THE SILENT CRY: HOW TO TURN TRANSLATIONAL MEDICINE TOWARDS PATIENTS AND UNMET MEDICAL NEEDS

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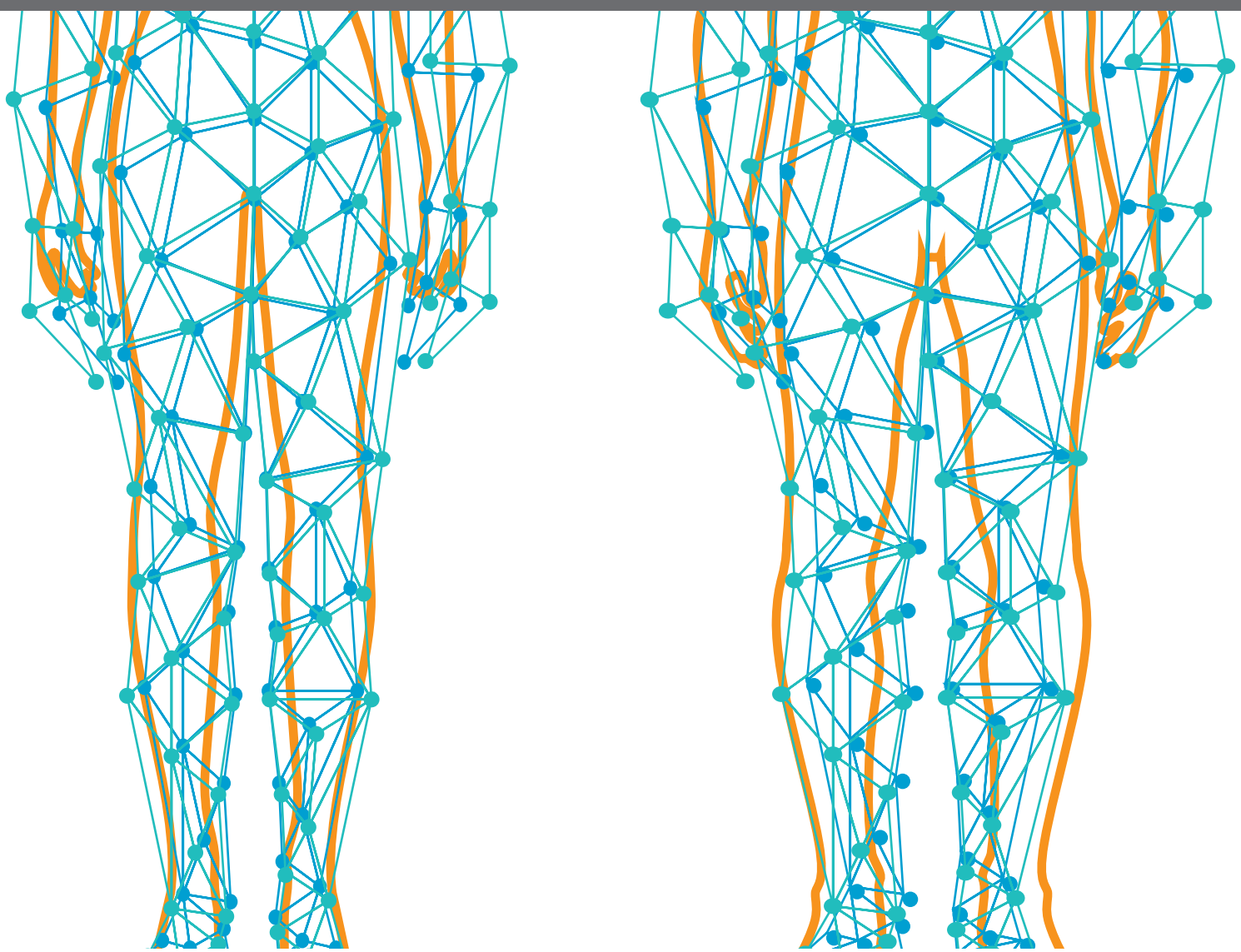

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THE SILENT CRY: HOW TO TURN TRANSLATIONAL MEDICINE TOWARDS PATIENTS AND UNMET MEDICAL NEEDS

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EDITORIAL
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Editorial: The Silent Cry: How to Turn Translational Medicine Towards Patients and Unmet Medical Needs

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Editorial on the Research Topic

The Silent Cry: How to Turn Translational Medicine Towards Patients and Unmet Medical Needs

Translational Medicine encompasses the continuum of activities that extend from the conception of an idea all the way till the development of new therapies and diagnostics for the benefit of patients. The purpose of this Research Topic "The Silent Cry: How to Turn Translational Medicine Towards Patients and Unmet Medical Needs" is to describe a new collaborative model of performing and teaching translational medicine revolving around an understanding of patient and societal needs, rather than on an exceptional idea desperately looking for a market need.

The translational medicine journey should ideally start with patients as engaged collaborators (Battaglia et al.), and continue to involve a myriad of stakeholders from basic scientists and physician scientists to intellectual property attorneys, regulatory professionals, and funders—including industry, as the innovation moves from "the bench to the bedside" (Tabori et al.). However, practically all translational medicine programmes to date have been driven by physician scientists and/or basic scientists with a personal passion, often working with minimal training and support, as their career-path doesn't align with that prescribed for either profession (van Dijk et al.), i.e., treating patients or publishing high impact papers. The dearth of patient inputs and of appropriate team-based problem-solving leads to potential medical solutions falling into unsurmountable "valleys of death," eventually resulting in wastage of talent, research, and funding.

The only way forward is to truly revolutionize translational medicine by making available appropriate education and support networks (Gohar, Gohar et al.). Training for translational medicine professionals requires not only the scientific and clinical skills that are currently taught in graduate or medical schools, but the soft skills required for creating an effective interface with society and patients as the primary stakeholders of an existing unmet need, as well as the managerial skills to orchestrate collaborations for the regulatory and business considerations (Gohar, Maschmeyer et al.). The curriculum should thus teach critical reflection and collaboration (Clay et al.), and include a "hidden" portion which teaches one to appreciate others' viewpoints as well as hones one's own communication skills (Foty et al.). The focus of both the training programs and environment in which translational medicine professionals work should be inter-disciplinary and focused on creating societal impact, rather than viewing publications as the last judgement (Kools et al.).

Efforts are underway to drive Translational Medicine toward this ideal (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419973/). Training programmes like the one run by Eureka Institute for Translational Medicine are currently providing the necessary education to a select cohort of professionals (Weggemans et al.). However, a change in how translational medicine is done and perceived by society will involve a change in thinking at a personal and institutional level. In today's data-driven world, both hospital systems and translational medicine professionals need to understand the considerations and implications of handling and mining vast patient datasets, and strive for a synergism between hypothesis-driven and data-driven experimentation to attain the best possible outcomes (Hulsen et al.). Translational Medicine professionals also need to be more actively engaged with social media to make sure advances are communicated with society accurately and to increase engagement with their stakeholders (Dijkstra et al.). Though basic scientists and physician scientists realize the potential of social media in making connections, for example between the innovators and physicians who run clinical trials, currently there is a lack of its practical use within the community (Sandalova et al.). Moreover, there is a need for creative problem solving during the translational medicine process (Goeltzenleuchter et al.), which will develop over time as the ecology matures and the various stakeholders truly appreciate each other's contributions and priorities while working together. To further strengthen team work and bring in different view points, there is also a need to create gender equity in the field, which can only be achieved by providing better societal support, hiring opportunities and mentoring for women in STEM (Bots et al.).

Despite the long road ahead, there are a number of successful translational medicine programmes that are already underway in a variety of disease areas. Immunomics in pediatric rheumatic disease has seen a number of advances in genomics, transcriptomics, epigenomics, proteomics, and cytomics—all unearthing new prognostic biomarkers and creating avenues for creating new therapies (Tay et al.). There are also trials underway to treat Type I Diabetes with immunotherapy (Coppieters and von Herrath), and currently innovative strategies such as combining immunotherapy with agents that promote Beta-cell survival are being tested. In the field of vaccine development, Controlled Human Infections (CHI) and question-based clinical development approaches are providing solutions to make vaccines more cost-effective and efficacious (Roestenberg et al.; Roestenberg et al.). The field of cognitive medicine is also progressing rapidly with advances in technologies like Diffusion Tensor Imaging (Lock et al.).

In summary, Translational Medicine is continuously evolving and as the field attracts more talented professionals with structured funding and career pathways available for their success, faster and better medical solutions will reach patients in need sooner. To fuel this Translational Medicine discipline, both physician scientists and basic scientists with a focus on patient-oriented research outcomes are needed. Early exposure to interdisciplinary environments and an organized institutional framework, including a dedicated program for translational medicine with accessible mentors is crucial. Reconsideration of the publication system and strategies for including important stakeholders throughout the process will put translational medicine advances in societal context, driving innovation in both directions.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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The Development of Immunotherapy Strategies for the Treatment of Type 1 Diabetes

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Optimized insulin therapies, increased use of continuous glucose monitoring/insulin pumps and most importantly the arrival of reliable closed loop systems will undeniably lead to a reduction in the burden of complications that arise from type 1 diabetes. However, insulin therapy will only ever treat the symptoms of the disease and will not alter the underlying pathology. The aim of immunotherapy treatment is to modulate the immune system, a strategy that has been successful in autoimmune conditions such as multiple sclerosis, rheumatoid arthritis and lupus. However, the success rate of immunotherapy treatment in type 1 diabetes has been low. There are several distinct stages of T1D development. In this review, we summarize the most important immunotherapeutic approaches tested thus far and focus on the characteristic features and unmet need within the different stages of the disease.

Keywords: type 1 diabets, immunotherapy of cancer, insulin, tolerance, trials

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RATIONALE FOR IMMUNOTHERAPY IN T1D

Background-T1D as an Autoimmune Disorder

Type 1 diabetes is characterized by the progressive loss of pancreatic beta cell function, eventually culminating in patients' dependence upon exogenous insulin to control blood glucose. Despite continuing improvements in insulin therapy, the majority of patients fail to adequately control their glucose homeostasis (1), resulting in both short-term (hypoglycemia) and long term (nephropathy, retinopathy, neuropathy, and others) complications. This well-documented fact leads to a significant unmet medical need and there is therefore an incentive to develop disease modifying therapies which could be used in addition to symptomatic treatments.

Disease modifying therapies by definition are designed to tackle the underlying cause of the condition. It has been known for decades that T1D is associated with autoantibodies (2) and inflammatory infiltration of the pancreatic islets (3). Early genetic evidence revealed a profound contribution of the HLA region, (and MHC class II in particular). With the advent of the GWAS era, many of the susceptibility regions were shown to code for proteins important in immune function and considerable overlap was found with the genetic signature of other autoimmune conditions (4). The combined evidence thus overwhelmingly favors a pivotal role of leukocytes, and especially T cells, during beta cell destruction.

The T cell repertoire associated with T1D development is by all accounts diverse and is directed against beta cell specific molecules such as insulin, as well as autoantigens that are also expressed in other tissues, such as GAD. Although some progress has been made in using T cell signatures as disease biomarkers in individual patients (5), the kinetics and composition of these repertoires still appear to be largely unpredictable.One of the reasons may

be that these parameters are typically measured in blood samples without the possibility of linking any observations to events at the target organ, which is extremely difficult to biopsy.

Finally, the autoimmune response and accompanying beta cell decay should be seen as a chronic, subclinical process that is initiated by unknown environmental factors long before clinical diagnosis. What has been unequivocally established is that autoantibodies serve as a reliable predictor of disease. Subjects with multiple autoantibody species carry a lifetime risk of developing T1D approaching 100% (6). This is a very powerful measure and it could be that high risk of T1D should be treated as a distinct, yet silent indication (6); much like hypertension is defined as a prodrome to stroke and myocardial infarction (7).

Immunotherapy From a Patient Perspective

Before looking into any potential immunotherapy targets, careful consideration should be given to the desired clinical outcomes. First and foremost, T1D presently is considered a chronic metabolic condition which can be adequately controlled with modern insulin therapy. Any disease modifying therapy administered at any given disease stage should therefore be exquisitely safe. This therefore excludes chronic immunosuppression regimens, which may have a safety/efficacy balance that is acceptable in situations of high risk (for instance transplantation), but carry side effects related to host defense and tumorogenicity that are unacceptable in T1D.

The clinically relevant efficacy outcomes for immunotherapy in T1D depend on the disease stage being treated. A consensus paper was recently published that defines four distinct stages of T1D development, three of which are situated prior to conventional diagnosis and one after (6). A close look at the characteristic features and unmet need within each of these stages helps to optimally frame experimental animal work and data interpretation.

Pre-stage 1: Genetic Susceptibility and Genetic Risk

At this stage individuals carrying T1D susceptibility alleles have not yet developed islet autoantibodies. The risk/benefit proposition to incentivize patients, physicians and payers to commence preventive therapy at this stage will depend on the individual degree of risk, which for instance in case of multiple affected first degree relatives only amounts to 20–25% (8). Furthermore, the progression rates vary wildly, with many years' difference in time of onset even between identical twins (9). As an example of screening efficiency, the German Fr1da study tested ∼27,000 children aged 2–5 years for antibodies at routine pediatric health exam visits and ended up with ∼0.4% harboring antibodies (10). This renders clinical development for this sub-indication a lengthy and costly endeavor, also taking into account that most subjects in this segment will be pediatric cases.

All the above implies that immunotherapy at this stage should be superiorly safe, convenient, and efficacious in delaying clinical diagnosis. On the other hand, this is arguably the stage that from a mechanistic immune modification/suppression perspective, treatment with immunotherapy would be most likely to be successful. Since no signs of active autoimmunity are present, one could argue that the autoreactive T cell repertoire has not expanded and adopted a memory phenotype, a state which many believe is hard to reverse. This notion is also supported by the vast majority of animal models studies, with many experimental therapies proving efficacious only when administered to neonatal or juvenile animals. We argue that some of the failures in clinical translation may stem from the inappropriate extrapolation of pre-clinical data situated within the animal model equivalent of Pre-Stage 1 into trial designs including exclusively Stage 3 patients. Antigen-specific therapies could be well suited for this stage and will be discussed below for the example of oral insulin.

Stage 1: Autoimmunity+ Normoglycemia (Presymptomatic)

This is the stage where individuals have developed measurable signs of autoimmunity in the form of autoantibodies. It can be inferred that some time before, seroconversion processes such as islet antigen presentation, T cell activation and plasma cell formation have taken place and that insulitis has been initiated in some parts of the pancreas. However, the histopathological experience from nPOD, the largest collaborative tissue database for T1D, indicates that very limited beta cell loss occurs prior to diagnosis (11). This may suggest that the bulk of immunological destruction occurs around diagnosis in response to a putative environmental trigger, such as a viral infection. Indeed, a study measuring enterovirus RNA or viral protein in blood, stool, or tissue of patients with pre-diabetes and diabetes found that there was a clinically significant association between enterovirus infection and T1D (12). Recent data support two clear phases of C-peptide decline following this initial event: an initial exponential fall over a 7-year period, followed by a prolonged stabilization where C-peptide levels no longer decline (13).

When multiple islet autoantibodies are detected, patients, physicians, and payers can be presented with the prospect of a lifetime risk approaching 100%. The antibody assays are currently used at the time of diagnosis but a consortium consisting of academic and industry partners led by the Critical Path Institute (https://c-path.org/) is currently working toward regulatory approval of these biomarkers for use in development programs in the presymptomatic stages of T1D.

This stage, along with Stage 2, can be experimentally modeled by including animals at a later age when the disease process is already advanced and the autoreactive T cell repertoire to some extent has expanded and adopted a memory phenotype. Whereas antigen-specific therapy would fulfill the requirements pertaining to safety, the thought is emerging that conventional antigenic tolerization strategies may be insufficient to tolerize T cells already committed to a functional activated memory lineage.

Stage 2: Autoimmunity+ Dysglycemia (Presymptomatic)

Much like in Pre-Stage 1, clinical development in Stage 1 is complicated by the long and varying progression rate to diagnosis, with 5-year and 10-year risks being ∼44 and 70%, respectively. By implementing glucose tolerance testing, 5-year risk can be increased to ∼75%, which reduces both trial size and

duration (6). An attractive proposition for both Stage 1 and 2 individuals would be to reduce disease risk by half or double the time to diagnosis. Other than treating as late as possible prior to hyperglycemia development, Stage 2 is not routinely separated from Stage 1 in animal models.

Stage 3: Autoimmunity+ Dysglycemia (Symptomatic)

By far the majority of development activity for immunotherapies in T1D has focused on this disease stage, immediately after diagnosis. At that point, patients are assumed to have lost up to 90% of their functional beta cell mass, yet many retain a fraction accounting for measurable C-peptide levels. The DCCT trial long ago indicated that patients benefit from this preserved endogenous insulin secretion through reduced risk for long and short term complications (14). It has therefore been proposed that immunotherapy, while not sufficient to restore normoglycemia, could be employed to preserve remaining beta cell function at clinical diagnosis.

The onset of clinical symptoms and the consequent need for exogenous insulin therapy result in a slightly less sensitive risk/benefit balance as compared with the presymptomatic stages. Since the disease has progressed to full-blown islet destruction driven by a fully activated autoreactive repertoire, antigen-specific monotherapy no longer is a viable option. To our knowledge, not a single antigen-specific therapy is able to reverse hyperglycemia in autoimmune diabetes models. The prevailing view is that the disease should at this stage be modified with a short course of pathway specific immune modulators such as biologicals, alone or preferably in combination with antigen-specific maintenance therapy.

From a value perspective, immunomodulatory strategies at this stage have come under pressure in recent years. The prognosis is that optimized insulin therapies, increased use of continuous glucose monitoring and insulin pumps and most importantly the arrival of reliable closed loop systems will reduce the burden of complications in T1D. The added value of maintaining endogenous C-peptide at the expense of diminished immune function, even if temporary, thus becomes less attractive. Nonetheless, owing to the more easily available patient population, this stage could in the future be utilized to obtain more rapid proof-of-concept results prior to embarking on more resource-draining prevention studies.

Disease Heterogeneity

Before transitioning to a discussion of some of the therapeutic concepts and studies situated in the 3 disease stages outlined above, the heterogeneous natural history of T1D deserves highlighting. It is clear that both rate of progression to clinical onset in the prevention stage and loss of C-peptide after onset show high inter-individual variation. Some underlying variables are well known such as the relationship between age at onset and rate of C-peptide decline. The majority of mechanistic factors underlying variability in disease course, however, remain poorly characterized.

This heterogeneity considerably affects trial size. For instance, while individuals with multiple autoantibodies have a near 100% lifetime disease risk, the 3- and 5-year risk which is relevant to outcome trials, happens to be much lower. The community has attempted to address this problem for instance by seeking to identify fast progressors via more comprehensive risk scores (15) or in stage 3 by correlating immune biomarkers with metabolic outcomes (16). This has proven to be extremely difficult in a polygenic autoimmune disease such as T1D, with hyperglycemia onset being the likely consequence of diverging immunopathological pathways.

Finally, biomarkers that are able to predict therapeutic responders would be the first step toward the holy grail of personalized medicine. Numerous attempts have been made with mostly some interesting *post-hoc* responder correlation findings (17, 18). We are, however, not aware of studies that managed to identify solid response biomarkers that would support use as an inclusion criterion for further studies. The market reality for industry is also such that, unless the target population can be cost-effectively identified with exquisite specificity and sensitivity, the business case for sub fractionation of an orphan indication such as recent-onset T1D becomes rather difficult and fragile. On the positive side, it is our belief that the well characterized prognostic value of islet autoantibodies calls for moving toward development of drugs into this space and eventually population wide risk screening (6).

A Look at the Present Development Landscape

Without intending to provide a complete overview [which can be found in Coppieters et al. (19)], we will discuss some of the more notable immunotherapies tested in T1D. Likely due to past failures and the limited financial case associated with treatment of a subgroup of T1D patients, few immunotherapy agents have been designed specifically for the treatment of T1D. Instead, most of the drugs tested in T1D have been repurposed from major autoimmune indications or the transplantation field.

Studies in the Presymptomatic Phase of T1D

Only a handful of trial consortia have consistently screened for and identified at-risk subjects, and therefore trial activities in the presympromatic stages have been relatively scarce. The most important consortium active in this space has been TrialNet (https://www.trialnet.org/), a US-based international clinical consortium that offers screening and trial inclusion. TrialNet has since its inception screened in excess of 160,000 subjects at a rate of ∼15,000/year.

The case of oral insulin tolerization will be discussed in detail in the next section. Two ongoing TrialNet prevention studies using biologicals are of interest. Abatacept, a CTLA-4Ig fusion molecule approved in several autoimmune indications, had been trialed earlier in Stage 3 patients (20). A delay in C-peptide decline was observed exclusively in the first 6 months after treatment initiation and the effect disappeared during subsequent dosing. Considering that CTLA-4Ig acts through costimulation blockade, as part of the early T cell activation process, it could be argued that such priming events predominantly take place earlier in the disease process. Based on this assumption, a prevention trial is currently enrolling Stage 1 subjects (NCT01773707).

However, CTLA-4 is expressed on the membrane of both conventional activated T cells and regulatory T cells, and so it is possible that using this approach in isolation, will not be successful.

One of those few dedicated T1D drugs with an elaborate pre-clinical and clinical history is the anti-CD3 monoclonal teplizumab. Once seen as the most promising immune modulator for T1D, it infamously failed in phase 3 trials in Stage 3 T1D (21, 22). Only treatment using the highest dose of teplizumab (and in particular in those randomized <6 weeks after diagnosis) led to preserved β-cell function for several months, maintaining significantly higher levels of C-peptide and allowing glycemic control to be achieved at a lower insulin dose in the teplizumab groups than in the placebo group. The somewhat contested composite endpoint of insulin usage and HbA1c (23) illustrates the issue raised above on attaining clinically relevant value, namely that an attractive and commercially viable product needs to offer more than C-peptide preservation. Anyhow, not unlike the rationale behind abatacept, it was reasoned that a course of T cell depletion earlier in the disease process may confer more meaningful benefit and an ongoing trial therefore targets Stage 2 T1D (NCT01030861).

Both the abatacept and teplizumab trials are expected to inform the R&D community on three key aspects of T1D drug development. First, one could question if potent T cell modulation or depletion with a proven drug does not delay the disease course, which type of T cell immunotherapy will? Second, if these trials succeed they validate the aforementioned strategy to use Stage 3 trial data as a gatekeeper for development in the pre-symptomatic phase. Lastly, positive data would validate the extensive pre-clinical datasets predicting the efficacy of T cell modulation, while negative data would cast doubt on their value.

A final trial worth mentioning is situated in the antigen-specific class. Diamyd® is a GAD-based vaccine formulated in alum adjuvant that previously failed to preserve C-peptide in Stage 3 patients during phase 3 development (24). The DIAPREV-IT trial was the first prevention study with Diamyd® and the results have been presented at ADA-2017 *(http://www.diabetes.org/newsroom/press-releases/2017/larsson-scientific-sessions-2017.html).* The trial enrolled subjects at Stage 1 and 2, who received 2 subcutaneous doses. 18 out of 50 subjects developed T1D in the observation period with no significant differences between treated and placebo and no effect on C-peptide or blood glucose. Newly published pre-clinical data also appear to question the potential of GAD based vaccination strategies (25).

Studies in the Symptomatic Phase of T1D

As outlined above, this is the most accessible stage of disease from a trial recruitment perspective and most of the clinical development activity in immunotherapies has occurred in this space. TrialNet and another public clinical trial consortium, the Immune Tolerance Network (ITN), have performed many of the pioneering studies. Almost all drugs tested had been approved in other autoimmune or transplantation indications and taken into T1D studies based on varying degrees of evidence for overlapping disease pathways. Examples include rituximab [anti-CD20 (26)], abatacept [CTLA-4Ig (20)], alefacept [anti-CD2 (27)], canakinumab [anti-IL-1 (28)], and anti-thymoglobulin (ATG, pan-T cell (27)].

The results using imatinib (Gleevec), a tyrosine-kinase inhibitor approved for chemotherapy in cancer indications, in Stage 3 T1D were just presented at ADA-2017. C-peptide levels were significantly preserved vs. placebo and reduced exogenous insulin usage was accomplished at the expense of mild to moderate AEs (infection, gastrointestinal,…).

Dedicated T1D agents, such as the anti-CD3 monoclonals teplizimab and otilixizumab (29, 30), as well as GAD-alum (Diamyd) have shown great promise in terms of C-peptide preservation in phase 2 trials but failed to meet endpoints in phase 3 development.

Collectively, it can be concluded from the moderate and transient C-peptide preservation observed in some of the above trials that immunotherapy is indeed capable of disease modification as late as in Stage 3. However, different study designs, and testing sequential or repeated treatment may be advised to improve efficacy.

An alternative strategy that has gained traction is to target complementary pathways through combination therapy. Low-dose proleukin (IL-2)+rapamycin (31) and daclizumab (anti-CD25)+mycophenylate (32) were combination therapy examples, with the former actually showing temporary disease acceleration. Thus, increasing efficacy by interfering with distinct immune functions does not necessarily result in improved safety and tolerability, or trial complexity for that matter. A more recent study exploring the combination angle was ATG+ Neulasta (G-CSF) which demonstrated beta cell preservation in Stage 3 patients (33, 34). In a way, the polyclonal Treg cell transfer technology currently tested by Caladrius (NCT02691247) in itself is also an example of combination therapy since expected to target multiple disease pathways downstream of the Treg.

A special category of combination therapy includes both an immunologic agent and one that acts to preserve beta cell health/function (35). The rationale behind such an immune-metabolic combination is that tackling the immune component of the disease with a cocktail of immune modifiers alone often comes at the expense of side effects related to immune suppression. Furthermore, even if the autoimmune part of the disease is adequately addressed, survival and functionality of the remaining beta cell pool may need to be targeted from a distinct therapeutic angle. One such example may consist of an immune modifier in combination with a GLP-1R agonist, a peptide drug class commonly prescribed in T2D. Several studies have suggested that GLP-1R agonism has protective effects on the beta cells, likely through mechanisms of ER stress relief (36, 37). The hypothesis then is that simultaneously dampening the autoimmune component with an immune modifier and relieving beta cell stress could lead to improved beta cell survival and functionality. A Novo Nordisk study using a neutralizing anti-IL-21 antibody in combination with the GLP-1R agonist liraglutide is underway (NCT02443155) (38).

Finally, significant progress has been made in recent years on the generation of stem cell derived beta cells and their implantation to replace lost beta cell mass. San Diego-based Viacyte has now conducted the first phase 1 trial on the concept (NCT02239354) and hopes are high that longstanding patients and especially "brittle" diabetic cases will benefit from this approach. However, depending on the success of accompanying encapsulation devices being able to protect the grafts from allo-rejection and autoimmunity, an effective, tolerable, and safe immunotherapy may actually also be needed in this niche.

CASE IN POINT: ORAL INSULIN TOLERIZATION

The concept of tolerization of the immune system through ingestion of antigenic substance dates back to ancient times. In the area of hypersensitivity and food allergies, the concept recently showed considerable promise with examples including protection against peanut (39) and egg white allergy (40). Within the context of autoimmunity, data from pre-clinical models and small proof-of-principle trials had suggested disease modifying action, which fueled larger scale trials. The company Autoimmune Inc., spun off from the results of Weiner and colleagues, tested oral tolerance therapy in major indications such as RA and MS but was ultimately unable to demonstrate significant disease amelioration (41).

A high profile endeavor in T1D was the clinical testing of oral insulin administration in at-risk subjects by TrialNet. The Diabetes Prevention Trial—Type 1 Diabetes (DPT-1) was the first major prevention trial with mass risk screening of relatives of T1D patients (42). Over 100.000 relatives were screened for islet autoantibodies and 372 were assigned to receive 7.5 mg /day oral insulin or placebo. At endpoint, the annualized rate of diabetes was similar in both groups. *Post-hoc* analysis did suggest that there was benefit in a subgroup with insulin autoantibodies (IAA), which formed the premise for a subsequent study in this population (43). Stage 1 participants with normal FPIR (first-phase insulin response) showed no delay or prevention. In a small subgroup (27 treated vs. placebo) with abnormal FPIR (=lower functioning beta-cells), oral insulin delayed T1D onset by an average of 31 months. The biological foundation for this observation remains unclear but it may point toward underlying heterogeneity of the disease.

Inspired by this long development history, we at Novo Nordisk recently concluded a careful experimental reassessment of the pre-clinical dataset on oral insulin in T1D (44). We first reasoned that timing of administration and dose are the most likely major variables that influence outcome. Considering the low-mg range doses typically given in mice, the 7.5 mg daily dose used in the DPT-1 trial does not represent the expected extrapolated dose going from animals to men.

Furthermore, many studies, including the original study by Weiner and colleagues, initiated treatment at 5 weeks of age in NOD mice (45). This age models Pre-stage 1 and we therefore found it important to assess disease prevention at 9 weeks of age, which would be the equivalent of Stage 1 as enrolled in DPT-1. Additional variables tested based on literature evidence were species origin of the insulin (46) and introduction of amino acid substitutions that rendered insulin metabolically inactive (47).

The sobering outcome was that none of the regimens tested in this treatment matrix resulted in disease protection (44). We found that orally administered insulin is degraded within minutes, which would also have been the case with the administration route used in DPT-1. A remarkable feature of gavaging insulin in large buffer volumes in mice was that the dosed solution travels immediately past the stomach into the small intestine, the purported site of action for oral tolerance induction. We therefore performed tolerance studies using endoscopic dosing of insulin in enteroprotective capsules in pigs but were unable to demonstrate any tolerizing effect (unpublished data).

Our negative oral insulin findings do not stand in isolation within the field of antigenic therapies for T1D. In collaboration with the Lenardo lab, we found no support for the tolerizing effect of parenteral, metabolically inactive insulin as had previously been reported (48). Likewise, published data on disease prevention using a strong agonist insulin mimetope did not appear to be reproducible (49).

What could be the reasons for these failures to reproduce pre-clinical data? Whereas the argument on animal colonies differing in terms of microbiome and disease penetrance might have basic scientific merit, it bears little relevance in view of the fact that therapies ultimately have to prove their value in an outbred human population within an uncontrolled environment. In other words, preclinical evidence should be robust enough to hold up in different vivariums. A possibility is that antigenic tolerance in general confers some degree of protection but is overall not potent enough to be universally reproducible. Thus, the labs where disease progression occurs less aggressively would be the ones observing benefits. For instance the original Weiner study had only 50% incidence in the control group, whereas we consistently reached around 70%.

Finally, it might be that, from a mechanistic point of view, antigen-specific monotherapy is unable to curb the established effector memory T cell responses that are characteristic for autoimmunity. The autoimmune response also qualitatively differs from the allergic response and that may be the reason why only the latter can still be modified late in the disease process. For T1D prevention, that is also what animal models have historically showed, namely that antigenic monotherapy only works in the very early disease stages equivalent to Pre-Stage 1. This hypothesis formed the rationale for the PRE-POINT study, which dosed Pre-Stage-1 in genetically at-risk, autoantibody negative children with oral insulin (max dose 67.5 mg) (50). Some immunological modification was observed upon dosing, and studies such as the Bavarian Fr1da insulin intervention study could elucidate whether this actually translates to prevention of seroconversion (NCT02620072). Rather than further narrowing down potential responder populations in later disease stages, we believe the Pre-stage 1 indication is the more applicable one

going forward also based on the available body of animal model data.

CONCLUSION

Immunotherapy for T1D has a checkered clinical history with a number of high-profile failures in the late development phase. In response, some have questioned the predictive value of animal models. We believe animal models continue to have their place in immunotherapy development for T1D, provided that they are used appropriately.

The current trend is toward combining drugs to enhance efficacy. An example would be Novo Nordisk's development program on anti-IL-21 program, where the original aim was to provide pre-clinical data in support of targeting a recent-onset T1D indication. While anti-IL-21 monotherapy potently prevents diabetes in the NOD model, it does not reverse.It was therefore opted to combine the GLP-1R agonist liraglutide with anti-IL-21, resulting in reversal after hyperglycemia onset in the NOD model. The program is currently in phase 2 in adult, recently diagnosed T1D patients, with primary endpoint on beta cell preservation (NCT02443155).

In conclusion, the past few decades have taught us that immunotherapy holds promise in T1D, but we haven't cracked the code yet in terms of acceptable safety/efficacy balance. We now have the knowledge to identify subjects earlier in the disease process before diagnosis, a disease state that might be easier to modulate. The near future will tell whether that hypothesis holds true, which would effectively turn T1D into a preventable condition.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CURRICULUM, INSTRUCTION, AND PEDAGOGY
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Thinking Critically: How to Teach Translational Medicine

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Translational Medicine (TM) is a comparatively new field of study that focusses on the continuum of activities from the conception of an idea, to advanced clinical testing and the development of a new medical technology or drug. In recent years, graduate education programs have been established internationally to train a new generation of professionals with specific skills necessary to navigate the translational landscape. Literature in the area highlights the importance of integrating specific competencies relevant to translational medicine as part of curriculum development. In addition to developing a working understanding of core knowledge (e.g., ethics, funding, regulation, policy, etc.), skills including effective communication, reflection, interdisciplinary, and interprofessional collaboration are critical components of a skilled TM professional. Curriculum development must focus on content, while carefully selecting the teaching strategies that are most effective to achieve the desired outcomes, which is for learners to comprehend the complex material. The following publication presents a series of vignettes that describe the experiences of an associate professor of molecular biology, who is looking to explore her role in translational medicine and develop skills for an innovative approach to problem-solving. The vignettes are focused on a variety of teaching and learning strategies that can be used to teach translational medicine. Each vignette includes a description of the experience from the perspective of the learner and the faculty as it pertains to the teaching strategy, method of delivery, and learning outcomes. TM is as complex to teach as it is to learn. The specialized skills and knowledges that are part of the TM toolbox cannot all be taught in a lecture format. Educators must consider multiple strategies and select those which are most effective for achieving the learning outcomes.

Keywords: education, curriculum design, translational medicine, hidden curriculum, communication, case study

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BACKGROUND

Translational Research (TR) is a comparatively new field of study that focuses on the process of moving scientific knowledge into real-world impact. A subdivision of TR, Translational Medicine (TM) specifically encompasses the continuum of activities from the conception of an idea to advanced clinical testing and ultimately, to the development of new medical technologies or drugs. The definition of these terms has been evolving in the literature for over a decade (1).

COMPETENCIES

Regardless of the definition, the ability to translate scientific knowledge into real-world health impact requires specialized core knowledges (Biomedical research, intellectual property, funding, regulation, legal issues, ethical issues, preclinical testing, design of preclinical, and clinical trials) and skills (networking, team-building, strategic thinking, creative problem-solving) (2). In addition to other programs in translational medicine, we have identified persuasive communication, as well as interdisciplinary and extraprofessional collaboration, as core skills. In recent years, graduate education programs have been established internationally to train a new generation of professionals with these specific skills necessary to navigate the translational landscape. Many teaching strategies have been proposed and employed to deliver this content. However, there is no consensus regarding the best methods of instruction.

Curriculum development in medical education is a process that combines educational theory and methodology with specific content, then evaluates its impact (3). The process equally focuses on content and the most effective teaching strategies for the learners to comprehend this complex material. Faculty in TM education programs are often recruited from academic medical centers for their content expertise and experience in delivering health care. However, they may not be trained in the competencies necessary for effective teaching, or curriculum development.

The pedagogical framework developed by Thomas (4) includes six essential steps to curriculum design in medical education: Step 1: Identify a problem; Step 2: Examine the particular needs of the audience; Step 3: Develop goals and measurable learning objectives; Step 4: Choose the educational strategies; Step 5: Devise steps for implementation, and; Step 6: Consider evaluation and feedback. The framework is a dynamic, interactive and systematic process, but do not always follow each other in sequence (3). One of our authors collaborated to create a curricular design based on Schwab (5) which focused on how we think critically about education and how we aim to teach TM. This design includes several educational strategies that integrate the hidden and the formal curriculum, and is a principle based curricula [**Table 1**; (6)]. The pedagogy is based on the constructivist learning theory (7) so that each participant has the opportunity to develop their own knowledge base in TM. Both large and small group case-based learning sessions are integrated into the curriculum along with short lectures, team-building and collaboration, recording of presentations, self-assessment, and mentoring groups that include mentoring from peers and expert faculty members.

RATIONALE

The innovative curricular design (**Figure 1**) presented below is aimed at teaching scientists and leaders who are working or intending to work, in the field of TM. In this article, we focus specifically on Step 4 of Kern's Model which addresses our educational objectives, our material, and our audience. We designed the curriculum to: (1) Analyze the business, scientific and regulatory aspects of TM; (2) Explore the challenges professionals encounter in TM including how to teach and learn; (3) Develop critical thinking skills to approach the challenges in TM, and; (4) Develop communication skills for presenting various topics to a broad spectrum of learners.

The skill of thinking critically in an open and safe learning environment is paramount in the curriculum as we focus on teaching to promote learning. We selected teaching strategies that enable students to master content using critical thinking skills. We designed the curriculum to teach material by enhancing the learners' ability to think and engage in their own learning, collaborate, and learn together.

LEARNING OBJECTIVES

The objectives of this article are to describe an innovative curriculum designed to teach TM, however, it could also be generalized to train other health professions. The following presents a series of vignettes that describe the experiences of a learner Susan Dias, Ph.D. Susan is an associate professor in molecular biology, who is attending a certificate program in TM as her first exposure to the discipline. She is a primary investigator within a hospital setting and has become increasingly frustrated. She is unsure that patient needs are driving her scientific questions, and she believes her narrow hypothesis-driven research is limited. Susan is looking for a different, more innovative approach to problem-solving. The vignettes are focused on a variety of teaching and learning strategies and theories that can be used to teach translational medicine and include case-study design, presentation skills, reflection, team-building, and the hidden curriculum. In addition to these vignettes, each section below will include key points for faculty to consider as it pertains to the respective teaching strategy, learning outcomes, and a personal reflection. All persons and data presented in this manuscript are fictional.

PART I-THE HIDDEN CURRICULUM (TABLE 2)

It's the morning of my first day at the certificate course in TM. I'm excited, albeit a little anxious to meet the other attendees and get started. The foyer of the building is filled with nervous energy; the room full is of people sipping espresso and making small talk. I grab a coffee just as we're asked to make our way into the lecture hall. As I walk through the doors, I'm taken aback. The room is less a lecture hall than a large dining room with 30 chairs arranged in a circle and no lectern or obvious indication of which way we should be facing. Intrigued and curious, I take a seat. When the room settles, the person seated to my right who I now realize is leading the session, welcomes us to the program. We are each given a notebook to use as our journal through this experience. In them, we are asked to write our reflection on each day's activities which will be used to frame an open discussion each morning in a debrief meeting with a faculty member. I'm intrigued by this reflection exercise. What exactly is it that they want us to write in our journals?

TABLE 1 | Chart of teaching strategies.

Strategy	Advantages	Disadvantages	Example situation
Lectures/Presentations	Good for primary explanation and clarifying concepts	Teacher-centerd, not learner-centerd; Generally, cannot review the presentation	Review of the Translational Medicine pathway
Case discussion	Useful for developing: problem-solving; critical thinking; demonstrating different points of view; effective communication; teamwork	May take time for the concepts to evolve; some members of the group may not participate	Case study to identify unmet patient needs; understand underlying problems; brainstorm possible solutions and implementation strategies
Questioning	Broadens/challenges ideas; involves the learner in the process	Skills are required to understand the range of question types	What is the participants knowledge of Translational Medicine?
Practicing	Begins to change behavior with personalized instruction; reinforces concepts	Takes time; may require observation by an instructor	Presentation workshop.
Feedback	Begins to change behavior; essential for learning	The teacher may not give useful or even any feedback	Peer review of presentation
Handouts/printed materials	Often used to illustrate initially and then useful for later reference	Information may not convey nuances; quantity of information may overwhelm	Graphic overview of Translational Medicine pathway
Computer-assisted instruction: e-learning	Good for initial instruction; practice; repetitions, and; future reference	The learner may need to obtain basic computer skills before using, may have mechanical" quality	Online materials required to establish a base knowledge of the day's topic before a seminar
Simulated cases/role play	Useful in helping learner apply material	Learners may feel threatened; may be difficult to relate to the character or situation	Practicing an elevator pitch; how to present to a chair or a foundation to obtain funding; Feedback is given
Video recordings	Useful in support of content presented in a lecture	Need audiovisual equipment, may be difficult to relate to the character or situation	A patient and family perspective
Slides	Visual reinforcement good for clarity; useful when presenting complex material	Information is very brief, cannot easily repeat the information	Introductory lecture on intellectual property law
Reading	Good for instruction, future reference, further exploration	No interaction with people	Reading in preparation, or as a follow-up to in-class discussion
Review, repetition	Reinforces concepts learned	Time-consuming	Having teams iterate on a conceptual prototype to achieve a solution to a patient need
Reflection	Examines aspects of an experience and develops reflective practice skills; allows expression and determines meaning	Time-consuming	Morning debrief sessions and journal writing

A flip chart is brought out, and we are each asked in turn to write down our names and tell an associated story. I'm already feeling a little nervous, although it has only been a few minutes. We spend quite a bit of time on these introductions, which actually turn out to be a fantastic ice-breaker. Something about seeing the names written down and associating them with a story made it very easy to remember everyone.

The next team-building activity is even more unusual. We stand up and are asked to converse with five different attendees, beginning each time with a different question: (1) Who are you? (Do this without discussing your name, job position, educational background, roles in life, and place of stay or birth); (2) Why did you start working where you work and why do you work here today? (3) What frustrates you the most about your work (concerning translational medicine)? (4) What gives you energy and fuels your engine through the day? (5) What is something small, or more significant you would like to change in your work environment concerning translational medicine? (9).

I hesitate. Discussing my passions, frustrations, and aspirations with a group of individuals I've just met is even more uncomfortable than the introductory exercise. Timidly, I approach one of the attendees, then another. I quickly realize that this is a very diverse group of people in different stages of life, from different backgrounds, disciplines, and professions. Despite these differences, I feel myself connecting with my new peers. We all share common challenges and frustrations; we are looking for ways to have a more positive and direct impact on patient health.

After a full day of sessions, the program has us head to a nearby restaurant for a dinner and social. Faculty and attendees are talking about the day, and our family lives back home. We're enjoying the night so much we hardly realize how late it is. Knowing we have an early morning ahead of us, we say our goodnights and retire for the evening.

Reflection and Journal Entry

It's my first day and I'm starting to feel a sense of connection with the other participants and the faculty. The morning introduction exercises and the informal interaction at dinner pushed me far outside my comfort zone. I registered in the program because I felt I needed a fresh approach to research. Maybe this is

Time Start	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
8:00	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:
8:15	Coffee & Networking	Coffee & Networking	Coffee & Networking	Coffee & Networking	Coffee & Networking	Coffee & Networking	Coffee & Networking
8:30	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:	Hidden Curriculum:
8:45	Debrief, Reflection,	Debrief, Reflection,	Debrief, Reflection,	Debrief, Reflection,	Debrief, Reflection,	Debrief, Reflection,	Debrief, Reflection,
9:00	Journal Entries	Journal Entries	Journal Entries	Journal Entries	Journal Entries	Journal Entries	Journal Entries
9:15							
9:30	Hidden Curriculum:	Off Campus	Interactive Lecture	Large Group Session	Large Group Session	Large Group Session	Large Group Session
9:45	Welcome & Intros	Team-Building Exercises		Creativity: Team Art Project			
10:00			Break				Break
10:15	Break		Interactive Lecture		Break		Presentation Video II
10:30	Large Group Session				Unfolding Case		& Feedback
10:45					Study II		
11:00							
11:15							
11:30			Hidden Curriculum:				
11:45			Group Lunch		Hidden Curriculum:	Hidden Curriculum:	
12:00				Hidden Curriculum:	Group Lunch	Group Lunch	
12:15				Group Lunch			
12:30	Hidden Curriculum:						Hidden Curriculum:
12:45	Group Lunch						Group Lunch
13:00			Presentation Video				
13:15			& Feedback		Large Group Session	Large Group Session	
13:30	Large Group Session			Large Group Session			
13:45				Stories of Success			Large Group Session
14:00							
14:15						Unfolding Case	
14:30	Interactive Lecture					Study III	Free Time
14:45					Personal Work Time		
15:00			Break	Break	for Presentations		
15:15			Large Group Session	Large Group Session		Break	
15:30	Break					Mentoring Session II	
15:45	Large Group Session						
16:00	Patient Perspective	Break					
16:15				Unfolding Case			
16:30				Study I	Break		
16:45					Speed Dating II		
17:00		Interactive Lecture					
17:15			Speed Dating I*				
17:30							
17:45				Intro to Mentoring			
18:00				Mentoring Session I			
18:15				Small group			
18:30				Peer & Faculty mentoring			
18:45		Hidden Curriculum:					
19:00	**Hidden Curriculum:**	**Evening social**	Free Evening		**Hidden Curriculum:**	Free Evening	**Hidden Curriculum:**
19:15	**Evening social**				**Evening social**		**Evening social**
19:30							
19:45							
20:00							

FIGURE 1 | Sample curriculum design for translational medicine. Shaded area indicates strategies that are highlighted in this publication. *Participants have the opportunity to voluntarily sign up and meet individually with a faculty member for 10 min.

TABLE 2 | Key points of the hidden curriculum.

1. Create a safe environment (team-building activities)
2. Intentional room setup (e.g., the orientation of chairs, the absence of computers or projectors)
3. Use multiple approaches to influence using the hidden curriculum (8)
   - Formally structured and intended social activities
   - Informal, unplanned, and unscripted social activities
   - Less tangible influences such as organizational culture
   - Debrief and journal entry

where it starts, and these activities are meant to create a safe environment where we feel comfortable to share, grow, and learn from each other. I wonder why this has not worked as effectively at other conferences or courses I have attended? I imagine it has something to do with these well-programmed interactions and having been taken away from our daily routines. This purposeful setup has most certainly contributed to building this fantastic network of new colleagues.

This must be the kind of reflection they're expecting of me. Sitting down in silence for 10 min to pen down my thoughts is refreshing. This is definitely something I am going to incorporate in my life back home.

PART II–THE UNFOLDING CASE (TABLE 3)

The next morning starts similarly with an early morning social over coffee. Groups of six participants are assigned to separate classrooms where we are greeted by two faculty members. This is the unfolding case, and the faculty members are to serve as facilitators to guide us.

We are presented with a case study on finding biomarkers for a new cancer drug that reads like a story. There is a protagonist, several supporting characters, a clear plot line, and it's actually quite engaging. The dilemma presented feels like a puzzle that I really want to solve.

The facilitators sit silently at the table, while we begin our discussion. Within minutes our entire group is speaking over each other, and each of us is offering a different opinion; each of us insistent that ours is the best way forward. After several minutes of this cacophony, I ask the facilitators if we are on the right track. They smile and suggest we begin by ensuring that everyone in the group understands the terminology in the case, and precisely what the question or dilemma is. Assuming we all understand the topic seems to be our first mistake. Once we reviewed the case and all understood the tasks at hand, the facilitators suggest we spend a few minutes familiarizing ourselves with each other's professional expertise. Amongst the other participants, there is a basic scientist, an epidemiologist and someone who works in marketing for pharmaceutical companies. Like me, these three participants have never seen a patient professionally. The final two participants are physician researchers involved in clinical trials.

Having a better handle on the various skills we had around the table, we begin to brainstorm the different angles of the problem. As a lab scientist, my thoughts immediately swing to the *in vitro* and *in vivo* experiments that must be done to better understand

TABLE 3 | Key points of the unfolding case.

1. Occurs over 2 or more sessions
2. Small groups of 4-6 people are ideal to have all participate.
3. The group members should have diverse expertise (interdisciplinary, interprofessional) complementary skills sets.
4. Role of the Facilitator(s):
   - Actively listen to the discussion to ensure the learning objectives are being met
   - Allow learners to set the agenda
   - If all the group members share similar opinions or arrive at a consensus too quickly, ask questions that require the group to approach the problem from different perspectives.
   - Encourage the group to voice conflicting viewpoints and support their own view.
5. A good case: (10–12)
   - Tells a story
   - Has a dilemma to be solved
   - Is relevant to the reader
   - Is real rather than fabricated
6. Specific to TM, a good case also:
   - Requires knowledge from multiple disciplines and professions
   - Has no single correct answer, but several paths to follow that may lead to a positive outcome
   - Requires learners to view problems from multiple perspectives
   - Draws on skills and knowledges that have been previously introduced, or
   - Is designed to introduce new skills and knowledges
   - Has specific learning objectives (e.g., Critical thinking, creative thinking, collaboration, effective communication)

the biologic question. However, I soon realize that there is much more at stake and that the lab component is merely one tiny slice of a much larger pie.

The case unfolds over three separate sessions. While I'm able to contribute to the conversation at the outset, I find myself reserved and quiet when the group begins to discuss issues around intellectual property, funding, clinical trials, patient involvement, companion diagnostics, ethics, and regulation. This case is much more complex than I had initially thought and I'm thankful we have so much diverse expertise sitting around the table.

Reflection and Journal Entry

When we started the case study, I thought the way forward was quite evident. The dilemma was rooted in basic science, and while I am well equipped to contribute to the problem-solving, I wondered what value an epidemiologist and marketing wizard might add to the discussion? Evidently, I was short-sighted. If I had approached the problem in my typical fashion, I would have missed many of the critical points raised by the other members of my group. I've never contemplated the importance of co-creating a research program with patients.

When we first started our discussion, each group member was sure they knew the correct answer. We jumped to solutions without ensuring we all understood the problem. We had failed to listen and engage each other. We weren't drawing on the

TABLE 4 | Key points of the presentation feedback.

Phase 1 - Encourage students to spend time planning:
• Know the purpose of your talk
• Know your audience
• Tell a story
• Be clear about the take-home messages
• Nervousness is normal. Practice! Practice! Practice!
Phase 2 - The exercise:
• Create a safe environment to practice skills and receive constructive feedback from peers
• Give the talk
• Record the talk
• Watch the talk privately and self-assess (students are often their own worst critic)
Phase 3 - Feedback:
• Share your self-assessment
• Receive peer and faculty feedback

collective skills sets we had around the table. I was also acutely aware of the amount of space each participant took up in the conversation. One participant, in particular, dominated most of the discussion. He presented many ideas and often interrupted others. I, on the other hand, tended to be more reserved with my comments, especially when the discussion moved into content areas in which I was less familiar. So much new information was thrown at me that I didn't have the chance to absorb and think critically. My mind was getting overloaded, and I was struggling to keep up. In retrospect, the suggestions made by the faculty to get us on track were so simple. I'm always in such a hurry to get to the answer; I should really spend more time contemplating the question.

I also realize translation requires a breadth of knowledge and many different skills. While I'm an expert in my field, there's just so much more I need to know to effectively translate my discoveries and improve the health of patients. I would have never been able to get through this case study without the other members of my group. Maybe it's time I start collaborating with my colleagues, rather than competing with them?

PART III–COMMUNICATION SKILLS (TABLE 4)

I was dreading the presentation skills session all week. While I often present my research to different audiences, I wasn't eager to have my presentation video recorded and scrutinized by the group. The night before the session, I spent about an hour preparing my 3-min talk: a short research pitch to a funding agency.

I stand in front of a small group of five participants. The faculty facilitator sets a laptop in front of me to record my presentation. My anxiety is increasing. I had never seen a recording of one of my presentations, and I feel self-conscious and uncomfortably aware of every aspect of my speech. Was I talking too quickly? Was I moving too much? Is anyone even interested?

At last, I finish the presentation. I'm asked to review the recording in the adjoining room while the group discusses my talk in detail. As I press play, I'm wondering who this person is on the screen. Watching myself immediately after having given the talk is startling, and it is clear to me that I could have been much smoother. I notice some nervous habits in my movements, and I can hear the hesitation in my voice throughout the presentation.

I make some notes and return to the group. The facilitator asks how I felt that it had gone. I share my observations and overall negative feelings about the presentation. To my surprise, no one feels that I had hesitated or paused too much during the talk, but they do mention my frequent use of "filler" words. They also suggest I work on eye contact with the group while presenting. I hadn't considered this during my own-self assessment, but I realize that I can quickly get caught up in my slides and not focus on the audience.

Reflection and Journal Entry

The communication exercise wasn't nearly as terrifying as I had feared. Having been videotaped was tremendously useful. I don't usually take the time to evaluate my presentations, and I rarely get direct feedback from my colleagues. As it turns out I'm not nearly as bad at presentations as I had thought, though the group did point out some nervous habits of mine like my use of filler words. I hadn't noticed this before, but as soon as it was pointed out, I realize that I could make my narrative sound smoother and more confident by eliminating words and phrases that don't add any value to the talk. I really need to work on that. Overall, the exercise was very valuable and far more helpful than I expected. I'm already feeling more confident, and I know the comments I received will strengthen my delivery. We're being given the opportunity to incorporate the feedback we received and present again to the group tomorrow. Time to start practicing!

DISCUSSION

In this publication, we have presented selected teaching strategies that are important in the instruction of TM. The above sections include key points for faculty to consider when using each strategy as well as vignettes that describe the experience from the learner's viewpoint. First, the hidden curriculum is designed to create a safe environment in which to build teams. The faculty gently pushed learners out of their comfort zones in many of the teaching strategies, to challenge them to have new experiences and examine these experiences from different perspectives. Second, the unfolding case uses active learning to engage students. The participants are challenged to learn from their own knowledge base—collaborate with the group to prioritize what is essential to learn, rather than relying on the faculty to indicate what is important. Effective case-based learning requires learners to communicate clearly, think critically and creatively and function as a team, using the strengths of the individual members to inform the best way forward. Third, persuasive communication is an essential part of the TM toolbox. Again, however, it has been historically overlooked in scientific education. In the lab, in the clinic, in grant applications, ethics reviews and even in front of the media, it is crucial for scientists

to be able to communicate clearly and succinctly in such a way that is accessible to their audience.

The common thread between each of these strategies is critical reflection. While content may be delivered using an appropriate strategy, the more profound learning opportunity lies in the learner's ability to reflect on how they experienced the curriculum and discover the relevance and importance of each activity. In the vignettes above, Susan was first asked to write her reflections on the day's events in her journal. The following day begins with a group discussion around the individual reflections. Discussing the experiences and reflections of our peers can help provide insights from different points of view and may aid in a more profound understanding of the experience.

In 2004, Ash and Clayton (13) developed the DEAL model for critical reflection. The model contains three steps: (1) Describe the experience in an objective and detailed manner; (2) Examine the experience as they relate to specific learning outcomes (e.g., personal growth, team dynamics, patient engagement) and; (3) Articulate the Learning and how it will be used in the future. A detailed and objective description of the experience gives the learner a firm foundation on which to look for meaning. Learners often overlook this step and choose instead to start the interpretation process immediately. In doing so, they may miss critical details of the experience. For instance, while it is important to know where the experience took place, who was there and what they did, it is equally important to ask who wasn't there and what didn't they do. In examining the experiences, the learners begin searching for meaning. This step is linked directly to the learning outcomes of the exercise. For example, if the goal is to reflect on a conflict that arose within a team, one may ask: What was the cause of the conflict? What was the trigger? What were the perspectives of each individual involved? How did the other party interpret those perspectives? It is also essential for the learner to be able to articulate what they have learned. The articulation should be actionable, such that it will provide further guidance to deepen and improve the quality of their learning and their future actions. This step consists of four prompts to guide the learner: (1) What did you learn? (2) How did you learn it? (3)Why does it matter? (4) What will you do in light of it?

The specialized skills and knowledges considered to be part of the TM toolbox cannot all be taught in a lecture format. Instead, educators must think carefully about which strategies are most effective for the anticipated outcomes. In **Figure 1** we present a curriculum which we designed for a 7-day TM program, but the curriculum could be modified to take place over a longer period of time. The curriculum includes several strategies in addition to the few we have highlighted in this publication. Design of this curriculum followed Kern's model and is the result of several years of an effective PDSA assessment theory approach of Plan, Do, Study, Act. TM is as complex to teach as it is to learn. Selecting the most effective teaching strategies that are carefully placed in a well-designed curriculum is key to achieving one's intended outcomes.

AUTHOR CONTRIBUTIONS

RF wrote the introduction and discussion sections, consolidated the remaining sections and was responsible for the final editing. MM wrote the section on the hidden curriculum and contributed to manuscript review and editing. EL wrote the section on the case discussion and contributed to manuscript review and editing. EG wrote the section on communication and contributed to manuscript review and editing. JH contributed to the conceptualization of the paper, the introduction, discussion, table creation, manuscript review and editing.

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OPINION
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The Translational Medicine Professional: A Bridge Between Bench and Bedside?

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Translational medicine (TM) can be defined as the interdisciplinary application of biomedical research for the improvement of health of patients and society. The focus of TM has so far been largely on the bench-to-bedside rather than bedside-community transition of research. Several "Valleys of Death" in this process have been described, identifying transitional failures that may halt or impede the pathway, which would otherwise lead to the development of medicines, technologies, and/or evidence based practice guidelines. In order to help bridge these gaps, increasing patient-orientated research at each stage could improve the success of projects and increase societal impact. Increasing the accessibility and involvement of patients in TM outside of traditional research centers, such as universities and teaching hospitals, is one crucial pre-requisite. For example, where clinical research units with active links to local universities have been set-up, research participation can be increased. Such non-traditional research centers (NRTCs) might include primary or secondary care services, or even social care institutions. TM professionals (TMPs) from multi-disciplinary backgrounds, with work experience in university or research centers and with experience of TM, could play a vital role in this organizational change. TMPs in NTRCs are well placed to collaborate with local universities, larger research centers and commercial research and development organizations. Exchanging information could benefit all shareholders involved. TMPs can also stimulate the education and innovative thinking that is required for TM to achieve its full societal impact. We discuss the scope of a potential role for TMPs in NTRCs, as well as the possible barriers and difficulties they might face, along with measures that could widen the accessibility of TM outside of the traditional setting.

The European Society for Translational Medicine defines translational medicine (TM) as being an interdisciplinary branch of biomedicine supported by three pillars: bench, bedside and community. It's goal is to improve the health of society by improving disease management, e.g., with new therapies (1).

TM has predominantly focused on the bench to bedside approach, with most research activities being conducted in traditional research centers such as specialist centers and universities. Several "Valleys of Death" in TM or the bench-bedside pathway, defined as the route between drug or technology development (the "bench") and its integration into clinical care (the "bedside"), have been described (2–4). The valleys represent gaps that impede the pathway, impacting the development of medicines, technologies and/or evidence based practice guidelines. Until now, less focus has been on the third pillar of TM: the involvement of the wider community, or "bedside to community" phase[1]. Multi-faceted organizational changes and innovation, for example in trial design, are required to bridge these valleys as success rates of products that reach the "end" clinical trial stage remain poor (2, 5, 6).

[1] *University of Glasgow - Postgraduate study - Taught Degree Programmes A-Z - Translational Medicine* (Accessed April 21, 2018). Available online at: https://www.gla.ac.uk/postgraduate/taught/translationalmedicine

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Increasing patient-orientated research at all stages could improve the success of research projects and increase societal impact. Research practice often focuses on select groups of patients, for example those with rare or financially or academically "attractive" diseases, and who are primarily treated in hospitals either in or linked to traditional research centers. Such organizational factors result in an inherently biased system in many respects, including in the setting of research agendas and allocation of funding for projects. Such factors could potentially explain the limited output of the TM pathway. Optimizing the accessibility for patients outside of traditional research centers is also a crucial pre-requisite to innovating TM for the benefit of the wider society. To tackle this problem, Clinical Research Units (CRUs) to link local universities and hospitals have been set-up. Funding through the European Clinical Research Infrastructures Network (ECRIN) has further encouraged the connection of research institutions including CRUs, also referred to as CTUs (Clinical Trial Units) or CRCs (Clinical Research Centers) into hubs and networks in 14 countries across Europe (7). Accessibility to research participation in other non-traditional research centers (NRTCs) such as primary or secondary care services, and social care institutions, should also be addressed. An onus on research funders to require evidence of early and consistent patient input beginning in the consultation phase could be an additional driver of change.

A range of professionals from basic scientists, laboratory members, regulatory agencies, educational facilities, members of ethics boards, and journals are involved in TM. Professionals with expertise in TM (Tranlational Medicine Professionals, TMPs) from multi-disciplinary backgrounds could play a central role in innovating TM (**Figure 1**). TMPs in NTRCs are well placed to collaborate with the traditional research centers and shareholders, and can coordinate the exchange of information as well as stimulate education and innovative thinking. While some clinical academic tracks for the training of TMPs exist, they may be informal and without a focus on TM. One example where TM and the training of future TMPs was a strong focus was the European Translational Training for Autoimmunity & Immune manipulation Network (EUTRAIN) research and training as part of the EU Marie Curie Initial Training Network programme (8, 9). Whilst most TMPs remain based in the organizations where they are trained, i.e., university and research centers, many will spend at least some of their training time in NTRCs. Encouraging such TMPs to continue research in such sites would have a dual effect of avoiding these skills going to waste and maximize the extension of TM into NTRCs. TMPs in NTRCs may even face less constraints on their work, for example with the freedom to conduct projects for societal benefit rather than to achieve prestige in terms of high impact publications and big grants, which may be the case in specialist research centers. In NTRCs, incorporating research into daily clinical practice allows the advantages of TM, such as increased job satisfaction and professional development, to also reach a wider group of professionals. However, TMPs in NTRCs face their own challenges, such as the long held misbelief that research activities should be secondary to the provision of good patient care and limited to research centers. TMPs should engage with colleagues to widen education about TM and its fundamental tenet of incorporating society. NTRCs could themselves drive the process by changing the culture to support and nurture the

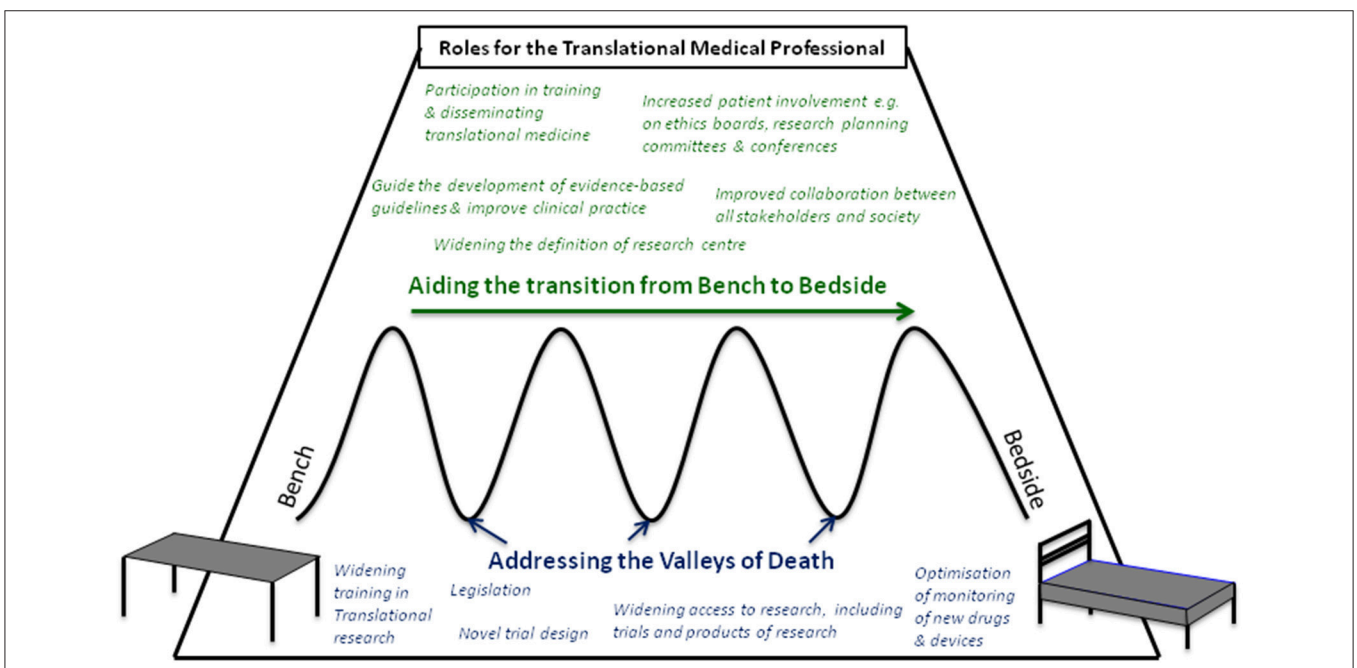

FIGURE 1 | Roles for the Translational Medical Professional in aiding the transition from bench to bedside (green text) and addressing potential points of failure, or "valleys of Death" (blue text).

process of research, for example by recruiting staff with a research interest or experience. The scope of a potential role for TMPs in NTRCs, particularly in (1) widening participation and (2) improving collaboration in TM outside of the traditional research setting will be discussed and are summarised in **Table 1**.

WIDENING PARTICIPATION

When research participation is excluded from the majority of NTRCs, a goal of wide societal impact and improvement of health is unlikely to be achieved. All members of society should be seen as potential research participants and receive the opportunity to take part in research (10). All members of society will be affected by healthcare provisions at some point of their life either as recipients of health interventions, or as carers for someone else receiving health care. Therefore, NTRCs should also include social care institutions such as hospices, rehabilitation centers, schools and care homes as well as primary and secondary care centers (10). In addition, some research questions are population based questions, and require broader patient inclusion to be adequately addressed. For this, the support of patient advocacy groups and ethical review boards is also vital, with TMPs supporting the case for widening TM participation in NTRCs.

Longer-term monitoring of drugs and product related adverse effects, for example after clinical trials are concluded or after the acute phase of a disease is over, might be better performed in NTRCs rather than in specialist centers. Whilst the reporting of drug side effects after licensing is encouraged and required in all countries, the monitoring of products is not monitored to the same extent (6). One recent example of the failure of adequate follow up and monitoring of devices is the mounting evidence that mesh used in the surgical management of pelvic organ prolapse has been responsible for many post-surgical complications and that the medical devices (the Mesh) was approved based on weak evidence leading to a large unexpected need for costly post-intervention care (11).

A programme of legislative support and training initiatives is required to support the process of patient engagement (12). Research activities are already being shifted to NTRCs, which can benefit from increased funding streams and patient access and also developing organizational links with local teaching hospitals and commercial research centers (13). Structural changes within NTRC, such as the setting up of research and development offices and facilities for clinical research, are also vital. While their financial set-up may not be under the control of TMPs, TMPs can support their development and help staff them. Clinical research centers often include outpatient facilities with consultation rooms and treatment beds as well as access to a laboratory which can perform basic research procedures such as Real-time PCR and flow cytometry, sample preparation for DNA extraction or serum bio-banking.

To be effective, TMPs should be adequately trained and be inter-disciplinary, including laboratory staff and research coordinators as well as specialist research and clinical nurses and doctors (14, 15). Therefore, a programme of widening participation for TMPs is also required. In the UK, academic clinical fellowships (ACF) during clinical training have improved access to research programmes for trainees. In contrast to the UK, a much greater proportion of medical students in the Netherlands will undertake PhDs during their study or early in their training. In Germany, to obtain the title "Dr. med" a period of research is also usually completed during university study, much akin to intercalated degree programmes in the UK. However, ACFs and most Dr. med. or Ph.D. and research programmes are based in research centers and include little or no focus on TM or inter-disciplinary working. Widening such programmes whether they are pre- or post-graduate based to multi-disciplinary participants and including time in the programme to develop and teach widening participation in research, novel trial design and collaboration and the inclusion of a period of training time in NTRCs is also vital. There is a general consensus that research and TM requires specially trained professionals, and there is increasingly financial and structural support for interdisciplinarity in clinical and research settings. Many universities have developed new institutes with industry partners as well as clinicians and researchers collaborating and

TABLE 1 | Specific roles the Translational Medical Professional could play in shifting the focus of the translational pathway from "bench to bedside" to "bench to society" by (1) widening participation to research and (2) improving collaboration.

Widening participation

• Encourage involvement in research activities in non-traditional research centers (NTRCs) and other partners including:
  ◦ social care institutions: e.g., hospices, rehabilitation centers, schools, and care homes
  ◦ primary care (general practitioner services)
  ◦ secondary care centers (specialist or teaching hospitals)
  ◦ industry partners
  ◦ universities
  ◦ patient groups
  ◦ ethics research committees

• Recruit and include patients outside of NTRCs in clinical trials and monitoring of medical devices
• Encourage the relocation of research and development offices and clinical research units into NTRCs, or take up roles in such centers or work independently but collaboratively with existing centers
• Take an organizational role in sharing of research facilities such as laboratory facilities
• Support and encourage the wider inclusion of patient advocates on ethical approval boards and grant approval committees
• Encourage new grants and apply for existing grants or other benefits, such as awards of a recognition of excellence to research centers that widen participation in TM could be a focus for TMPs in NTRCs.
• Participation in, and encourage new educational programmes, pre- and postgraduate as well as on-going clinical educational opportunities to address challenges facing translational medicine professionals (TMPs).
Improving collaboration
• Communication and outreach activities to connect different research partners and participants
• Organization of collaborative forums and meetings
• Development and participation in mentorship programmes
• Setting up and maintenance of shared biobank facilities
• Organization of the use of specialist research equipment between different centers
• Mentoring and supporting non-TMP colleagues in realizing the potential personal and wider benefits of TM.

now also offer translational study programmes[1,2](6). However, one of the largest challenges in widening participation in TM in NTRCs is achieving the organizational changes to support such a transition.

IMPROVING COLLABORATION

TMPs could foster links between NTRCs and local research centers which excel in a particular field or service by driving collaborations as well as widening research participation. Practical measures may include the organization of regular open meetings, with an open forum to present ideas and updates for new or on-going research projects that could help overcome problems or barriers that projects may be facing. This inter-disciplinary sharing of information could drive innovation and benefit all parties involved, e.g., by pooling potential research participants and sharing access to technology or specialists. Common goals and challenges could help lead to solutions such as the recruitment of a suitable control group. Collaboration between departments from different centers, or even between departments from the same center that may have been unaware of pre-existing research facilities or goals available in-house could be improved upon. Open and equal exchanges of ideas, which is the basis of inter-disciplinary research, opens the door to broader sources of funding. Traditional hierarchies of power, which still often exist in traditional research centers, may also be more effectively challenged when committees are inter-disciplinary. Collaboration between NTRCs and established research centers could also be organized in the form of "outreach programmes" which might include the development of mentorship programmes. Taking an active role in the development and running of such integration and outreach activities could provide career benefits to early-stage TMPs, providing earlier opportunities to undertake leadership roles.

CHALLENGES FACING TMPS

Some challenges facing TMPs focus around accepting the idea of TM in NTRCs. Many TMPs will have trained with a specialist focus. For their new role in NTRCs, TMPs will need to maintain this focus on detail but also develop wider research skills including novel trial design and collaborative work, which takes public health into account. The role of a TMP will comprise many challenges, including that they must work hard in their NTRCs to be seen as effective and successful in both their clinical and research activities. TMPs must also cross barriers such as addressing common misconceptions including that research has no place in clinical training programmes and be able to engage colleagues to also drive good research practices in their workplace (13). The main barrier will be to change perceptions so that research is seen as a part of daily practice in NTRCs and not as a supplementary or a career progress driven activity. TMPs will also need to develop time management skills as well as leadership and delegation if they are to achieve all the activities associated with TM including: teaching, publishing papers, writing research grants. Balancing expectations from colleagues, supervisors and patients will also be vital.

In order to achieve the variety of goals we have discussed as well as to excel in communication and drive innovation, TMPs must be creative—a skill which is difficult to teach and measure. This creativity is fundamental to driving new concepts in the design and practice of trials as well as of medical products and the TM pathway itself (6). TMPs must also use their creativity to develop collaborations with research centers, universities and commercial centers. This can all be achieved with support from colleagues, mentors, and collaborative practices as discussed above.

SUMMARY

In conclusion, greater focus on the societal aspect in TM is required to tackle the so-called "valleys of death." The TMP could be a potentially vital driver of innovation and the organizational processes that are required. However, whilst the focus on TM and the number of TMPs might be increasing, TMPs still face multiple challenges but there are many ways in which they can help widen access of TM and improve collaboration within TM.

AUTHOR CONTRIBUTIONS

FG conceived the study and performed the literature review. All authors contributed to the writing of the manuscript and made substantial contributions to the content and approved the final version.

[2]*Institute of Translational Medicine - University of Liverpool* (Accessed April 21, 2018). Available online at: https://www.liverpool.ac.uk/translational-medicine/about-us/

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REVIEW
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Controlled Human Infections As a Tool to Reduce Uncertainty in Clinical Vaccine Development

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Vaccines can be extremely cost-effective public health measures. Unfortunately the research and development (R&D) of novel vaccines is suffering from rising costs and declining success rates. Because many vaccines target low- and middle income markets (LMIC), output needs to be maintained at a constrained budget. In addition, scientific neglect and political uncertainty around reimbursement decisions make it an unattractive arena for private investors. The vaccine development pipeline for LMIC thus is in need for a different, sustainable, and cost-effective development model. In conventional vaccine development, objectives for every clinical development phase have been predefined. However, given the scarcity of resources, the most efficient clinical development path should identify vaccine candidates with the highest potential impact as soon as possible. We argue for a custom-made question-based development path based on the scientific questions, success probabilities and investments required. One question can be addressed by several studies and one study can provide partial answers to multiple questions. An example of a question-based approach is the implementation of a controlled human malaria infection model (CHMI). Malaria vaccine R&D faces major scientific challenges and has limited resources. Therefore, early preliminary efficacy data needs to be obtained in order to reallocate resources as efficiently as possible and reduce clinical development costs. To meet this demand, novel malaria vaccines are tested for efficacy in so-called CHMI trials in which small groups of healthy volunteers are vaccinated and subsequently infected with malaria. Early evaluation studies of critical questions, such as CHMI, are highly rewarding, since they prevent expenditures on projects that are unlikely to succeed. Each set of estimated probabilities and costs (combined with market value) will have its own optimal priority sequence of questions to address. Algorithms can be designed to determine the optimal order in which questions should be addressed. Experimental infections of healthy volunteers is an example of how a question-based approach to vaccine development can be implemented and has the potential to change the arena of clinical vaccine development.

Keywords: vaccine, malaria, product development (PD) process, clinical development, low-income access

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INTRODUCTION

Vaccines are one of the world's most important and cost-effective public health measures and have proven to generate vast socio-economic benefits (1). The elimination of smallpox and the near-elimination of polio as a consequence of global use of vaccines demonstrates the potential impact of these pharmaceuticals. As such, prophylactic vaccines have a unique niche in the pharmaceutical industry. Unfortunately, the rising development costs needed to maintain a constant output of new drugs over the past decades has affected the vaccine portfolio of major pharmaceutical companies.

Initially, investors perceived vaccine development to be riskier than other products, but this view has changed over the past years (2). Unfortunately, the overall probability of success of around 11% is not unlike any other pharmaceutical agent (2). Because the development of new vaccines is often complex, average development timelines are between 8 and 18.5 years, and estimated costs are substantial ($200 million to $900 million) (3, 4). Remarkable examples in this respect are the accelerated development of an Ebola vaccine and the long timelines in the development of an HIV vaccine. The risk of failure is particularly high in later stages of clinical development when vaccines are tested for their immunogenicity and protective efficacy in larger (target) populations (2, 4). Given the fierce competition, the fact that so-called "low-hanging fruits" have been picked, and in the aftermath of the global financial crisis, the vaccine development pipeline seems to encounter greater challenges than ever before (3).

CHALLENGES ASSOCIATED WITH VACCINES FOR LOW- AND MIDDLE-INCOME MARKETS

Because the global viral, bacterial, and parasitic infectious disease burden nowadays is primarily borne by low- and middle- income countries (LMIC), novel vaccines need to target LMIC markets. The limited financial capacity of such nations puts constraints on the vaccine market prices. Advanced scientific technologies in areas such as immunology, chemistry and molecular biology have accelerated vaccine development through, for example, increased understanding of population differences in vaccine efficacy (3) or identification of correlates of protection (4). While improving existing vaccines using incremental innovations can be done relatively fast, the remaining infectious diseases predominantly prevalent in LMIC require development of a novel category of vaccines, the foundation of which need to be laid by fundamental scientists. Whereas governments, non-governmental organizations and international donors play a central role in pre-clinical and early clinical development stages of vaccines, it is likely that private partners are eventually needed to successfully develop a vaccine for the (LMIC) market.

Predicting vaccine demand in the LMIC countries is difficult because the infrastructure needed to provide necessary epidemiological data and information on immunization coverage and wastage is sometimes lacking. In addition, vaccine uptake in the Global Alliance for Vaccines and Immunization (GAVI)-eligible countries may lag behind demand forecasts (3). The political uncertainty in reimbursement decisions and the public pressure to reduce prices limits the enthusiasm for private investors to enter this arena. The current procurement systems and strong downward price pressures further increase the uncertainty of recovering costs of development and goods (5). Lastly, differential pricing, despite its proven public health success, has been jeopardized by so-called "external price referencing," whereby high-income countries seek to benefit from the lower prices offered to countries with weaker economic profiles (3).

Given the current vaccine development landscape, the market-driven business model will need to be revisited in order to provide a feasible, sustainable, and cost- effective structure for a global population.

IMPROVING THE BUSINESS CASE FOR VACCINE DEVELOPMENT

Global recognition of the challenges in vaccine development for LMIC has increased the support of donors for vaccine research, particularly from the Bill and Melinda Gates Foundation (6). These and other direct grants and investment in product development partnerships (PDPs) have enabled a more active participation of public partners later in the clinical development pipeline. Public investments reduce R&D costs and improve the business case for private partners. Developing country manufacturers have been able to reduce the production costs of several vaccines, substantially increasing vaccine cost-effectiveness and ultimately the population reached. However, the involvement of large pharmaceutical companies, including developing country manufacturers, is substantially higher at later stages of clinical development, reflecting the preference of private investors for lower risk development. Forty percent (40%) of the R&D efforts currently invested in neglected diseases is conducted through product development partnerships (PDPs) (3). However, also public donors increasingly demand success given hundreds of vaccine candidates in development globally (7). Considering the resource constraints, there is a growing need to rationally identify the approaches that are most likely to succeed and then prioritize among these candidates (8).

Alternatively, market-based "pull" mechanisms—where donors stimulate demand for new technologies through purchase commitments and volume guarantees—incentivize vaccine research and development by fuelling the business case from the revenue side. Similarly, effort is put into defining target product profiles for new vaccines early in the development process, aiming to reduce risks of late failures by being explicit about the requirements for novel category vaccines (5). However, "pull" mechanisms work best when the concept of a new vaccine is proven and the intrinsic development risks are reduced to acceptable, technical risks (3).

In conclusion, managing costs and risks of vaccines for LMIC is challenging. Providing early proof-of-concept of these vaccines is essential in order to prioritize and ensure

donor enthusiasm, raise funds from private investors or fuel collaborations with companies. Obviously, any product will have intrinsic development risks which are technical in nature. However, additional uncertainty may be introduced by the lack of scientific insights which need to be valued within the vaccine portfolio. Unfortunately, investment decisions on R&D projects in life sciences are frequently based on Net Present Value (NPV) calculations that depend heavily on assumptions of technical risks, costs and future profits while scientific considerations are not taken into account. NPV analysis just indicates that such evaluation studies cost time and money and disregards the increases in knowledge which is obtained when scientific questions are adequately addressed. Particularly in vaccine development for LMIC scientific advances are fundamental to game-changing novel technologies.

QUESTION BASED CLINICAL VACCINE DEVELOPMENT

Classically, the clinical development program of a vaccine is divided in four phases:

- Phase 1: Research using small groups of healthy volunteers. Traditionally, this phase mainly focuses on vaccine safety, may explore its immunogenicity, and targets to finding a dose where the level of tolerance is acceptable. In general, this phase takes about 1–2 years.
- Phase 2: Clinical trials are larger and the first proof for immunogenicity is established. More characteristics of the vaccine are determined and a safe and well-tolerated dose is determined where the drug is immunogenic.
- Phase 3: The potential new vaccine is tested on thousands of patients in an endemic setting to investigate its safety in more detail. Furthermore, the efficacy of the vaccine at the determined dose is determined. Further research is conducted to investigate possible side effects after long-term treatment and development of the drug for different indications is investigated.
- Phase 4: The registered and introduced vaccine is monitored closely to examine the occurrence of unexpected side-effects and interactions with other vaccines.

The description of these phases is typically process oriented and contains very little information about which scientific aspects are actually covered during the clinical development. Alternatively, the clinical vaccine development pipeline can be centered around key scientific questions which need to be addressed in the most optimal order applicable to the individual investigational vaccine (**Figure 1**). Examples of such questions are:

- *Does the vaccine formulation induce an immune response ("**Immunogenicity**")?*

This main generic question contains several issues that need to be addressed such as the route and site of vaccine administration. Not only the immunogenicity of the vaccine antigen, but also any possible adjuvants, vectors or conjugates could be included in answering this question.

- *Does the vaccine formulation induce a disease correlate of protection ("**Disease correlate**")?*

Answering this question includes the demonstration of the immunological mechanism of action for the investigational vaccine. As stated previously, R&D investments into mechanisms of disease and correlates of protection are essential to help answer this question and as such the associated development risks in this area may vary considerably. Addressing this question may be very instrumental in addressing the other questions also. In diseases where a correlate of protection is lacking, e.g., malaria or HIV, protective efficacy trials bear substantial risks which have impeded vaccine development.

- *Does the vaccine formulation confer protective efficacy to the target disease ("**Protective efficacy**")?*

This question reflects the need to establish beneficial effects on the incidence or prevalence disease but also the alteration of other physiological systems resulting in clinical side effects. Depending on the infection incidence, these trials can be particularly large in vaccine development in order to achieve sufficient power to detect efficacy.

- *What is the lowest dose and number of doses at which the vaccine which still induces protective immunity ("**Therapeutic window**")?*

The therapeutic window of each investigational vaccine needs to be established in order to select the optimal dose that is clinically optimally efficacious at well tolerated levels. This question includes important sub-questions: how many vaccine doses need to be given at what interval? Can vaccine formulation decrease the need for booster doses?

- *How do the sources of variability in vaccine response in the target population affect the development of the product ("**Target population**")?*

This question should include: Are there any specific factors in the target population that may affect immunogenicity? Particularly in vaccine development for LMIC this can be a significant hurdle given the generally decreased efficacy of vaccines in resource-poor settings (9). Co-infections, previous exposure to the target disease or malnutrition may be factors which hamper immunogenicity in the target population (10, 11).

The abovementioned questions can be ranked based on their risk profile and examined in different sequence orders. For example, if we examine the clinical development path for a hypothetical malaria vaccine using overall probability of success of 5%, development costs of 90 €M and revenues of 800 €M. Equal distribution of the risks and costs over the five proposed questions would amount to a 55% probability of success and 18 M€ costs for each question. The resulting question-based decision tree (**Figure 2A**) reflects the true scientific risks and uncertainties that are faced in the development of an individual vaccine based on estimations of risks associated with the postulated questions.

Because it is unlikely that all five questions would contribute evenly to the overall risks, we now unevenly distribute risks and

FIGURE 1 | The question optimizing tool, where estimated costs and probabil ities of success can be entered per question, generating a question-based decision tree with the most optimal order of questions. https://www.pauljanssenfuturelab.eu/our-tools/.

costs in our example (**Figure 2B**). Despite similar overall costs and risks, the project value can vary substantially depending on the distribution of question-associated risks and costs. Similarly, the order of questions strongly determines the project value as illustrated by the dramatic drop in project value if the user-defined "Therapeutic window" is the first question to be addressed with these input variables. In this case, the overall project value actually drops below zero, implying that risks and investments do not outweigh the potential revenues.

Furthermore, the question-based approach illustrates how the project value can increase by performing an additional early phase evaluation study that helps to adequately answer a critical question. If an additional 1 M€ costs and a 5% increased probability of successfully answering the "Disease correlate" question is added, the overall project value increases by more than 50% (**Figure 2C**), despite the fact that the overall probability of success increases with only 0.17–5.17% and overall costs increase by 1–91 M€.

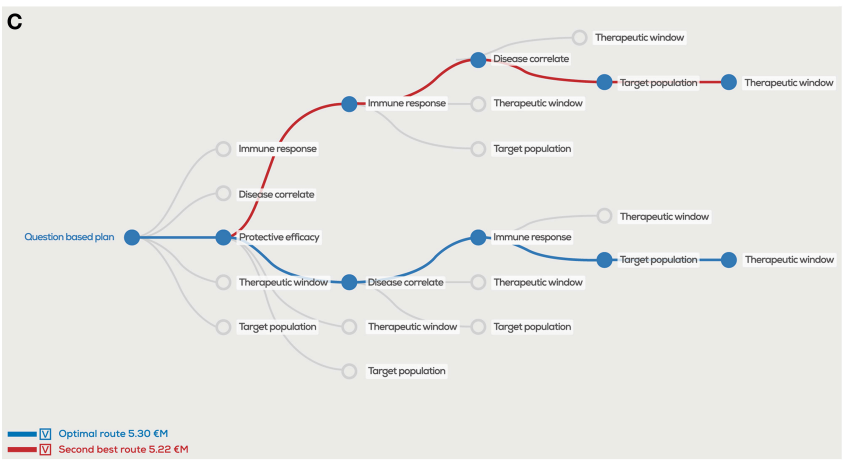
By defining the costs and probabilities of success and constructing the decision tree for every new vaccine, the bottleneck in the development of each individual vaccine will be identified. Presumably for most vaccines the "Disease correlate" and "Protective efficacy" questions will have the lowest probability of success. As explained earlier, the increasing recognition of this critical bottleneck in vaccine development has led to a demand for proof-of-concept clinical trials showing early efficacy for the candidate vaccine technology. In the next section, we will take the example of malaria vaccine development to illustrate how question-based product development has changed malaria vaccine development and fostered novel technology development in this field.

THE EXAMPLE OF MALARIA VACCINE DEVELOPMENT AND THE ROLE OF CONTROLLED HUMAN MALARIA INFECTIONS

Despite the fact that half the world's population is at risk for malaria with an extremely high global burden of 200 million malaria cases annually and nearly 500,000 deaths among children, the vast majority of the burden is borne by resource-poor countries in Sub-Saharan Africa (12). Most malaria deaths are caused by one microbial species: the protozoan *Plasmodium falciparum (Pf)*. This organism displays extracellular and intracellular developmental stages and transforms within

	PoS	Costs
Immunogenicity	55%	18€M
Correlate	55%	18€M
Efficacy	55%	18€M
Window	55%	18€M
Population	55%	18€M

	PoS	Costs
Immunogenicity	60%	16€M
Correlate	44%	19€M
Efficacy	55%	18€M
Window	64%	19€M
Population	55%	18€M



	PoS	Costs
Immunogenicity	60%	16€M
Correlate	49%	20€M
Efficacy	55%	18€M
Window	64%	19€M
Population	55%	18€M

FIGURE 2 | Decision tree showing the optimal order of questions to generate the highest project value, given estimated probability of success (PoS) and costs (million euro, €M) per scientific question. In the case PoS and costs for every question are equal, the order does not matter for the project value **(A)**, however unequal distributions will clearly show different project values for the optimal order in blue, second best order in red and user defined order in green **(B)**. A 1 €M additional investment in "correlates" has a major effect on the optimal order and project value **(C)**.

the human host, creating a challenge for the immune system and therefore also a scientific challenge for malaria vaccine development. Because there are no prior registered vaccines for parasitic diseases, malaria vaccine development cannot draw on experience from other disease areas. In addition, despite decades of vaccine research, there are no correlates of protection for

Pf malaria. Lastly, *Pf* strains worldwide display considerable genetic variability which may affect local vaccine efficacy. As a consequence, the probability of successful market entry for malaria vaccines is extremely low even after 7–8 years of clinical development (4) and the investment into malaria vaccines is extremely small as compared to other disease areas such as influenza or HIV/AIDS (4). A radical approach to tackle R&D uncertainty and boost scientific advances is thus urgently needed.

Initially developed as a treatment for neurosyphilis before the discovery of penicillin, the methods for experimental infection of volunteers with malaria have been adapted as a tool to serve the malaria vaccine pipeline (13). The human infection model was standardized by means of (automated) parasite cultures and laboratory-bred mosquito colonies (14, 15). Nowadays, both the blood-stage as well as the mosquito stage of the Pf parasite can be GMP manufactured and injected for this purpose (16, 17). The model is known as "controlled human malaria infection (CHMI)" to stress the importance of the standardization and the highly controlled follow-up which ensures that severe malaria does not occur and participants are treated as early as possible.

Within the vaccine development pipeline, CHMI has been increasingly used to address the "Disease correlate" question in the absence of a known correlate of protection. Despite the fact that a formal validation was never done, CHMI trials are nowadays widely accepted as a critical step in the clinical development path. Using the CHMI model, one vaccine—GlaxoSmithKline Mosquirix—has received marked authorization in 2016 following a proof-of-concept clinical trial more than 10 years earlier (18). An implementation pilot to evaluate its use in the field is currently ongoing. The product development partnership "Malaria Vaccine Initiative," has very successfully advanced this vaccine for the public sector and simultaneously managed global access and IP issues with commercial partners (5). CHMI has also fostered unconventional approaches to vaccine development such as the live-attenuated malaria vaccine PfSPZ Vaccine which is entering phase 3 clinical trials, led by the US biotech company Sanaria (17). Furthermore, disappointing CHMI results have stopped the development other candidate malaria vaccines (19).

The CHMI trials are thus a prime example how questions with the lowest probability of success can be addressed in early clinical development. Because of their invasive nature and the requirement for healthy volunteers, which seemingly contradict the principle of "primum non nocere," CHMI trials initially raised ethical debate but nowadays have gained acceptance through demonstrating their accelerating scientific potential and the fact that CHMIs have been safely performed in >3,000 volunteers worldwide (20).

Following the example of malaria, the experimental infection of volunteers are also being used as a tool for the development of novel products in other infectious disease areas such as influenza, rhinovirus or cholera (21). In exceptional cases, such as the cholera vaccine VaxChora, this trial was the basis for registration of a novel vaccine (21). However, the position of CHI trials within the vaccine development pipeline and their value in mitigating the development risk is highly dependent on its scientific validity. Therefore, attention should be paid to the scientific details of the CHI trial setup, in particular to the proposed vaccine mechanism of action, the vaccine target population and the position of the CHI model within the vaccine product pipeline. Specific points to be considered are outlined below.

RESTRICTIONS AND SOLUTIONS FOR CHI MODELS

Mechanism of Action

Vaccines consist of one or multiple antigens and as such target prevention of disease, infection or colonization. Because CHI trials are often designed as preliminary experiments which only include a very small group of volunteers, endpoints should be selected based on their power to discriminate vaccine effects. Preferably, these trials target a relevant (clinical) endpoint, addressing a claim in the vaccine target product profile, such as diarrhea in the case of cholera CHI (22) or fever in the case of typhoid CHI (23). Alternatively, an intermediate (microbiological) endpoint may be selected, such as viremia in the dengue model (24) or parasitemia in the malaria model. However, for malaria, infection does not always parallel disease particularly in endemic areas (25). Depending on the target disease the CHI endpoint as such may be a surrogate to clinical endpoint and will need to be validated in epidemiological studies or in later field trials (**Table 1**).

In addition, the vaccine antigen(s) should be sufficiently present in the CHI model to measure protective effects. For example, in the malaria case, a liver-stage malaria vaccine can be tested for its preliminary efficacy by a mosquito-bite CHMI. However, for blood stage malaria vaccines, this model is less suitable because blood stage parasitemia will be limited to only a very short (3–4 day) timeframe in a mosquito bite CHMI (26).

TABLE 1 | Examples of potential restrictions and solutions for CHI models within the vaccine product pipeline.

Topic	Restriction	Solutions
Mechanism of action	Model endpoint does not reflect vaccine efficacy endpoint	Define endpoints to balance clinical relevance and feasibility in small groups. Validation of endpoints in epidemiological studies.
	Challenge strain does not express vaccine antigen, or correct strain not available	Design of fit-for-purpose challenge strains or models
Model validation	Model population does not reflect target population	Transfer of CHI trials to endemic areas and susceptible populations
	Challenge strain does not reflect circulating field strains	Increase portfolio of challenge strains to reflect natural infections
Position of CHI in product development pipeline	False negative result in CHI trial leads to no-go decision for further development of potentially valuable product	Clear definition of the research question which the model addresses
	Acceptance of CHI data in registration dossiers	Early involvement of regulators

Therefore, the CHMI model was adapted to accommodate a longer phase of blood stage parasitemia. This blood stage CHMI has the possibility to detect small alterations in blood stage development of malaria parasites (16).

Model Validation

Generally, CHI trials are performed in healthy adult volunteers which do not necessarily reflect the target population, which is typically much more heterogeneous. In order to overcome these differences, CHI trials can also be performed in more susceptible (target) populations such as COPD patients for rhinovirus (27) or malaria infections in Sub-Saharan Africa (28). Interestingly, controlled human malaria infections in non-endemic high-income settings have a much higher clinical attack rate and parasitemia as compared to rural African populations. In the latter population parasitemia is much more variable, and clinical disease may be lacking despite parasitemia (25). It is plausible that this reflects different immunological responses, which may be unraveled in the future.

Given the invasive nature of the CHI trial, regulatory authorities will often demand strictly controlled production of challenge material. In addition to the fact that such processes may be difficult, expensive and time-consuming, the process itself may render the challenge material less representative of microbes circulating in the field. For example, passage of virus strains through well-characterized cell lines to produce Good Manufacturing Practice compliant strains, will unequivocally alter the genetic makeup of the virus. Alternatively, the well-characterized laboratory strains such as the Quailes strain used for typhoid CHI (23) or the NF54/3D7 strain for *Pf* CHI (20) may not reflect the heterogeneity of field strains which impacts the scientific value of the model to predict field efficacy.

Position of CHI in the Product Development Pipeline

Depending on the scientific and clinical details of the CHI model mentioned above, the CHI model can be used as a tool to answer one or multiple questions in the product development pipeline. Determining the most optimal order in which these questions should be addressed, will aid in positioning the CHI model in the pipeline. Because CHI models often address high-risk clinical development questions, they are optimally performed early in clinical development. Previously, this has led to hesitancy by vaccine developers, who fear that negative results will result in a "no-go" decision for a vaccine which may actually be efficacious in later trials. However, as in any other model, the results of the model system should be valued for its merits within the scientific question which it addresses. For example, a CHMI trial may enable identification of an immunological correlate of protection in a trial which shows only partial efficacy. The correlate will de-risk other clinical development questions. Depending on the outcome of the trial, these need to be reassessed and risks adjusted to come up with the then optimal order based on the required investments and updated probability of success.

Increasing familiarity of CHI models by regulators as well as vaccine developers increases acceptance of these trials as part of the regulatory package which is submitted for licensure. However, given the restrictions of CHI models, continuous education of regulators, and vaccine developers to increase the scientific understanding of these models is essential to ensure that data from these trials are interpreted appropriately. In the end, regulation follows science, not the other way around. The malaria example shows how a well-designed CHI trial early in clinical development can dramatically improve the business case of the experimental vaccine and ultimately lead to registration of a LMIC vaccine with global impact.

CONCLUSIONS

In conclusion, global vaccine development faces major challenges, particularly for LMIC settings. Initiatives to improve the business case for vaccine development including so-called "pull" mechanisms to ensure pricing and guarantee demand are needed but will not provide the ultimate solution. A question-based clinical development approach can provide the insights on critical steps in the development path for novel vaccines and will help display the priorities within the program. Controlled human infections, if well designed, are an excellent example of how question based product development has led to adjustments to the product development pipeline and the way to prioritize vaccine candidates, accelerate novel vaccines, reallocate resources and foster novel technologies. During development, the estimations in the question based approach require constant evaluation and adjustment in order to keep development on the optimal path. Ultimately, this approach has the potential to more quickly improve global health and hopefully increase the appetite for private investors to enter the arena of clinical vaccine development and work together with public funders to target low income markets despite small profit margins. In addition, it will foster scientific advances which are needed to turn the tide on the development of vaccines for neglected infections of global importance, increase enthusiasm for public investments and the public pressure needed to stimulate societal corporate responsibility.

AUTHOR CONTRIBUTIONS

MR drafted the manuscript. IK and SdV reviewed and finalized the manuscript.

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CORRECTION
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Corrigendum: Controlled Human Infections As a Tool to Reduce Uncertainty in Clinical Vaccine Development

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A Corrigendum on

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In the original article, there was a mistake in "Figure 2C" as published. In the figure legend, the incorrect number was used to indicate the second-best route and should have been "5.22 €M" instead of "5.97 €M". The corrected **Figure 2C** appears below.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

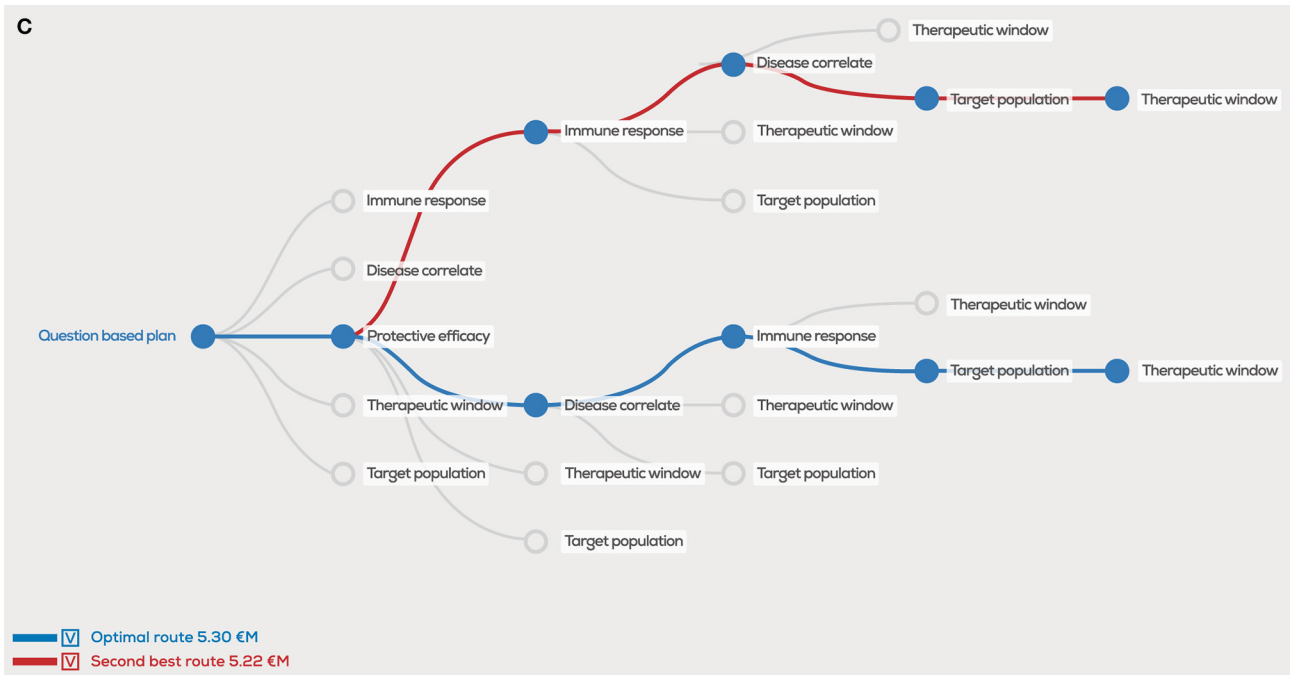

FIGURE 2 | Decision tree showing the optimal order of questions to generate the highest project value, given estimated probability of success (PoS) and costs (million euro, €M) per scientific question. In the case PoS and costs for every question are equal, the order does not matter for the project value **(A)**, however unequal distributions will clearly show different project values for the optimal order in blue, second best order in red and user defined order in green **(B)**. A 1 €M additional investment in "correlates" has a major effect on the optimal order and project value **(C)**.

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ORIGINAL RESEARCH
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Preventing Translational Scientists From Extinction: The Long-Term Impact of a Personalized Training Program in Translational Medicine on the Careers of Translational Scientists

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Far too much biomedical research is wasted and ends in the so called "Valley of Death": the gap that exists between biomedical research and its clinical application. While the translational process requires collaboration between many disciplines, current translational medicine focuses on single disciplines. Therefore, educational pathways that integrate clinical and research skills in interdisciplinary and interprofessional contexts are needed. The Eureka institute (http://www.eurekainstitute.org/) was founded to address these issues. The institute organizes an annual 1-week international certificate course to educate professionals in the domains of translational medicine.

Study design: This study set out to investigate the impact of the Eureka certificate course on the alumni, focusing on their ability to engage in translational activities and thus become more proficient translational professionals. An explanatory, mixed-methods study was executed.

Data collection: A questionnaire was distributed to collect quantitative data on the number of alumni who were able to apply what they learned during the Eureka course and engage in translational activities. Questionnaire data were also used to inform the semi-structured interviews that were conducted subsequently.

Results: Fifty-one percent of the alumni reported that participating in the Eureka course played a role in their decision to change to a different job or in the way they were accomplishing their everyday work. Ten conditions for change that either hampered or supported the Eureka alumni's engagement in translational research activities were identified. Further, the learning outcomes of the Eureka course that impacted the alumni's professional activities were explored using Personal Professional Theory (PPT). The insight that alumni gained in the full translational spectrum and stakeholders involved

stimulated reflection on their own role within that pathway. Further, according to the alumni, the course provided them with the skills and confidence to pursue a career as translational professional. These learning outcomes, in combination with conditions that supported alumni's engagement in translational activities, such as supportive professional partners, opportunities to network or collaborate, and a translational work environment, contributed to the large number of alumni that were able to engage in translational activities.

Keywords: translational medicine, clinician-scientist, translational scientist, translational research, training, education, personal professional theory, program evaluation

INTRODUCTION

For several decades, concerns have been raised about the large amount of biomedical research that end in the so-called "Valley of Death": the gap that exists between biomedical research and its clinical application (1, 2). Modern medicine fails to translate innovations at the bench to tangible products at the bedside, leading to an estimated waste in research of 85% of all research funding (3). Although some waste in research is inevitable, the real concern is that a large part of this waste is due to structural issues in the research ecosystem and could be avoided (3–5). The cause of this problem is multidimensional and crosses the domains of academia, industry, and government (6, 7). Indeed, academic, commercial, and political interests often influence decisions about what is studied and how this research is executed, while users of research evidence, such as patients and clinicians, are rarely involved in these decisions (4).

To better align biomedical research with clinical needs and allow for translation of discoveries to clinical practice, there is a need for improved collaboration between all disciplines that are part of the translational process (4, 6) This requires central figures with a full understanding of the translational spectrum, who are able to integrate the perspectives and needs of all involved. These translational scientists—either PhDs with an interest in clinical research or clinician-scientists—need to have a broad set of knowledge and skills to help breaking down the barriers between the different disciplines and foster interdisciplinary communication and collaboration (8–10).

Educational pathways, such as MD/PhD-programs, have been developed to encourage training of physician-scientists. However, obtaining both a clinical and research degree does not necessarily create a physician-scientist, as clinical and research degrees are based on approaches that are fundamentally different (11). Many dual-degree programs lack integration of these different ways of thinking. Often, the full breadth of translational medicine, the perspectives of academia, industry, government, and patients, and the skills needed to work in multidisciplinary teams are not addressed. In addition to dual-degree programs there is a wealth of postgraduate training programs that focus their content on knowledge of translational medicine. The majority of these programs do not address the full range of competencies needed to become a lead figure in translational medicine. They often focus on a more specific skills set, such as postgraduate research training for clinicians or programs that focus on biomedical technology (10, 12, 13).

Most programs lack role modeling and mentorship (11, 14). Although mentorship for medical students is generally deemed important, students aiming for a translational scientist career are particularly in need of role models and mentors, because of the many challenges they need to face during their careers (15). It is often difficult to find a clinical job that allows for protected time for research, and funding and reward systems focus on publications and citation scores while translational research consists of longer periods that produce no or only lower-impact papers (16). Because of these challenges in the training and career pathways for translational scientists, the number of researchers and clinicians pursuing such a career has been static over the past decades, with an average age that continues to rise. All in all, regardless of the need for a growing number of translational scientists to advance medicine, this professional figure seems to be in danger of becoming extinct (16, 17).

The Eureka institute for Translational Medicine (http://www.eurekainstitute.org/) was founded in 2007 based on the realization that international, system-wide networks to train and sustain translational scientists did not exist. The Eureka institute aims to build an interdisciplinary community of translational professionals that are equipped to promote the development of true translational studies. The international certificate course that is organized on a yearly basis addresses the educational needs of Eureka's mission. During the course, participants are educated in knowledge domains of translational medicine through formal (e.g., workshops and seminars) and informal (networking opportunities with faculty) curriculum elements, and with mentoring from experts in translational medicine and education. Course evaluations directly after the course revealed high scores for both formal and informal curriculum elements. Participants reported a "paradigm shift" in their scientific knowledge and beliefs. The present study aims to investigate whether alumni of the Eureka certificate course are indeed better able to engage in translational research activities and how this can be supported. The research questions are: (1) *Are alumni of the Eureka certificate course better able to engage in translational activities?*, (2) *What conditions for change hamper or support Eureka alumni's engagement in translational research activities?* and (3) *What are the learning outcomes for Eureka alumni that impacted (one of) their professional activities (e.g., research, clinical work, education, management)?*

THEORETICAL FRAMEWORK

The learning outcomes of the Eureka certificate course were expected to be complex in nature because the course curriculum covers various types of knowledge, for instance explicit knowledge regarding the health professions and personal knowledge of (partly) tacit nature. Further, the course builds forward on prior training and work experiences of the participants and combines knowledge and skills development. Therefore, personal professional theory (PPT) was used to understand the learning outcomes for Eureka alumni. The PPT concept was investigated by Schaap et al. (18) in the field of competence-based vocational education, where moving toward a competence-based model brought along issues with the definition and assessment of learning outcomes in which knowledge, skills, and attitudes were addressed as integrated wholes (19). Schaap et al. (18) define a PPT as "a personal professional knowledge base that serves as frame of reference in the process of internalizing professional knowledge and beliefs." This process of internalization requires critical reflection on previous experiences, knowledge, and beliefs, and adopting shared knowledge and collective norms, values and beliefs of a vocational community so that they become personalized. The content of PPTs involves propositional knowledge, conceptual knowledge and personal beliefs. Propositional knowledge consists of discipline-based theories and concepts (20). Conceptual knowledge contains knowledge about facts, concepts and principles that can be applied in a specific domain. Personal knowledge is what an individual knows and is able to do (20). PPTs can act as a frame of reference through which new knowledge and beliefs can be acquired and interpreted and direct professional behavior.

The content of a PPT is divided into six objects: vocational domain, organizations, social environment, target group, technical-instrumental processes, and professional development. Together, these objects encompass the vocational knowledge, including knowledge on the professional environment and professional development, that is needed to perform adequately in a specific vocation (18).

METHODS

Context

The Eureka institute defines translational medicine as the continuum from a scientific idea or finding to a diagnostic tool and/or therapy applied to human diseases. This means that translational scientists need to have a comprehensive understanding of the aspects of the translational process, including molecular medicine, intellectual property, financing, regulation, and pre-clinical and clinical studies, without necessarily being a specialist in any of those fields. Knowledge and beliefs of these different domains and disciplines are acquired during the certificate course through seminars, workshops, and case-studies that are facilitated by leaders in translational medicine and educational experts. As it remains impossible for one single person to be an expert of all aspects of the translational itinerary, the course also largely focuses on developing the skills to navigate this itinerary, namely communication, networking, and connecting the different domains and disciplines. Teambuilding activities and group assignments are designed to develop the skills to foster innovative teams, critical thinking, problem solving, and communicating effectively across broad audiences. Furthermore, the Eureka course has a personalized learning approach in which challenges and experiences of the participants are central in all sessions. Mentoring and speed-dating sessions with faculty are focused to provide individual advice on issues the participant raises from their working environment or related to career development.

The Eureka certificate course was first organized in 2009 and aims at mid-level career professionals who are working in the field of translational medicine. It is organized on an annual basis for an international group of around 30 participants and lasts 1 week. For the present study, all alumni who attended the certificate course from 2009 up to and including 2014 were approached (144 alumni in total).

Design

An explanatory, mixed-methods design was selected and conducted in two phases (21). In the first phase a questionnaire was distributed among all 144 alumni of the Eureka certificate course. A questionnaire was chosen as the preferred method in the first phase because it would provide quantitative data on the number of alumni that indicated that their participation in the course had helped them to engage in translational activities. The responses to this questionnaire informed the development of a semi-structured interview guide and coding schemes for the second phase of this study. The interview approach was chosen to gain a better understanding of the conditions for change that hampered or supported the engagement in translational research activities and the learning outcomes for Eureka alumni that impacted their professional activities. Ethical approval for this study was obtained from the Ethical Review Board of the Netherlands Association for Medical Education (NERB#403).

Participants

From 2009 to 2014, 144 participants took part in the Eureka certificate course. In March 2015 the questionnaire of the first phase of this study was sent to all 144 alumni. Seventy-eight alumni (54%) completed the questionnaire. In October 2016 the same 144 alumni were invited over email to participate in a semi-structured interview. In total, 14 alumni (8 male, 6 female) volunteered to participate, representing a variety of institutions from four continents. They were working as either a physician-scientist, full-time scientist, or manager of (translational) research. Fictitious names are used for quotes throughout this paper to indicate the gender of the alumni.

Instrumentation

The questionnaire was developed by three of the researchers (BP, NR, and MW). Two of them (BP and NR) are experts in the field of translational medicine and one (MW) is the primary researcher and is not related to the Eureka institute. The questionnaire was pilot tested with five alumni of the Eureka certificate course. The input from these alumni led to minor

changes to the wording of the questions. The final questionnaire consisted of the questions: *Were you able to apply what you learned at the Eureka course in your home environment? If yes, what allowed you to? If no, what prevented it?* and *Did your experience at the Eureka course change the jobs you've held or what you're doing in your work? If yes, please explain what changed?*

The semi-structured interviews were developed by the same three researchers and informed by the results of the questionnaire. The interviews covered 12 questions regarding learning outcomes of the Eureka course, intentions for practice and changes in practice after the Eureka course, conditions for change to engage in translational activities, and questions related to the interviewees engagement in translational networks.

Data Collection

The final questionnaire was distributed via email to alumni who had participated in the course anywhere from 1 to 6 years (mean 2.9 years, SD 1.6 years) since completion. The questionnaire was anonymous and all respondents provided informed consent before starting the questionnaire. The interviews were conducted by one of the researchers (MW) who is not associated with the Eureka institute, varying from two to seven years after alumni's participation in the course. Eleven of the 14 interviews were completed using Skype technology and three were conducted face-to-face. All interviews lasted up to 1 h, were audio recorded with the permission of the interviewees and transcribed verbatim without identifying data. The final questionnaire, interview scheme and coding schemes can be found in the **Appendix**.

Data Analysis

The transcripts of the semi-structured interviews were coded and analyzed by one of the researchers (MW) together with a research assistant. Both were not associated with the Eureka institute. Two coding schemes were developed, using directed content analysis methodology (22). This means that coding schemes were developed before the start of data analysis using prior research (coding scheme I) or existing theory (coding scheme II) (22). Coding scheme I regarded the second research question and thus focused on conditions for change that underlie the engagement of Eureka alumni in translational research activities. For the development of this coding scheme the descriptive qualitative responses to the questionnaire were coded, which led to the identification of six conditions for change. Coding scheme II concerned the third research question. This scheme was developed based on the work of Bakkenes et al. (23) in which four main categories of learning outcomes for teacher learning were defined and validated (as opposed to student learning in which case learning outcomes are often conceptualized as exam or test scores). The four categories of learning outcomes in our coding scheme II were: changes in knowledge and beliefs, intentions for practice, changes in practice, and changes in emotions. Each learning outcome category was subdivided into the six objects that form the content of a PPT: vocational domain, organizations, social environment, target group, technical-instrumental processes, and professional development (18). The initial coding schemes were applied by both coders independently to four randomly selected interviews (28%). Segmentation was initiated at utterance level (24). After each interview both coders met to compare the results of their coding, resolve differences by consensus discussion, and further develop the coding schemes. Coding scheme II only required minor changes for clarification in the operationalization of the codes. Coding scheme I was further expanded due to new themes that emerged, leading to the definition of additional codes, namely "(lack of) personal characteristics," "(lack of) training in how to engage in translational research activities," "(lack of) supportive funding and reward system," and "(lack of) feasibility to conduct translational research." After coding of the first five interviews was completed no new codes emerged.

The final coding schemes were checked for reliability in coding by determining interrater agreement. Both researchers independently coded two more interviews to account for more than 10% of the data (25). Interrater reliabilities were calculated separately for each coding scheme and showed an adequate level of agreement (inter-rater reliability 71 and 81%, and Cohen's kappa 0.77 and 0.88 for coding schemes I and II, respectively) (26). The final coding schemes were applied to the remaining seven transcripts by the research assistant.

RESULTS

Questionnaire

Eighty-six percent of the alumni indicated that they had been able to apply what they learned at the Eureka certificate course in their (professional) home environment. For 51% participating in the Eureka course had played a role in the decision to change to a different job or in the way they were accomplishing their everyday work.

Interviews

Conditions for Change

One aim of the interviews that were held with 14 alumni was to understand the conditions that made it either possible or impossible for Eureka alumni to engage in translational research activities. This led to the identification of ten conditions for change underlying their engagement in translational activities, which are summarized in **Table 1** and will be described in more detail below. All conditions for change start with "(lack of)" to indicate that the presence of the conditions supports engagement in translational activities while the absence of a condition hampers thisengagement. For most conditions, both absence and presence of a condition had been experienced by different alumni.

(Lack of) latitude to conduct translational research

Alumni described how having the opportunity to initiate research projects and collaborations was an important determinant for their ability to engage in translational research. Others, on the contrary, pointed out how they felt restricted to do so within their professional environment.

> "I think my job is quite, I mean, I'm still within a 5 year contract that was very much, let's say, set in stone and it was clear what I

TABLE 1 | Conditions for change underlying the engagement in translational research activities of alumni of the Eureka certificate course.

1.	(Lack of) latitude to conduct translational research
2.	(Lack of) motivation to conduct translational research
3.	(Lack of) opportunities to network and/or collaborate
4.	(Lack of) research time and/or money
5.	(Lack of) supportive professional partners
6.	(Lack of) translational work environment (general)
7.	(Lack of) personal characteristics
8.	(Lack of) training in how to engage in translational research activities
9.	(Lack of) supportive funding and reward system
10.	(Lack of) feasibility to conduct translational research

was supposed to achieve and what to do. And I don't think I had any power to change this." (Maria)

(Lack of) motivation to conduct translational research

The wish to contribute to better patient outcomes was described as a great motivator for almost all of the alumni. Doing research with the patient in mind was said to give additional meaning and relevance to their work and felt more rewarding than research without clinical application.

> "I still want to fight for a better outcome for my patients so I keep on doing this, and I like it, you know, if you don't like it you're not going to stay in this game." (Anna)

(Lack of) opportunities to network and/or collaborate

The importance of being able to contact other people in the field of translational medicine was emphasized by most of the alumni. Examples of experienced benefits were finding a new job through contacts within the alumni's network, knowing more senior translational professionals who can act as mentors, receiving input on research proposals from peers, establishing collaborations for research and educational activities, and being stimulated and inspired by people who share the same objectives.

The lack of a collaborative atmosphere, or more specifically a competitive atmosphere, was said to be counterproductive as it leads to delays in research and increases in research costs.

> "So that is someone who has more power for his experiments, but we believe that over there they draw conclusions too quickly. But if we could collaborate, we could talk about these things and exert some influence. And then we would not have to spend money on the same research twice." (Julie)

(Lack of) research time and/or money

Having protected time for research was regarded as an essential factor by most of the alumni. Although this seems to be most obvious for clinician-scientists, as clinical duties often take priority over research, also fulltime scientists experience a lack of time due to teaching and management obligations. Job profiles that prescribe a certain percentage of time that is (contractually) protected for research seem to be successful examples in some institutions. The issue of funding for research was often related to the issue of time, as being dependent on grants for research funding is time consuming, especially with success rates that have gone down considerably over the years. Working in labs that have sufficient funding and institutions that provide support for early-career researchers or start-up funding were therefore considered to be very helpful.

> "So there's start-up funding that was made available to me both from the hospital department of pediatrics and from the research institute, and that has been critical, because as I said grant funding is hard to get and when it runs out it runs out and then there is nothing. Yet you have a lot of fixed costs…yeah." (Luke)

(Lack of) supportive professional partners

Alumni described how the support of professional partners was very important for their ability to engage in translational research. Partners that were mentioned were superiors, clinicians, researchers, colleagues from different departments or disciplines, mentors, and students.

> "I have my position, my current position now in large part because I entered a purely clinical division and they were very interested in having a research component, like a science translational component […] and so that team, you know, was very open to having me join them and they have been very strong advocates for me and I wouldn't have this position without them." (Laura)

(Lack of) translational work environment

Many examples were given during the interviews of how a "translational philosophy," and the presence of "visionary people" who contribute to the realization of such a translational work environment, influence the alumni's ability to engage in translational research. One such example is having established collaborations between hospitals and universities as it provides an infrastructure that enables translational research: it is easier for clinicians and scientists to collaborate and understand each other, improves access to data and (clinical) samples, and provides more opportunities for patients to participate in trials from which they may benefit. Furthermore, it prevents clinician-scientists from feeling torn when they have to choose whether an article or grant should count for the hospital or the university.

Supportive Human Resource Management practices and support for early career researchers were also mentioned, as is exemplified in the following fragment:

> "There are moments in our career when we need more support and that will pay of later on. But…at an early stage of your career, that you have to be as good as a well-established professor in terms of, you know, bringing revenues for research and publishing, that's a bit unfair." (Maria)

(Lack of) personal characteristics

Most alumni mentioned a number of personal characteristics that are required to succeed in translational research. They mentioned that translational professionals need to be very good communicators and collaborators that function well in multidisciplinary teams, rather than striving to succeed in individual, goal driven research. Since many described how

working in translational medicine can be challenging and stressful, commitment, perseverance, time-management and being able to ensure a good work-life balance were also mentioned as important factors for success.

> "I see these as people who have a cohesive team around them. They have a really clear focus on an important health issue. They know how to communicate well, so for example, there is a group who is getting huge amounts of funding for diabetes, you know translational work in diabetes, huge amounts, millions of dollars, but they have really, they've got their collaborators from all over the country, they're actually bringing all the people in that they need, they've got a really tight team around them, they've brought in all the assets that they need to make their work happen. So they're quite entrepreneurial in their approach. The people who are less entrepreneurial, so who are much more inward looking, are not as successful." (Emma)

(Lack of) training in how to engage in translational research activities

The issue of training in translational research was mentioned in several interviews. Some said that it was not until their participation in the Eureka certificate course that they gained a full understanding of the translational pathway. Looking back, they would have liked to have received this kind of training earlier on in their careers, for example during graduate training or while working on their PhD. Others noted how difficult it is to find students who are interested in translational medicine because they are very "polarized" when they finish their undergraduate degrees due to the focus of these programs on either basic science or medicine. For students who do pursue a combined training path, such as an MD-PhD program, alumni felt it was difficult to see the goal at the end of that pathway due to limited opportunities to work as clinician-investigator or clinician-scientist.

> "But I also think that training is really important, and I think potentially even introducing new approaches to PhD training, so really starting to train young researchers earlier and not just young researchers, but young clinicians, you know, really bringing them together with researchers, to work out how do they prioritize the questions that they are asking, and how do they achieve the best outcome for their patients? Because that's what they want, that's what the researchers and clinicians want, that's the thing that drives them." (Emma)

(Lack of) supportive funding and reward system

Current funding and reward systems that focus on prominent author positions on high-impact papers were often seen as a difficulty in succeeding in translational research. As successful translational work is often the result of a collaboration between scientists and clinicians, and often additional partners, metrics in terms of author positions on papers and impact factor do not adequately reflect the work that was put in. One interviewee called the current system "anti-collaborative" and "anti-translational." Many alumni felt that every author position on a paper should be valued and that, in addition to publications, translational outcomes should be demonstrated and rewarded.

Some alumni also described how they felt restricted to engage in translational activities by these systems as grants and job evaluations often depend on these author positions, number of publications and impact factor. Because that is the case, they felt pressed to spend time on projects that are less translational, but lead to faster results and can be published in higher impact papers.

> "Because at the end of the day, no matter if someone is in industry or somebody is in university, we all answer to somebody and if we don't answer to that person or entity the way that we need to, we cease to have the position. You know, so there's always conflicting priorities. So I think it would be brilliant if there could be some shift away from, in my world academics, the traditional metrics of publications, grants, and presentations to something that values collaborative work and ideas more than it is today. And now I feel that it's only valued when it turns in to the traditional types of academic output, which inherently puts a constraint on even the kinds of translational ideas that you can think about." (Luke)

(Lack of) feasibility to conduct translational research

Some alumni mentioned factors that were difficult to influence, but could determine whether their efforts would be successful. Examples include ending up at the right institution, meeting the right people at a conference, and ending up with a patentable discovery.

> "So I was really at a moment in my life where I was questioning where I wanted to go and the truth is, a friend saw the advertisement for [my current position] and said it is not for me but maybe you should look at it, because it might be interesting for you. And I looked at it and I liked what they were doing and the position, so I applied but it was really by chance. Also, I think at that time I was ready for a next move in my career, it came at a point where I was ready to take this step." (Sophie)

Learning Outcomes

In this part we describe how the learning outcomes of the alumni of the Eureka certificate course contributed to their engagement in translational activities, which was the second aim of the semi-structured interviews. Results are described for each of the four categories of learning outcomes, and – when applicable – each of the six objects of PPT.

Changes in knowledge and beliefs

Vocational domain Almost all alumni reported that obtaining a clear perspective on the full spectrum of translational medicine was one of the most valuable outcomes of the Eureka course. Alumni were generally not aware of the entire translational process prior to the course or had used the term "translational research" for different types of research, as one alumnus explains:

> "It really struck me that that's a mistake I think is often made, and this phrase 'translational research' is really misinterpreted and misused very frequently. So I used to say that I did [do translational research], but actually what I was doing was basic research that was with some human cells now and then, rather than kind of thinking through, you know, a much more complex process, which is actually what translation is." (Tom)

This insight in the full translational pathway influenced what alumni regarded as end point of their research and how they felt about the need for inter-professional collaborations. Gaining a better understanding of the drug development pathway, the importance of intellectual property (IP) and patenting in order to be an interesting partner for industry, and the importance of interfacing with people who are making (health) policy decisions directed their focus toward the implementation of research outcomes, rather than publication of results only.

> "So I think where Eureka has influenced my thinking maybe is what I'm going to do with the results of my studies and how I'm going to think about translating that into, you know, something beyond just 'here's the paper reporting the results'." (Luke)

Moreover, the clear perspective on the full translational spectrum and stakeholders involved allowed participants to reflect on their own role and where they wanted to be within that spectrum:

> "I think since Eureka, you know I'm very clear that I'm a, you know I'm a basic and a translational scientist, that I started to use that word and feel more comfortable saying that you know, that I'm a translational scientist, that translation isn't just something you do. You can actually sort of be that person that takes care of that type of research." (Laura)

Organizations One alumnus said that the personalized approach of the Eureka course led to new insights in how to manage people in research:

> "For me, the most important insight was actually the way the course was set up, connecting the human dimension, like personal growth and development and how people interact with each other as persons instead of professionals, to connect that to the challenges in the field research." (Alex)

Social environment For most alumni the course helped to gain an overview of the people involved in translational medicine, which helped to understand the need to collaborate with people and with organizations.

> "I have a much more well thought out understanding of how this all works and where I fit within it, and what needs to be done for me to make a connection, if I need to make the connection, and how to build bridges. So I think you know Eureka provided a lot of time for thinking and time for talking to people from different areas, who have, even though they are form different areas, have similar experiences and similar frustrations and road blocks, and I think it gained a lot more insight." (Luke)

Furthermore, the interaction with other participants fostered a greater understanding of translational professionals from different backgrounds.

> "I think that, to understand what motivates different people, you know what's motivating a scientist vs. a clinician when they approach a problem, understanding how those sort of, our training makes us sometimes good collaborators, and not so great collaborators." (Laura)

Personal development Alumni described that the course showed them the difficulties in communication and collaboration, which enabled them to reflect on their own communication and collaboration styles.

> "It provided me a lot of insight in the way people can behave very different in a group [. . .] and how that's fine. So it is important to have diversity within a group and for everyone to have different characteristics." (Julie)

Intentions for practice

Vocational domain A few alumni described how, immediately after the course, they had planned to look back at projects they had undertaken in the past to see whether the results could be translated into clinical practice. In general, however, alumni seemed to have little recollection of the intentions they had at the end of the course. Other intentions had turned into changes in practice by the time of the interview and will be discussed under 1.3.

Social environment The network of alumni of the Eureka certificate course was mentioned during all of the interviews. Almost all alumni mentioned that they wanted to stay in touch with the Eureka community, usually because of a combination of the friendships that had formed during the course and the want to be in contact with peers or mentors. Although most alumni were still in contact with at least some of the Eureka alumni or faculty, it was also indicated that they did not form a cohesive network. Possible explanations that were provided during the interviews were physical distance (as the Eureka alumni form an international group), restrictions in time, limited follow-up by the Eureka institute, and the difficulty of connecting over a common theme that is as broad as translational research without a specific project binding them:

> "And at least in my case, whenever I've built meaningful professional connections, that have blossomed into something long-term, and actually had tangible benefits, it's always been or almost always been around specific work that we've done together. As opposed to just 'hey you're an interesting person in a different discipline, let's translate together'." (Kevin)

Changes in practice

Vocational domain Three different types of changes in practice within the vocational domain were described by the alumni: changes in professional appointment, changes in research activities, and changes in teaching styles or methods.

Participating in the Eureka course led to a change in professional appointment for some of the alumni, because they felt restricted in their abilities to do translational research in their previous positions. These changes in positions were either within academia toward a more translational environment, or from academia to industry as is the case in the following example:

> "So I've actually very recently accepted a new position at a company, and that has certainly been influenced by my experience at Eureka. And so from January I'll be moving to a technology development company that is more focused on translation, you

> know from a bit more commercial rather than an academic side, but it's what I want to do because I am so interested in actually delivering something that you know success or fail, at least you take it to those steps to test that. And that definitely has been Eureka, has had an impact on that decision." (Tom)

Others described how their research activities have become more translational, for example by setting up collaborations with clinical departments to be able to use clinical samples rather than animal models or by deliberately choosing research projects that may benefit patients over research projects that may lead to publications on the short term.

Alumni also reported changes in practice outside the translational domain: specific teaching methods and elements of the personalized teaching style that is applied during the Eureka course have been used by alumni in their own teaching activities and in interactions with colleagues and other people. Also, some alumni organized courses and workshops that were inspired by the Eureka certificate course.

Organizations Alumni described how the Eureka course helped them to create a research team, acknowledging what people did for the team and helping them to develop themselves. One alumnus described how he restructured a research department:

> "We work with approximately 40 researchers in the lab and 40 clinical researchers, and then the clinical department is even bigger. So I think the setting up a structure in which people, despite them working on very different topics without speaking one another's language, do collaborate and believe it to be an integrated and meaningful experience, that is something that I, for the better part, gained from the Eureka course." (Alex)

Personal development Alumni described how they gained the skills to communicate around the impact and relevance of their work, to reflect on their careers and take leadership in professional decisions, thanks to the confidence they gained in their roles as translational professional during the Eureka course.

Changes in emotions

Vocational domain Alumni described that the course increased their motivation to become translational professionals, because they felt inspired by the faculty and other participants, who showed them that it was possible to succeed in translational medicine, and because of the inspiration for new projects and possibilities to make their own work more translational. For others, the Eureka course came at a time where they were deciding on future directions for their careers, for which the Eureka course offered them the ideas, contacts or confidence.

DISCUSSION

This study set out to investigate whether alumni of the Eureka course were better able to engage in translational activities, the conditions for change that hampered or supported Eureka alumni's engagement in translational research activities, and the learning outcomes of the Eureka certificate course that impacted their professional activities.

Two to seven years after the course alumni reported high impact of the course on their professional activities, both in terms of applying what was learned (89%) as well as on job crafting (51%). Though by no means of proof of the efficacy of the course, this finding is remarkable in the light of what we know about the professional struggles of translational scientists.

Ten conditions for change were identified that had either hampered or supported the engagement of alumni in translational activities. Two conditions that mainly hampered this engagement focused on the lack of (dedicated) time and funding for research and the current funding and rewards systems. These issues have frequently been addressed in the literature (3, 16, 27). Research requires protected time, but often this time is limited due to patient care, management activities or teaching expectations. Funding for research largely depends on grants, which further draws away from the already limited time for research. Further, academic promotions are ultimately based on publications, citation indices, and related metrics such as the Hirsch-index, discouraging publishing on the implementation of research findings in practice as this type of research takes considerable more time to produce (3, 16). The results of the questionnaire, however, indicated that a large number of alumni succeeded to engage in translational research despite these systems. Our results suggest that this was likely due to a combination of conditions that are supportive for engaging in translational activities, such as supportive professional partners and working in a translational work environment, and the learning outcomes that resulted from alumni's participation in the Eureka certificate course.

The concept of PPT was used to understand the learning outcomes and how they enabled alumni to further develop as translational professionals. Gaining a full understanding of the whole translational pathway and the stakeholders that are involved in this pathway seem to be the most important insights that alumni gained from the Eureka certificate course. It enabled them to reflect on their own role within that pathway and stimulated them to more consciously make decisions on the type of research they wanted to engage in, the environment they wanted to work in, and the people they wanted to collaborate with. Moreover, it was mentioned how the course gave them the skills and confidence to pursue a career as a translational professional. Alumni indicated how they would have liked to gain this insight earlier on in their careers and addressed the need for more education on translational research in graduate training and PhD programs.

No learning outcomes were reported in the objects "technical-instrumental processes" and "target group." This is likely due to the fact that this type of knowledge falls outside the scope of the Eureka course, but rather is addressed during prior (bio)medical training or PhD tracks. These objects focus on discipline specific knowledge, while the participants of the Eureka course represent a diverse and multidisciplinary group.

A remarkable outcome was the number of alumni who mentioned how the teaching style of the Eureka course had

impacted their own teaching activities. For some alumni it had influenced the way they were interacting with colleagues or organized a research unit.

This study was not set up to compare the Eureka certificate course with other graduate and postgraduate training programs on translational research. Still, a number of differences can be observed. Many of the shorter courses focus on technical skill development, business management and leadership, or knowledge on the translational spectrum without integrating this knowledge with interdisciplinary skills development, mentoring, and community building. For most of these programs data regarding the long-term impact of these courses for comparison are not (yet) available (10, 12, 13). Other programs that do combine multiple components are often master or postgraduate training programs of much longer duration, varying in length from multiple weeks up to 6 years. An example is the National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) mentored career development program (https://ncats.nih.gov/training-education) that supports translational scientists in the transition from mentored to independent research funding (28).

Building a community of interdisciplinary translational professionals, one of the goals of the Eureka institute, seems to be the most challenging. Although most alumni were still in contact with at least some alumni or faculty this has not led to the formation of a structured network yet. As fostering community to prevent isolation has often been described as a necessity for translational scientists (29–31) this is an aspect that can still be improved and may contribute to a further increase in alumni's ability to engage in translational activities.

This study has a number of limitations. Although the use of a questionnaire and interviews was deemed most suitable to address our research questions, this may have led to a response bias in favor of alumni who benefitted most from their participation in the Eureka certificate course. Also, our questionnaire and interviews focused on the perspectives of the alumni. The outcomes of the course were not observed or measured. Due to the explanatory nature of this study we do however feel that this did not have substantial impact on our results.

CONCLUSION AND RECOMMENDATIONS

Current translational medicine needs translational professionals with a broad set of knowledge and skills to help breaking down the barriers between the different disciplines that are involved in the translational pathway. Becoming such a translational professional, however, is challenging due to the lack of training programs, the current funding and reward systems, and the lack of support for (especially early-career) translational professionals in terms of start-up funding and dedicated time for research. Although these systems are influenced by economical, political, social and cultural factors (3) and are therefore not easily changed, this study showed that education in translational medicine can have a large impact on the careers of translational professionals. Together with the conditions for change that have been identified in this study this may enable young translational professionals to succeed in their translational activities, and thus help to close the gap between biomedical research and its clinical application, and reduce the waste in research funding.

AUTHOR CONTRIBUTIONS

MW, BP, and NR designed the study and developed the questionnaire and semi-structured interview guide. MW analyzed the results together with a research assistant. MW wrote the first draft of the paper, with extensive feedback from MvdS and BP. All authors provided critical comments and revisions and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2018.00298/full#supplementary-material

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OPINION
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Publications Are Not the Finish Line: Focusing on Societal Rather Than Publication Impact

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INTRODUCTION

Have bibliographical quantification of publications and the subsequent accompanying rewards perverted the incentives of scientists? Are we lost in a publish-or-perish research culture? Alarmingly, ample (bio)medical research findings intended to improve patient outcomes and lead to innovations in patient care never leave the lab (1–3). This widening gap between discovery and implementation undermines the social responsibility of scientists and erodes their public stature. When research findings have the potential to improve the health and well-being of society but are not translated into real-world benefits, it represents a failure of the system and a failure to society.

A re-evaluation of the parameters that define scientific success is imperative. Climbing the academic ladder and securing financial support relies heavily on a scientist's productivity, which is typically defined by the number of publications and their bibliometric scores (4, 5). Several groups are working toward developing novel measures for impact, but so far traditional bibliometric evaluation criteria prevail (6, 7). Whilst understandable that a quantitative system of evaluation might fulfill a desire for objectivity, this creates an intrinsically competitive culture in which regularly publishing ever-novel work is key to individual career success and open collaboration is undermined.

When novel discoveries are incentivized over refinement and implementation, it becomes strategically disadvantageous to do the work needed to translate discoveries into working strategies that benefit patients, the ultimate goal of translational medicine (1–3). Proper recognition and rewards for aiding efforts to achieve this goal must be advocated for, guided by the principles of social accountability and fostered by the support of key stakeholders (8).

JOURNALS AS GATEKEEPERS

One way in which the scientific community is not serving society well is reflected in the current publishing environment. The pressure to publish quantity over quality in order to build a successful scientific career has cultivated a rapidly-expanding ecosystem of thousands of journals publishing millions of papers per year (9). Many of these papers are seldom read or cited, and many contain non-reproducible or even fraudulent data (10, 11). Simultaneously, and partially because of the proliferating abundance of journals, there is increased pressure to publish in so-called "high-impact" journals, which have achieved recognition

in the (bio)medical field as being highly desirable to publish in (12–16). Through their selection of what to publish and what not, these "high-impact" journals often become gatekeepers that define what is seen as "good" science by not only the research community, but also the general public. In an effort to impress the editors of these aggrandized journals, scientists increasingly focus on "cutting-edge" questions, rather than validating previous results or pushing them toward further development. Thus, there is a paradoxical problem of too many publications in too many journals, but also too much pressure to publish in too few journals. This creates a conflict where potential scientific advances are lost in the increasingly distracting background noise.

Similar to the role of the free press, scientific journals have a responsibility to the public: to objectively communicate advancements in scientific research and to foster productive exchange of ideas and information. How can journals fulfill this great responsibility? First, by realizing the impact their selection bias has and how strongly it shapes the global scientific research culture. Translational research cannot be accomplished by one individual at a time, it relies heavily on interdisciplinary collaboration and studies at all stages of the research pipeline deserve to be appreciated and rewarded. Second, by helping to shift the focus away from individual achievements and vacuous publication or citation counting, but conversely onto a common goal of achieving real societal impact through collaboration. Encouraging open-access platforms that provide full data sets helps ensure the full use of generated data, reducing scientific waste (17, 18). Web platforms could also implement new evaluation systems, rating scientists on their interdisciplinarity and collaborations. Finally, by revising the peer-review system. Despite holding a very important role in the publishing process, the current system offers little incentive for quality reviewing (19). Unmasking peer-review and rewarding the intellectual contribution and time dedicated by reviewers may promote a more fair process that is in line with the mission of the work. Adding an assessment of the potential for knowledge utilization and societal impact to be published alongside the article would also promote a healthier science culture.

If journals are gatekeepers through which all (bio)medical research must pass, it is time to redefine their role and influence. Translational medicine involves much work beyond initial discovery. The long and tedious but vitally important process of seeing research findings through to clinical practice is one of the field's most overwhelmingly difficult yet largely under-appreciated burdens (20, 21).

THE ROLE OF INDUSTRY, COMMUNITY AND OTHER STAKEHOLDERS

In the case of (bio)medicine, there is a long and risky path from discovery to real-world clinical implementation (22). One research group cannot do all of this alone, especially since the later stages require partnership among many stakeholders (23, 24). If the goal of translational medicine is to implement research that has a meaningful societal impact, academia must collaborate more closely with all stakeholders involved, including industry, patients, and community leaders (6).

A current obstacle to translation is that partnerships among stakeholders are difficult to establish and maintain (25). Specifically, better partnerships between academia and industry would be instrumental to more time- and cost-efficient implementation of research findings (26). Although setting up shared platforms may demand sizeable initial investments, timely and continuing validation of research findings according to companies' pre-approved standards can save time and expenses at later stages of the translation process. More importantly, this facilitates a more efficient pipeline from discovery to societal benefit.

On a more individual scale, Technical Transfer Offices (TTOs), and similar programs housed within academic institutions can also help bridge the gap between academia and industry (27), yet this can be difficult if they are not involved early in the research process and do not remain engaged throughout. Therefore, academic institutions must create awareness amongst scientists and TTOs about their respective value. Specific programs, such as scouting systems to identify potentially impactful research findings, educational initiatives that promote the latest developments, and including TTOs as part of trans-institutional partnerships, might more efficiently establish a pipeline for ideas and networks including international collaborations. Funders could facilitate this by making an assessment of knowledge utilization and societal impact by a third party, e.g., TTO or patient organization, mandatory in annual reports. Sponsored networking events and training programs may also help overcome barriers and facilitate knowledge exchange between these key stakeholders. Developing a more collegial relationship based on shared goals can add momentum to this cooperative process and strengthen the scientific infrastructure as a whole.

Better engagement with other stakeholder groups will facilitate other aspects of the translational enterprise. Patient groups are an increasingly integral part of the scientific process, driving scientific questions (28–30). The voice of the patient in translational research is extremely important and must play a crucial role in the whole process (28). In a similar way, translational medicine has eschewed approaches such as community-based participatory research (CBPR) or community-engaged research (CER) (31, 32). These types of studies, which include community members in the generation of research questions and implementation of research studies, are a valuable approach toward improving the quality and value of the science itself. Involving the community may lead to the identification of underrecognized or underappreciated problems faced by the community, which in turn drives innovation. It may also serve to give a voice to underrepresented and disadvantaged groups that typically fall off the radar. These approaches not only improve scientific validity, innovation, and feasibility, but by including the community as a partner in the work, they kindle a bidirectional dialogue between scientists and society, which is ever more needed.

SCIENTIFIC COMMUNICATION

Science in general is facing a growing problem of insufficient resources and eroding public appreciation (33–35). One reason for this is that the public, and funding bodies that often represent the public, are increasingly skeptical about the return on their investment (33, 36). A bench-to-bedside approach to research can help bridge gaps among basic discovery, clinical investigation, implementation, and application in society (37, 38). Effective communication with the public is an important part of this process.

As patients are increasingly confronted by misinformation and charlatanism, the public expresses a desire for clear-cut answers to what they perceive are clear-cut questions. But scientists notoriously provide overly-nuanced and seemingly-obfuscated conclusions. This creates a situation where media reporting of science tends toward overextrapolation and oversimplification which, in turn, leads to scientists being unenthusiastic about engagement with the media or public and the public's distrust of science growing as inaccuracies and exaggerations are borne out, e.g., "miracle cures" that aren't miracles. It is essential that scientists take on their role in guiding the scientific discourse. This is especially true in the field of translational medicine, where discoveries have the potential to directly impact lives.

Communicating science in a way that maintains accuracy, context, and nuance, is accessible to a non-scientific audience, and is as brief as a short news article is difficult, even for seasoned journalists. Additionally, journalists who are expected to cover a wide variety of topics often don't have the expertise or time to assess an individual study's relevance or integrity. It is up to the academics, who have a responsibility to maintain scientific integrity, to accurately interact with the press and advocate for appropriate representation of their work. If academics neglect this role, it will be filled by others who may not hold themselves to the same standards. Yet, scientists are often actively discouraged by peers from collaborating with the media. It is often seen as a distraction or, worse, as unprofessional. Currently though, the ability of scientists to engage the public is greater than it has ever been. More and more news outlets are seeking content, more people than ever are seeking information, and more direct lines of

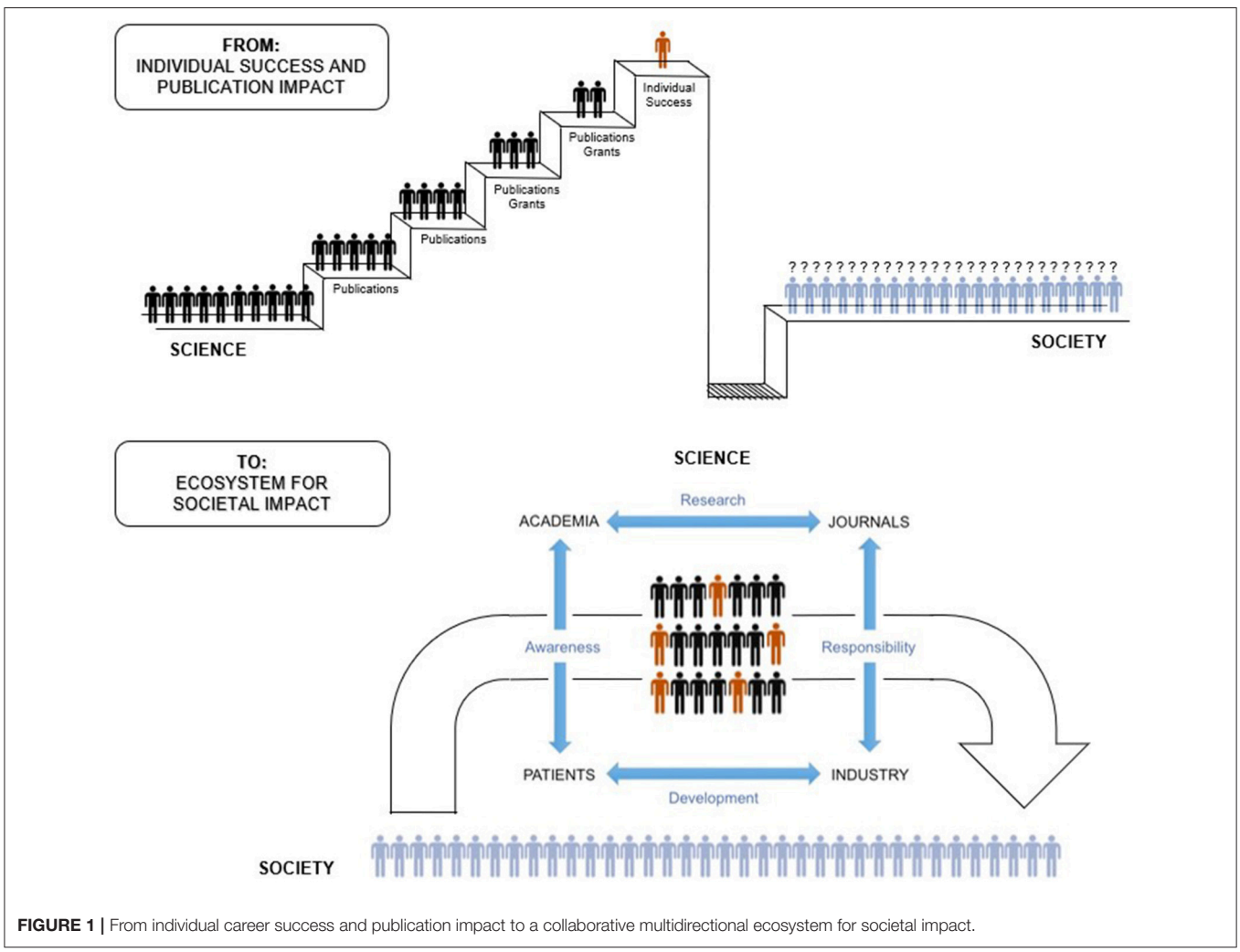

FIGURE 1 | From individual career success and publication impact to a collaborative multidirectional ecosystem for societal impact.

communication are available than there have ever been, e.g., social media.

Issues regarding scientific communication require initiatives at several levels. Academic institutions should better teach scientists how to communicate with the public, ensure that any press releases fairly represent their work, and also powerfully convey relevance to a lay audience. News organizations should collaborate more closely with academia to ensure that reported findings are not overly sensationalized. The public should be encouraged to engage with research with the understanding that while science is rigid in some ways, it reflects a constantly evolving process and an everchanging knowledge base. Improving scientific communication is a critical step in informing everyone, including patients and caregivers, on the relevance and merits of translational medicine. The importance of scientific literacy in communicating the societal impact of research is often and wrongfully neglected.

CONCLUSION

Society expects translational scientists to address relevant matters that aim to improve human health and well-being. Indeed, successful translational research has resulted in the clinical application of promising therapies such as CAR-T cell immunotherapy in leukemia and novel HIV antivirals (39, 40). However, the gap between society and academics is widening. Scientists find themselves enthralled in a vicious exercise: publish, secure funding, repeat. The public and other stakeholders are largely absent from this process. Scientists have become so accustomed to this unhealthy system, that they equate "success" with mere survival in the current publish-or-perish culture. Additionally, the perception of science by society and vice versa is dangerously perturbed.

Breaking free from the current failing system will require disrupting this vicious cycle and realigning (bio)medical research with its original mission (**Figure 1**). This requires reconsideration of the publication system and strategies for including important stakeholders throughout the process. Society must be better informed about the importance of research and play a larger role in its advancement. To accomplish this, scientists and other stakeholders need to take more responsibility in facilitating discussion in a way that effectively communicates and serves the public, while maintaining scientific integrity. Translational scientists should also remember the societal context of their work, recognizing their social accountability and the need for proper two-way dialogue with the public, driving innovation in both directions.

In conclusion, publication should not be the finish line scientists strive to, it should be a stepping stone toward a greater good.

AUTHOR CONTRIBUTIONS

FK, SM, and SH-B conducted literature research and authored the manuscript. SN and GC advised and guided the writing process. MG revised and edited the final manuscript.

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PERSPECTIVE
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Possibilities and Pitfalls of Social Media for Translational Medicine

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We live in an age where the sharing of scientific findings and ideas is no longer confined to people with access to academic libraries or scientific journals. Social media have permitted for knowledge and ideas to be shared with an unprecedented speed and magnitude. This has made it possible for research findings to have a greater impact and to be rapidly implemented in society. However, the spread of unfiltered, unreferenced, and non-peer-reviewed articles through social media comes with dangers as well. In this perspective article, we aim to address both the possibilities and pitfalls of social media for translational medicine. We describe how social media can be used for patient engagement, publicity, transparency, sharing of knowledge, and implementing findings in society. Moreover, we warn about the potential pitfalls of social media, which can cause research to be misinterpreted and false beliefs to be spread. We conclude by giving advice on how social media can be harnessed to combat the pitfalls and provide a new avenue for community engagement in translational medicine.

Keywords: translational medicine, translational research, social media, research dissemination, patient engagement, science communication

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INTRODUCTION

The emergence of social media has changed the way we communicate and allows for knowledge and ideas to be shared with an unprecedented speed and magnitude. Similarly, an exponentially increasing amount of research about social media is being published (**Figure 1**). Social media come in a variety of forms, including collaborative projects such as Wikipedia, (micro)blogs like Twitter, content communities like YouTube, social networking sites like Facebook, and gaming communities like Second Life (1). These platforms are accessible to all and provide forums where people can freely share thoughts, opinions, and knowledge without—in general—any form of censorship or fact-checking.

Several groups have addressed how social media are used by the research and medical communities. Medical researchers have shown doubt about professional use of social media, describing it to be incompatible with research (2). Social media are mostly used for personal and less for professional purposes (3, 4). Yet, on the level of society, social media have great potential. There are many examples of its use for public health and prevention purposes (5, 6). Additionally, the rapid dissemination of research findings and the spreading of knowledge to society has increased public interest and involvement in research. Consequently, patients increasingly can and want to be part of developing solutions for their illness (3, 7).

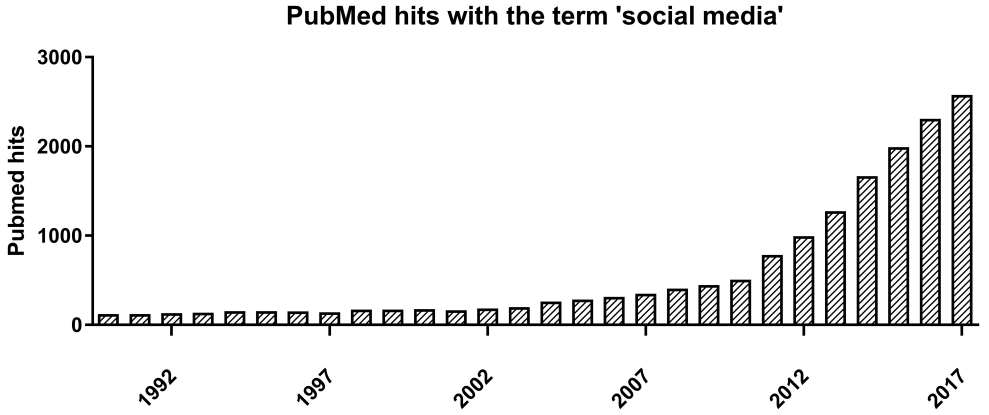

FIGURE 1 | Number of publications found on PubMed with the search term "social media," as shown by publication year.

The use of social media for purposes of implementation and translation of research is still in its early stages. At the same time, social media are clearly being used by both patients and professionals for personal content and information sharing. Various efforts of using social media for research are also increasing. Thus, it is important to raise awareness and understanding of the possibilities and pitfalls that social media present to the research and medical communities as well as to regulatory bodies, patients, and industries. Therefore, in this study, we aimed to address both the possibilities and potential pitfalls of social media for translational medicine. We aimed to provide a brief and broad overview of this topic that could steer the community to be more mindful when using social media. A comprehensive review of all different aspects relating to social media and translational medicine is beyond the scope of this perspective article.

POSSIBILITIES OF SOCIAL MEDIA FOR TRANSLATIONAL MEDICINE

Rapid and Easy Dissemination of Research

Social media are widely used all over the world. Facebook, for example, had an average of 1.45 billion daily active users and 2.20 billion monthly active users in March 2018 (8). With this many users, social media provide platforms for researchers and institutes to quickly disseminate their research plans and findings to a greater public. Through online pages of journals, associations, newsgroups, and direct-sharing, it is relatively easy for researchers to reach a broad audience compared to the more "conventional" sharing of knowledge through publishing in scientific journals. Relevant research findings that are interesting to the community may rapidly spread through social media and go viral. This way, social media may be used to rapidly spread and implement public health findings to the general public. An additional benefit is the easier recruitment of traditionally "hard to reach" populations for medical research (9–11). Furthermore, it increases the chances of research being picked up by peers and stakeholders (4). Faster dissemination of research findings might also prevent other research groups from repeating the same research, decreasing the potential waste of resources. Recently, tools were developed that visualize the magnitude of impact of social media on scientific publications. This is important, as number of tweets within the first 3 days after publication of an article was found to predict which articles would be highly cited on Google Scholar or Scopus (12). The most commonly used tracking tool is Altmetric, which tracks the amount of rumor about an article on nearly all professional and social media outlets (13). For example, an article about the association of fats and carbohydrates with cardiovascular disease published in medical journal *The Lancet* was at time of writing only cited by 21 articles (14). However, the real "buzz" was generated by 8,313 tweets, 450 Facebook posts and 168 news stories, adding it to the top 5% of the most discussed publications of the year (14).

Critical Review of Existing Articles and Raw Data Sets

In this era of exponentially increasing numbers of publications, using the reviewing power of the scientific community is an opportunity that should not be missed in order to improve overall research quality. As an extension of recent developments toward more transparent peer reviewing, several social platforms that allow open peer review have been developed, encouraging readers to critique existing publications in-depth. In addition, users are stimulated to upload raw data sets as well, including negative results that might otherwise never have been published, thereby counteracting the effect of publication bias (15). However, the scale of impact of open review might be limited to high-profile work that raises concerns, as those are more likely to attract attention (16).

Possibilities for Raising Funds for Research

With its fast dissemination of information and large number of users, social media platforms have the potential to broadly raise awareness for medical research and specific diseases. Social media platforms have been demonstrated to play an important role in

reaching potential donors and raising money in crowd funding campaigns (17). In 2014, $115 million was raised from the *Ice Bucket Challenge* on Facebook for research into new treatment strategies for Amyotrophic Lateral Sclerosis (ALS) (18). In 2016, a 6-year old Dutch boy who was recently diagnosed with a pontine glioma raised € 2.6 million for the Dutch Red Cross by daring people to paint their nails and post a picture on social media (19, 20). Moreover, a social media-based fundraising contest launched by the University of California San Francisco (UCSF) raised more than $1 million for the UCSF Benioff Children's Hospital, surpassing their initial fundraising goal 10-fold (21, 22). Thus, with the large audience that can be reached through social media, new opportunities for raising funds arise.

Networking Between Clinicians, Researchers, and Patient Groups

Keeping an up-to-date online presence on social media may prove valuable for clinicians and researchers. Social media create an accessible platform for peer-to-peer discussions and form an increasingly important networking tool. Depending on the platform used, potential target audiences include professionals as well as patient representatives.

Social media outlets also enable patients and patient representatives to efficiently unite into groups. This may be especially beneficial for patients with novel or rare diseases (23). In addition to providing guidance, advice, and support to peers, these platforms may be used to exchange and seek medical information from each other and from medical professionals (24). A unique opportunity for clinicians and/or researchers lies in initiating these groups, which facilitates immediate contact with patient groups. This can provide the researcher with valuable first-hand information and enable patients and their representatives to directly influence research and prioritize projects (25). Similar collaborations on social media between patients, clinicians, and researchers have been shown to contribute to overall scientific knowledge (25).

Big Data Analytics for Prediction Models and Assessing Trends/Outbreaks

Social media outlets have the potential to be used as exponentially growing, observational datasets (26, 27). A well-known example of big data research performed on online data is the prediction of global influenza outbreaks by analyzing the number of searches of the word "influenza" or symptoms of influenza-like illness on Google (also known as *Google Flu Trends*, currently discontinued) (28). The same can be done using data social media such as Twitter. For example, based on data from Twitter posts (tweets) researchers were able to detect increases and decreases in influenza prevalence with a 85% accuracy (29). Another example is a study that found that a model that analyzed language expressed on Twitter was better at predicting atherosclerotic heart disease mortality than a model that combined 10 common risk factors such as smoking, diabetes, and hypertension (30). Social media have also been demonstrated to contain information on health-related behaviors, such as smoking (31), sexual risk behavior (32), and sedentary behavior (33). Finally, they could be used to monitor public opinion on important health topics, such as vaccines (34) and opinions on specific projects or studies (35).

POTENTIAL PITFALLS OF SOCIAL MEDIA FOR TRANSLATIONAL MEDICINE

Lack of Peer Review and Filtering of Quality

The increased speed and magnitude of the spread of scientific findings through social media comes at a price. There is no system for peer review or filtering of social media, which means that any idea can be spread; even if it is fabricated or not supported by evidence. The vast majority of social media users do not have a scientific background and may be ill-equipped to judge the quality of evidence and sources. For example, people might perceive a blog or advertisement stating "proven by science" as just as trustworthy as a research paper in a peer reviewed scientific journal. However, most people will never read the latter; full research articles are simply not as fun and easy to read as readily digestible news items on social media.

Fake News Spreads Fast and Is Difficult to Refute

Fake news often disseminates rapidly through social media. A recent study compared the differential diffusion of ∼126,000 verified true and false news stories through Twitter. Worryingly, the study revealed that false stories spread much faster, further and more broadly than did true news stories. True news stories rarely spread to more than 1,000 people, whereas false stories often reached up to a 100 times more people (36). Similarly, false stories spread several times faster (36), proving what Charles Spurgeon's already asserted in 1855 "a lie will go around the world while truth is pulling its boots on" (37). False stories are generally more novel and trendy than true stories, which are often more sober and nuanced, and it is part of human nature to be attracted to novelty (38). Novel information is most valuable to decision-making (39), and surprising content can induce physiological arousal that encourages people to spread information and cause content to go "viral" (40).

Once a fake story has spread, it becomes increasingly difficult to refute it. This principle is generally known as Brandolini's law, or the "Bullshit Asymmetry Principle": the amount of energy needed to refute bullshit is an order of magnitude bigger than that needed to produce it (41). Often, the fake news being spread is relatively harmless and primarily amusing. For example, a story by a doctor about a baby boom in Iceland 9 months after a football victory has gone viral, even though it was debunked by statistical analyses (42). Unfortunately, there are also examples of pervasive fake news stories that endanger public health. Perhaps the most famous of these stories is the case of Dr. Wakefield, who wrote an article that suggested a link between the MMR-vaccine and autism (43). The study was soon discovered to be fraudulent, the article was officially retracted, and Dr. Wakefield's UK medical license was retracted (44). It is now 14 years after the retraction of this article, but its fraudulent results continue to refrain people from taking vaccinations (45). A search on

Facebook reveals 109 public pages and 94 discussion groups about vaccines with collectively more than a million members and followers, such as *@thetruthaboutvaccines* (136 k followers) where daily memes are posted to warn people about putative risks of vaccination, including autism. Psychological studies have shown that incorrect memories continue to influence decision making even when you are aware that the memory is false (46), which may explain part of the persistence of these stories. Similarly, most strategies to correct vaccine misinformation are ineffective and could even backfire (47). With fake news being this difficult to refute, it invites the question whether the dangers of the fast and broad dissemination on social media outweigh the advantages.

Misinterpretation of Research

Aside from fake or fraudulent research being spread on social media, there is also the risk of genuine research findings to be misinterpreted. Conclusions of research findings are often simplified and overly extrapolated in the media. A prime example of this happened in 2015, when a study on cancer risk was published (48). The authors concluded that 65% of the variation in cancer risk among different tissues could be explained by the total number of stem cell divisions and thus "bad luck" (i.e., random mutations arising during DNA replication in normal, non-cancerous stem cells). Even though the study did not explore the causes of cancer, major news headlines (mis)interpreted: "most cancers are caused by bad luck–not bad judgement, says study" (49), "most cancers are 'caused by bad luck–not lifestyle'" (50), and similar titles (51). Six days after publication, an additional press release addressed these erroneous conclusions, but they had already been shared on social media extensively. This exemplifies the damage that can be done when research findings are misinterpreted and spread to the general public.

Dissemination of Pseudoscience Through Social Media

The line between science and pseudoscience is often blurred and it is difficult to determine what is true and false (52, 53). Sometimes, pseudoscientific information can give false hope to patients with disease. Moreover, while pseudoscientific supplements are often relatively harmless, there are also dangerous advices and practices, which are readily being spread through social media. For example, the use of alternative treatments and supplements without proven efficacy (52) are often promoted through social media. Moreover, multiple procedures for tampering with existing drugs can be obtained via the internet (53). These procedures are illegal and unconfirmed to result in the drug formulation of interest, which in some cases can even lead to (fatal) intoxications (54). This makes the spreading of pseudoscientific findings a potentially harmful situation.

With the increased use of social media, the public is paying closer attention to bloggers and celebrities—regardless of their medical or scientific background—than to experts in their respective fields of interest. For example, Dr. Mercola, an osteopathic physician, has almost 2 million followers on Facebook, a strong online presence and daily emails to subscribers where he pushes "alternative" or "miracle" supplements to the masses. However, in 2016, Dr. Mercola, was ordered to refund customers up to $5.3 million for the false advertisement of his own company's tanning beds that he claimed would reduce chances of getting cancer. This was not his first trouble with regulators: the US Food and Drug Administration (FDA) warned him three times between 2005 and 2011 for violating federal laws for marketing a device he claimed was an alternative to mammograms and for making unproven claims about dietary supplements (55). Dr. Oz is another proponent of pseudoscience and "miracle cures" for an array of conditions. He has 6 million Facebook followers and his own television show. Perhaps most notable is his persistent advertising of "miracle" weight loss supplements that will be effective with little to no exercise. He was criticized by the Senate in 2014 for such unsupported claims for specific supplements and was called to be removed from the faculty at Columbia University, where he worked as a cardiothoracic surgeon. During his testimony, Dr. Oz acknowledged that many supplements he lends support to would not stand up to scientific scrutiny (56) and a recent study confirmed that most of his claims were not supported and, in some instances, contradicted by evidence (57). These instances are just the tip of the iceberg when it comes to examples of pseudoscientific ideas being spread to a large audience.

HOW TO BEST USE SOCIAL MEDIA

In 2016, politician Michael Gove famously claimed "people have had enough of experts" (58). This assertion was confirmed when the majority of the UK voted to leave the EU against all expert advice. What does this mean for us as a research community, the "experts" on healthcare, and how can we use social media to combat fake news and pseudoscience that could endanger translational medicine and public health?

We believe that we, as a research community, have a responsibility to use social media to spread research findings of public interest and to combat fake news that can be harmful to society. One way to counter the dangerous spread of misinformation is for scientists to critically evaluate the scientific

TABLE 1 | Possibilities and pitfalls of social media use for translational medicine.

	Possibilities	Pitfalls
1	Rapid and easy dissemination of research	Lack of peer review and filtering of quality
2	Critical review of existing articles and raw data sets	Fake news spreads fast and is difficult to refute
3	Possibilities for raising funds for research	Misinterpretation of research
4	Publicity of researchers/institutes	Dissemination of pseudoscience through social media
5	Networking between clinicians, researchers and patient groups	
6	Big data analytics for prediction models and assessing trends/outbreaks	

news stories and report inaccuracies in order to correct or refute them. As news media outlets are more likely to report data that are compelling or sensational, it is essential to provide information that is interesting to the general public while at same time maintaining standards for reporting the accuracy of the relayed information (59). Another possibility is for the scientific community to use a rating and online review system similar to travel-review websites such as TripAdvisor, in order to establish consensus about the validity and quality of research and health claims that are circulating on the internet (41). Moreover, several social media groups have been established specifically for refuting false news, such as the Facebook and Twitter group "Refutations to Anti-Vaccine Memes" (*@RtAVM*), which has 233,871 members that aim to refute fake news stories about anti-vaccine movements by responding with rational arguments and counter-memes that dispel false-beliefs. However, confirmation bias can be strong and it remains to be seen whether people with opposing views will be convinced or even read such pages with opposing views.

Another approach for scientists to reach people with opposing views is to think small and to begin with sharing information within their immediate social network. Many scientists have several hundreds of social media connections, 519 on average, and these personal connections could mean that people trust and value their opinions, especially in their field. It has been suggested that every scientist can be a "nerd of trust" within their network of friends and family, and collectively, we as a scientific community could have the potential to influence the opinion of a large part of society (60).

CONCLUSION

We live in an exciting age, where social media allow for unrestricted spreading of scientific findings at an extraordinary pace, which brings major advantages for translational medicine, but comes with several potential dangers and pitfalls as well (as summarized in **Table 1**). We hope that this perspective article helps translational researchers to tackle the challenges and harness the possibilities of social media for the advancement of science.

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SD, GK, JL, ES and RS contributed to the conceptualization and writing of this study. SD, GK, and RS wrote and edited the final manuscript. RS coordinated the study. SD and GK contributed equally to this work.

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Women in Translational Medicine: Tools to Break the Glass Ceiling

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Despite the recent movements for female equality and empowerment, few women occupy top positions in scientific decision-making. The challenges women face during their career may arise from societal biases and the current scientific culture. We discuss the effect of such biases at three different levels of the career and provide suggestions to tackle them. At the societal level, gender roles can create a negative feedback loop in which women are discouraged from attaining top positions and men are discouraged from choosing a home-centred lifestyle. This loop can be broken early in life by providing children with female role models that have a work-centred life and opening up the discussion about gender roles at a young age. At the level of hiring, unconscious biases can lead to a preference for male candidates. The introduction of (unbiased) artificial intelligence algorithms and gender champions in the hiring process may restore the balance and give men and women an equal chance. At the level of coaching and evaluation, barriers that women face should be addressed on a personal level through the introduction of coaching and mentoring programmes. In addition, women may play a pivotal role in shifting the perception of scientific success away from bibliometric outcomes only towards a more diverse assessment of quality and societal relevance. Taken together, these suggestions may break the glass ceiling in the scientific world for women; create more gender diversity at the top and improve translational science in medicine.

Keywords: glass ceiling, gender, translational medicine, gender roles, gender champions

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INTRODUCTION

Translational medicine is a rapidly growing field of scientific research. For this research discipline to be successful, a multi-disciplinary, and highly collaborative approach is required. Both men and women are needed to contribute to this important field of research. However, women and men are different. Not only in terms of the biology of sex hormones and sex chromosomes but also in terms of gender roles in society. Acknowledging that these differences matter has brought about an inspirational movement of sex and gender integration in biomedical research (1). Funding agencies and journals now guide and instruct authors to include sex and gender in their analyses to improve biomedical research and healthcare provision. In addition, gender diversity in leadership has become a serious target for many organisations, not in the least because there is a growing body of evidence that gender diversity in executive teams positively correlates with (financial) performance[1] and that gender-diverse teams produce better quality science (2).

Despite the recent movements for female equality and empowerment, it is clear that gender bias still exists. A Dutch study (3) shows that while younger women (aged < 45) are more highly educated than men in the same age category, they seem to be unable to translate their educational advantage into better career chances. The 2018 Global Education Monitoring Report showed that women were underrepresented in university leadership positions across the globe (4). Particularly in science, despite fairly balanced ratios of male-to-female undergraduates and post-graduates, women are less likely to progress through the career ladder than men, resulting in a low representation of women in senior positions. For instance, a report from the Association of the American Medical Colleges (5) indicates unequal distribution of chairs by gender basis, with a total of 15.8% women in Academic Medicine in 2015.

So what are the obstacles that prevent so many female scientists from occupying top positions in scientific decision-making? How can we explain the steep fall in percentage of women with each step up on the career ladder (6)? Finally, which structural interventions can be implemented at the institutional level to promote women's careers in science? We believe there is a need for a multilevel approach consisting of a combination of bold methods that address the deeply rooted causes that lead to gender disparity in the selection procedures for professorships and the most senior positions within companies. In this article, we discuss possible reasons for gender disparity at three levels or stages in the career. The first and broadest is the societal level, which influences the career of women throughout their lives. The second and more specific level covers bias in hiring practices, which is most important at the start of one's career. The third discusses the effect coaching and evaluation may have during the career. We will also propose suggestions that may tackle some of the inherent biases present in each stage.

THE SOCIETAL LEVEL: THE EFFECT OF GENDER ROLES

The hampered progression of women in science is known as the "glass ceiling," which is the resistance women (and minorities) face when they attempt to reach the top ranks of management in organisations. One of the deeply rooted causes for this glass ceiling may be the societal role of women, which dictates gender-specific and accepted behavioural patterns. Men are naturally expected to be the main provider for the family, whereas women are expected to take care of the family and household. These societal expectations are reflected in the work environment. The current organisation culture values masculine traits and is therefore more attractive for and more facilitating towards men. One intrinsic hurdle of this culture for women is the effect pregnancy has on the progression of their careers. Women who either are pregnant, are planning to get pregnant or recently had a child often face negative consequences in their careers such as the termination of their contract or being denied a promotion because of the implicit expectation that they will need to take time off and reduce their work effort due to their maternal duties. This happens to 43% of women in the Netherlands (3). Another example comes from Japan, where one university deliberately excluded female applicants from medical school because they were expected to take time off during their studies for family-related duties.[2]

These kind of intrinsic mechanisms and other parts of the glass ceiling feed into a downward spiral. Women make different choices during their career based on societal and work-related expectations and often end up with more limited choices in the end compared to men. One example of this is that senior positions are made available during the years in which women tend to have children and are thus likely to be given to their male counterparts. However, on the other hand, when a woman goes against societal expectations of maternal duties, they receive stigma and criticism from society. This makes it difficult to break the vicious cycle and leads to women preferring jobs that enable a good work-life balance. These preferences in turn lead to crowding, in which female-dominated jobs are valued less compared to male-dominated jobs demonstrated by lower salaries, few stable long-term contracts, and an abundance of part-time jobs (7).

This feedback loop may start already early in life. According to the *preference theory* (8), women make their choice between family and business based on their preference for a particular lifestyle: work-centred, home-centred, or adaptive (combining paid work and family time). Women might adjust their preferences as a response to gender inequality, adapting to the current social disparities and expectations. These preferences feed into the vicious cycle described above and are formed early on in life. This makes it difficult to later redistribute roles and responsibilities more equally between men and women, which ultimately negatively impacts women's career prospects and possibly their mental health (9). The same

[1] https://www.mckinsey.com/business-functions/organisation/our-insights/why-diversity-matters

[2] https://www.natureindex.com/news-blog/lost-in-japan-a-generation-of-brilliant-women

is true for men who go against societal expectations by adopting a home-centred lifestyle instead of a work-centred one.

Therefore, we call for a societal change on the views of gender roles. The double-duty that women often do in terms of unpaid domestic labour and progression of scientific careers highlights their capability and creativity, which should be valued by our society. Female translational scientists should be aware of behavioural differences between men and women and should use this knowledge to adapt accordingly. While masculinising their behaviour can help to be taken more seriously, it can also have negative effects on how women are perceived socially. Both women themselves and society should thus value female-specific behavioural traits and use these to their advantage.

Changing the societal role of women is an ongoing process and will take time and effort to be accomplished. A gender-balanced educational workforce at different educational stages, from school to university and workplace, may help the progression of women's self-awareness and careers. Schools can play an important role in breaking the vicious cycle early on. Teachers should be made aware of unconscious biases present in their teaching material and update them accordingly (10). Schools can invite female scientists to talk about their work and act as role models for young girls who aspire a career in science (11). Mainstream media is also an important source of inspiration and empowerment for young and adolescent girls. The introduction of strong female superheroes such as *Wonder Woman* provides girls with role models that break traditional gender roles (12). Opening up the discussion about gender roles at a younger age and providing girls with enough female role models may empower them to challenge and go beyond societal expectations.

HIRING PRACTICES: LOOKING BEYOND GENDER BIAS

People make decisions that are often incorrect and not based on facts, even though we sincerely think that we objectively made the best choice. Deep-rooted prejudices around male leadership and the belief that men are better at math and science continue to influence hiring practices (13, 14). These ideas are perpetuated by key public figures in science such as a former Harvard President (in 2005) and the former President of the Royal Academy of Sciences of the Netherlands (in 2018). They attribute the underrepresentation of women in science and scientific institutions to "issues of intrinsic aptitude" and "lack of willingness to put in the required hard work which is needed for scientific excellence."

The first step towards dealing with heuristics and biases is to acknowledge they exist and understand how they work. The next step is to overcome them, for example through changing current selection procedures. We highlight three possible measures that can be used to create more female-friendly selection procedures in scientific institutes.

Using Artificial Intelligence to Pre-Select Suitable Candidates

Organisations outside of the scientific world have already experimented with new recruitment approaches that might improve the gender balance of selected candidates. One example of this is Unilever, one of the world's leading consumer-goods conglomerates with 170,000 employees worldwide. They integrated machine learning approaches in their talent recruitment programme, using neuroscience-based games, and LinkedIn profile information to determine whether a given candidate fits the job requirements[3]. Each candidate had to complete a standardised online interview and their responses were analysed using artificial intelligence. Afterwards, the hiring managers were given a detailed list of candidates the programme deemed most suitable for the position. By using such algorithms to aid the selection process, Unilever hired their most diverse class to date not only regarding gender, but also ethnicity and socioeconomic class[2]. Adopting this type of algorithm-based pre-selection system would allow scientific institutions and universities to streamline their hiring processes in an unbiased manner. Because human judgment still plays an important role in the final decision to hire a candidate, it is also important to educate recruiters and human resources staff on how to retain diversity during the hiring process. Both adding technology to the screening process and increasing awareness under recruiting staff about gender biases may help to make hiring practices more gender-balanced.

Training of Selection Committees Through Gender Champions

Selection criteria for job candidates and decisions made during the selection process lack transparency and are too often made by male-dominated committees with an explicit preference for men (15). Interestingly, women in leading positions of masculine organisations more often choose a male candidate over a female one because they have internalised the masculine behaviour of their peers (the "Queen Bee" effect). In contrast, women in leading positions of more gender-balanced organisations are more open to mentorship and sponsorship of other women (16). Because both men and women are biased towards male candidates in a male-dominated atmosphere, adding more women to the selection committee may even out the playing field. A successful example of this approach comes from intervention studies in hiring committees to select young faculty (17).

Inspired by the integration of gender in biomedical research, we propose to implement institutional gender champions (18). These gender champions, defined as decision-makers with expertise regarding the role of gender in hiring practices, will be included in selection panels to point out any biases in the panel's decision making. In addition, selection panel members will be trained in various aspects that help increase bias awareness, including items such as tests to gain insight in personal unconscious biases[4], serious games to highlight common

[3]https://www.businessinsider.nl/unilever-artificial-intelligence-hiring-process-2017-6/?international=true&r=US

[4]https://mindbugstest.nl/mindbugstest/gender-leiderschap/

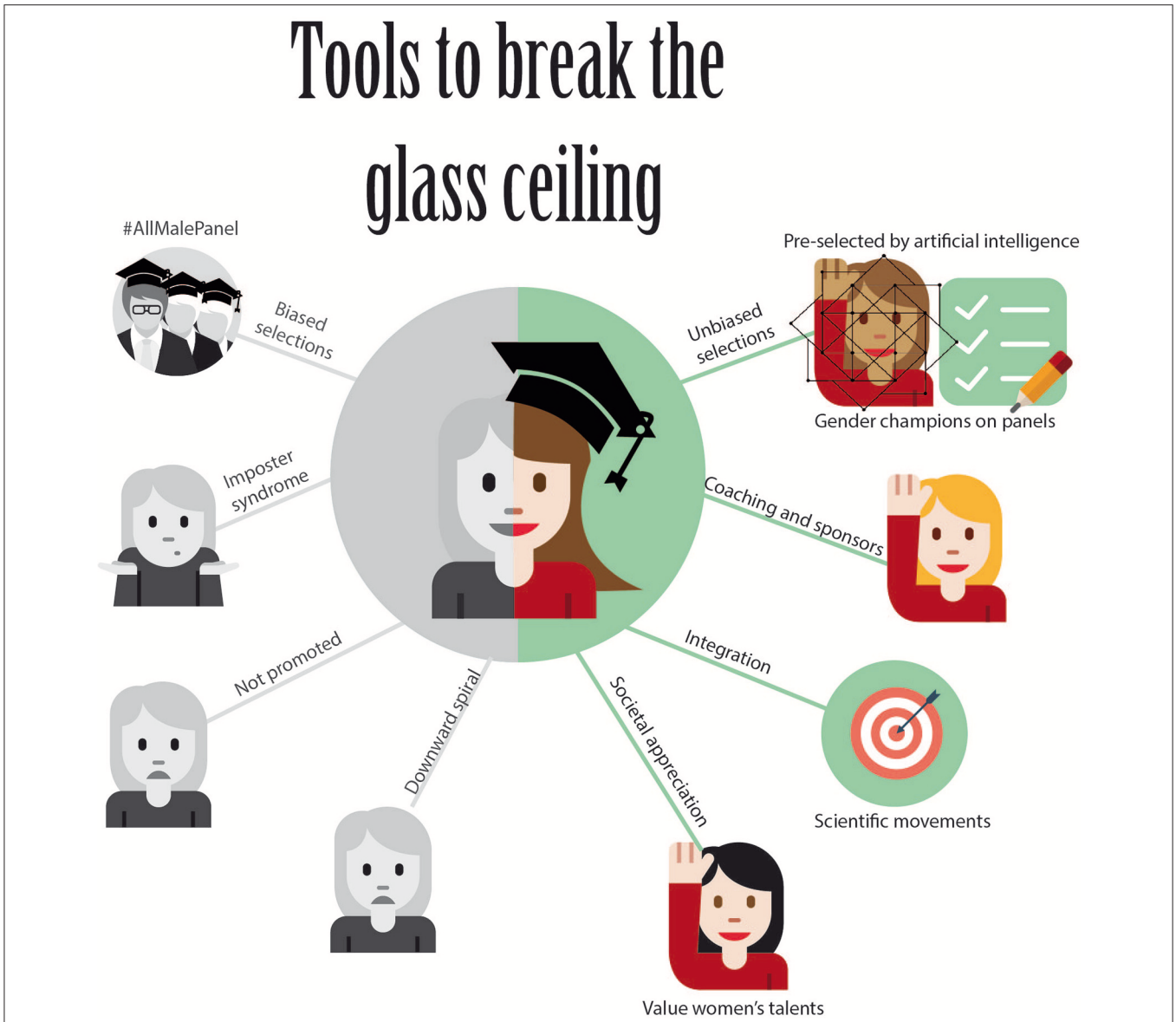

FIGURE 1 | Infographic summarising approaches to break the glass ceiling.

interview situations and interpretations, and showcasing the success of female professors. Decision support tools can also support committees by making selection criteria more objective and reach a more structured and transparent decision based on facts instead of feelings.

COACHING AND EVALUATION: TOWARDS A LEVEL PLAYING FIELD

Low self-confidence and self-perception among women may be another cause of gender disparity. Girls from six years of age are already less likely to perceive themselves as brilliant than boys of the same age (19). Small and unintended implicit suggestions on male superiority in our society may engrain the idea that men and boys are superior in leadership positions from a very young age. This is perfectly illustrated by the recently withdrawn girls shoe line by Clarks® called "Dolly Babe," for which the equivalent version for boys (which is still available) was called "Leader." Over time, women may internalise the feelings of professional inferiority that are implicitly suggested by such incidents and grow to believe themselves underequipped for their job or academic studies. This is also known as the *imposter syndrome* (20). Early research into this condition labeled it as a female condition; however, although men are less likely to report it due to stigma, more recent research has shown that they struggle with imposter syndrome as well (21). People suffering from imposter syndrome may not pursue the career they wish to have due to their feelings of inaptitude, instead settling for less. Early recognition of the condition and appropriate support can

help individuals deal with these feelings and thus help them reach their full potential (21).

Expanding Coaching and Sponsoring Programmes

We therefore propose to expand coaching and sponsor programmes to better suit the needs of women (and men) aspiring a career in science. In 2012, the University Medical Center Utrecht (The Netherlands) implemented a talent programme to promote scientific careers of women called the Steyn Parvé programme. Five years later, the percentage of female professors had increased from 18 to 26%. A similar trend was seen at Vita-Salute San Raffaele University (Milan, Italy), where the percentage of female professors increased from 12 to 25% in the 10-year period. This increase occurred naturally, without the need for adopting any institutional policy to promote gender equality. The British Medical Association (BMA) in the United Kingdom (UK) organises an annual one-day conference celebrating and promoting women in science[5]. The association also advocates the use of role models so that women early on in their career have an inspirational figure to look up to for direction and for examples of what can be and how it can be achieved. Recent data from the Wellcome Genome Campus in the UK show that the implementation of an integrated "Sex in Science" programme, including mentoring and addressing unconscious biases in hiring practices, helped increase the percentage of female employees overall and the percentage of female speakers at seminars and conferences (22). Introduction of a mentoring programme at the Flinders University in Australia markedly improved both the success and the self-esteem of junior academic women (23). The extension of mentoring programmes may be one of the key determinants of academic success in medicine (24), thus good mentoring and having female role models may encourage women to proceed in science. We believe that the development of professional mentoring skills should be implemented as early as possible in career tracks. Mentoring programmes or workshops should address amongst other qualities of a good mentor, mutual responsibilities, giving feedback, bias and diversity, and mentorship pitfalls. The chance that one person can fulfill all mentoring needs in any phase of a career is small and mentorship programmes should also support the development of mentor networks (25). With a mentor network, mentorship can be diverse in age (e.g., peer-mentoring), rank, area of expertise, and gender and may therefore be more effective (25). This is in line with the policy of gender equality promotion supported by the League of European Research University (LERU), a network of research-intensive universities based in Europe. They have recommended measures, such as defining clear selection criteria, educating selection committees on implicit gender bias, and involving external evaluators, which should be implemented in all research institutes (26).

Next to mentors, sponsors may also play an important role in advancing to an academic leadership position. Sponsors have the power and position to advocate for unrecognised talent in discussions on executive leadership positions (27) and can play a crucial role in identification, visibility, and training of female talents. However, women are less likely than men to have a sponsor (28). Therefore, sponsorship of women should be promoted, for example by asking every senior leader to adopt at least one female talent. Mentoring and sponsorship should be complemented by funding. Institutes should receive financial incentives to perform research if gender equality policies are to be effectively implemented. In the UK, for example, the Athena SWAN programme gives out gender equality awards to institutes or departments who commit to advance gender equality for academic staff. To be considered for funding from the National Institute for Health Research, institutes should have at least a silver-level Athena SWAN award. Similar incentive structures could be implemented in research institutes across the world.

Changing the Measure of Scientific Success

Scientific success is often measured using bibliometrics such as the h-index, although the discontent about these measures is growing in the scientific community because they are heavily dependent on the quantity of output instead of the quality. The focus on quantity puts women at a disadvantage, as they have been shown to on average publish less papers compared to their male counterparts throughout their scientific careers (29). However, the papers women publish seem on average to be of higher quality than those of men, suggesting that the lower productivity of women is not due to lack of aptitude (29). Incorporating such insights into the metrics for scientific success may help to level the playing field for women scientists. This would also fit into the general movement beyond metrics that is currently going on in science, which can be referred to as "Science in Transition" (30).

CONCLUSION

We have discussed several aspects that may prevent female translational scientists from embarking on successful career paths and we have proposed possible solutions to break these barriers (see **Figure 1**). The approaches described above take gender as the starting point, but are equally applicable to dealing with other disadvantaged minority groups. This application would thus not only improve gender diversity in leadership but diversity in general, increasing the chance of successful translational medicine.

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AUTHOR CONTRIBUTIONS

All authors listed have contributed to the research underlying and writing of the article. All authors approved the article for publication.

[5]https://www.bma.org.uk/collective-voice/committees/medical-academics-committee/women-in-academic-medicine

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DTI Profiles for Rapid Description of Cohorts at the Clinical-Research Interface

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Normal pressure hydrocephalus (NPH) is a syndrome comprising gait disturbance, cognitive decline and urinary incontinence that is an unique model of reversible brain injury, but it presents as a challenging spectrum of disease cohorts. Diffusion Tensor Imaging (DTI), with its ability to interrogate structural white matter patterns at a microarchitectural level, is a potentially useful tool for the confirmation and characterization of disease cohorts at the clinical-research interface. However, obstacles to its widespread use involve the need for consistent DTI analysis and interpretation tools across collaborator sites. We present the use of DTI profiles, a simplistic methodology to interpret white matter injury patterns based on the morphology of diffusivity parameters. We examined 13 patients with complex NPH, i.e., patients with NPH and overlay from multiple comorbidities, including vascular risk burden and neurodegenerative disease, undergoing extended CSF drainage, clinical assessments, and multi-modal MR imaging. Following appropriate exclusions, we compared the morphology of DTI profiles in such complex NPH patients ($n = 12$, comprising 4 responders and 8 non-responders) to exemplar DTI profiles from a cohort of classic NPH patients ($n = 16$) demonstrating responsiveness of white matter injury to ventriculo-peritoneal shunting. In the cohort of complex NPH patients, mean age was 71.3 ± 7.6 years (10 males, 2 females) with a mean MMSE score of 21.1. There were 5 age-matched healthy controls, mean age was 73.4 ± 7.2 years (1 male, 4 females) and mean MMSE score was 26.8. In the exemplar cohort of classic NPH patients, mean age was 74.7 ± 5.9 years (10 males, 6 females) and mean MMSE score was 24.1. There were 9 age-matched healthy controls, mean age was 69.4 ± 9.7 years (4 males, 5 females) and mean MMSE score was 28.6. We found that, despite the challenges of acquiring DTI metrics from differing scanners across collaborator sites and NPH patients presenting as differing cohorts along the spectrum of disease, DTI profiles for responsiveness to interventions were comparable. Distinct DTI characteristics were demonstrated for complex NPH responders vs. non-responders. The morphology of DTI profiles for complex NPH responders mimicked DTI patterns

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found in predominantly shunt-responsive patients undergoing intervention for classic NPH. However, DTI profiles for complex NPH non-responders was suggestive of atrophy. Our findings suggest that it is possible to use DTI profiles to provide a methodology for rapid description of differing cohorts of disease at the clinical-research interface. By describing DTI measures morphologically, it was possible to consistently compare white matter injury patterns across international collaborator datasets.

Keywords: normal pressure hydrocephalus, complex, comorbidities, MRI, DTI

INTRODUCTION

NPH was first described in 1965 by Hakim and Adams as a condition of "symptomatic occult hydrocephalus with 'normal' cerebrospinal fluid (CSF) pressures" (1, 2). It classically comprises of a triad of gait disturbance, cognitive decline and urinary incontinence associated with ventriculomegaly in the absence of persistently elevated intraventricular CSF pressures. The diagnostic challenge is that the clinical features of NPH are commonly found in functional decline from aging or other neurodegenerative conditions. It is therefore possible that "many patients with a potentially reversible condition are misdiagnosed as having Alzheimer's disease or vascular dementia and *vice versa*" (3, 4). Although NPH is an apparently rare condition accounting for an estimated 5% of dementias, it is more likely that its true incidence is underestimated, due to the confounding factors of multiple comorbidities in the elderly population (5). However, unlike other conditions within the dementia spectrum, features of the NPH syndrome may be reversed by the insertion of a CSF shunt.

There is published data demonstrating that the condition is reversible across differing populations worldwide. Recent neurology practice guidelines concluded that there was evidence for "96% chance subjective improvement and 83% chance improvement on timed walk test at 6 months" and that shunting was possibly effective in idiopathic NPH (6). Somewhat surprisingly, increasing age in NPH does not decrease the chance of shunting being successful. Few conditions in the elderly are known to demonstrate such levels of response to intervention. This should therefore elevate the importance of the study of NPH within aging research as an urgent priority (7).

NPH presents as a challenging collection of patient cohorts along a spectrum of disease. Neuropsychological profiling, gait/balance measurements and CSF infusion studies may help predict which patients have the potential to improve with surgical intervention. However, such techniques require significant patient cooperation for meaningful testing to occur. This may not be possible for patients presenting at the late or complex part of the NPH spectrum who are less able to participate in active testing methods. In these types of NPH cohorts, supplementary imaging methods to confirm and characterize NPH features are of critical importance. These methods provide supporting information in evaluating the NPH component remediable to CSF diversion in order to balance the risks vs. benefits of surgical intervention in patients where multiple clinical confounders co-exist.

Yet, one of the major obstacles in the development of novel tools for the interpretation of NPH imaging findings is that the pathogenesis for classic NPH is still unknown. Published data have been contradictory across different imaging modalities [see Keong et al., 2016 (8) for a comprehensive review]. Studies have demonstrated congruence with different hypotheses involving structural changes, cerebral blood flow and CSF hydrodynamics (9). It is thought that biomechanical forces, such as tissue distortion caused by ventricular dilatation may result in CSF and interstitial fluid stasis. This causes an increase of interstitial fluid pressure, leading to reversal of fluid flow, which then results in the failure of drainage of neurotoxic compounds such as amyloid-β (10, 11). Studies have also demonstrated reduced periventricular blood flow and impaired cerebrovascular autoregulation in NPH, suggesting that watershed ischaemia in the deep white matter and/or leakiness of damaged vasculature may be the starting point for the process of accumulation of toxic waste products that results in the increase of interstitial fluid pressure (11, 12). Conversely, increased CSF stroke volume through the aqueduct has been found in the NPH population (13–15) despite normal CSF pressures. These processes, or a combination of them, may disrupt the cerebral mantle and the white matter tract connections serving the cortex in a spectrum of injury processes. It is possible that "some types of disruption may be more tolerable (i.e., more reversible) than others" (16). Imaging methodology that is able to simultaneously document differing injury patterns, such as axonal loss, compression, stretching and/or oedema would be greatly advantageous in understanding the cohorts presenting with NPH.

Diffusion Tensor Imaging (DTI) is a methodology that lends itself to the understanding of intricate structural changes at a microarchitectural level by using mathematical modeling of water diffusion properties. As the displacement of fluid in compartments is critical within the NPH spectrum, studies have shown that DTI has been able to demonstrate different patterns of white matter injury consistent with the symptomatology of the NPH disorder (16). DTI has also been found to differentiate NPH from other cohorts such as those with other types of ventriculomegaly, chronic hydrocephalus as well as Alzheimer's disease, Parkinson's disease, and other dementias (17–19). However, there are challenges in DTI acquisition and interpretation that prevent its more widespread uptake at the clinical-research interface. As DTI imaging is performed at different technical specifications across multiple scanners and sites, there is a lack of understanding of how to harmonize interpretation of DTI measures and so, derive knowledge of

injury patterns from different cohorts of disease. DTI post-processing and analysis methods may also be dependent on availability of software tools and computing infrastructure. This confounds the efforts of interested collaborators to share common findings across international working groups and to discover new targets for intervention.

In this study, we present the use of a novel methodological tool for DTI interpretation that illustrates the ideal of the new praxis of translational medicine, in which a patient-centered approach to disease is promoted and prioritized. In such an ideal, NPH patients within their respective patient cohorts presenting to international collaborators would have access to the same DTI interpretation and understanding of their disease process, through an ability to share common knowledge of imaging markers for thresholds of reversible vs. irreversible brain injury. In order to overcome the challenges of applying DTI interpretation techniques across collaborator sites, new tools are needed to address our gaps of understanding. We present the use of a simplistic DTI interpretation methodology that leverages on existing capabilities at the clinical/research interface to convert DTI measures into a consistent morphological classification for more rapid comparisons of clinical cohorts across sites.

MATERIALS AND METHODS

The study comprised a prospective cohort of patients with complex NPH undergoing management at the National Neuroscience Institute (NNI), Singapore. The study protocol was approved by the local research ethics committee (CIRB 2016/2627). A cohort of healthy controls was recruited under a subsequent study (CIRB 2017/2854). Written informed consent was obtained from all participants or, in cases of dementia (MMSE <24/30), their legal representatives, for inclusion in the study.

Subjects

Thirteen patients diagnosed with complex NPH undergoing the extended CSF drainage protocol were selected for the study from the NPH programme at the National Neuroscience Institute, Singapore between 2016 and 2017. Participants were recruited with a particular focus on the complex NPH subtype (further described below), and therefore presented with multiple comorbidities co-existing. Additionally, five age-matched healthy controls who were functionally independent and had no neurological conditions were recruited from the population. A comparator dataset of a cohort of 16 patients with classic NPH attending Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust and nine age-matched healthy controls, served as the exemplar for the analysis and interpretation of DTI profiles. Details of patient characteristics, study protocol, and ethical approval for the exemplar dataset, who were studied pre- and 2 weeks post-operatively after successful shunting, have been previously published (16).

Protocol for NPH Programme

Patients accepted for testing in the NPH protocol had clinical descriptions consistent with either probable or possible NPH, according to criteria in published guidelines (20). All patients demonstrated communicating hydrocephalus, with ventriculomegaly defined as an Evans' index (maximum width of frontal horns of the lateral ventricles divided by the transverse inner diameter of the skull) $\geq$0.30, or a Bicaudate index (minimum intercaudate distance divided by the brain width along the same line) $\geq$0.25. Patients with probable NPH had at least two out of three features of the NPH triad of gait disturbance, cognitive impairment, and urinary incontinence. Patients with possible NPH either had (a) incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance or (b) gait disturbance or dementia alone. Within the NPH programme, we termed patients amenable to standard testing and management according to international guidelines as having "classic NPH." Typically, these patients demonstrated significantly positive responses to high-volume tap testing and were offered shunt insertion without further supplementary testing. However, patients who demonstrated low/ borderline positive results on tap testing or had comorbidities confounding the assessment of short-term responsiveness to CSF drainage were offered the extended CSF drainage protocol.

We also identified a separate subtype of NPH patients presenting with multiple comorbidities co-existing, in particular overlay from vascular risk burden and neurodegenerative diseases. These patients had clinical symptoms and signs consistent with probable/possible NPH according to international and Japanese guidelines (20–22), and had strong neuroradiological features supportive of the NPH diagnosis. However, due to overlay, testing their CSF responsiveness was difficult. We termed this subtype as "complex NPH." Further management was required to identify and optimize other concurrent conditions before testing. "Where NPH features coexisted with other neurological, psychiatric, or general medical disorders, symptoms must be deemed not to be entirely attributable to these conditions" (20). In cases with neurodegenerative overlay, patients were referred for further evaluation via the NPH programme following confirmation that they did not fit diagnostic criteria for Alzheimer's and Parkinson's diseases, and/or had; limited response to disease-modifying drugs such as levodopa. Patients with cardiac risk were assessed as being of no higher than moderate risk for surgical intervention prior to being offered testing in the NPH programme.

All participants in this study had complex NPH and underwent insertion of a lumbar drain to facilitate the extended CSF drainage protocol. In two participants, failure of drainage led to the conversion of the lumbar drain to insertion of an Ommaya reservoir for testing. In one of the latter, significant psycho-behavioral issues resulted in failed MR imaging; this patient was subsequently excluded from the analysis. CSF drainage in this patient resulted in improvement in behavioral symptoms and the patient underwent completion of ventriculo-peritoneal shunting following their exit from the study.

The remaining 12 participants underwent the full NPH programme for CSF drainage, including clinical gait and cognitive testing, as well as pre- and post-drainage inpatient

MR imaging. Patients with a lumbar drain *in-situ* underwent a 3-day drainage/7-day global assessment protocol, achieving ≥300 mls total CSF withdrawal whereas the patient undergoing serial reservoir taps had a modified protocol achieving ≥150–200 mls total CSF withdrawal to account for the tolerance needed for more rapid drainage and increased infection risk.

Imaging Acquisition and Post-processing

All MR imaging data for this study were acquired with a 3.0-T MR scanner (Ingenia, Philips Medical Systems, Best, the Netherlands), including 3D T1, T2, FLAIR, and DTI sequences. DTI was obtained using a single-shot echo-planar sequence with a slice thickness of 2.3 mm. Images were acquired in 20 gradient directions with the following parameters: $b = 0$ and 1,000 s/mm^2, TR = 7,274 ms; TE = 80 ms; FOV 220 × 220 mm; and matrix = 96 × 96, resulting in a voxel size of 2.3 × 2.3 × 2.3 mm, with SENSE factor of 2.5. A few patients were downgraded to the 1.5-T scanner at equivalent specifications due to MR safety concerns. All DTI processing was performed by using ExploreDTI (ExploreDTI, PROVIDI Lab, Utrecht, the Netherlands).

DTI Analysis

Following corrections of subject motion and eddy current distortions, tract pathways were reconstructed using whole brain tractography. Due to dual technical constraints of scanning specifications and fiber distortion in the presence of significant ventriculomegaly, automated tractography extraction only reliably generated key periventricular white matter tracts. This "at-risk" model of white matter, including projection fibers (corticospinal tract), commissural/callosal fibers (corpus callosum, anterior commissure), and key association tracts (typically inferior longitudinal, fronto-occipital, and uncinate fasciculi) but excluding short association fibers, was found to be reproducible in all participants.

We performed DTI analysis and interpretation according to published methodology. We also derived disease-specific ($n = 16$) and human control exemplar data ($n = 9$) for DTI profiles from the published dataset (16). DTI measures, involving six similar regions-of-interest (ROI), were used to generate an overall estimate of the exemplar for mean DTI measures of periventricular white matter. We have previously confirmed the comparability and reliability of DTI measures, extracted using ROI methodology, across different preferred software tools (16).

Gait, Balance, and Cognitive Assessments

Patients underwent physiotherapy-led examinations of the 10 m walking test, Tinetti gait and balance examination, and had a Mini-Mental State Examination (MMSE) carried out by occupational therapists. Inpatient assessment was further corroborated with the patient's own reported measures of functional performance at home in the early period following discharge. Using a simple report scale (from – to +100% levels), patients and/or caregivers were asked to grade their own perceived levels of improvement or deterioration at home to the nearest 10%, with 0 being no perceivable difference, following

TABLE 1 | Clinical characteristics of complex NPH patients.

	Age	Sex	MMSE	NPH symptoms	Other comorbidities
NNPH01	77	M	16	Gait disturbance, memory impairment, urinary incontinence	Hypertension, diabetes mellitus, IHD, multifactorial dementia, CKD
NNPH03	74	M	26	Predominantly gait disturbance	Hypertension, parkinsonism
NNPH04	72	M	28	Predominantly gait disturbance	Parkinsonism, previous stroke
NNPH05	74	F	11	Gait disturbance, memory impairment, urinary incontinence	Hypertension, hyperlipidaemia, diabetes mellitus, vascular parkinsonism, dementia
NNPH06	73	F	15	Gait disturbance, memory impairment, urinary incontinence	Hypertension, hyperlipidaemia, diabetes mellitus, vascular dementia, bladder dysfunction
NNPH07	67	M	21	Gait disturbance, memory impairment, urinary incontinence	Hypertension, hyperlipidaemia, lumbar spondylosis, and degenerative disc disease
NNPH08	71	M	28	Predominantly gait disturbance, mild memory impairment, urinary frequency	Hypertension, hyperlipidaemia, diabetes mellitus, IHD, SIADH
NNPH09	81	M	29	Gait disturbance, urinary incontinence	Hypertension, hyperlipidaemia, parkinsonism, cervical spondylosis
NNPH10	67	M	20	Gait disturbance, memory impairment, urinary incontinence	Hypertension, hyperlipidaemia, diabetes mellitus, aortic sclerosis, cervical spondylosis
NNPH11	55	M	12	Gait disturbance, memory impairment, urinary incontinence	Hypertension, Korsakoff's syndrome, behavioral disturbance
NNPH12	82	M	17	Predominantly gait and cognitive disturbance	Hypertension, hyperlipidaemia, IHD, parkinsonism, COPD
NNPH13	63	M	30	Predominantly gait disturbance, urinary frequency	Hyperlipidaemia, cervical and lumbar spondylosis

IHD, ischaemic heart disease; CKD, chronic kidney disease; SIADH, Syndrome of inappropriate antidiuretic hormone secretion; COPD, Chronic obstructive pulmonary disease.

admission for CSF drainage. A positive response to CSF drainage was defined as an increase of ≥10% in any measure of inpatient gait, balance or cognitive testing (23) and ≥20% functional improvement on the patient's own self-report measure.

Statistical Analyses

Analyses were performed using SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). Between-group and within-group comparisons for DTI measures were tested with paired-samples and independent-samples *t*-test. Mann–Whitney U and Wilcoxon signed-rank tests were used for other variables. Spearman's rank correlation was used for correlations. All statistical tests were two-tailed and significance level was set at $p < 0.05$. All group means and DTI profile graphs were generated with Microsoft Excel Version 15.23 (Microsoft Corp., Redmond, WA, USA).

RESULTS

Clinical Characteristics

Following one exclusion, the study cohort included 12 participants (10 males, 2 females) with mean age 71.3 ± 7.6 years. All patients presented with gait disturbance, 58.3% had cognitive impairment, and 58.3% had urinary incontinence or known bladder dysfunction (**Table 1**). All patients with complex NPH completed a baseline MMSE pre-drainage; mean MMSE was 21.1. MMSE scores were not significantly different between responder (Mean MMSE = 23.3) and non-responder (Mean MMSE = 20.0) groups. The cohort of complex NPH patients in the Singapore study was similar in clinical composition to the exemplar dataset derived from the Cambridge study of classic NPH patients ($n = 16$) in terms of gender (10 male, 6 female) and age (mean age of 74.7 ± 5.9 years), but differed in ethnicity. Classic NPH patients presented with mean MMSE = 24.1, just

TABLE 2 | Difference in DTI measures between complex NPH and healthy controls.

DTI measure		MR1	*p*-value	MR2	*p*-value
FA	% difference between Complex NPH (all) vs. HC	0.225	*0.921*	−0.450	*0.881*
	% difference between Complex NPH responders vs. HC	2.928	*0.323*	−0.901	*0.820*
	% difference between Complex NPH non-responders vs. HC	−1.126	*0.716*	−0.225	*0.939*
MD	% difference between Complex NPH (all) vs. HC	14.461	***0.023***	12.815	***0.019***
	% difference between Complex NPH responders vs. HC	9.236	***0.049***	11.038	***0.035***
	% difference between Complex NPH non-responders vs. HC	17.079	***0.012***	13.704	***0.036***
L1	% difference between Complex NPH (all) vs. HC	14.272	***0.008***	12.236	***0.009***
	% difference between Complex NPH responders vs. HC	10.310	***0.015***	10.270	***0.019***
	% difference between Complex NPH non-responders vs. HC	16.261	***0.005***	13.210	***0.019***
L2and3	% difference between Complex NPH (all) vs. HC	15.070	***0.043***	13.803	***0.031***
	% difference between Complex NPH responders vs. HC	8.525	*0.107*	12.212	*0.050*
	% difference between Complex NPH non-responders vs. HC	18.334	***0.020***	14.599	*0.056*

Italics indicate p-values; bold indicate significant p-values at a significance level of 0.05.

TABLE 3 | Pre-lumbar drain vs. post-lumbar drain DTI; mean (SD).

DTI measure	Cohort	WBT Pre-LD	WBT Post-LD	% change	*p*-value
FA	NNI Complex NPH (all)	0.445 (0.021)	0.442 (0.023)	−0.674	*0.514*
	NNI Complex NPH responders	0.457 (0.011)	0.440 (0.019)	−3.720	***0.044***
	NNI Complex NPH non-responders	0.439 (0.023)	0.443 (0.026)	0.911	*0.450*
MD	NNI Complex NPH (all)	9.530 (0.993)	9.393 (0.828)	−1.438	*0.385*
	NNI Complex NPH responders	9.095 (0.404)	9.245 (0.515)	1.649	*0.363*
	NNI Complex NPH non-responders	9.748 (1.148)	9.467 (0.973)	−2.883	*0.210*
L1	NNI Complex NPH (all)	14.420 (1.233)	14.163 (1.056)	−1.782	*0.251*
	NNI Complex NPH responders	13.920 (0.529)	13.915 (0.613)	−0.036	*0.978*
	NNI Complex NPH non-responders	14.671 (1.434)	14.286 (1.240)	−2.624	*0.251*
L2and3	NNI Complex NPH (all)	7.086 (0.874)	7.008 (0.728)	−1.101	*0.555*
	NNI Complex NPH responders	6.683 (0.344)	6.910 (0.472)	−0.036	*0.179*
	NNI Complex NPH non-responders	7.287 (1.006)	7.057 (0.854)	−2.624	*0.187*

Italics indicate p-values; bold indicate significant p-values at a significance level of 0.05.

above the dementing range. The age-matched healthy controls in the Singapore study (1 male, 4 female) had a mean age of 73.4 ± 7.2 years and mean MMSE was 26.8. The Cambridge exemplar dataset had nine age-matched healthy controls (4 males, 5 females; mean age of 69.4 ± 9.7 years) and mean MMSE = 28.6, the best of all available cohorts.

In the current study, eight out of the 12 patients were able to complete a 10 m walking test at 0, 48, and 72 h CSF drainage. One patient could not be assessed at 48 h and their response was assessed purely on the last measure. One patient missed their baseline assessment and two patients were not able to undergo any gait testing; their scores were excluded from gait analysis and their response assessed based on other domains and functional improvement, such as level of dependence for sit/stand transfers or balance. Median time for the 10 m walk was 12.9 s (IQR = 11.8–28.5 s) at 0 h and 14.8 s (IQR = 12.8–19.1 s) at 72 h CSF drainage.

Comparisons Between DTI Parameters

As expected, the majority of the cohort of complex NPH patients were non-responders. Of the 12 participants who were included in the analysis, four responded to CSF drainage and were subsequently offered definitive surgical intervention in the form of ventriculo-peritoneal shunting. We confirmed that DTI measures (FA, MD, L1, and L2and3) were statistically different between cohorts [complex NPH vs. classic NPH patients ($p < 0.001$), healthy controls in Cambridge vs. Singapore ($p \leq 0.001$)]. When patients were compared to healthy controls within the individual sites, nearly all DTI measures were significantly different between groups. Pre-drainage, both complex NPH responders and non-responders demonstrated significant differences in MD (axonal disruption) and L1 (stretch/compression) compared to healthy controls. However, there were only significant differences in L2and3 compared to healthy controls in the complex NPH non-responder group (**Table 2**), suggesting that the white matter microstructure in the complex NPH responders was better preserved (less stretch/oedema). Following CSF drainage, only the group of complex NPH responders demonstrated changes in DTI measures sufficient to cause a significant overall change in FA (**Table 3**).

DTI Profiles Across NPH Cohorts

Differing NPH patient cohorts and healthy controls could be differentiated by the position of their DTI profiles within the spectrum of diffusivity measures (see **Figures 1**, **2**). As NPH patients displayed worsening functional performance along the disease spectrum (for example, mean MMSE = 24.1 vs. 21.1 for Classic vs. Complex NPH, respectively), their DTI profiles concurrently worsened to match, across all diffusivity measures. The morphology of DTI profiles also matched the performance of healthy controls (mean MMSE = 28.6 vs. 26.8 for Cambridge vs. Singapore healthy controls). Nevertheless, in individual collaborator sites, DTI profiles for patients were consistently worse than controls across all diffusivity measures. When pre-intervention DTI profiles for complex NPH patients were plotted as percentage differences between patients and healthy controls

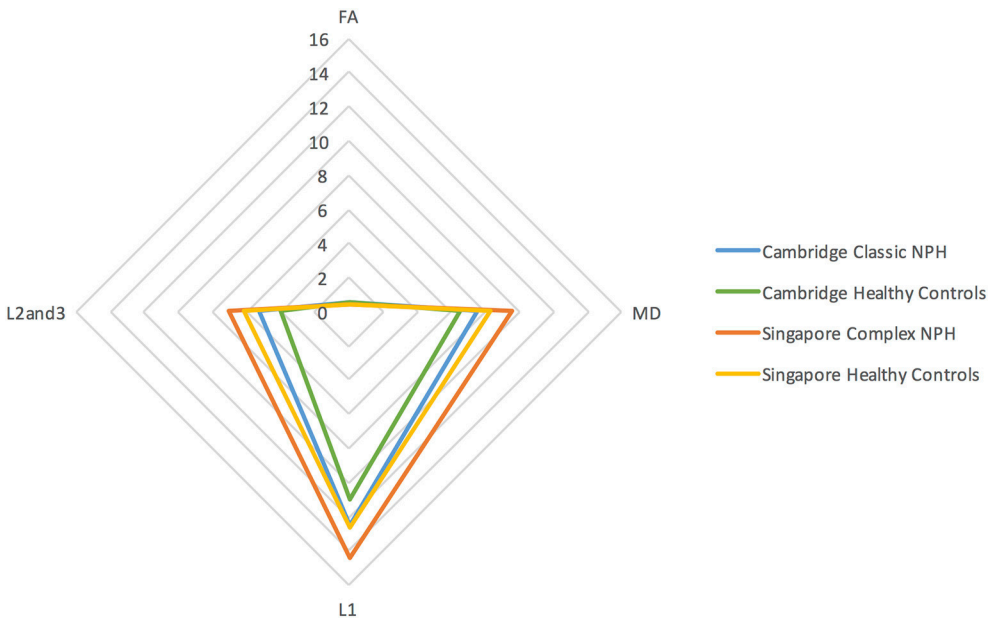

FIGURE 1 | DTI profiles as radar graphs representing differences across classic NPH, complex NPH, and healthy control cohorts. Due to variations in scanning acquisition between collaborator sites, differences in DTI metrics may not be statistically meaningful. However, DTI profiles provide a methodological tool for comparability across cohorts. As NPH patients displayed worsening functional performance along the disease spectrum (for example, mean MMSE = 24.1 vs. 21.1 for classic vs. complex NPH, respectively), their DTI profiles concurrently worsened to match, across all diffusivity measures. The morphology of DTI profiles also matched the performance of healthy controls (mean MMSE = 28.6 vs. 26.8 for Cambridge vs. Singapore healthy controls).

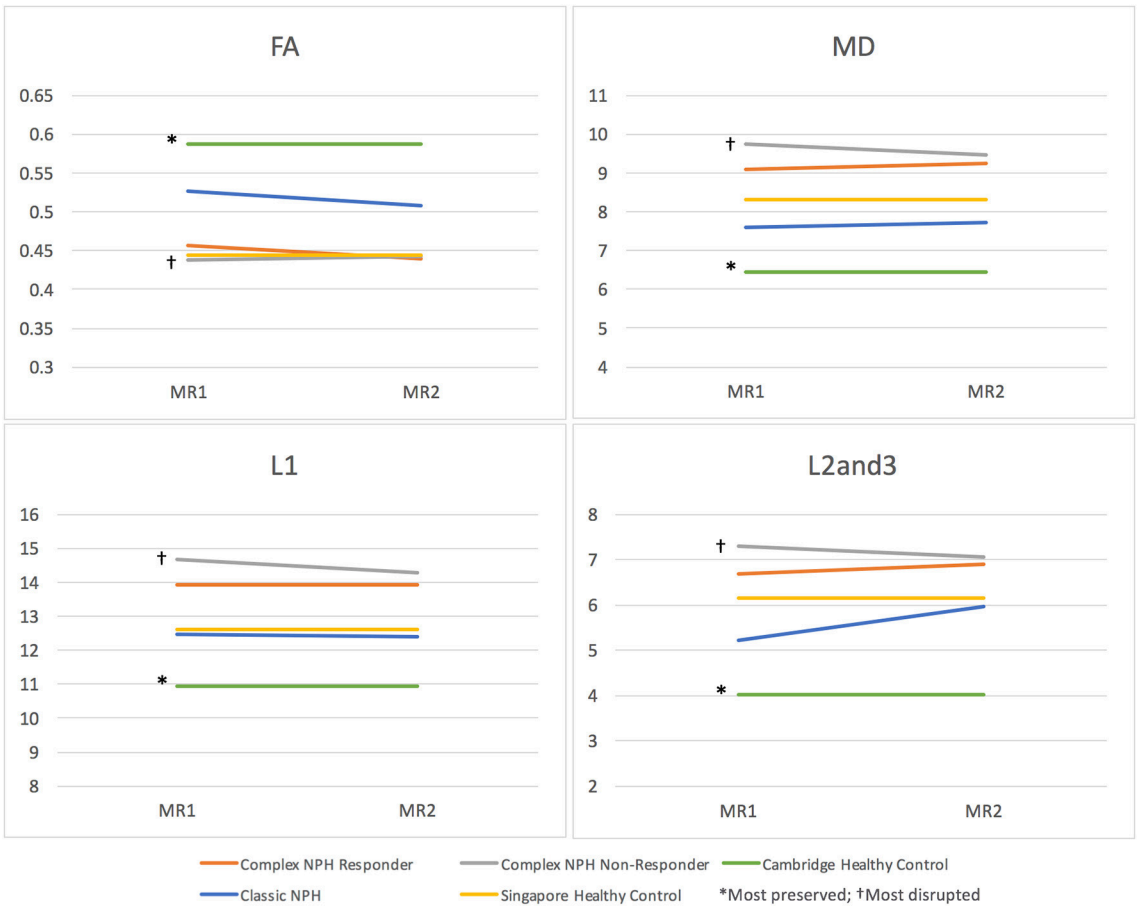

FIGURE 2 | DTI profiles as line graphs across classic NPH, complex NPH (responder and non-responder), and healthy control cohorts. Differing NPH patient cohorts and healthy controls could be differentiated by the position of their DTI profiles within the spectrum of diffusivity measures. DTI profiles for Cambridge healthy controls* were the most preserved (highest FA, lowest MD, L1, and L2and3), whereas DTI profiles for complex NPH non-responders† were the most disrupted (lowest FA, highest MD, L1 and L2and3).

(see **Figure 3**), DTI profiles for complex NPH responders were more preserved compared to non-responders at baseline.

Morphology of DTI Profiles for Responders vs. Non-responders

When the responses of NPH patients to CSF drainage were plotted as percentage changes between pre- and post-intervention diffusivity measures, the morphology of DTI profiles for complex NPH patients responding to CSF drainage matched that of classic NPH patients responding to successful shunting in the exemplar dataset, albeit with a differing magnitude of changes (see **Figure 4**). However, when the percentage changes pre- and post-intervention were plotted for complex NPH non-responders, DTI profiles demonstrated entirely different morphology compared to responders from either complex or classic NPH cohorts. When the means of diffusivity parameters were considered concurrently, changes in DTI profiles for complex NPH responders in Singapore undergoing extended CSF drainage mimicked patterns of changes seen in predominantly shunt-responsive patients with classic NPH in Cambridge. Such patterns [decreased fractional anisotropy (FA), increased mean diffusivity (MD), decreased axial (L1) with increased radial diffusivities (L2and3)] were seen consistently across all diffusivity measures (see **Figures 5**, **6**). Furthermore, such patterns were not seen in complex NPH non-responders, who often exhibited changes in the exact opposite direction to responders. Instead, the changes seen in non-responders (an increase in fractional anisotropy (FA), with passive reduction of all other diffusivity measures following CSF drainage) were consistent with water diffusivity patterns in the presence of atrophy. The interpretation of diffusivity measures using DTI profiles also corresponded with visual representations of tractography models for responders vs. non-responders (**Figure 5**).

Correlation of CSF Responsiveness From Lumbar Drainage With Surgical Outcome

Five patients (four responders and one patient excluded from analysis due to lack of imaging compliance) underwent surgical intervention, with six ventriculo-peritoneal shunts placed. All

responders maintained their predicted responses following shunting. One responder developed a delayed abdominal pseudocyst with subacute infection. He had no evidence of infection on CSF sampling but had drainage of the pseudocyst with temporary shunt externalization, due to concerns of ascending infection. He subsequently had a shunt reinsertion on the contralateral side without neurological deterioration. Two responders reported post-operative improvement exceeding that of testing levels. At 1 year post-shunting, all complex and classic NPH responders maintained their good outcomes. Good outcomes were primarily reflected in improvement of gait symptoms. In terms of urinary symptoms, one responder had subjective improvement in incontinence and two responders reported no change; one responder had known pre-existing bladder dysfunction. One non-responder subsequently died from a cerebrovascular accident, a known comorbidity, outside the study. Another had delayed improvement at home but declined surgery.

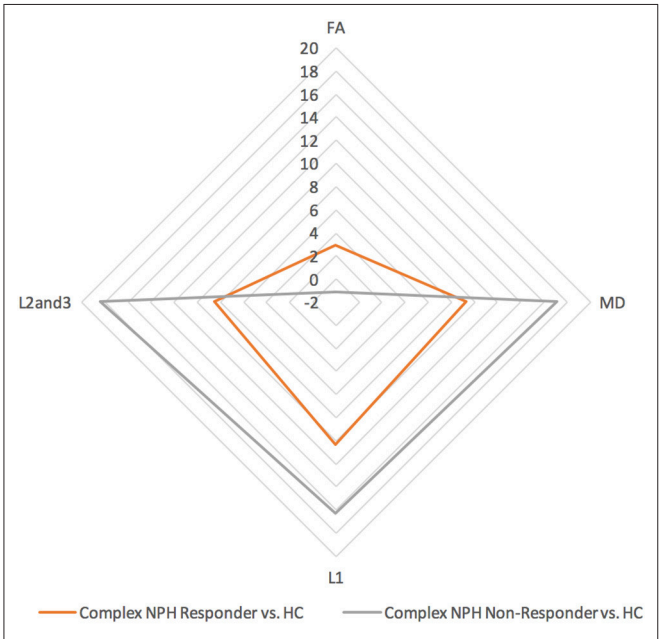

FIGURE 3 | DTI profiles for complex NPH vs. healthy controls—radar graphs represent percentage (%) differences between pre-intervention patients and controls, differentiated by their post-intervention responses. The larger the DTI radar graph, the greater the differences between patients and controls. This graph demonstrates that compared to healthy controls, DTI profiles for complex NPH responders were more preserved compared to non-responders at baseline.

DISCUSSION

In this study, we demonstrate the utility of using the morphology of DTI parameters to compare DTI profiles across collaborator sites, despite significantly different datasets. Due to the differing MR scanners and specifications unique to each collaborator site, it would not ordinarily be possible to directly compare DTI findings. The methodology of DTI profiles provides a framework for the rapid characterization of diffusivity measures to describe patient cohorts at the clinical-research interface that supports the new praxis of patient-centered international collaborative research.

Technical Challenges of Data Harmonization

The challenges of comparing imaging datasets between differing collaborating units are well-accepted. Apart from MR field

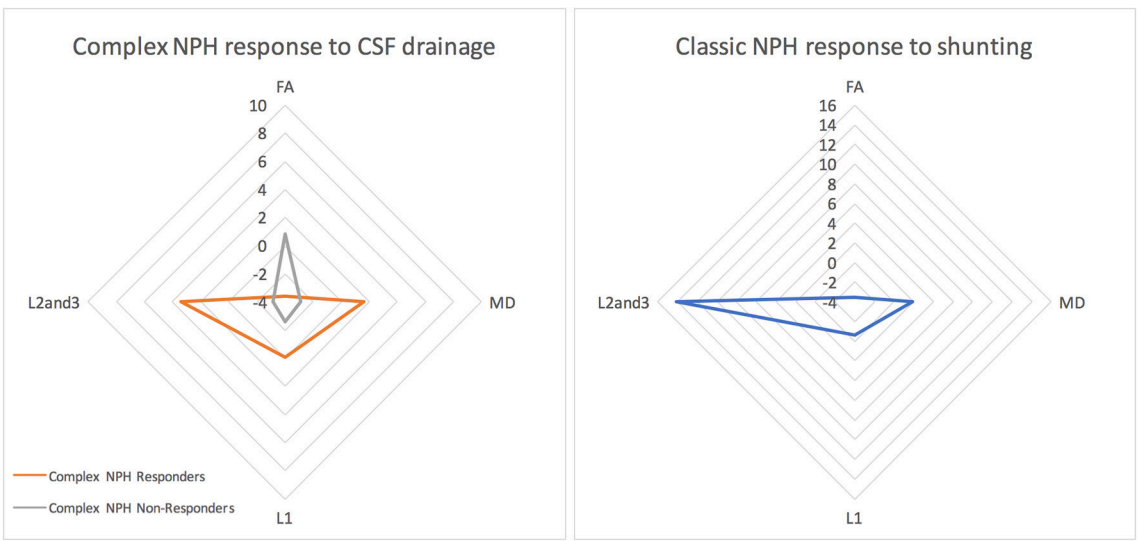

FIGURE 4 | The morphology of DTI responses to CSF drainage—radar graphs represent percentage (%) changes between pre- and post-intervention DTI profiles in patients. The morphology of DTI profiles for complex NPH responders matched that of classic NPH responders, albeit with a differing magnitude of changes. DTI profiles for complex non-responders demonstrated entirely different morphology to responders with either complex or classic NPH.

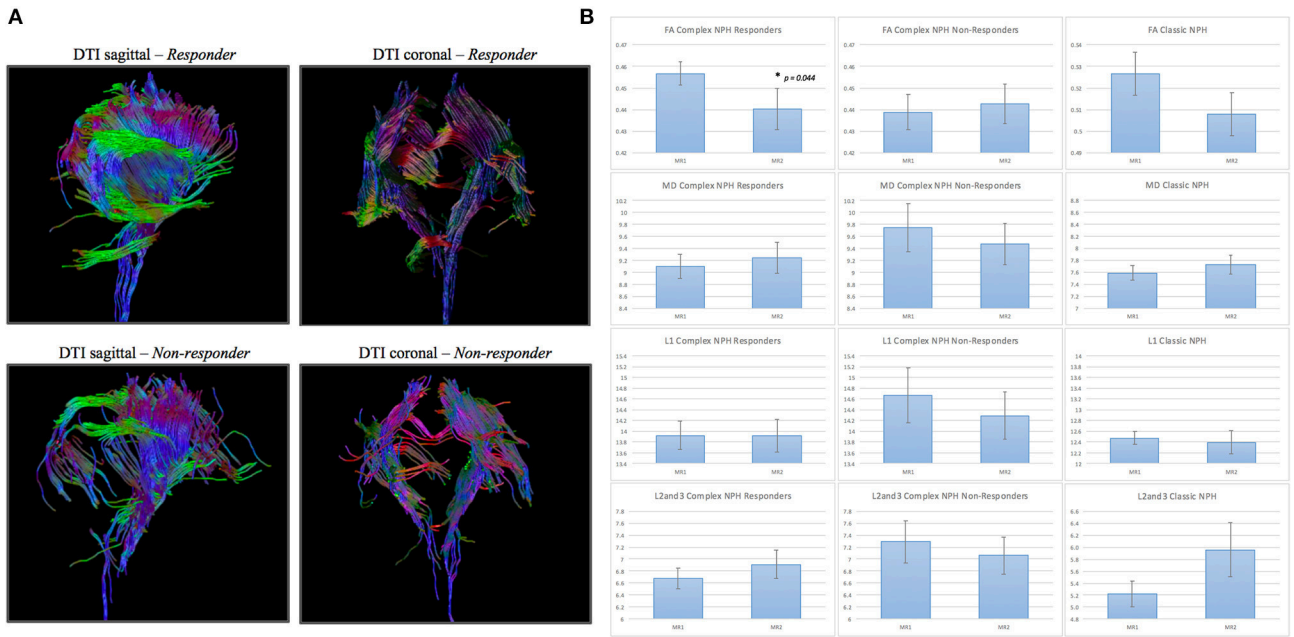

FIGURE 5 | (A) DTI periventricular white matter tractography model. (Above, left) A typical complex NPH responder demonstrating structural integrity despite white matter disruption. (Below, left) A typical complex NPH non-responder demonstrating severe paucity of tracts and white matter damage. **(B)** DTI profiles (means with standard error bars) for complex NPH responders, non-responders and classic NPH cohorts. Patterns of directional changes in diffusivity measures for complex NPH responders were consistent with classic NPH, whereas directional changes for non-responders were suggestive of atrophy. MR1 = pre-intervention; MR2 = post-intervention.

strengths, an analysis study by Cetin Karayumak et al. (24) illustrated differences in inter- and intra- specific scanners. For accurate analysis, harmonization and resolution of differences both across and within scanners are usually required. Inter-scanner differences can be found in both DTI measures such as fractional anisotropy and mean diffusivity, and structural measures, such as cortical thickness, and range from tissue-specific to regional differences. Types of intra-scanner differences include variability in receiver coils, reconstruction algorithms, magnetic fields, and acquisition parameters (25). Several methods have been developed to correct such issues. To combat structural variability, it is possible to use a physical phantom framework for monitoring and detection of scanner-related changes (26). Techniques such as generation of z-scores (27–29) and regression of covariates (30, 31) have been used to statistically resolve the differences in specific diffusion measures. These challenges can confound the establishment of international thresholds for comparison of cohorts within a spectrum of disease.

Whilst such work is still necessary, good scan-rescan repeatability and cross-scanner comparability have already been confirmed across differing sites and scanners, supporting the feasibility of using DTI measures derived from multiple collaborating sites (32). Ongoing efforts have focused upon achieving harmonizing of acquisition parameters and applying relevant corrections to the generation of DTI metrics. However, few studies have sought to understand the comparability of using the morphology of DTI changes as a form of consistent DTI interpretation across scanner sites. In this study, we present a simplistic methodology for use at the clinical-research interface that does not seek to directly address correction of diffusivity measures *per se*. Instead, we propose the use of DTI profiles to enable collaborators to confirm and characterize the comparability of their cohorts by providing a further layer of transparency, prior to the application of higher statistical methods. The checks afforded by DTI profiles also enable rapid detection of outliers for diffusivity parameters expected for local cohorts and allows individual units to ascertain if their presenting disease cohorts are comparable to international or open-access datasets of disease. The ability to perform these checks at the clinical-research interface contributes to the development of patient-centered collaborative research networks.

NPH as a Model of Disease Cohorts

NPH as a disease continuum is critical to the development and study of DTI profiles because it serves as a both a model of reversible and irreversible brain injury. In our previous work in classic NPH patients, we have shown that it is possible to use DTI methodology to confirm and characterize differing pathophysiological processes occurring concurrently (16). Compared to age-matched healthy controls, NPH patients exhibited "distinct profiles of white matter injury." These profiles could be entirely described by changes in anisotropic indices that are specific to the individual white matter tracts. We found that patterns of changes were influenced by measurable neuroanatomical factors and that some patterns of injury demonstrated a greater potential for reversibility than others

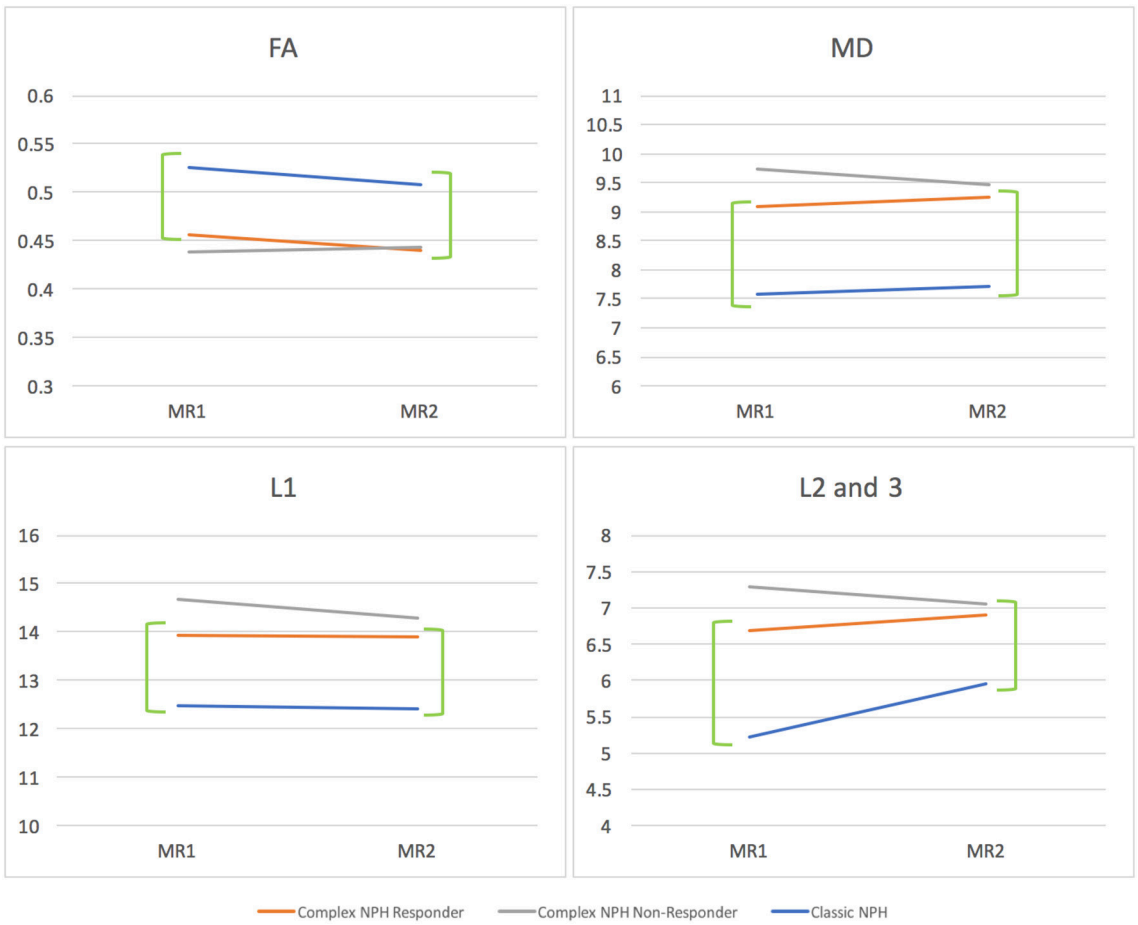

FIGURE 6 | DTI profiles as line graphs comparing NPH cohorts across the spectrum (complex vs. classic NPH). DTI profiles for complex NPH responders mimicked patterns of changes seen in classic NPH patients across all diffusivity measures (green brackets). MR1 = pre-intervention; MR2 = post-intervention.

(16). Predominant transependymal diffusion and stretch/oedema patterns found in the corpus callosum and inferior fronto-occipital/uncinate fasciculi, were less amenable to surgical intervention. By contrast, in white matter tracts where a pattern of stretch/compression was present, such as in the inferior longitudinal fasciculus, or where stretch/compression was the predominant pattern, such as in the posterior limb of the internal capsule, it was possible to demonstrate significant changes as early as 2 weeks following surgery (16). These changes, consistent with improvement, preceded changes in clinical outcome and were ultimately predictive of them. In this study, we have similarly demonstrated that certain patterns of DTI morphology are more responsive to CSF drainage than others. Complex NPH patients who did not respond to extended CSF drainage exhibited patterns consistent with axonal disruption and stretch/oedema (increased mean (MD), axial and radial (L1 and L2and3) diffusivities compared to healthy controls). Complex NPH responders demonstrated worse DTI measures that patients with classic NPH. However, white matter patterns in responders appeared to be more preserved, consistent with axonal disruption and stretch/compression [increased mean and axial diffusivities (MD and L1) but radial diffusivities (L2and3) not significantly different to healthy controls]. By plotting changes in DTI measures concurrently as profiles, it is possible to overcome the methodological challenges of comparing statistically significant datasets.

DTI Profiles for the Rapid Comparison of Cohorts

Similarly, we have found, using DTI profiles, that despite confounding factors such as comorbidities involving cardiovascular risk burden and overlay from neurodegenerative disease, complex NPH responders can be shown to demonstrate patterns that mimic classic NPH responders across all diffusivity measures. The changes exhibited by non-responders are different and exhibit DTI morphology that are distinct from responders. DTI is useful because of its ability to characterize microarchitectural changes within white matter. The application of DTI profiles allows for the interpretation of contrasting pathological mechanisms without assumed prior knowledge of the predominant patterns of changes leading to its clinical syndrome. Our methodology of DTI profiles provides a mechanism for describing morphological changes common to different cohorts within the same spectrum of disease. This

shorthand does not require that such groups are homogenous; we have demonstrated its utility within separate and significantly different patient cohorts within NPH, suggesting the DTI profiles for the disease process is proportionately more important than variations of the disease phenotype within its spectrum.

Limitations

Our study has several methodological shortcomings. Firstly, our sample size is small, albeit relevant for the disease in question. The current study reflects improvements in DTI acquisition and analysis that is in some ways superior to that of the exemplar dataset. An optimal comparator study would involve simultaneous recruitment of different patient cohorts across both collaborator sites, and would require harmonization of DTI acquisition protocols in real time. Further validation work regarding the use of DTI profiles in comparison with international open-access datasets would be most helpful in this regard.

In conclusion, comparability of DTI measures across disease cohorts and collaborative sites is an obstacle to its usability and application at the clinical-research interface. Our findings suggest that it is possible to overcome such challenges by the use of DTI profiles to understand the morphology of microstructural changes and to apply such characterization in consistent terms to international collaborator datasets. The use of such methodology should be considered within the context of interdisciplinary collaboration as part of the new praxis of translational medicine.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the SingHealth Centralized Institutional Review Board (CIRB) with written informed consent from all subjects or their legal representatives, in the event that the subjects were not able to consent for themselves. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the SingHealth Centralized Institutional Review Board.

AUTHOR CONTRIBUTIONS

NCK and CL contributed to the conceptualization and design of the study and wrote the manuscript. JK coordinated study procedures and scanning for the study. JK and CL contributed to the collection, analysis and interpretation of study data. NCK supervised study procedures and data collection for the study, and contributed to the analysis and interpretation of study data. SK contributed to design of imaging acquisition parameters and optimization of the study protocol as well as interpretation. NK, E-KT, and AN contributed to the clinical and research characterizations of the complex NPH patients. JP, MC, and ZC contributed to the exemplar dataset of the classic NPH patients. VN, AA-A, AN, and YJT contributed to the validation of the methodology of DTI characterization of the complex NPH patients using fluid markers (not presented in this manuscript). All co-authors contributed to revisions of the manuscript.

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OPINION
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Driving Medical Innovation Through Interdisciplinarity: Unique Opportunities and Challenges

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INTRODUCTION

Many health problems facing society are multifactorial and often require social and political input as well as interventions from medical and technological experts. For example, the treatment of chronic pain requires expertise from multiple disciplines: imaging technology, cellular electrophysiology, neurochemistry, genetics, social, psychological, and cultural studies (1). While these activities are coordinated by the treating physician, they usually remain parallel and are never fully integrated to create an innovative therapy for the patient. From a research standpoint, we argue that for these new solutions to emerge, there needs to be a concerted effort to move from multidisciplinarity to interdisciplinarity.

Multidisciplinary research is defined as work involving researchers from different fields who "remain conceptually and methodologically anchored in their respective fields" (2). In contrast, interdisciplinary research is defined as "a mode of research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge, to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or area of research practice" (3). It may lead to the creation of a new scientific field, such as environmental humanities (4–6).

The major difference between the two types of research is that while interdisciplinarity involves deep and robust integration of distinct disciplines, multidisciplinarity implicates juxtaposition of a variety of expertises (5). By these definitions, both research types are clearly valuable, but interdisciplinary research should drive more impactful results for complicated problems. These advances come at a cost for researchers because interdisciplinarity has its own set of unique challenges, ranging from communication issues to allocation of credits among a team. In this article, we discuss these hurdles and potential solutions to raise awareness amongst researchers keen to lead a successful interdisciplinary project.

CHARACTERISTICS OF AN INTERDISCIPLINARY TEAM

Collaborative teams consist of individuals from different fields working toward a common goal that transcends the borders of a single discipline. Exactly who will comprise the members of an interdisciplinary and multidisciplinary team must be individually determined for each project according to the specific needs. It is almost a certainty in research projects that individuals will face hurdles that can only be solved with group support, leading to a widespread feeling among members of being out of one's comfort zone (7). Communication can be challenging when a team involves members from a variety of disciplines. A classic strategy employed to dominate the discourse and decision-making process is to use highly technical language specific to one's field of expertise. Bammer proposed the creation of a new role for integration and implementation scientists (8). Such experts would contribute to teams tackling complex problems by assessing the problems and their interconnections, and by identifying strategies for approaching them. These implementation scientists could define the level of involvement of the different stakeholders and strategize how to incorporate the various disciplines and stakeholder objectives. Furthermore, they can identify knowledge gaps and predict evolving problems, whilst providing support throughout the process. Two major hurdles can be identified: first in identifying a universal requirement for experts in this role, and secondly establishing a clear identity for scientists in this role with a clear consensus on methods and processes to be used for example in training for such a role (9).

In the same direction, a new field of research is developing, which was first termed "the science of team science" or SciTS in 2006. This field focuses on systematic efforts to overcome barriers in collaborative work, and how to achieve the targeted research outcomes. Other goals of SciTS are to support scientists in creating and working effectively within a team. However, above a certain team size (different for each research setting and question) output decreases and bureaucracy increases, with potential conflicts arising within teams. Therefore, in a world of limited resources, important questions for researchers also include the question of resource allocation i.e., when to decide if external collaborators or cross-disciplinary support is required and how to fund this adequately (10).

Efficient coordination of project tasks is vital for progress to occur. In large teams, a power struggle for the "lead" role may emerge when several individuals have equal seniority or leadership experience. The team leader must match responsibilities to expertise and time commitment, to plan a schedule that is realistic yet ambitious, and to provide ample opportunities for team members to share updates and knowledge. The team leader also often plays a key role in designing the research plan and in identifying potential team members with complementary knowledge and skills. "The science of team science" is a new field of research that aims to provide evidence to support scientists responsible for these tasks and helps them to overcome barriers (11).

A survey of researchers revealed that successful interdisciplinary work often includes mutual respect, comfort, or already established positive relationships (12). These concepts gave rise to a new ethical framework known as relational ethics, stemming from the fact that all ethics are grounded in relations, interdependency, engagement and the importance of community (13). This framework suggests that a climate of safety, trust, respect and equality is necessary to effectively challenge the *status quo* (14, 15).

Successful solutions to complex problems can be achieved when a team is comprised of individuals with complementary expertises, interests, ideas, and/or professional goals. An example is the creation of arterio-venous fistulas for hemodialysis access using an innovative endovascular catheter-based system: this system was conceived and implemented by a team of interventional radiologists, vascular surgeons, biomedical, and industrial engineers (16). Another example is the invention of a blood-resistant biodegradable surgical glue by a team of pediatric cardiologists, cardiac surgeons, biomedical, biological, and chemical engineers (12). In both cases, long-identified unmet medical needs became solvable because of well-directed interdisciplinary efforts over many years.

ADVANTAGES AND HURDLES OF WORKING IN INTERDISCIPLINARY PROJECTS

The interpretation of the concept interdisciplinarity varies among individuals. It is reported that researchers face challenges in justifying the benefit of interdisciplinary interactions against their perception of increased time and resource requirements. In a study by Roy et al. both natural and social scientists identified departmental or institutional difficulties, communication difficulties and differing disciplinary approaches as significant challenges (17).

In another descriptive study, 19 researchers indicated that they conducted interdisciplinary research specifically because of their individual lack of knowledge in some sectors (7). Other benefits were the generation of new knowledge, exposure to new methods or theories, and the opportunity to make a bigger impact. However, the respondents also indicated caveats to performing interdisciplinary work, such as the need to allocate more time compared to their usual line of research as well as limited credits for academic promotion. Other issues highlighted included the significantly greater effort needed to understand interpersonal dynamics, to clarify leadership roles, and to determine the contributions of each team member. Finally, some researchers noted that some individuals may be marginalized as a result of power imbalances (18).

Funding agencies have traditionally rewarded independent scientists proposing research in their field of expertise rather than teams of researchers offering to conduct interdisciplinary projects. Over time, complex problems such as climate change led to increased funding for inter- or multidisciplinary research teams. Some researchers have argued that efforts to make

research funding contingent on inclusion of interdisciplinarity leads to inefficiency (7). How successful such interdisciplinary focused funding approaches are remains unclear: the US National Institutes of Health (NIH) reports slightly better outcomes for funding fostering interdisciplinary funded programmes vs. conventional, projects of independent research, whereas the opposite is true for the European Research Council (ERC) (18). Funding for collaborative projects are increasingly available and are internationally well supported. For example, the European Framework Program for Research and Innovation, which includes the "Horizon 2020" (H2020) program, is the world's largest interdisciplinary funding program (19). In the USA, the National Science Foundation (NSF) (20) and the Clinical and Translational Science Awards (CTSA) Program supports national networks of medical research institutions that collaborate to improve the efficiency of translational research, promoting the integration of underserved populations, and train future translational researchers (21).

In summary, many researchers hold negative perceptions about interdisciplinary research. However, these perceptions could be overcome by adopting strategies such as advanced planning of the study, including whether a project is to be multi- or interdisciplinary (see **Figure 1**), and by including a balanced team with the abilities required for the project (see **Table 1**).

INTERDISCIPLINARY RESEARCH IN EARLY CAREER STAGES AND FOR CAREER PROGRESSION

The World Health Organization (WHO) has recently concluded that effective interdisciplinary education facilitates later collaborative practice (22). Introducing the interdisciplinarity concept early in a scientist's career promotes the later unconscious incorporation of it into their future research (23). As a result, this early practical exposure ensures the new generation of researchers is better equipped to manage the challenges of interdisciplinarity. The integration of interdisciplinarity into higher education could be driven by educational institutions, the UK Research Excellence Framework being a good model (24).

A more structured approach is the formation of multidisciplinary translational teams (MTT) as a training and mentoring approach focusing on translational innovation by research capacity building, interprofessional integration, and team-based mentoring approaches. This methodology enhances the development of translational research competencies and productivity in terms of collaborative publications (25, 26). Another innovative structured approach is industry-based studentships, as recommended by the Canadian Academy of Health Sciences (CAHS) after an in-depth assessment of interdisciplinary health research (27). An argument against this model of training is that it increases pressure and constraints placed on trainees by adding an additional layer of training and evaluation to their portfolio.

For challenging topics with dedicated grants and that require interdisciplinary approaches, evaluation of teams supersedes the evaluation of individuals. Yet, the coordinator carries most of the evaluation pressure, since their track record needs to show they have coordinated interdisciplinary teams and trained next-generation scientists to implement interdisciplinary research. It is true that progression from early stage to established scientists requires continuous evaluation with the "expertise" binoculars, yet one needs to start somewhere. The pressure is on early-stage researchers to acquire "expertise" in order to progress, yet, be open to learning and implementing interdisciplinary methods in preparation for the tackling of complex problems.

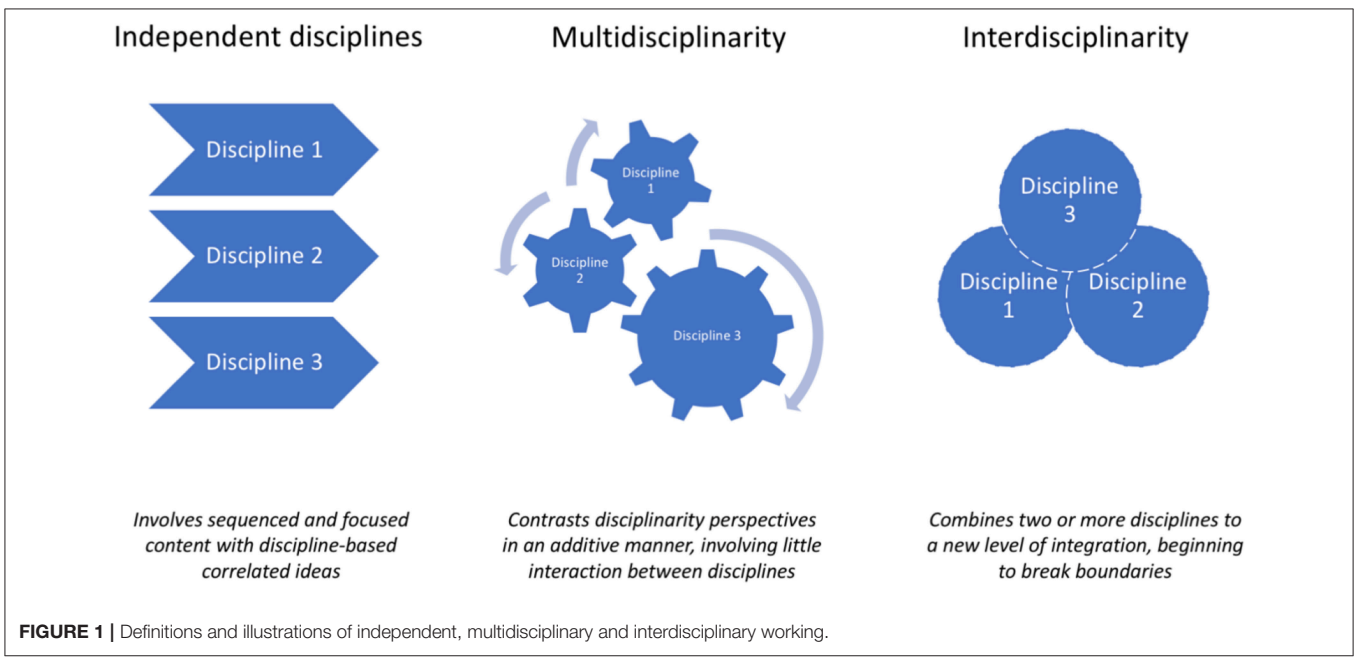

FIGURE 1 | Definitions and illustrations of independent, multidisciplinary and interdisciplinary working.

TABLE 1 | Recommendations to stimulate sustainable interdisciplinary research environments.

Pre-project
Include a trainee or have a future team member seek additional training in a program with a focus on interdisciplinary research.
Determine the extent of collaboration wished (inter- vs. multi-disciplinary).
Plan the team composition, the balance of abilities and role delegation. Consider including a scientist in an integration and implementation role.
During the project
Allocate the supervisor role to someone with experience of interdisciplinary project supervision, not necessarily the most senior.
Plan early for potential project hurdles, such as funding issues, allocation of funds, credits etc.
Plan the allocation of credits, such as the authorship order, early.
Focus on the training of inexperienced project members.
Consider the implementation of a team-based mentoring program and integrate team-based evaluation.
Post-project
Ask for anonymous feedback from all team members on what worked well and what could be done better to provide helpful hints to improve the team performance.
Consider success of the project to be not only based upon achievement of publication in high-impact journals, but rather achievement of societal goals and wider translational objectives.
All team members actively engage in knowledge translation to promote the project in their own field, including considering the use of "newer" resources or publication modes such as interactive Journals or Social Media.

Throughout their careers, scientists are traditionally evaluated based on the quality of their output. Articles only "count" in the academic tally if the scientist is first or last author. Middle authorships are reflexively disqualified irrespective of the nature of the contribution or the importance of the discovery. Scientists interested to work as part of interdisciplinary teams may be discouraged to do so when realizing that they will be at a significant disadvantage compared to others who prefer "flying solo." McLeish and Strang identify "Individual Career Progression" as one of the crucial levels at which there is an immediate need for an effective evaluation method for interdisciplinarity (28).

Furthermore, from their experience as evaluators, the authors report enormous pressures on researchers to establish a distinct identity, fueling the claim that career progression is hampered by interdisciplinary research and potentiated by single-discipline work. Nevertheless, some successful interdisciplinary translational researchers counter-argue that their aim is impact, a goal favored by several institutions. "*Resisting the concept of focusing in research meant to surround myself with collaborators of different skills to fill the gaps in knowledge and exploring constantly new areas. One's focus gets defined by products* (29) *and technologies they put on the market that have large impact on patients' lives*"—personal communication, Dr. Jeffrey Karp from Brigham and Women's Hospital, Boston (MA) (30).

WHAT IS THE BEST APPROACH FOR TRAINING FUTURE SCIENTISTS?

While it is critical to continue training scientists who are highly knowledgeable in one specific field, it is important to expose them early on to the notions of multi- and inter-disciplinarity. Ideally, this exposure would be an integral part of their didactic and practical training. It is also critical to strive to train individuals with broader interests by allowing them to straddle a few fields during their training, with the understanding that their training is likely to be substantially longer than usual (and thus will require unusually long periods of support from funding bodies). The clinician-scientist training model is an example of this approach since it generates a workforce that is conversant in the language of both clinical and basic science. This will facilitate the dialogue between the disciplines and render a deeper mutual understanding. There are now a large number of training programs for non-physicians that aim to specifically train researchers focused on interdisciplinarity in a given discipline such as cancer or cardiovascular diseases, although no specific standards for training exist to which these programs can be evaluated by.

INDEPENDENT VS. TEAM VS. INTERDISCIPLINARY SCIENCE

It is important to emphasize that our goal is not to dismiss independent or team science. These two approaches, which rely on work within a more narrow scientific perspective, are distinguished by the number of independent teams involved. There are many important research questions that are best addressed using either of these traditional approaches. For example, assessing the impact of a genetic deficiency on human physiology using genetically engineered cellular or animal models. Reductionism is often a critical heuristic device to solve these scientific problems. In contrast, interdisciplinary science is most useful to answer research questions nested in complex structures. By definition, they cannot be answered by relying only on reductionistic methods but rather require integrated, multi-pronged approaches. For example, multifactorial conditions that are caused by the confluence of multiple genetic and environmental factors

have been notoriously difficult to study. This has long been a frustrating situation since many diseases under this banner are prime public health problems (e.g., diabetes, atheroembolism, hypertension, or dementia). While there is no guarantee of success, the fresh look provided by interdisciplinary science is likely to yield insights and breakthroughs that may not be otherwise possible.

CONCLUSION

Whilst remembering the overarching goal of interdisciplinarity research is impact, research teams should be carefully constructed, led, and organized to allow for the fulfillment of individual objectives required for personal development, as well as for overall project success and achievement of the project aims. Effective collaborative practices are enabled by effective interdisciplinary education and can be promoted by the active provision of funding streams, in order to drive creative interdisciplinarity in academia.

AUTHOR CONTRIBUTIONS

FG, PM, BM, and ML made equal contributions in writing the paper. LW, MR, and AvR-K also wrote the manuscript and supervised the project.

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REVIEW
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From Big Data to Precision Medicine

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For over a decade the term "Big data" has been used to describe the rapid increase in volume, variety and velocity of information available, not just in medical research but in almost every aspect of our lives. As scientists, we now have the capacity to rapidly generate, store and analyse data that, only a few years ago, would have taken many years to compile. However, "Big data" no longer means what it once did. The term has expanded and now refers not to just large data volume, but to our increasing ability to analyse and interpret those data. Tautologies such as "data analytics" and "data science" have emerged to describe approaches to the volume of available information as it grows ever larger. New methods dedicated to improving data collection, storage, cleaning, processing and interpretation continue to be developed, although not always by, or for, medical researchers. Exploiting new tools to extract meaning from large volume information has the potential to drive real change in clinical practice, from personalized therapy and intelligent drug design to population screening and electronic health record mining. As ever, where new technology promises "Big Advances," significant challenges remain. Here we discuss both the opportunities and challenges posed to biomedical research by our increasing ability to tackle large datasets. Important challenges include the need for standardization of data content, format, and clinical definitions, a heightened need for collaborative networks with sharing of both data and expertise and, perhaps most importantly, a need to reconsider how and when analytic methodology is taught to medical researchers. We also set "Big data" analytics in context: recent advances may appear to promise a revolution, sweeping away conventional approaches to medical science. However, their real promise lies in their synergy with, not replacement of, classical hypothesis-driven methods. The generation of novel, data-driven hypotheses based on interpretable models will always require stringent validation and experimental testing. Thus, hypothesis-generating research founded on large datasets adds to, rather than replaces, traditional hypothesis driven science. Each can benefit from the other and it is through using both that we can improve clinical practice.

Keywords: big data, precision medicine, translational medicine, data science, big data analytics

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INTRODUCTION

Advances in technology have created—and continue to create—an increasing ability to multiplex measurements on a single sample. This may result in hundreds, thousands or even millions of measurements being made concurrently, often combining technologies to give simultaneous measures of DNA, RNA, protein, function alongside clinical features including measures of disease activity, progression and related metadata. However, "Big data" is best considered not in terms of its size but of its purpose (somewhat ironically given the now ubiquitous use of the "Big" epithet; however we will retain the capital "B" to honor it). The defining characteristic of such experimental approaches is not the extended scale of measurement but the hypothesis-free approach to the underlying experimental design. Throughout this review we define "Big data" experiments as hypothesis generating rather than hypothesis driven studies. While they inevitably involve simultaneous measurement of many variables—and hence are typically "Bigger" than their counterparts driven by an *a priori* hypothesis—they do so in an attempt to describe and probe the unknown workings of complex systems: if we can measure it all, maybe we can understand it all. By definition, this approach is less dependent on prior knowledge and therefore has great potential to indicate hitherto unsuspected pathways relevant to disease. As is often the case with advances in technology, the rise of hypothesis-free methods was initially greeted with a polarized mixture of overblown enthusiasm and inappropriate nihilism: some believed that *a priori* hypotheses were no longer necessary (1), while others argued that new approaches were an irrelevant distraction from established methods (2). With the vantage point of history, it is clear that neither extreme was accurate. Hypothesis-generating approaches are not only synergistic with traditional methods, they are dependent upon them: after all, once generated, a hypothesis must be tested (**Figure 1**). In this way, Big data analyses can be used to ask novel questions, with conventional experimental techniques remaining just as relevant for testing them.

However, lost under a deluge of data, the goal of understanding may often seem just as distant as when we only had more limited numbers of measurements to contend with. If our goal is to understand the complexity of disease, we must be able to make sense of the complex volumes of data that can now be rapidly generated. Indeed, there are few systems more complex than those encountered in the field of biomedicine. The idea that human biology is composed of a complex network of interconnected systems is not new. The concept of interconnected "biological levels" was introduced in the 1940s (3) although a reductionist approach to biology can trace roots back as far as Descartes, with the analogy of deconstructing a clockwork mechanism prevalent from Newton (4) to Dawkins (5). Such ideas have informed the development of "systems biology," in which we aim to arrive at mechanistic explanations for higher biological functions in terms of the "parts" of the biological machine (6).

The development of Big data approaches has greatly enhanced our ability to probe which "parts" of biology may be dysfunctional. The goal of precision medicine aims to take this approach one step further, by making that information of pragmatic value to the practicing clinician. Precision medicine can be succinctly defined as an approach to provide the right treatments to the right patients at the right time (7). However, for most clinical problems, precision strategies remain aspirational. The challenge of reducing biology to its component parts, then identifying which can and should be measured to choose an optimal intervention, the patient population that will benefit and when they will benefit most cannot be overstated. Yet the increasing use of hypothesis-free, Big data approaches promises to help us reach this aspirational goal.

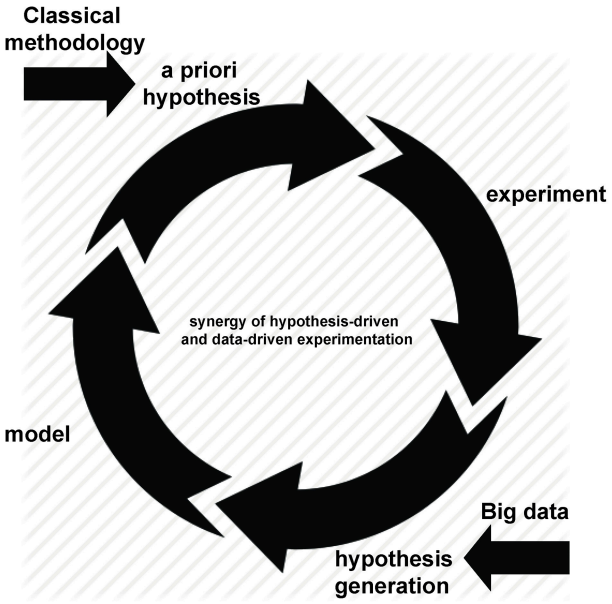

FIGURE 1 | The synergistic cycle of hypothesis-driven and data-driven experimentation.

In this review we summarize a number of the key challenges in using Big data analysis to facilitate precision medicine. Technical and methodological approaches have been systemically discussed elsewhere and we direct the reader to these excellent reviews (8–10). Here we identify key conceptual and infrastructural challenges and provide a perspective on how advances can be and are being used to arrive at precision medicine strategies with specific examples.

ACCESS AND TECHNICAL CONSIDERATIONS FOR HARNESSING MEDICAL BIG DATA

The concept of Big data in medicine is not difficult to grasp: use large volumes of medical information to look for trends or associations that are not otherwise evident in smaller data sets. So why has Big data not been more widely leveraged? What is the difference between industries such as Google, Netflix and Amazon that have harnessed Big data to provide accurate and personalized real time information from on line searching and purchasing activities, and the health care system? Analysis of these successful industries reveals they have free and open

access to data, which are provided willingly by the customer and delivered directly and centrally to the company. These deep data indicate personal likes and dislikes, enabling accurate predictions for future on-line interactions. Is it possible that large volume medical information from individual patient data could be used to identify novel risks or therapeutic options that can then be applied at the individual level to improve outcomes? Compared with industry, for the most part, the situation is different in healthcare. Medical records, representing deep private personal information, is carefully guarded and not openly available; data are usually siloed in clinic or hospital charts with no central sharing to allow the velocity or volume of data required to exploit Big data methods. Medical data is also complex and less "usable" compared with that being provided to large companies and therefore requires processing to provide a readily usable form. The technical infrastructure even to allow movement, manipulation and management of medical data is not readily available.

Broadly speaking, major barriers exist in the access to data, which are both philosophical and practical. To improve the translation of existing data into new healthcare solutions, a number of areas need to be addressed. These include, but are not limited to, the collection and standardization of heterogeneous datasets, the curation of the resultant clean data, prior informed consent for use of de-identified data, and the ability to provide these data back to the healthcare and research communities for further use.

Industry vs. Medicine: Barriers and Opportunities

By understanding the similarities and the differences between clinical Big data and that used in other industries it is possible to better appreciate some opportunities that exist in the clinical field. It is also possible to understand why the uptake and translation of these techniques has not been a simple transfer from one domain to another. Industry uses data that can truly be defined as Big (exhibiting large volume, high velocity, and variety) but tends to be of low information density. These data are usually free, arising from an individual's incidental digital footprint in exchange for services. These data provide a surrogate marker of an activity that allows the prediction of patterns, trends, and outcomes. Fundamentally, data is acquired at the time services are accessed, with those data being either present or absent. Such data does exist in the clinical setting. Examples include physiological monitoring during an operation from multiple monitors providing high volume, high velocity and varied data that requires real time handling for the detection of data falling outside of a threshold that alerts the attending clinician. An example of lower volume data is the day to day accumulation of clinical tests that add to prior investigations providing updated diagnoses and medical management. Similarly, the handling of population based clinical data has the ability to predict trends in public health such as the timing of infectious disease epidemics. For these data the velocity provides "real time" prospective information and allows trend prediction. The output is referable to the source of the data, i.e., a patient in the operating room or a specific geographical population experiencing the winter flu season [Google Flu Trends (11)].

This real time information is primarily used to predict future trends (predictive modeling) without trying to provide any reasons for the findings. A more immediate target for Big data is the wealth of clinical data already housed in hospitals that help answer the question as to why particular events are occurring. These data have the potential, if they could be integrated and analyzed appropriately, to give insights into the causes of disease, allow their detection and diagnosis, guide therapy, and management, plus the development of future drugs and interventions. To assimilate this data will require massive computing far beyond an individual's capability thus fulfilling the definition of Big data. The data will largely be derived from and specific to populations and then applied to individuals (e.g., patient groups with different disease types or processes provide new insights for the benefit of individuals), and will be retrospectively collected rather than prospectively acquired. Finally, while non-medical Big data has largely been incidental, at no charge and with low information density, the Big data of the clinical world will be acquired intentionally, costly (to someone) with high information density. This is therefore more akin to business intelligence which requires Big data techniques to derive measurements, and to detect trends (not just predict them), which are otherwise not visible or manageable by human inspection alone.

The clinical domain has a number of similarities with the business intelligence model of Big data which potentially provides an approach to clinical data handling already tested in the business world.

Within the electronic health record, as in business, data are both structured and non-structured and technologies to deal with both will be required to allow easy interpretation. In business, this allows the identification of new opportunities and development of new strategies which can be translated clinically as new understanding of disease and development of new treatments. Big data provides the ability to combine data from numerous sources both internal and external to business; similarly, multiple data sources (clinical, laboratory tests, imaging, genetics, etc.) may be combined in the clinical domain and provide "intelligence" not derived from any single data source, invisible to routine observation. A central data warehouse provides a site for integrating this varied data allowing curation, combination and analysis. Currently such centralized repositories do not commonly exist in clinical information technology infrastructure within hospitals. These data repositories have been designed and built in the pre-Big data era being standalone and siloed, with no intention of allowing the data to be combined and then analyzed in conjunction with various data sets. There is a need for newly installed information technology systems within clinical domains to ensure there is a means to share data between systems.

Philosophy of Data Ownership

Patient data of any sort, because it is held within medical institutions, appears to belong to that institution. However, these institutions merely act as the custodians of this data—the data is the property of the patient and the access and use of that data outside of the clinical realm requires patient consent. This immediately puts a brake on the rapid exploitation of the large volume of data already held in clinical records. While retrospective hypothesis driven research can be undertaken on specific, anonymized data as with any research, once the study has ended the data should be destroyed. For Big data techniques using thousands to millions of data points, which may have required considerable processing, the prospect of losing such valuable data at the end of the project is counter-intuitive for the advancement of medical knowledge. Prospective consent of the patient to store and use their data is therefore a more powerful model and allows the accumulation of large data sets then allowing the application of hypothesis driven research questions to those data. While not using the vast wealth of retrospective data feels wasteful, the rate (velocity) at which new data are accrued in the medical setting is sufficiently rapid that the resultant consented data is far more valuable. This added step of acquiring consent from patients likely requires on site manpower to interact with patients. Alternatively, options such as patients providing blanket consent for use of their data may be an option but will need fully informed consent. This dilemma has been brought to the fore by the EU General Data Protection Regulation (GDPR) which entered into force in 2018, initiating an international debate on Big data sharing in health (12).

Regulations Regarding Data Sharing

On April 27, 2016, the European Union approved a new set of regulations around privacy: the General Data Protection Regulation (GDPR) (13), which is in effect since May 25, 2018. The GDPR applies if the data controller (the organization that collects data), data processor (the organization that processes data on behalf of the data controller) or data subject is based in the EU. For science, this means that all studies performed by European institutes/companies and/or on European citizens, will be subject to the GDPR, with the exception of data that is fully anonymized (14). The GDPR sets out seven key principles: lawfulness, fairness and transparency; purpose limitation; data minimization; accuracy; storage limitation; integrity and confidentiality (security); and accountability. The GDPR puts some constraints on data sharing, e.g., if a data controller wants to share data with another data controller, he/she needs to have an appropriate contract in place, particularly if that other data controller is located outside the EU (15). If a data controller wants to share data with a third party, and that third party is a processor, then a Data Processor Agreement (DPA) needs to be made. Apart from this DPA, the informed consent that the patient signs before participating in a study, needs to state clearly for what purposes their data will be used (16). Penalties for non-compliance can be significant, GDPR fines are up to €20 million or 4% of annual turnover. Considering the fact that health data are "sensitive," potential discrimination has been addressed in legislation and a more proportionate approach is applied to balance privacy rights against the potential benefits of data sharing in science (12). In fact, processing of "data concerning health," "genetic data," and "biometric data" is prohibited unless one of several conditions applies: data subject gives "explicit consent," processing is necessary for the purposes of provision of services or management of health system (etc.), or processing is necessary for reasons of public interest in the area of public health.

The question of "explicit consent" of patients for their healthcare data to be used for research purposes provoked intense debate already during negotiations for GDPR, but finally these research groups lost the argument in the European political arena to advocacy groups of greater privacy. Research groups lobbied that restricting access to billions of terabytes of data would hold back research e.g., into cancer in Europe. The fear as concluded by Professor Subhajit Basu, from Leeds University, is that "GDPR will make healthcare innovation more laborious in Europe as lots of people won't give their consent. It will also add another layer of staff to take consent, making it more expensive. We already have stricter data protection laws than the US and China, who are moving ahead in producing innovative healthcare technology." (17)

Within the GDPR, the data subject also has the "right to be forgotten": he/she can withdraw the consent, after which the data controller needs to remove all his/her personal data (18). Because of all issues around data sharing, scientists might consider (whenever possible) to share only aggregated data which cannot be traced back to individual data subjects, or to raise the abstraction level, sharing insights instead of data (19).

While the implementation of GDPR has brought this issue into sharp focus, it has not resolved a fundamental dilemma. As clinicians and scientists, we face an increasingly urgent need to balance the opportunity Big data provides for improving healthcare, against the right of individuals to control their own data. It is our responsibility to only use data with appropriate consent, but it is also our responsibility to maximize our ability to improve health. Balancing these two will remain an increasing challenge for all precision medicine strategies.

Sharing of Data, Experience and Training—FAIR Principles

The sharing of data only makes sense when these data are structured properly [preferably using an ontology such as BFO, OBO, or RO (20)], contains detailed descriptions about what each field means (metadata) and can be combined with other data types in a reliable manner. These tasks are usually performed by a data manager or data steward (21), a function that has been gaining importance over the past years, due to the rise of "Big data." Until recently, data managers and data stewards had to do their job without having a clear set of rules to guide them. In 2016 however, the FAIR Guiding Principles for scientific data management and stewardship (22) were published. FAIR stands for the four foundational principles—Findability, Accessibility,

TABLE 1 | FAIR principles for data management and stewardship.

1	Findability: (meta)data are assigned a globally unique and persistent identifier; data are described with rich metadata; metadata clearly and explicitly include the identifier of the data it describes; (meta)data are registered or indexed in a searchable resource
2	Accessibility: (meta)data are retrievable by their identifier using a standardized communications protocol; this protocol is open, free, and universally implementable, and allows for an authentication and authorization procedure, where necessary; metadata are accessible, even when the data are no longer available
3	Interoperability: (meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation; they use vocabularies that follow FAIR principles; they include qualified references to other (meta)data
4	Reusability: (meta)data are richly described with a plurality of accurate and relevant attributes; they are released with a clear and accessible data usage license; they are associated with detailed provenance; they meet domain-relevant community standards

Interoperability, and Reusability—that serve to guide data producers and publishers as they navigate around the obstacles around data management and stewardship. The publication offers guidelines around these four principles (**Table 1**).

Physical Infrastructure

On first impression, healthcare institutions are well equipped with information technology. However, this has been designed to support the clinical environment and billing, but not the research environment of Big data. Exploitation of this new research environment will require a unique environment to store, handle, combine, curate and analyse large volumes of data. Clinical systems are built to isolate different data sets such as imaging, pathology and laboratory tests, whereas the Big data domain requires the integration of data. The EHR may provide some of this cross referencing of unstructured data but does not give the opportunity for deriving more complex data from datasets such as imaging and pathology which gives the opportunity for further analysis beyond the written report. To do this, as mentioned above, a data warehouse provides a "third space" for housing diverse data that normally resides elsewhere. This allows the handling of multiple individuals at the same time, grouped by some common feature such as disease type or imaging appearance, which is the opposite of a clinical system which usually is interested in varied data from one patient at a time.

A data warehouse allows secondary handling to generate cleaner, more information-rich data as seen when applying annotations and segmentation in pathological and radiological images. In order to achieve this, the data warehouse needs to provide the interface with multiple software applications. Within the warehouse, the researcher can gather varied, high volume data that can then undergo various pre-processing techniques in readiness for the application of Big data techniques including artificial intelligence and machine learning. The latter needs specialized high-powered computing to achieve rapid processing. Graphic processing units (GPUs) allow the handling of very large batches of data, and undertake repetitive operations that can accelerate processing by up to a hundred times compared to standard central processing units (CPU's). As previously stated, current data handling systems are not yet equipped with these processors requiring upgrading of hardware infrastructure to translate these new techniques into the clinical domain. The connection of these supercomputing stacks to the data can potentially be achieved via the central data warehouse containing the pre-processed data drawn from many sources.

Clinical Translation

A significant barrier to the application of new Big data techniques into clinical practice is the positioning of these techniques in the current clinical work environment. New and disruptive technologies provided by Big data analytics are likely to be just that… disruptive. Current clinical practice will need to undergo change to incorporate these new data driven techniques. There may need to be sufficient periods of testing of new techniques, especially those which in some way replace a human action and speed the clinical process. Those that aid this process by prioritizing worklists or flagging urgent findings are likely to diffuse rapidly into day to day usage. Similarly, techniques not previously possible because of the sheer size of data being handled are likely to gain early adoption. A major player in achieving this process will be industry which will enable the incorporation of hardware and software to support Big data handling in the current workflow. If access to data and its analysis is difficult and requires interruption of the normal clinical process, uptake will be slow or non-existent. A push button application on a computer screen however, as on an x-ray image viewer that seamlessly activates the program in the background is far more likely to be adopted. Greater success will be achieved with the automatic running of programs triggered by image content and specific imaging examinations. As previously mentioned, these programs could potentially provide identification of suspicious regions in complex images requiring further scrutiny or undertake quantitative measurements in the background which are then presented through visualization techniques in conjunction with the qualitative structured report. Furthermore, quantitative data can then be compared with that from large populations to define its position in the normal range and, from this and other clinical data, provide predictive data regarding drug response, progression and outcome. Part of the attraction for industry in this rapidly expanding arena will obviously be the generation of Intellectual Property (IP). Development of new techniques useful to clinical departments will require close collaboration between industry and clinical researchers to ensure developments are relevant and rigorously tested in real life scenarios.

IP protection—provided mainly via patents—is the pillar of national research policies and essential to effectively translate innovation by commercialization. In the absence of such protection, companies are unlikely to invest in the development of diagnostic tests or treatments (23). However, the operation of the IP system is being fundamentally changed by Big data based technical solutions. Due to free and open source software tools for patent analytics (24) and technical advances in patent searches such as visualization techniques it is easy

to gain access to high quality inventions and intellectual property being developed and to understand the findings. Today, unlike a traditional state-of-the-art search which provides relevant information in text format, patent landscape analysis provides graphics and charts that demonstrate patenting trends, leading patent assignees, collaboration partners, white space analysis, technology evaluations (25). By using network based and Big data analysis, important patent information including owner, inventor, attorney, patent examiner or technology can be determined instantly. Presently, patent portfolios are being unlocked and democratized due to free access to patent analysis. In the near future, automated patent landscaping may generate high-quality patent landscapes with minimal effort with the help of heuristics based on patent metadata and machine learning thereby increasing the access to conducting patent landscape analysis (26). Although such changes within the operation of the IP system gives new possibilities to researchers, it is hard to forecast the long-term effect, whether and how incentives in health research will be shifted (encouraging/discouraging innovation).

The Bigger the Better? Challenges in Translating From Big Data

Just as the volume of data that can be generated has increased exponentially, so the complexity of those data have increased. It is no longer enough to sequence all variants in a human genome, now we can relate them to transcript levels, protein levels, metabolites or functional and phenotypic traits also. Moreover, it has become clear that reconstruction of single cell data may provide significantly more insight into biological processes as compared to bulk analysis of mixed populations of cells (27). It is now possible to measure concurrent transcriptomes and genetics [so-called G&T seq (28)] or epigenetic modifications (29) on a single cell. So, as the volume of data increases, so does its complexity. Integrating varied Big data from a set of samples, or from a partially overlapping set of samples, has become a new frontier of method development. It is not the goal of this review to provide a comprehensive review of such methods [which have been comprehensively and accessibly reviewed elsewhere (8)] but instead to highlight core challenges for generating, integrating, and analysing data such that it can prove useful for precision medicine.

Forged in the Fire of Validation: The Requirement for Replication

While new technologies have greatly increased our ability to generate data, old problems persist and are arguably accentuated by hypothesis-generating methods. A fundamental scientific tenet holds that, for a result to be robust, it must be reproducible. However, it has been reported that results from a concerning proportion of even the highest ranking scientific articles may not be reproduced [∼11% only were (30)]. Granted this was a restricted set of highly novel preclinical findings and the experimental methods being used were in some cases advanced enough to require a not always accessible mastery/sophistication for proper execution. Still, the likelihood that such independent validation will even be attempted, let alone achieved, inevitably falls as the time, energy and cost of generating data increases. Big data is often expensive data but we should not allow a shift toward hypothesis-free experimentation to erode confidence in the conclusions being made. The best—arguably the only—way to improve confidence in the findings from Big data is to work to facilitate transparent validation of findings.

Where the number of measures (p) greatly outstrips the number of samples they are made on (n), the risk of "overfitting" becomes of paramount importance. Such "p >> n" problems are common in hypothesis-generating research. When an analytical model is developed, or "fitted," on a set of Big data (the "training" set), the risk is that the model will perform extremely well on that particular dataset, finding the exact features required to do so from the extensive range available. However, for that model to perform even acceptably on a new dataset (the "test" set), it cannot fit the training set *too* well (i.e., be "over-fitted," **Figure 2**). A model must be found that both reflects the data and is likely to generalize to new samples, without compromising too much the performance on the training set. This problem, called model "regularization," is common to many machine-learning

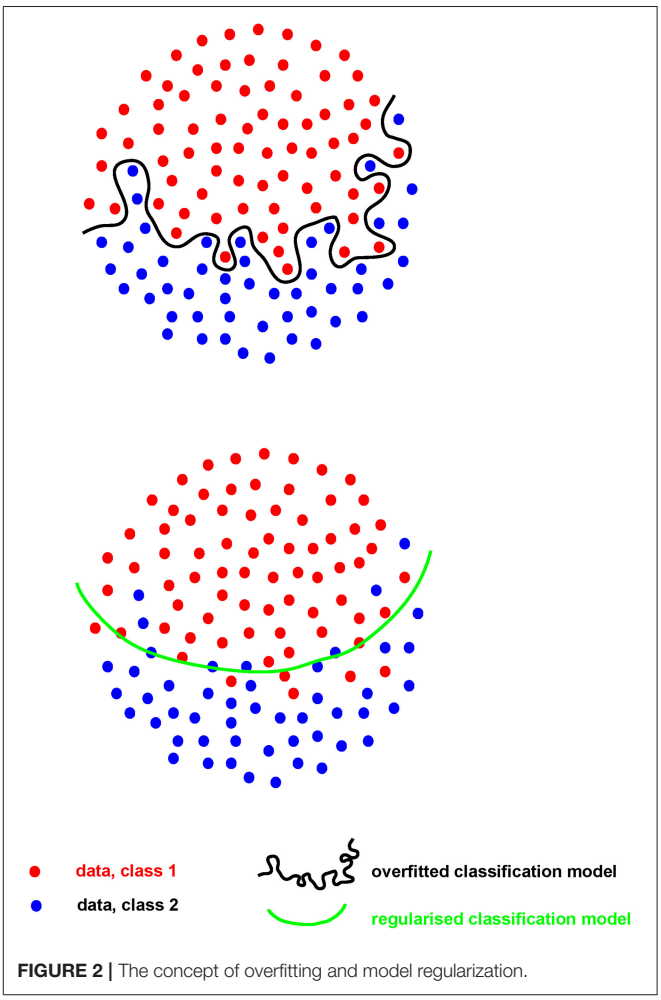

FIGURE 2 | The concept of overfitting and model regularization.

approaches (31) and is of increasing importance as data volume and complexity increases.

For example, if a large dataset (perhaps 100 k gene expression measures on 100 patients/controls by RNA sequencing) is analyzed, a clear model may be found using 20 genes whose expression allows clean separation of those with/without disease. This may appear to be a useful advance, allowing clean diagnosis if the relevant genes are measured. While the result is encouraging, it is impossible to tell at this stage whether the discriminating model will prove useful or not: its performance can only be assessed on samples that were not used to generate the model in the first place. Otherwise, it looks (and is) too good to be true. Thus, replication in a new, independent data set is absolutely required in order to obtain a robust estimate of that models performance (**Figure 3**).

While this example is overly simplistic, overfitting remains an insidious obstacle to the translation of robust, reproducible hypotheses from biomedical Big data. Overfitting occurs easily and is all the more dangerous because it tells us what we want to hear, suggesting we have an interesting result, a strong association. Risk of overfitting is also likely to increase as the complexity of data available increases, i.e., as p increases. To counter that, increasing the number of independent samples (n) becomes fundamental. As surprising at it may seem, in the early days of RNA-seq, experiments were performed with no replicates, leading to prominent genomic statisticians to remind the community that next-generation sequencing platforms are simply high-throughput measurement platforms still requiring biological replication (32). As we accumulate genomics data of several kinds across a spectrum of diseases, estimating effect sizes becomes more accurate and more accessible. In turn, realistic effect sizes enable *a priori* power calculations and/or simulations, which help reveal whether a study is sufficiently sensitive, or rather doomed by either false negatives or spurious correlations.

Yet generating sufficient samples and funds to process independent cohorts can be challenging at the level of an individual academic lab. That is why performing science at the scale of networks of labs or even larger international consortia is essential to generate reliable, robust and truly *big* (as in *big n*, not *big p*) biomedical/genomic datasets. Funding agencies have widely embraced this concept with collaborative funding models such as the U and P grant series, and large-scale initiatives such as ENCODE, TCGA, BRAIN from the NIH or Blueprint in the EU, to mention just a few. Training

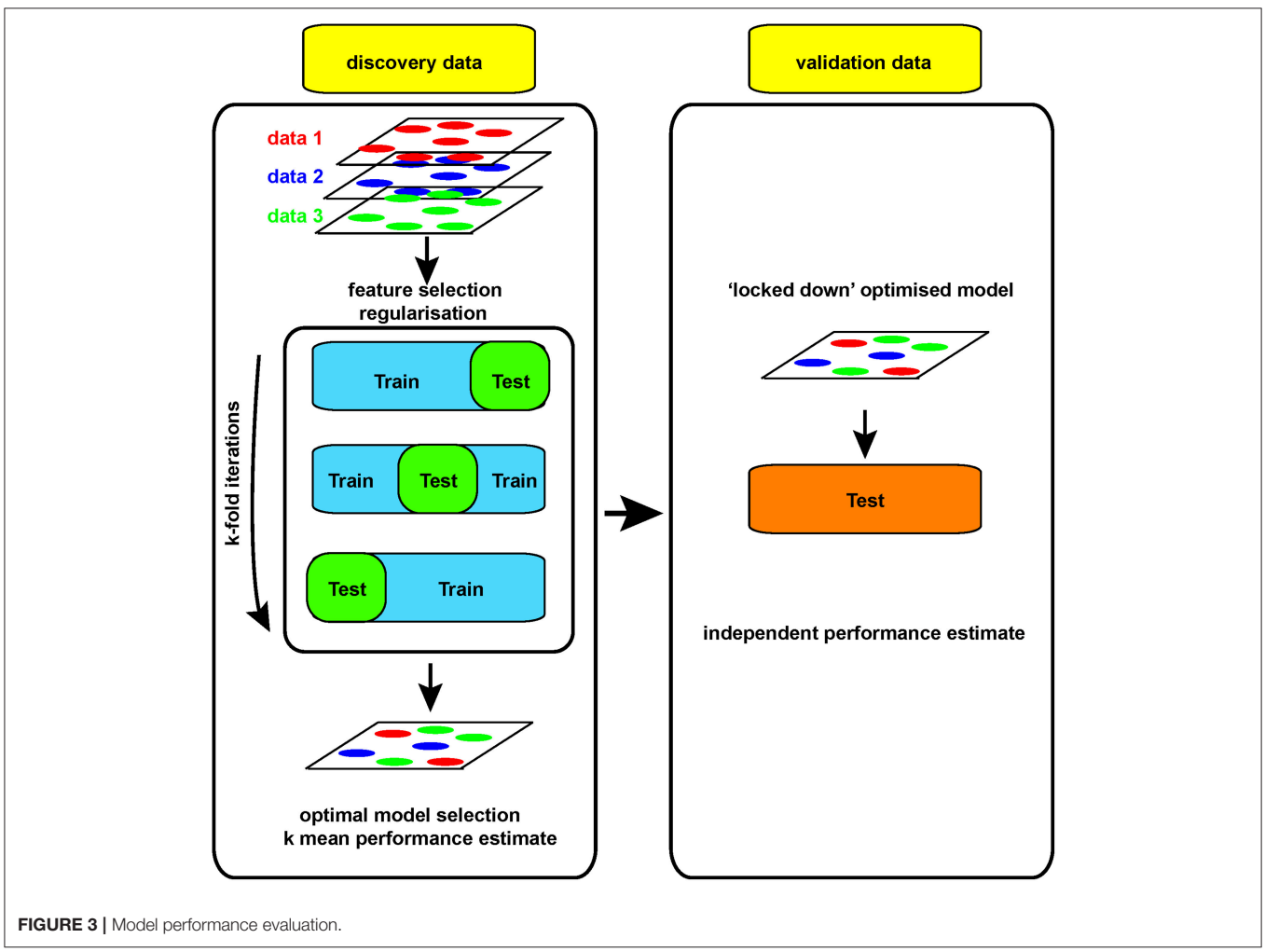

FIGURE 3 | Model performance evaluation.

datasets need to be large enough to allow discovery, with comparable test datasets available for independent validation. Leave-one-out cross-validation approaches (LOOCV, where one sample is re-iteratively withheld from the training set during model development to allow an independent estimate of performance) are useful and can be built into regularization strategies (31) (**Figure 3**). However, changes in the way the biomedical community works, with increasing collaboration and communication is also facilitating validation of models built on Big data.

Community Service: The Bigger the Better?

The development of international consortia and networks facilitating sample collection and distribution facilitate access to precious biomaterials from patients. Such biorepositories can provide access to carefully annotated samples, often including a wide range of assay materials and with detailed metadata. This can rapidly expand the pool of samples available for the generation of large datasets. Examples include the TEDDY and TrialNet consortia in diabetes (33, 34), the UK Biobank (35) and the Immune Tolerance Network (ITN), in which samples from completed clinical trials can be accessed by collaborators in conjunction with detailed clinical metadata through the TrialShare platform (36). This allows clinical trials to create value far beyond answering a focused primary or restricted secondary endpoints. This model is further extended in attempts to build similar biorepositories from pharmaceutical industry trials in which the placebo arms can be compiled into a single meta-study for new discovery work (37). A positive side-effect of large international consortia is that the complexity of coordination requires developing well-defined standard operating procedures (SOPs) for both experimental and analytical procedures. Because consortia group together so many experts in a particular field, the resulting (public) SOPs often become the standard *de facto* resource for the task at hand. For example, ChIP-seq protocols from the ENCODE initiative (http://www.encodeproject.org/data-standards), as well as its bioinformatics pipelines (http://www.encodeproject.org/pipelines), are often referred to by a constellation of published studies having no formal connection with the primary initiative.

It is not just biosamples that are increasingly being shared, but also data. In addition to the example networks above, the Cancer Genome Atlas has generated—and made publicly available—integrated molecular data on over 10,000 samples from 33 different tumor types. This huge, collaborative project not only references genetic, epigenetic, transcriptomic, histologic, proteomic, and detailed clinical data but does so in the context of an accessible data portal facilitating access and use (38). Most importantly, there is clear evidence that this approach can work, with cancer-associated mutation identification driving target identification and precision medicine trials (39).

Forming a community of researchers can do more than simply collect samples to be used in data generation. Harnessing the analytical experience of a community of researchers is the explicit goal of crowdsourcing approaches such as that used by the DREAM challenges [Dialogue for Research Engineering Assessments and Methods (40)]. This alternative model of data sharing and analysis effectively reverses the conventional flow of data between repositories and analysts. Community sourced, registered users can access data and effectively compete against each other to train optimal models. Importantly, the ultimate "winner" is determined by validation on independent "containerized" datasets, controlling the risk of overfitting during development. This innovative approach has facilitated not only broader access to key datasets but has also engaged the analytic community broadly with notable successes (41). Indeed, following centralized cloud-based processing of several challenges, consistent themes have emerged from successful models. Core principles of successful models have been their simplicity and inclusion of approaches either integrating different models or prior knowledge of the relevant field (8). In particular, this last observation has important ramifications for the integration of biomedical and analytical training (see below).

Arguably the most remarkable success in the field of Big data receives almost no attention. Despite significant potential for the creation of protectable value, software developers have almost universally made source code freely available through open-source tools that are frequently adapted and improved by the scientific community (42). Encouraged by organizations such as the Open Bioinformatics Foundation and the International Society for Computational Biology, this quiet revolution has undoubtedly had a huge impact on the rate of progress and our ability to harness the potential of Big data and continues to do so.

Setting Standards

In order for robust validation to work, it is necessary to ensure that measurements made in a training cohort are comparable to those made in a test set. This sounds straightforward, but isn't. Robust analysis can fail to validate just as easily as overfitted analysis, particularly where patients may come from different healthcare systems, samples may be collected in different ways and data may be generated using different protocols.

While there has been remarkable progress in detection of disease using a single blood sample (such as genome sequencing in affected individuals, circulating cell free tumor DNA in oncology, non-invasive prenatal testing in pregnancy, among others), it is no longer enough to provide all the information about an individual with respect to one's health. There is an increased understanding of the need for repeat sampling to gather longitudinal data, to measure changes over time with or without a significant exposure (43, 44). More importantly, the ability to interrogate single cells has spurred a need to identify and isolate the tissue of interest and select appropriate samples from within that tissue (45). Tissue samples include blood, saliva, buccal swabs, organ-specific such as in tumors, as well as stool samples for the newly emerging field of microbiome.

Over the past two decades, methods have been established to ensure standardization of extracted genomic material such as DNA from blood and other fresh tissues, including automation

(46). However, other samples such as DNA from paraffin embedded tissue, RNA, protein are more sensitive to type of tissue and tissue handling, and may not be robust enough for replication studies. For Big data science to work, one of the key ingredients is robust and reproducible input data. In this regard, there have been recent advancements in attempts to standardize the way these samples are collected for generating "omics" data (47–49). Basic experimental methodologies involved in sample collection or generation are crucial for the quality of genomics datasets, yet, in practice, they are often neglected. Twenty-First century omics-generating platforms are often perceived to be so advanced and complex, particularly to the novice, that should draw most of the planning effort, leaving details on trivial Twentieth-century steps (cell culture, cell freezing, nucleic acid isolation) comparatively overlooked. If anything, while experiments performed on poorly generated material would yield only a handful of flawed data points in the pre-genomics era, they would bias thousands of data points at once in the big data era. When thinking at the reasons underlying failed or low-quality omics experiments in daily practice, it is easy to realize that trivialities and logistics played a major role, while sequencing and proteomics platforms are seldom the culprit.

Similar considerations apply when choosing the starting biologic material for a big data experiments. Because of its accessibility, blood is still the most widely available tissue in human research and is often well suited for investigating immune-related diseases. However, peripheral blood mononuclear cells (PBMCs) are a complex mixture of immune cell types. Immune profiling using omics technologies is overwhelmingly performed on total PBMCs, as opposed to more uniform cell subsets. While cutting-edge single-cell platforms can deal with complex mixtures of cell types, the more widespread bulk platforms, such as Illumina's sequencers, can only measure averages from a cell population. Unfortunately, such averages are a function of both differential regulation of mechanisms of interest (such as gene expression) and the often-uninteresting differential prevalence of each cell type—this latter effectively qualifying as unwanted noise, from an experimentalist's standpoint. This issue is often either unappreciated or disregarded as solvable by deconvolution algorithms, that is software that attempts to recover the unmeasured signal from contributing subsets to the measured mean. However, deconvolution software often deals with just the main white blood cell subsets, leading to coarse resolution; is usually trained on healthy controls, limiting its usefulness in diseases substantially altering molecular fingerprints, such as cancer; and its accuracy is severely limited (an extreme example being CD4+ and CD8+ T cells, lymphocytes with a clear immunological distinction, but sharing so much of the epigenetics and transcriptional landscape to be very hard to deconvolve separately) (50, 51).

Lastly, standardization of samples also allows for data generated from one individual/ cohort to be used in other related studies and obviates the need to generate the same data over and over again. While this has to be within the remit of ethics and data sharing regulations for each institution/ country, it allows for better use of limited resources (such as clinical material) and funds.

Data Comparability

The past decade has seen remarkable progress in development of standard genomic data formats including FASTQ, BAM/CRAM, and VCF files (52). However, such standardization is incomplete and may lead to incompatibility between inputs and outputs of different bioinformatics tools, or, worse, inaccurate results. An example is the quality encoding format of FASTQ files, which is not captured by the file itself, and must be either inferred or transmitted as accompanying metadata with the file itself. Still, even an imperfect standardization has allowed for sharing of genomic data across institutions into either aggregated databases such as ExAC, GNOMAD (53) or as federated database such as Beacon Network (54). These databases allow for understanding of genetic variations that are common across different ethnic groups but also identifies variants that are unique within a specific ethnic group (53). However, despite these successes with upstream genomic data formats, key challenges remain regarding further downstream data formats. This often leads to non-uniform analysis, and indeed, re-analysis of the same data using different pipelines yields different results (55, 56).

Similar efforts have been developed in the field of proteomics (57) and microbiomics (49). In view of the increasing recognition of a need for such standards. The American College of Medical Genetics released guidelines to aid interpretation of genomic variants (58), the ClinGen workgroup has released a framework to establish gene-disease relationship (59) and Global Alliance for Genomics and Health (GA4GH), in collaboration with National Institute of Health (NIH), have developed genomic data toolkit which includes standards for storage and retrieval of genomic data (54).

Clinical and Phenotypic Definitions

One of the largest challenges with harmonizing Big data is definition of cases (disease) and controls (health) (60). Stating the obvious, no one is healthy for ever. Using strict definitions based on consensus statements allow comparability of diseases across different populations. There have been several initiatives to standardize phenotypic terminology including Human Phenotype Ontology (HPO), Monarch Initiative, among others (61, 62). In addition, standard diagnostic codes such as SNOMED CT, ICD-10, etc. provide for computer processable codes which standardize medical terms and diagnosis, and lead to consistent information exchange across different systems (63). As we move toward use of machine learning and artificial intelligence, the use of controlled vocabularies is critical. Even more important is the need for robust definitions of the clinical phenotypes and diagnosis that accompany these samples so as to ensure accurate comparison between cases and controls. The often heard phrase "Garbage in, Garbage out" is ever more relevant in the days of Big data science (64). Establishing clear principles on data access and sharing is a key step in establishing and maintaining community-wide access to the kind of collaborative sample sharing required to facilitate both discovery and validation.

Opportunities for Clinical Big Data: Leveraging the Electronic Health Record

The EHR is an intrinsically large resource as the majority of patients in the developed world are treated in this context. There is a staggering amount of information collected longitudinally on each individual, including laboratory test results, diagnoses, free text, and imaging. This existing wealth of information is available at virtually zero cost, collected systematically for decades. Whereas the EHR has classically been used in clinical care, billing, and auditing, it is increasingly used to generate evidence on a large scale (65). Population-based studies tend to be disease-specific, but the EHR is largely disease agnostic. Thus the EHR provides opportunities to study virtually any disease as well as pleiotropic influences of risk factors such as genetic variation. Since the EHR was not originally designed for evidence generation, leveraging these data is fraught with challenges related to the collection, standardization, and curation of data. While opportunities exist to study a spectrum of phenotypes, data contained in the EHR is generally not as rigorous or complete as that collected in a cohort-based study. Nevertheless, these EHRs provide potential solutions to problems involving Big data, including the reliability and standardization of data and the accuracy of EHR phenotyping. As discussed below, there are multiple examples of how these challenges are being met by researchers and clinicians across the globe.

Among the formidable challenges related to leveraging the resources of the EHR is assurance of data quality. Missing data abounds in these records and the study of many conditions relies on mining narrative text with natural language processing rather than more objective testing such as laboratory measures and genomic sequencing. Misclassification is often encountered within the electronic health record such as with International Classification of Diseases-10th Revision (ICD-10) codes. EHR data would also be improved by recording of lifestyle choices such as diet and exercise, family history and relationships between individuals, race and ethnicity, adherence to prescribed drugs, allergies, and data from wearable technologies. Standardization of data is also an issue. The EHR includes structured data such as Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT) terms and ICD-10 codes as well as unstructured data such as medical history, discharge summaries, and imaging reports in unformatted free text (65). Standardization across multiple countries and EHR software tools provides a vast opportunity for scalability. As the technical issues with EHR data are addressed, legal and ethical frameworks will be necessary to build and maintain public trust and ensure equitable data access.

Despite the many challenges that have yet to be addressed, the EHR provides a wide variety of opportunities for improving human health. The wealth of existing data that the EHR provides enables richer profiles for health and disease that can be studied on a population level. There is much effort in standardization of EHR phenotyping, which has the potential to create sub-categories of disease and eventually re-taxonomise diseases. (66, 67) The EHR affords an opportunity for efficient and cost effective implementation, allowing efficient return of data to patient and provider. The integration of pharmacogenomics testing into patient care is an example of the translational power of the EHR (68, 69).

EHR data is increasingly being coupled to biorepositories, creating opportunities to leverage "-omic" data in combination with EHR phenotyping. Noteworthy examples include the UK biobank and eMERGE Network (35, 70). With these new resources, new and innovative tools are being developed, such as the phenome-wide association study (PheWAS) (71, 72). Using the PheWAS approach, genomic variation form biorepository is systematically tested for association across phenotypes in the EHR. The PheWAS approach presents a useful approach to assess pleiotropy of genomic variants, allows the study of human knockouts, and is a new approach to drug discovery and drug repurposing. The coupling of EHR and -omic data also enables translation of discovery back to the clinic. Such biorepositories can mine genomic variation to confirm disease diagnoses or re-diagnose/re-classify patients in a clinical setting. In a recent study, combinations of rare genetic variants were used to identify subsets of patients with distinct genetic causes for common diseases that suffered severe outcomes such as organ transplants (73). While illustrating the power of these biorepositories, it is worth noting that these results were not returnable to patients due to restrictions around the ethical approval of the biorepository.

Artificial Intelligence and Clinical Imaging

While health improvements brought about by the application of Big data techniques are still, largely, yet to translate into clinical practice, the possible benefits of doing so can be seen in those clinical areas already with large, easily available and usable data sets. One such area is in clinical imaging where data is invariably digitized and housed in dedicated picture archiving systems. In addition, this imaging data is connected with clinical data in the form of image reports, the electronic health record and also carries its own metadata. Because of the ease of handling of this data, it has been possible to show, at least experimentally, that artificial intelligence through machine learning techniques, can exploit Big data to provide clinical benefit. The need for these high-powered computing techniques in part reflects the need to extract hidden information from images which is not readily available from the original datasets. This is in contrast to simple parametric data within the clinical record including physiological readings such as pulse rate or blood pressure, or results from blood tests. The need for similar data processing is also seen in digitized pathology image specimens.

Big data can provide annotated data sets to be used to train artificial intelligence algorithms to recognize clinically relevant conditions or features. In order for the algorithm to learn the relevant features, which are not pre-programmed, significant numbers of cases with the feature or condition under scrutiny are required. Subsequently, similar, but different large volumes of cases are used to test the algorithm against gold standard annotations. Once trained to an acceptable level these techniques have the opportunity to provide pre-screening of images to look for cases with high likelihood of disease allowing prioritization of formal reading. Screening tests such as breast mammography could undergo pre-reading by artificial intelligence/machine

learning to identify the few positive cases among the many normal studies allowing rapid identification and turnaround. Pre-screening of complex high acuity cases as seen in the trauma setting also allow a focused approach to identify and review areas of concern as a priority. Quantification of structures within an image such as tumor volume, monitoring growth or response to therapy, or cardiac ejection volume, to manage drug therapy of heart failure or following heart attack, can be incorporated into artificial intelligence/machine learning algorithms so they are undertaken automatically rather than requiring painstaking manual segmentation of structures.

As artificial intelligence/machine learning continues to improve it has the ability to recognize image features without any pre-training through the application of neural networks which can assimilate different sets of clinical data. The resultant algorithms can then be applied to similar, new clinical information to predict individual patient responses based on large prior patient cohorts. Alternatively, similar techniques can be applied to images to identify sub populations that are otherwise too complex to recognize. Furthermore, artificial intelligence/machine learning may find a role in hypothesis generation by identifying unrecognized, unique image features or combination of features that relate to disease progression or outcome. For instance, a subset of patients with memory loss that potentially progress to dementia may have features detectable prior to symptom development. This approach allows large volume population interrogation with prospective clinical follow up and identification of the most clinically relevant image fingerprints, rather than analysis of small volume retrospective data in patients who have already developed symptomatic degenerative brain disease.

Despite the vast wealth of data contained in the clinical information technology systems within hospitals, extraction of usable data from the clinical domain is not a trivial task. This is for a number of diverse reasons including: philosophy of data handling; physical data handling infrastructure; the data format; and translation of new advances into the clinical domain. These problems must be addressed prior to successful application of these new methodologies.

New Data, New Methods, New Training

It is clear that sample and phenotypic standardization provide clear opportunities to add value and robust validation through collaboration. However, increasing availability of data has been matched by a shortage of those with the skills to analyse and interpret those data. Data volume has increased faster than predicted and, although the current shortage of bioinformaticians was foreseen (74), corrective measures are still required to encourage skilled analysts to work on biomedical problems. Including prior knowledge of relevant domains demonstrably improves the performance of models built on Big data (8, 31), suggesting that, ideally, analysts should not only be trained in informatics but in biomedicine also.

Studies in the field of translational research usually collect an abundance of data types: clinical data (demographics, death/survival data, questionnaires, etc.), imaging data (MR, UltraSound, PET, CT, and derived values), biosample data (values from blood, urine, etc.), molecular data (genomics, proteomics, etc.), digital pathology data, data from wearables (blood pressure, heart rate, insulin level, etc.) and much more. To combine and integrate these data types, the scientist needs to understand both informatics (data science, data management, and data curation) and the specific disease area. As there are very many disease areas which all require their own expertise, we will focus here on the informatics side: data integration in translational research. Although this field is relatively new, there are a number of online and offline trainings available. As for the online trainings, Coursera offers a course on "Big Data Integration and Processing" (75). The i2b2 tranSMART Foundation, which is developing an open-source/open-data community around the i2b2, tranSMART and OpenBEL translational research platforms, has an extensive training program available as well (76). As for the offline trainings, ELIXIR offers a number of trainings around data management (77). The European Bioinformatics Institute (EBI) has created a 4-day course specific for multiomics data integration (78).

REWARD AND ASSESSMENT OF TRANSLATIONAL WORK

In order for the long, collaborative process of discovery toward precision medicine to succeed, it is essential that all involved receive proper recognition and reward. Increasing collaboration means increasing length of authorship which, in turn, highlights the increasing challenges inherent in conventional rewards for intellectual contribution to a publication: in plain terms, if there are over 5,000 authors (79), do only first and last really count? The problem is particularly acute for those working in bioinformatics (80). Encouraging early-career analysts to pursue a biomedical career is challenging if the best they can hope to receive is a mid-author position in a large study. The backdrop to this problem is that similar analyst shortages in other industries have resulted in more alternative options, often better compensated than those in biomedicine (80). Reversing this trend will require substantial changes to biomedical training, with greater emphasis on analysis along with a revised approach to incentives from academic institutions. Trainings such as these in the analysis of big data would enable physicians and

TABLE 2 | Key proposed principles when assessing scientists.

1. Addressing societal needs is an important goal of scholarship.
2. Assessing faculty should be based on responsible indicators that reflect fully the contribution to the scientific enterprise.
3. Publishing all research completely and transparently, regardless of the results, should be rewarded.
4. The culture of Open Research needs to be rewarded
5. It is important to fund research that can provide an evidence base to inform optimal ways to assess science and faculty.
6 Funding out-of-the-box ideas needs to be valued in promotion and tenure decisions.

researchers to not only enter the Big Data Cycle (**Figure 1**) on the hypothesis-driven side, but also on the hypothesis-generating side. There is an increasing recognition that traditional methods of assessment and reward are outdated, with an international expert panel convening in 2017 to define six guiding principles toward identifying appropriate incentives and rewards for life and clinical researchers [**Table 2** (81)]. While these principles represent a laudable goal, it remains to be seen if and how they might be realized. At some institutions, computational biologists are now promoted for contributing to team scientist as middle authors while producing original work around developing novel approaches to data analysis. Therefore, we would propose adding a seventh principle here: "Developing novel approaches to data analysis."

SUMMARY AND CONCLUSIONS

In recent years the field of biomedical research has seen an explosion in the volume, velocity and variety of information available, something that has collectively become known as "Big data." This hypothesis-generating approach to science is arguably best considered, not as a simple expansion of what has always been done, but rather a complementary means of identifying and inferring meaning from patterns in data. An increasing range of "machine learning" methods allow these patterns or trends to be directly learned from the data itself, rather than pre-specified by researchers relying on prior knowledge. Together, these advances are cause for great optimism. By definition, they are less reliant on prior knowledge and hence can facilitate advances in our understanding of biological mechanism through a reductionist "systems medicine" approach. They can also identify patterns in biomedical data that can inform development of clinical biomarkers or indicate unsuspected treatment targets, expediting a goal of precision medicine.

However, in order to fully realize the potential inherent in the Big data we can now generate, we must alter the way we work. Forming collaborative networks—sharing samples, data, and methods—is now more important than ever and increasingly requires building bridges to less traditional collaborating specialities such as engineering, computer science and to industry. Such increased interaction is unavoidable if we are to ensure that mechanistic inferences drawn from Big data are robust and reproducible. Infrastructure capacity will require constant updating, while regulation and stewardship must reassure the patients from whom it is sourced that their information is handled responsibly. Importantly, this must be achieved without introducing stringency measures that threaten the access that is necessary for progress to flourish. Finally, it is clear that the rapid growth in information is going to continue: Big data is going to keep getting Bigger and the way we teach biomedical science must adapt too. Encouragingly, there is clear evidence that each of these challenges can be and is being met in at least some areas. Making the most of Big data will be no mean feat, but the potential benefits are Bigger still.

AUTHOR CONTRIBUTIONS

All authors wrote sections of the manuscript. TH and EM put the sections together and finalized the manuscript. DH edited the manuscript.

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Developing Reflection and Collaboration in Translational Medicine Toward Patients and Unmet Medical Needs

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This perspective article aims to highlight the importance of values-driven personal reflection and collaboration for effective translational medicine training. We frame the dilemma in translational medicine and provide an approach for solution emphasizing collaboration and co-creation for innovative change in translational medicine. We cite the science in transition literature suggesting why personal reflection and a collaborative approach is important. We identify the problem with publication pressures and the bibliometric mindset. We focus on motivation to seek and find results that really matter for patients and individuals to maintain health in the real world. We review how the international *EUREKA Institute for Translational Medicine* (established in 2007) works with students, to harness their core values and develop personal growth skills to improve their leadership effectiveness, to work toward collaborative gain and potentially more meaningful results for patients and medical needs. We describe how the *EUREKA Institute's* unique setting, curriculum and hidden curriculum aspects effectively train program participants. The article highlights creating an immersive safe space, personal reflection, connection, structured brainstorming, group problem solving, collaboration and co-creation to facilitate innovation in translational medicine. The article relates program features to their theoretical underpinnings such as Theory U, Mediation Theory and Strategic Innovation Theory. The six authors from different global regions, ages, career stages, translational medicine contexts and years of attendance at the EUREKA Institute provide their reflections on training impact. Lessons learned and recommendations for research and application are discussed.

Keywords: reflection, team, growth, collaboration, co-creation, transformation

INTRODUCTION—DILEMMA

Translational medicine focuses on the continuum from scientific discovery to its clinical application (1). An increasing number of articles published in prestigious journals address controversies concerning the "crisis in science" and its impact on society, as well as difficulties researchers must overcome in their everyday practice (2–5). It has been suggested that a majority of identified problems, like reproducibility and waste, may originate with publication pressures placed on researchers to assure funding for their endeavors and their career advancement. This tension compels them to forget about real world needs, and to commit themselves to "fashionable science" in order to secure smooth publication. Many scientists in the biomedical field tend to direct their research toward the elucidation of disease mechanism and discovery of new treatment options. While cure is the ultimate goal for every patient, there are also many other needs associated with improving quality of life, that are seldom addressed among researchers of different domains and which someone not spending time with patients cannot fully understand. The dilemma is the widening gap between scientists and patients, as well as between research discoveries and their clinical application. Groups of esteemed and accomplished scientists have therefore created specific guidelines to establish a new scientific system which will have higher impact on health related issues that really matter to distinct communities (6–8). This could mean new promising treatments and/or better quality of life. In order to achieve this, it is important for scientists to strengthen their connections with those whom they plan to serve, such as patient organizations, and to seek out new and non-obvious collaborations among different professionals. It is also essential to change the way research impact and researchers are being measured in order to allocate limited research resources, maximize research benefit and minimize research waste (9–13). Finally, in parallel with large scale changes, the most important initiative and inevitable step toward shedding the narrow bibliographic mindset is personal introspection of every person regarding their role in this theater that we call science. In this article, we describe the process of one translational medicine educational program model. Complementing the recent mixed methods Weggemans et al. study (1), participant reflections in this perspectives article answer, "How has this program had an influence on you and how have you translated that to your work/ personal life?" We will present critical lessons which we have learned from this program model, that provide a means for addressing this crisis in science, including the importance of self-reflection, self-awareness and collaboration to break through siloed thinking and the need for effective engagement across disciplines and between professionals and patients.

PROGRAM MODEL

The *Eureka Institute for Translational Medicine* certificate program was established in 2007 to educate and build an international interdisciplinary translational medicine community prepared to spearhead application of discoveries that truly improve human health. Funded by university partners, medical journals, and research institutes internationally, it provides an intensive 1-week experience with both content-driven formal curriculum and informal hidden curriculum for practitioners of translational medicine internationally. Researchers such as Hafler et al have identified the hidden curriculum as informal arenas of influence such as unplanned social activities as well as "organizational culture and place that are more invisible and ethereal in their presence and impact" (14). Participants include practicing clinicians, researchers, clinical researchers, basic scientists and industry professionals. *Eureka* partner institutions have a search and selection process focused on selecting faculty members who are investigators and who would benefit from the course and likely to engage in follow up Eureka hub activities locally. Most trainees who attend the course are from the partners; a small number of trainees are selected by the *Eureka* board via an open competition.

Eureka goals are to harness student core values and personal strengths, to work toward collaborative gain and meaningful results for patients and medical needs. Weggemans et al demonstrate that over half of institute alumni report its influence on their commitment to translational medicine. They also report Eureka's influence on how they conduct translational medicine, their engagement with stakeholders and a broader international network that provides a base of support for their translational work (1). "Why translational medicine fails -and what to do about it," an intensive 1-week course of the UMC Utrecht, Netherlands University Summer school established in 2016, is also an integral component of the *Eureka Institute for Translational Medicine*, reaching international students with an emerging interest in translational medicine early in their careers. The course recruits Ph.D. and postdoc trainees from around the world. Reflections in this article are a result of the authors' experiences as students and faculty in these two related programs of the Eureka Institute. It describes how the unique features and path shared by both these international translational medicine programs present a model to address the challenges faced by the translational medicine community.

PROGRAM FEATURES—UNIQUE SETTING

The setting for the *Eureka Institute Certificate Program* is unique with the intention of providing a nurturing and vibrant learning environment for the intense, content driven curriculum and hidden curriculum. Faculty and students interact in a setting of fresco lined vaulted ceilings in a large session space and break out rooms for small group discussion held in the round. The venue is the Borgia Casa tucked away just off the main piazza in Ortigia, Syracusa, southern port and site of ancient ruins and the abode of Archimedes. Sessions are peppered with luscious meals of pasta, fresh market foods, wine, and short breaks with cappuccino or gelato. In the Utrecht, Netherlands Summer school, students meet in an open glass-surrounded classroom, a country estate with break out groups on its immense grounds, or in the modern rooms of a nutrition research science park with beer and bites and dinner along the canal.

The social environment reinforces shared experience, values and beliefs of the formal and informal hidden curriculum. Each physical setting is slightly out of the ordinary creating a unique immersive safe space for personal reflection, connection, structured brainstorming, "out-of-the-box" thinking, group problem solving, collaboration, and co-creation to push the envelope and to facilitate innovation in translational medicine. What is essential to these physical contexts, is creating a positive safe space and protected (uninterrupted) time.

PROGRAM FEATURES—PROFESSIONAL LEADERSHIP CURRICULUM

In parallel with the science content-driven program is the professional leadership curriculum component that moves from personal growth to connection and collaboration establishing an atmosphere of trust. This is an essential first step (15) toward creating collaborations not previously achieved (i.e., *Eureka Institute* certificate program or summer school students with each other, with faculty, patient physician teams, clinical research teams, lab teams, or industry clinical research teams), potentially breaking silos in the competitive translational medicine context.

PROGRAM FEATURES—INSTRUCTIONS AND OUTCOMES

The program does not provide students with specific instructions on how to achieve its goals. Instead, it gives them a unique experience which enables them to identify and understand a problem, think about possible solutions and most importantly, engage in joint activities with other students and faculty. Although outcomes of this approach are difficult to measure, they allow each participant to make the most of their experience gained. Finally, this helps to create a global network providing a context from which real, meaningful, and much-needed changes could arise.

What follows are reflections of the professional leadership curriculum incorporating personal growth and collaboration and its subsequent influence as described by faculty and students of these programs.

FACULTY REFLECTION, NETHERLANDS—PERSONAL GROWTH TOWARD INNOVATION

Having once upon a time studied medicine and later pursued a career working on change within healthcare, I have wondered and asked myself what role I can play in bringing research to practice? Invited in 2017 to become a part of the faculty of the *Eureka Institute Certificate Program*, I was tasked to find a way for people to connect more with each other, develop their leadership skills and give tools to effect change in their particular setting.

It starts with asking some fundamental questions of ourselves (16): "Who am I?", "Why do I do the work I do?", "What does translational medicine mean to me?", "What gives me both energy and frustrates me about the current landscape of translational medicine?", and "What do I want to change or have an influence on when it comes to Translational medicine." As we explore these core questions, there is a model that we utilize to understand the process that "Eurekans" go through during their immersive 1-week study experience. Theory U is a change management process that very naturally and organically can depict how we as individuals and groups go through a process of letting go of our old ways of thinking and opening us up to new perceptions (17). This process starts with learning the art of active listening through facilitated deep conversations, after which the participants are prompted to reflect on both what they said and heard, to understand and empathize with each other and to become aware of challenges that each person faces with respect to Translational Medicine. After this phase of 'co-creation," each participant will work on constructive solutions to create a positive change within their own working environment. As a result, Theory U helps in visualizing how we learn to let go of previous preconceptions and patterns, develop a manner of seeing and sensing with a fresh perspective, co-creating with the people we are teaming up with, and allowing a new way of thinking and working to emerge.

FACULTY REFLECTION, CANADA—COLLABORATIVE INTERACTION TOWARD INNOVATION

I am an educator and sociolinguist whose work is to connect members of different cultural groups so they are authentically represented in educational and arts institutions (theater companies, museums, TV and broadcast companies) and one of the few non-medical faculty members in the *Eureka Institute Certificate Program* (since 2014) and in the *Eureka Institute Summer School* (since 2016). I have been struck by the similarity in issues facing translational medical researchers with professionals in the arts world wishing to create more effective institutions that not only serve but also grow out of the priorities, interests and values of those whom they serve. Fear and turf protection hamper progress in both the arts and science. Soul searching, building foundations of trust, increased positive relationships, finding shared values, and creative exploration of solutions reliably enhance breakthroughs in problem solving in both the arts and medical science for true institutional transformation.

Theoretical underpinnings of *Eureka Institute* reflection and collaboration include strategic design for innovative change (18) and mediation theory (19). Students create their own personal *Incomplete Manifesto* based on reflections of their core values (18). They discover their communication interaction strengths in different situations based on communication styles questionnaires used by mediators, similar to the *Myers Briggs Type Indicator* (20). Students gain insights on how they approach conflict from the *Thomas Kilmann Conflict Mode Instrument*, strategies for dealing with cross-cultural interactions, conflict, themes that emerge in translational medicine and how to effectively problem solve using constructive negotiation in the arena of shared interests. This allows for breaking through

pre-determined positions to generate new shared solutions and to co-create cultural shift for transformations both personally and institutionally.

STUDENT REFLECTION, CROATIA—FOCUS ON WELL-BEING

I went to Eureka to better understand and respond to growing skepticism about science in my surroundings, but also in me. During and after my medical education I realized that science, an elaborate system crafted for providing answers which could make a difference, became an aim in itself. Amid these contemporary circumstances, many use scientific research just for their advantage, neglecting its primordial purpose—to enhance well-being for all. Scientific endeavors are often determined by personal interest, and not based on the potential applicability of the results. However, Eureka offered some solutions for these seemingly insurmountable predicaments that are challenging scientists across the globe. This intensive 1-week course has illuminated the wrongdoings that have driven science to this point, and more importantly, has instructed the participants on how to leverage the lost order in which science can make our lives better. Hearing the anecdotes of patients and their families have raised the issue that their needs might often be much more elementary than scientists imagine. Throughout the course, the importance of maintaining a healthy life and work balance was emphasized as one of the most prominent difficulties scientists face on a personal level. Introspective exercises done throughout the course have highlighted the practical value of reconciling inner harmony with everyday strivings. Finally, the time spent together during the formal program of the course, as well as throughout informal gatherings, created strong bonds among participants which are nourished long after the course has ended. After finishing the program, I feel more competent to exploit my merits as a physician-scientist, to commence a meaningful transformation in my vicinity and to contribute to the efforts of a thriving community of responsible researchers that are part of the Eureka Institute global network.

STUDENT REFLECTION, AUSTRALIA—A JOURNEY BEYOND SCIENTIFIC CONTENT

I went to Eureka, as a research strategy expert, curious to understand more about translational medicine and how I could support my organization and its researchers in this vital endeavor.

There was a diverse group of students from all over the world from different disciplines and career stages. We all shared a hunger for driving discoveries into new medicines or diagnostics. There was a similar number of Faculty—all leaders in their field from some of the top institutions involved in translational medicine world-wide. *Eureka* was a "microcosm" of the highly diverse network required to drive translational medicine.

Eureka is about the translational medicine journey. The Greek mythology tale of Sisyphus, condemned to an eternity of rolling a boulder uphill then watching it roll back down again, was unfolded during the week to highlight how translational medicine can be an uphill battle. Successfully translating a research finding into a diagnostic or therapeutic tool is getting the right help at the right time from the right people who share your goal of "getting the boulder to the top of the hill."

Eureka taught me that translational medicine is not just about scientific content. It is also about character, connections and self-awareness. Many of the elements of the Eureka continue to influence me, 8 years after my participation. Team building a tent blind-folded under the direction of one team member without a blind-fold showed how a diverse group of people can come together to problem solve and achieve a goal in challenging circumstances. The group exercises, working with peers and two members of Faculty, to develop various elements of the translational medicine process such as building a narrative for funding, were extremely valuable. The journaling aspect of the program was powerful and a practice I continue to this day, as was brainstorming with peers and connecting with an ecology of translational medicine students and Faculty (of diverse backgrounds and disciplines).

STUDENT REFLECTION, CANADA—NEW APPROACHES

Eureka has both an explicit curriculum focused on bridging basic science discovery with improved public health, and a hidden curriculum. After my week at *Eureka*, I found myself returning to those informal lessons from faculty and fellow participants, on the link between self-awareness and research success. In our mentoring small groups, we were encouraged to share our personal challenges in establishing our research programs. These were provocative sessions that pushed each of us to reflect and reveal our vulnerabilities, which created opportunities for solutions. It was clear that those challenges were shared across institutions and continents, as were the guiding principles for success.

As an early career MD, Ph.D., in a large, Canadian tertiary care center, I must balance my roles as researcher, clinician, teacher, wife, mother and daughter. Often compartmentalizing time has the unintended effect of placing my personal life at odds with my professional work. Through the *Eureka* sessions and discussions on the impact of individual experience on leadership effectiveness, the shared principles and strategies for successfully managing personal and professional demands became obvious. Reframing my approach, and emphasizing the whole-self, lead to my most vital link between personal growth and professional leadership effectiveness.

When I returned home, I sought ways to foster the optimistic "*Eurekan* spirit" and began making changes in my lab. I engaged each research team member differently, with greater consideration for their individual attributes and goals, hence finding new working connections. I experimented with new teaching techniques in my university classes, and I worked with *Eureka* alumni at my institution to promote the program to a wider audience of those with the drive to pursue further translational medicine training.

Personally, we are encouraging our children to be productive, contributing members of society. Similarly for myself, I am striving to be an agent of positive change, in fostering a scientific community that values collaboration and connection as a means for united success.

STUDENT REFLECTION, EGYPT—FOCUS

Perhaps my encounter with *Eureka* is quite different. I am a rheumatologist at Cairo University with a research career far from the lab. Driven by my deep passion for immunology and its intersection with translational medicine, I attended *Eureka* in 2017. Gladly, my learning expectations were replaced by extraordinary concepts embraced by *Eureka*, such as "structured brainstorming" and "hidden curricula."

Although many of these concepts struck me as pivotal, they are seldom implemented professionally and personally. This is simply because it's not that easy, never was and never will be. Moreover, absorbing these strategies during the intense and bedazzling 1-week experience is one thing, and incorporating them into one's mindset amidst the chaos of our lives and careers is quite another.

Overcoming this challenge is definitely strenuous and elusive yet is a priority to me. It could be achieved through disseminating and applying these paradigm-shifting concepts to our research, careers, fellows, and lives back home; which again brings me to my peculiarity among other *Eurekan* colleagues.

Egypt, a new member of the *Eureka* network, is a country where research is rapidly evolving; with a tighter clinging to dogmatic molds of academia, such as shooting impact factors and numerous publications. Sisyphean and important as these success definitions and aspirations are, they are not the most important. Hence, my role to convey the ultimate principal nurtured by Eureka, which is to focus on constructive and visionary research serving patients' quality of life.

SUMMARY

A summary of the key personal and program elements impacting the authors' personal evolution to create change in their respective work environments, translational medicine approach and results, can be seen in the key words below. Key words were based on the process we described in this article, namely the journey of participating in *Eureka Institute* programs. Words selected were agreed by author consensus to be most representative of the authors' collective EUREKA Institute experience. They are organized thematically and chronologically to show the development as the program progresses.

Dilemma—Skepticism in Science, Crisis in Science, Challenges, Dogma-Mindset
Program Setting—Safe Space and Protected Time
Journey—Formal Curriculum and Hidden Curriculum—Personal Growth and Team Growth
Personal Reflection—Self-Awareness, Whole-Self, Personal Sharing, Let Go of Old Constructs, Purpose of Science Fundamental, Communication Interaction Styles

FIGURE 1 | EUREKA Institute - Expansive Experience.

Group Process—Strategic Design for Innovative Change, Strategy
Structured Brainstorming, Communicating, Connecting
Conflict Management, Cross-Cultural Interaction
Shared Goals, Shared Values, Help
Collaboration, Co-Create
Outcome—New Ideas Emerge, New "Ways of Doing" Emerge, Reconnection, Transformation

In keeping with *Eureka's* creative approach to problem solving as a way to think outside of the box and expand our perspectives, **Figure 1**, provides a visual metaphor for personal and team growth rather than a standard logic model of the Eureka Institute Program experience and its impact. The key elements summary is intended to be a descriptive tool while **Figure 1** is intended to be inspirational for others wishing to develop similar programs that meet their needs or to attend or create a *Eureka Institute Hub*.

Effective *Eureka* experiences have a synergy between the formal curriculum and the hidden informal curriculum which run in parallel. There is also a synergy between the scientific content components of the Eureka Institute

program/s with the personal and team growth approach in the program. The elements integrate like leaves swaying together on branches of a tree. The synergies allow for something expansive to happen leading to a reflection that broadens the picture.

Taken together, the tree and its reflection become a different and more beautiful picture, than that of the tree or its reflection alone.

It's the synergy that makes a learning experience that is both meaningful and impactful on both an individual and collective level. This taken together, creates expansive opportunities for true change in translation medicine, research approaches and outcomes. *Eureka* participants can bring these new reflections and the wholeness of the experience to their lives and work at home.

LESSONS LEARNED AND RECOMMENDATIONS FOR FUTURE RESEARCH AND APPLICATION

Lessons Learned

1. The Eureka Institute program creates an environment that demonstrates the importance of self-reflection and collaboration, via exercises anchored in a scientific curriculum.
2. Self-reflection and self-awareness are essential components for effective leadership in translational medicine and research. Knowledge of one's own goals, motivations, biases and limitations, and those of team members and collaborators, positively impacts relationships. This leads to improved communication and productivity.
3. Engaging all stakeholders (i.e., clinicians, researchers, patients, families, industry, and government) at all stages of research, from inception to care delivery, is essential for ensuring the work is relevant and impactful to the emerging medical challenges, that are reflections of patients' needs.

Recommendations Moving Forward: Call to Action

We recommend identifying and acknowledging your personal motivations for your actions in pursuing translational medicine continually along your journey OR ask yourself, "How can I identify and acknowledge my personal motivations for my actions as I pursue translational medicine?"

Find a context in which you can acknowledge and act upon the personal motivations in yourself as well as in others, in order to strengthen collaborations across disciplines and with patients and connections with the work and process.

Create regular reminders of your core values and discover others' core values to help maintain your priorities, focus and sense of meaningful achievement leading to potentially greater research significance and success in terms of meaningful, impactful health care.

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OPINION
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When Parallel Roads Meet: Orchestrating Collaborations Between Regulatory, Ethical, and Business Partners in Translational Medicine

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The exponential growth in technological abilities and biological understanding of diseases result in the advancement of novel interventions and therapeutics which may dramatically impact patients. Despite this significant progress in biomedical science and technology, the efficiency of clinical product development (i.e., drugs, medical devices, and medical procedures) is not improving and may actually be decreasing. Innovations arising from medical research are nowadays facing important hurdles that prevent their timely implementation into patient management, treatment and health policies (1).

Although promotion of standards, recording and reporting information is a key stepping stone to an effective and safe healthcare system, the high volume of bureaucracy hinders an early introduction into the market (1–3). At the same time, the costs of drug development continue to rise.

We require a team of stakeholders to translate the overwhelming rate of inventions into clinical care (**Figure 1**). The five components of such a team are (1) The innovators, most commonly the Academia, (2) Industry, key to fund and facilitate the innovation, (3) The research ethics board, mostly located in clinical institutions and responsible for the safety of patients and society and (4) The national/regional regulatory agencies which take into account ethical, feasibility and financial aspects important for the ultimate implementation. The last (5) and perhaps the most important stakeholder are the patients and their representatives.

This paper is a part of a Frontiers research topic entitled "The Silent Cry: How to Turn Translational Medicine Toward Patients and Unmet Medical Needs" which is a larger series collecting other position papers addressing issues related to early discovery, patenting, animal work, preclinical and other aspects of clinical trials. Coming from the observation that translational process is highly inefficient in the current healthcare state, this series was created to raise awareness on the different hurdles of the process. The list of all topics developed in the *silent cry* series can be found on the Frontiers webpage: (4). Nonetheless, the focus point of this article is the relationships between the academic, the business, the ethical and the regulatory partners.

Together, the tension between potential benefits from innovation and the fallout upon mistakes in safety, legal repercussions or financial loss results in a rough path of progress and frustrations for all sides in this endeavor. For each of the partners there are specific benefits but most importantly risks to be aware of. The unique risks for each partner result in delays and are considered

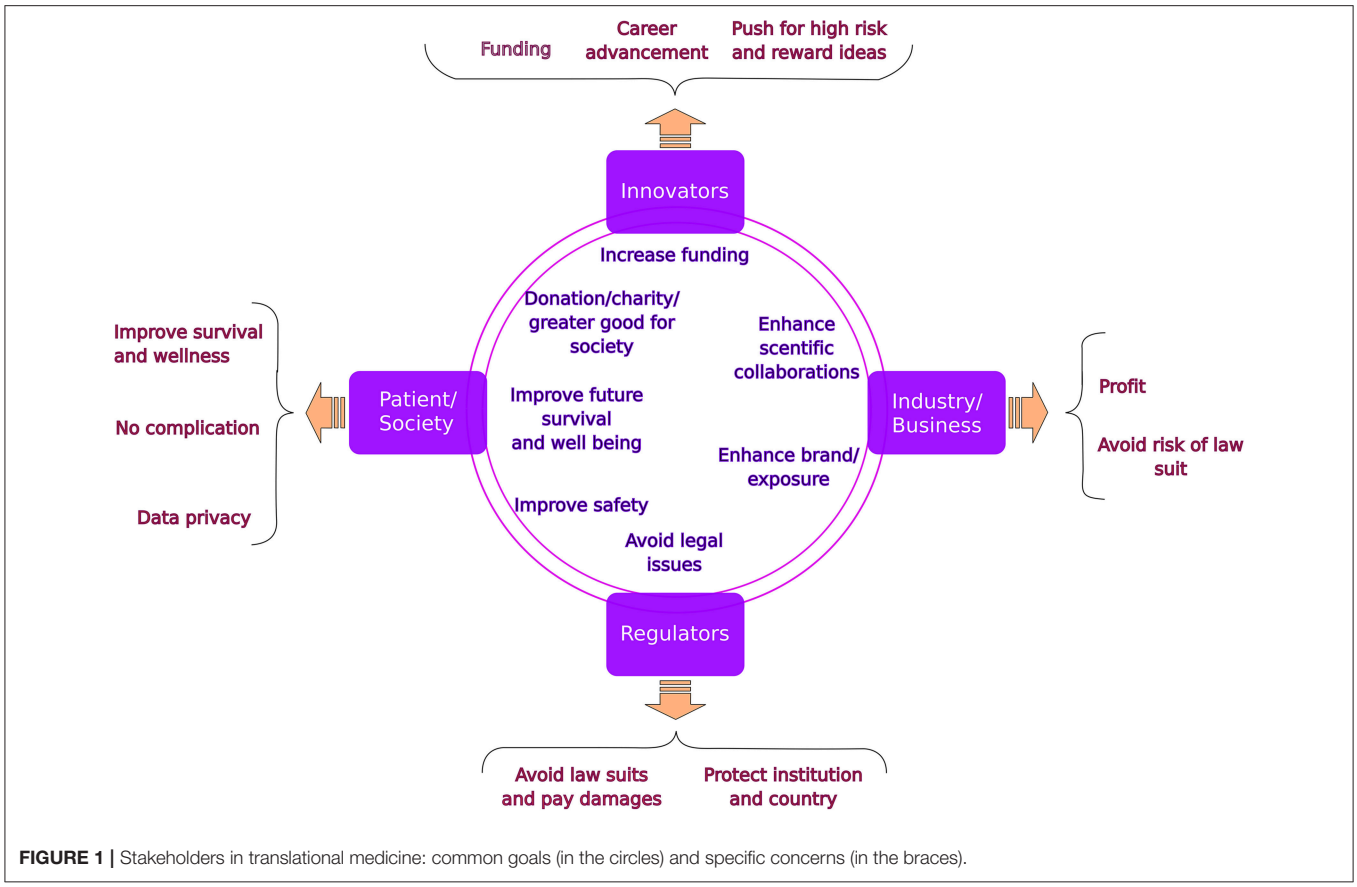

FIGURE 1 | Stakeholders in translational medicine: common goals (in the circles) and specific concerns (in the braces).

bureaucratic hurdles in the translational medicine path. Only by understanding the risks and benefits for each partner, a project can be successful in a timely manner (5, 6).

In the present paper we lay out the individual concerns of each partner as well as the common beneficial components (**Figure 1**), which will potentially help improving the interactions and easing the path to translate innovations into clinical practice. Other major hurdles which exist in this path from early discovery to clinical trial and ultimately implementation are discussed in related articles to the *silent cry* series.

The initial stakeholders are the researchers who cherish the invention as their own "child" and strive to get the discovery published in a high impact journal while applying for funding. In their view, the potential benefit to patients makes it "unethical" not to proceed with patient interaction early on. It is common that they overlook important steps such as patent, appropriate financing, necessary technical and regulatory steps and ultimately the distribution of the innovation to the public. This can affect the maturation of their "child".

Each business partner, on the other hand, needs to observe the invention through the lens of financial gain. Protection of any invention by intellectual property is necessary but by itself not sufficient for industry to invest in the product. Unidentified risks and lack of clear benefits can discourage the Industry partner from joining this endeavor. Industry usually wants to see a clear horizon of patient-numbers, benefits, safety and economic value (e.g., will a drug warrant reimbursement by payers and will it be beneficial enough to sell on the market). Therefore, innovations in small populations such as most childhood diseases are a major hurdle. Potentially small volumes of cases, possible legal ramifications and reputational damage of adverse events in children, competition with larger (adult) indication groups result in tensions between the innovator and the business partner.

Although the mandate of the Instutional Review Board (IRB) is to advance research in a safe and ethical way toward patient and society, the institutional protection and avoidance of potential individual law suits commonly interfere with this initial mission. The more innovative and invasive the discovery, the higher is the risk for the IRB. This tension creates automatically a higher need for safety measures resulting in the much discussed bureaucratic hurdles observed by the innovators. Furthermore, if potential financial profit is involved, further tension raises between the IRB and the industry partner.

Last but not least are the regulatory agencies responsible for protecting the population from adverse events while also considering both clinical and financial implications. Importantly, the extensive testing for new therapeutics or medical devices often represents large and risky financial commitments from manufacturers (7). Only well established companies are able to absorb these level of costs, which prevents new players from entering the market competition. The risks without yet clear long term benefit to the patients and society result in risk

aversion even more so when approvals require additional steps, time and costs in high-risk products. The tension between the innovator/industry and the regulatory agencies is also increased when the decision process is not transparent and/or the individuals responsible for these decisions cannot be contacted.

In order to improve the integration between the abovementioned four partners in this part of translational medicine, it is important for all stakeholders to first appreciate each partner's roles and priorities, and to guarantee their independency and role in the process. To achieve efficient project progression it is essential to increase risk tolerance and emphasize the potential short and long term benefits to each partner. Specific tools to achieve these goals include a "concierge service" which means early on involvement of industry partnership and research collaboration experts. These experts, speaking the same industry jargon, will know how and when to approach the right business partners. They can also be involved in the regulatory issues further in the process. One should not hold back on approaching high up individuals in the involved companies to ensure sustained partnership.

Many countries are moving into regional and nationwide IRB agencies which will reduce diversity and increase transparency in decision making and shorten times for large projects. Involvement of innovators in the IRB committees and continuous learning and discussions with IRB chairs will also facilitate trust and reduce risk aversion. When approaching the regulatory agencies, seeking experts and meeting the individuals responsible for specific applications will result in better and faster outcomes. The use of external experts and advocates might also support this goal.

Finally, patient advocates (8, 9) are extremely important from early on as they also play key role in the discussions with IRB and regulatory agencies. They can guide the innovator and industry in the priorities of the end users of the product. Specific care should be spent on the role of smart (dynamic) consents covering the current issues as well as the future potential use of patient data and tissues. One should explore the potential collaborations with industry and non-academic stakeholders.

When balancing technological innovations, new medical concepts and deeper understanding of human biology translational projects can transform disease management and thereby improve patient outcome. Ethics, health and economics are all at stake and therefore a careful approach including participation of all stakeholders is required. Understanding the risk and benefits for each partner in this journey and keeping active representation of each of the partners in every decision making step will reduce the tension and is the most fruitful way forward.

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PERSPECTIVE
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Improving the Translational Medicine Process: Moving Patients From "End-Users" to "Engaged Collaborators"

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Translational medicine works through the definition of unmet medical needs, their understanding and final resolution. In this complex and multi-disciplinary process patients have always been regarded as "end-users" or no more than "data provider." Considering that the translational practice is nowadays highly inefficient (i.e., large intellectual and economical resources are wasted with limited impact on people health) here we propose to reverse the process: start from patients, engage them, and keep them at the center. A new partnership needs to be formed between the patients and the health care professionals, as well as the treating physicians, to make the most out of the current "health resources." New patient-centric approaches are emerging but they remain isolated phenomena often difficult to implement. Here—with this perspective—we aim at thinking differently and learning from new experiences. We will provide some successful examples of change, and we will discuss new approaches to create a radical change in the way translational medicine is managed and how this would significantly impact people health and health care systems.

Keywords: translational medicine, patient-centric approaches, shared decision medicine, the innovation journey, patient advocacy

INTRODUCTION

The European Society for Translational Medicine has defined translational medicine as an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside, and community. The goal of translational medicine is to combine disciplines, resources, expertise, and techniques within these pillars to translate efficiently and effectively scientific research findings relevant to human diseases into knowledge that is beneficial for patients via new drugs, devices, or treatment options (1). Accordingly, translational medicine is a highly interdisciplinary field and includes academia, industry, and regulatory institutions. However, patients (who are the direct beneficiaries of translational medicine) are often excluded by this complex process.

In this perspective paper, we will discuss the impasse of translational medicine, the role that patients should have in this process (with concrete examples of success) and the future directions with the aim at fostering a science that really impacts on patients' life.

THE IMPASSE OF TRANSLATIONAL MEDICINE

Translational medicine is a process fundamental for the society as it aims at developing new interventions beneficial to the patients. However, translational medicine is at a historic moment of crisis. The process is becoming unsustainable in spite of enormous technological advances, since the technological explosion has not been accompanied by a reinforcement of quality in experimental designs, especially in the discovery phases. However, there is no clear path neither for clinicians nor for scientists regarding the process of how a discovery leads to an approved drug. The high level of failure of clinical trials in Phase II/III swallows up economic resources, generates exhaustion among researchers and clinicians and, most importantly, induces frustration among patients who see their hopes for a new drug to treat their disease, disappear (2). The high failure of clinical trials can be due to the inadequate study design, incorporating endpoints that provide limited or misleading information regarding the efficacy of the test agent, to the limited reproducibility of data, or also due to the high variability between tested subjects regarding their genetic background or the heterogeneity of their disease and also their comorbidities (3). Although it is now clear that even the failure of well-designed studies benefits both researchers and healthcare systems by, for example, generating evidence about disease theories and demonstrating the limits of proven drugs (4).

The Food and Drug Administration (FDA) publishes every year a list of all the drugs released on the market [1]. Backtracking the initial publication on the mechanism or molecule leading to drug development shows—for the drugs released between January and September 2018—a median interval of 10 years (range: 5–37 years) before the drug is reaching the patient. This is becoming unsustainable as it creates tremendous social distress. At a time of global financial crisis, citizens perceive that vital resources are not being used efficiently and scientists fear to enter in a career path that is uncertain and not properly rewarded.

Thus, there is a great need to reconsider the translational medicine process and we do believe that moving the patients from "end-users" to "engaged collaborators" would transform them into agents of change. The standard business model is indeed to speak to the consumer. Apple for instance understands its consumer: it must first identify the customer, talk about the product and ask if the intended consumer would value the product. Is it any wonder why Apple is the first billion-dollar company? They know their consumer! In translational medicine, this concept is ignored. Patients are the ultimate users of health technologies and they can advocate and promote models for patient involvement among other stakeholders. Nothing will facilitate the dialogue among scientists, clinicians, and society more effectively than the creation of a pathway, constructed together, and bound by a common objective. This should lead to improved translational medicine efficiency and reduced waste of resources and energies.

CURRENT ADVANCES

The doctor-patient relationship in western countries has significantly evolved over the years. Prior to the last two decades the relationship followed a paternalistic model, where the patient sought help and the doctors used their skills to choose the necessary interventions or treatments to restore or improve patients' health. Decisions of the doctors were silently complied by the patient (5). The social system has been challenged over the last 20 years: society has changed (being now multicultural), access to information is broader (social), media allow easier contact between patients and thus facilitated creation of patient's organization. Therefore, critics have emerged, demanding a more active, autonomous and thus centered role for the patient who advocates greater control, reduced physician dominance, and more mutual participation.

This has led to the idea of the Shared Decision Medicine (SDM), which is a process promoted by the Institute of Medicine (IOM) as part of the strategy to improve the quality of health care in the United States. The IOM recommended that healthcare should be customized based on the patient's needs and values, the patient should be given adequate knowledge and control to make decisions that affect his/her health, patients and healthcare providers should communicate and share information, and patients should receive information that allows them to make informed decisions. To this end, SDM is the joint involvement of patients and healthcare providers in making healthcare decisions that are informed by the best available evidence in regards to possible options, potential benefits and harms, and that consider patient preferences and values. SDM ensures patients get no more and no less of the care they need and want (6, 7). However, despite attention to principles and competences, there remains a lack of clear guidance about how to accomplish SDM in routine practice. Studies have not yet addressed the question about the impact on professionals. There might be the need to coach patients to be able to assess the value, risks, benefits, and burden of interventions. For organizations, a consistent shared decision-making might change patient experience evaluations and lead to a "satisfied patient" and fewer complaints or even legal issues. Clear outcome measurements of shared decision-making are needed as they would provide a more substantive evidence base to guide implementation (6).

Another, more recent, approach to bring the patients closer to the science that could impact their life is the "plan S." Research funders from France, the United Kingdom, the Netherlands, and eight other European nations have unveiled a radical open-access initiative; they will mandate that, from 2020, the scientists they fund must make resulting papers free to read immediately on publication. The scientific papers would have a liberal publishing license that would allow anyone to download, read it or otherwise reuse the work leading to a science no more locked behind paywalls and freely available for everybody (8).

[1] https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100246/lutathera-lutetium-lu-177-dotatate

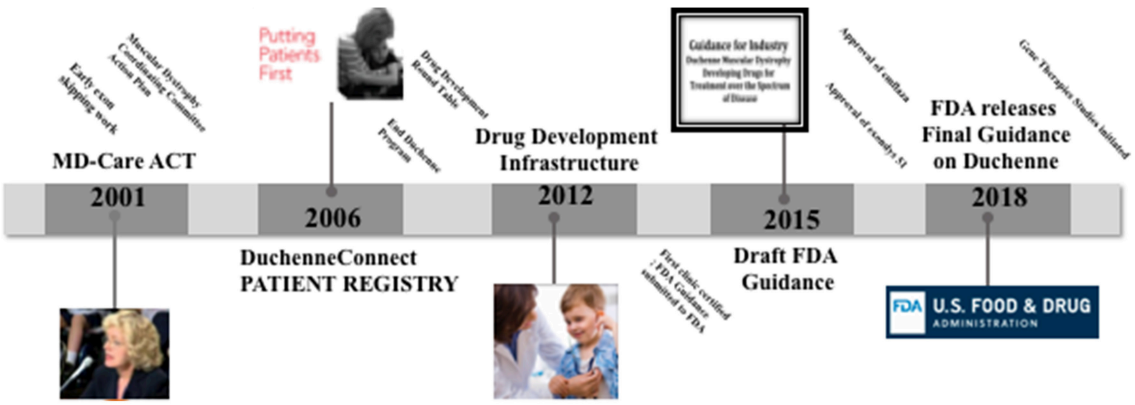

FIGURE 1 | Time line of the parent project muscular dystrophy (PPMD) contributions to Duchenne care and treatment.

Increasingly, funding opportunities for translational biomedical research require studies to engage community partners, patients, or other stakeholders in the research process to address their concerns. However, there is little evidence on strategies to prepare teams of academic and community partners to collaborate on grants. A well-planned and feasible educational program designed to help community organizations and academic institutions to build infrastructure for collaborative research projects using a partnered approach is needed and some institutions are already investing in this important activities (9, 10).

Industry is today also very open to view patients as close collaborators and aims at connecting with them throughout the innovation journey, starting with validation of new concepts to the design of patient-centric trials. The customer journey is a term from marketing, describing the 5 cycles, which a client passes through before he decides to buy a product, or in medical terms, before he decides for one or the other therapy. Five phases mark this journey: awareness, favorability, consideration, intent to purchase (or in medical terms, intent to treat), conversion (decision to treat). For most pharma companies, this represents a major shift in thinking. It requires putting not the product but the customer at the center of the launch, and addressing customers' emotional and behavioral needs as well as their clinical ones.

There are also tangible examples of success on how to move the patients at the center of the translational medicine process. Here we report two specific cases.

The Remarkable Story of a Mother and the Parent Project Muscolar Dystrophy

When doctors diagnosed her two sons, Christopher and Patrick, with Duchenne muscular dystrophy (DMD) in 1984, Pat Furlong didn't accept the therapeutic nihilism, the fatalistic message from their doctor "there is no hope and little help." DMD is the most common, lethal genetic disease diagnosed in childhood; it is an aggressive and ultimately fatal muscle wasting disease that primarily affects boys and it results in a progressive loss of muscle strength. Individuals with DMD lose ambulation in the early teens, require ventilation in the mid-teens and die before reaching the 3rd decade. Families who receive the diagnosis are in a race against time. They await new knowledge and scientific breakthroughs, possibilities to slow the degeneration. As of today, steroids are used to slow the decline, but there are no cures for DMD. In 1994, together with other parents, Pat Furlong founded Parent Project Muscular Dystrophy (PPMD) to change the course of the disease and ultimately end DMD. PPMD is today the largest most comprehensive non-profit organization in the United States focused on finding a cure for DMD [2]. In her quest for a cure, she first realized that there simply wasn't enough research into the disease and too many questions being left unanswered. Her first efforts focused on small investments in academic research and leveraging those investments. Due to the rarity of the disease (1 in 4600−5600 boys) and hence lack of potential profits there had been little interest at the onset from major pharmaceutical companies. Early in the fight, PPMD realized that the greatest source of advancement in basic science surrounding DMD would be through an investment by the National Institutes of Health (NIH) and related agencies. In 2000, the Duchenne community, through PPMD, employed a firm to lobby on their behalf in Washington DC and scored major legislative success with the introduction of legislation, intended to require government agencies such as NIH to significantly increase its investment in and coordination of research into the muscular dystrophy's. That same year, at the insistence of PPMD, NIH held a scientific workshop on Duchenne, bringing in scientists from all over the world to advance the cause. This was a workshop of major significance in which attending scientists' and researchers came to the realization that with the knowledge of the genetic basis of the disease and through multidisciplinary collaboration, something could be done to improve the quality of life and extend the lifespan of boys with DMD. On the tails of the earlier success with NIH, PPMD continued its Washington DC advocacy agenda and achieved another stirring victory. In December 2001, the Muscular Dystrophy CARE ACT was signed into law. This legislation dramatically increased NIHs investment in Muscular dystrophy research (from ∼$17

[2]https://www.parentprojectmd.org/

millions to over $750 millions), including the funding of six Centers of Excellence. All of that, in addition to the earlier orphan drug act of 1983 incentivizing companies to invest in rare disease research, resulted in significant breakthroughs and new knowledge to fully characterize the pathology of DMD and to encourage industry interest in targeting relevant pathways. Today there are more than 40 ongoing clinical trials, whereas in 1999 there was 1 trial. Additionally, today there are more than 45 pharmaceutical companies investing in DMD. Current market estimates an 8-Billion-dollar investment in drug development. PPMD is currently working with FDA to develop a Master Protocol to enable access to trials across the Duchenne community, potentially leading to combination therapies and reach the highest priority of families (**Figure 1**).

Patient advocacy has come of age. Foundations focused on a specific disease provide substantial investments in research, organize the patient community, collect data to better understand disease progression, support the development of biobanks, inform regulatory interactions and assist patients navigate the healthcare environment. Advocacy efforts lead the ecosystem of research, therapy development, access and reimbursement. Her sons lost their battle with DMD in their teenage years, but Pat Furlong continues to fight—in their honor and for all the community to this day.

The Development of a Patient Council Within a Clinical Department

Another, yet different, example of success comes from the Department of Pediatric Rheumatology at the Wilhelmina Children's University Hospital in Utrecht (The Netherland) focused on the study and cure of Juvenile idiopathic arthritis (JIA). JIA is the most common chronic rheumatic disorder in children and is a major cause of short-term and long-term disability. JIA is defined as having an inflamed joint before the age of 16 without a clear cause that persists for more than 6 weeks; it is a chronic disorder, which if neglected, can lead to serious complications.

In developing a network for biological research for patients with Childhood Arthritis doctors and scientists at the Wilhelmina Center of Excellence strongly think that input from and collaboration with patients and patient organizations is crucial. Patients, their parents, doctors and researchers all share the same common goal, namely that progress in basic science is translated in real tangible products for patients with childhood arthritis. In 2013 a patient council was formed in this Department. Together with professionals the JIA patient council explore research priority setting by reviewing the research topics, safety and efficacy of immunizations, as well as stopping medications. In addition to this, a jointly written application was obtained for a project with focus groups for patients that was also led by a parent. The patient council selected a topic which was the most frequent concern expressed by patients: the uncertainty patients feel due to the impact of the unpredictable course of their disease (pain, relapses) in their activities of daily life (activities at school for younger children and later work, sports and social contacts). Focus groups further analyzed the effects of the unpredictable course of the disease. Information was written for websites and two youtube movies were made. The group made of Dutch organizations of patients, parents and clinicians will collaboratively develop a research agenda for JIA, following the James Lind Alliance (JLA) methodology [3]. The JLA is a non-profit making initiative established in 2004 and it brings patients, caregivers and clinicians together in Priority Setting Partnerships (PSPs) to identify and prioritize the top 10 uncertainties, or unanswered questions, about the effects of treatments. The aim of this is to make sure that health research funders are aware of the issues that matter most to patients and clinicians. In this process the input from clinicians, patients and their caregivers will be equally valued. Additionally, focus groups will be organized to involve young people with JIA. The involvement of all contributors will be monitored and evaluated. In this manner, the project will contribute to the growing body of literature on how to involve young people in agenda setting in a meaningful way.

This approach, despite still at its infancy, will inform researchers and research funders about the most important research questions for JIA and this will hopefully lead research agenda for research that really matters (11).

CURRENT OBSTACLES AND FUTURE DIRECTIONS

The examples provided show how patients and their care givers can be the catalysts of a change that is highly needed in translational medicine but they remain, as per today, sporadic cases led by unique human beings or by particularly inspired institutions. Many obstacles remain. Qualitative research showed that the involvement of patients and caregivers is challenging: real co-design does not happen by itself (12). First, specific educational programs are needed to improve the process of shared decision-making, for both partners, the patient and the physician. These programs are missing and importantly clinicians are often limited in their time-management. Educate and engage patients is a time-consuming process but health insurances—as well as hospitals—push more and more to reduce the time spent with patients, as costs of medication, exams, and personnel are dramatically increasing.

Scientists are even farther away from this process, as they often do not have direct contact with the patients. Current criteria for promotion in the medical field still rely heavily on individual research output such as high impact publications, h-index, grants, and invited lectures. There is tremendous pressure and on top of this pressure, there is really no space for a patient-centric view that needs time, patience and dedication. Especially in a system where these activities are not properly recognized and, as a consequence, rewarded. To change this, institutions need to ensure that their tenure and promotions systems are able to evaluate and recognize the contributions investigators conducting translational medicine make. Many institutions are working in this direction and, for instance, signed the Declaration

[3]http://www.jla.nihr.ac.uk/about-the-james-lind-alliance/about-psps.htm

on Research Assessment (DORA). DORA recognizes the need to improve the ways in which the outputs of scholarly research are evaluated. The declaration was developed in 2012 during the Annual Meeting of the American Society for Cell Biology in San Francisco[4]. It is a worldwide initiative covering all scholarly disciplines and all key stakeholders including funders, publishers, professional societies, institutions, and researchers. It is a first step toward assessing research based on its own merits rather than on the basis of the journal in which the research is published.

In conclusion, translational medicine is a very complex branch of medicine. The constant challenges of teaching, researching, publishing, and competing for limited sources of funding, coupled with pursuing career aims and ambitions, can seem daunting. On top of this, we are also adding the patient-centric view, which adds another level of complexity. However, we believe that once the obstacles are overcome, the real inclusion of patients in the process of translational medicine will improve healthcare delivery to patients.

[4]https://sfdora.org/

AUTHOR CONTRIBUTIONS

MB conceived the topic, contributed to the topic discussion and wrote the manuscript. PF and NW contributed to the topic discussion and contributed to manuscript writing. FB contributed to the topic discussion and wrote the manuscript.

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REVIEW
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Immunomics in Pediatric Rheumatic Diseases

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The inherent complexity in the immune landscape of pediatric rheumatic disease necessitates a holistic system approach. Uncertainty in the mechanistic workings and etiological driving forces presents difficulty in personalized treatments. The development and progression of immunomics are well suited to deal with this complexity. Immunomics encompasses a spectrum of biological processes that entail genomics, transcriptomics, epigenomics, proteomics, and cytomics. In this review, we will discuss how various high dimensional technologies in immunomics have helped to grow a wealth of data that provide salient clues and biological insights into the pathogenesis of autoimmunity. Interfaced with critical unresolved clinical questions and unmet medical needs, these platforms have helped to identify candidate immune targets, refine patient stratification, and understand treatment response or resistance. Yet the unprecedented growth in data has presented both opportunities and challenges. Researchers are now facing huge heterogeneous data sets from different origins that need to be integrated and exploited for further data mining. We believe that the utilization and integration of these platforms will help unravel the complexities and expedite both discovery and validation of clinical targets.

Keywords: immunomics, rheumatology, genomics, transcriptomics, proteomics, cytomics, epigenomics

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INTRODUCTION

Unraveling the etiology of pediatric rheumatic diseases exposes the complex heterogeneity inherent within the networks of immune pathophysiology. This mechanistic complexity underscores the challenge and uncertainty in precise disease characterization or sub-stratification. One illustrative example is the International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA) which serves to discriminate seven categories through a combination of clinical presentations, family history, serum, and genetic markers (1). Yet recent advances have shown that the disease mechanisms in JIA patients may be far more diverse (2). The clinical inability to deal with disease heterogeneity manifests as difficulties in confidently predicting responses and matching patients to current available treatment modalities (3). Furthermore, the development of future better-fit therapeutics will require dissecting the plethora of available immunological data through the lens of individual patient-specific clinical information. Cross comparisons of immunological data between different diseases could reveal underlying similarity in immune architecture that would facilitate opportunistic repurposing of existing drugs that have passed phase 1–3 clinical trials (4) and ultimately reduce drug development costs. These challenges and clinical unmet needs necessitate a different approach.

Immunomics can be understood as the application of high dimensional technologies that aim to harvest information across a spectrum of biological processes, encompassing (a) genomics, (b) transcriptomics, (c) epigenomics, (d) proteomics, and (e) cytomics (**Figure 1**). This holistic approach is well-suited to distilling key mechanistic information from complex immune networks, thus providing insights that may well otherwise be hidden. For instance, with greater dimensional resolution, we can now decipher key subtle mechanistic differences away from background stochastic immune features, and increasingly obtain better understanding of intra- and inter-individual pathological diversity.

In this review, we will discuss how conventional high dimensional immunomics platforms, and recent emerging technologies in single cell immune profiling (mass cytometry and single cell transcriptomics) have been deployed in pediatric rheumatic diseases. The resultant explosion of biological information entails corresponding challenges in bioinformatics analysis and public data sharing platforms, and how these issues are addressed will be examined. We believe the incorporation and integration of immunomics platforms in the research community will serve to illuminate and expedite both discovery and clinical validations.

GENOMICS

Genetic susceptibility is a cardinal aspect of pediatric rheumatic diseases, and comprehension of how individual genetic variants influence pathogenesis will subsequently guide prognostication and disease management. However, the challenge with pediatric rheumatic diseases is underpinned by its heterogeneity in disease susceptibility, clinical presentations as well as treatment outcomes. Genomics is well-placed to address this quandary by (a) identifying candidate genetic susceptibility loci through an unsupervised genome wide interrogation and (b) by streamlining disease classification into more homogenous subtypes, so that disease pathways may be elucidated and therapeutic selection more personalized. Another facet of immunological heterogeneity pertains to the inter-individual differences in immune repertoire present in T cell receptors (TCR). Advancements in TCR repertoire sequencing will add another dimension in the understanding of why certain individuals develop autoimmune diseases and maintain disease persistence. Major insights have since been gleaned from genetic studies across multiple pediatric rheumatic diseases, thereby augmenting our understanding of these diseases.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) are hypothesis-free studies in which a dense array of genetic markers, achieving significant representation in the genomic sequence, are instructive for a trait of interest (5). A typical genetic marker is the single nucleotide polymorphism (SNP), which is a variation in a single nucleotide occurring at a specific position along the genome, and some SNPs will be co-inherited with the trait of interest due to proximity along a contiguous stretch of genomic sequence. By detecting these associations between specific SNPs and disease on a population scale and deeming them robust if differences in allelic frequency between cases and controls exceed a statistical genome-wide significance threshold, susceptibility effects can hence be mapped. Given that pediatric rheumatic diseases are genetically complex with multiple genes of low effect sizes as well as gene-gene and gene-environment interactions, GWAS represent a major step forward from prior candidate gene studies and low-powered family linkage studies (**Table 1**).

An early success of GWAS in pediatric rheumatic diseases was the discovery of *VTCN1*, implicated in immune attenuation through B/T lymphocytes, as a novel JIA susceptibility locus in a 2009 study involving 279 JIA cases in the discovery cohort and 321 JIA cases in the validation cohort (7). Several contemporary JIA GWAS studies also built upon the findings of the Wellcome Trust Case Control Consortium Study to add both human leukocyte antigen (HLA) and non-HLA loci to the list, for which the latter included genes involved in T cell regulation and signaling; *STAT4*, *TRAF1/C5*, *PTPN22*, *PTPN2, CD80,* and *JMJDC1* (6, 8–10). This experience is mirrored by the Myositis Genetics Consortium (MYOGEN), through an international collaborative effort that revealed the presence of *HLA DRB1*03:01* as a disease susceptibility locus for juvenile dermatomyositis (JDM) (17). Since then, the advent of large consortia with their corresponding larger sample sizes, meta-analyses tapping on global databases as well as improvements in GWAS technology have further enhanced our knowledge on disease pathways, classification, and management.

Large-scale meta-analyses, which are statistical studies interrogating the combined results from multiple independent studies, have permitted analysis at an increased power and hence detection of signals that would have otherwise be missed due to their small effect sizes in underpowered single GWAS. This has been of great use in JIA, whereby two studies identified novel susceptibility loci for different subtypes of the disease: *HLA-DRB1*11* was uncovered as a strong systemic JIA (sJIA) risk factor following a meta-analysis of 9 independent case-control populations consisting 982 patients and 431 healthy children (11), while 9 new oligoarticular and rheumatoid factor (RF)-negative polyarticular JIA loci including *PRR9_LOR* and *ILDR1_CD86* were identified from three cohorts comprising of 2,751 patients and 15,886 controls (13).

Given that associations identified following GWAS and meta-analysis tend to implicate several genetic variants in disease susceptibility, it is imperative to determine the loci with the strongest evidence for candidate causal association. The realization that there is significant overlap in genetic susceptibilities across different autoimmune diseases led to the development of the Immunochip, which is a dedicated SNP array created for fine-mapping 186 autoimmunity loci established from prior GWAS (27). The use of the Immunochip has helped to refine peaks of association identified in previous GWAS and increase sensitivity in discovering new risk loci; in a well-powered study of ∼2,000 patients with either oligoarticular or rheumatoid factor (RF)-negative polyarticular JIA, three known JIA risk loci (the HLA region, *PTPN22*, and *PTPN2*) and 14 novel loci reaching genome-wide significance ($p < 1 \times 10^{-6}$) were uncovered for the first time (14). The same fine-mapping

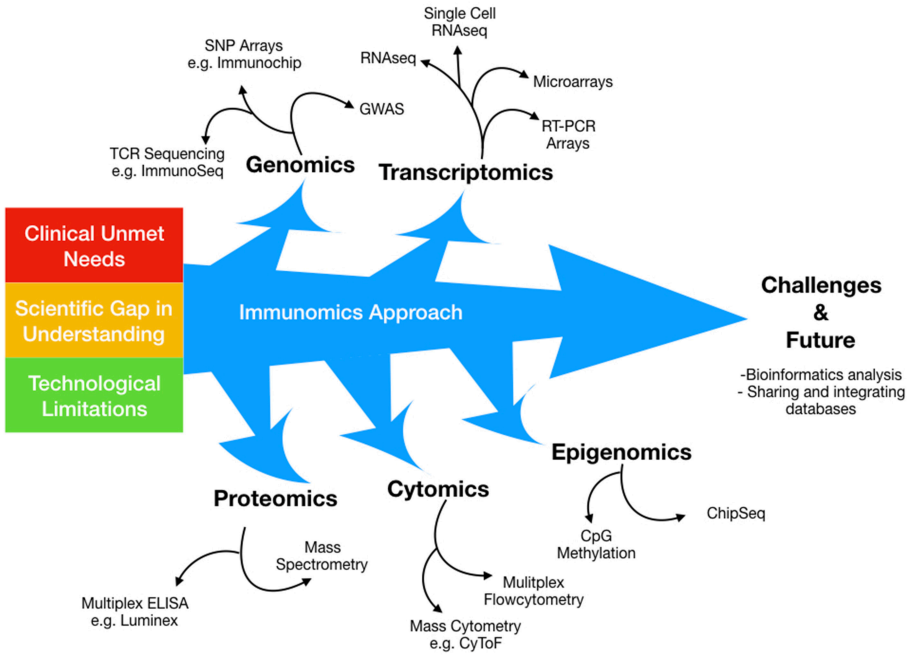

FIGURE 1 | The immunomics approach has evolved over time to surmount technological limitations in a broad attempt to answer several clinical and scientific unmet needs. Immunomics can be conceptualized as the application of high dimensional technologies that aim to harvest information across a spectrum of biological processes, encompassing; genomics, transcriptomics, epigenomics, proteomics and cytomics. This holistic approach is well suited in deciphering key mechanistic information from complex immune networks, thus unveiling insights that may well otherwise be hidden.

approach, in a separate study involving 14 countries, also supported association of the HLA and *PTPN22* regions for susceptibility to idiopathic inflammatory myopathies (IIM), of which JDM is a major subtype (18). In a systemic lupus erythematosus (SLE) Korean cohort with 781 patients, a hybrid approach with a GWAS array and Immunochip genotyping allowed for the sensitive detection of two SLE risk loci, *XKR6* and *GLT1D1*, which were found to be significantly higher in childhood-onset SLE (19).

In tandem, efforts involving large-scale sequencing projects such as the 1000 Genomes Project have continued to expand the catalog of known population variants, which in turn provide multi-ancestral reference populations from which control genotypes can be readily used from their public databases (28). For instance, a GWAS study conducted on IgA vasculitis, also known as Henoch-Schönlein purpura (HSP) and commonly found in children, with the aid of reference panels from the 1000 Genomes Project, revealed the HLA class II region as the major susceptibility locus (21).

Such advances in the validity of GWAS data and availability of public reference databases have renewed interest in the incorporation of this genetic information in pediatric rheumatic disease classification. The current categorization of JIA is primarily based on clinical signs and symptoms, such as the number of joints affected and the extent of extra-articular manifestations (1), but fails to account for underlying disease pathogenesis and hence helps in neither prognostication nor therapy selection. In particular, sJIA's autoinflammatory inflammatory phenotype clearly distinguishes it from the other 6 subtypes (29). Thus, GWAS comparing genetic variation across different JIA subtypes can help to highlight differences in genetic architecture that can potentially explain the distinct presentation of sJIA. A recent study on 770 patients with sJIA from 9 populations of European ancestry demonstrated a lack of shared genetic susceptibility loci with other JIA subtypes (oligoarthritis and RF-negative polyarthritis), with two susceptibility loci exceeding genome-wide significance: the major histocompatibility complex (MHC) II/III and a region located 20 kb upstream of *LOC284661* (a long intergenic non-coding RNA) loci (30). This is in line with the discovery of *HLA-DRB1*11* as a strong sJIA risk factor with an overall Odds Ratio (OR) of 2.3, and *HLA-DRB1*04* with a pooled OR of 1.9 from a meta-analysis of prior candidate gene studies of MHC II in JIA (11, 12). The implications of this result are 2-fold as it not only highlights the genetic dissimilarity between sJIA and other JIA subtypes, but also proposes the concurrent involvement of the adaptive immune system on top of a dysregulated innate immunity in disease pathogenesis. Thus, this paves the way for future mechanistic studies of these susceptibility loci to further elucidate sJIA pathophysiology and subsequently identify better targets for therapy.

GWAS findings have also provided insights into disease outcomes, with both HLA and non-HLA gene polymorphisms emerging as risk factors for certain disease manifestations as well as predictors of therapeutic response. The presence of amino acid serine at position 11 in HLA-DRB1 was shown

TABLE 1 | Summary of recent immunomics applications and their impact on our understanding of pediatric rheumatic disease (I).

Immunomics techniques	Clinical application and discovery	References
Genomics		
Genome Wide Association Studies (GWAS) with/without Immunochip	JIA susceptibility	
	Multiple HLA loci	(6)
	VTCN1, STAT4, TRAF1/C5, PTPN22, PTPN2, CD8, and JMJDC1	(6–10)
	JIA classification	
	*HLA-DRB1*11*, *HLA-DRB1*04* (systemic JIA), *PTPN22, ATP8B2_IL6R, STAT4, IL2_IL21, ERAP2_LNPEP, HLA, IL2RA, COG6, PTPN2, PRR9_LOR and ILDR1_CD86* (oligoarthritis and RF-negative polyarthritis)	(11–14)
	VTCN1 (uveitis)	(15)
	JIA with methotrexate response	
	TGF-beta signaling pathway	(16)
	JDM susceptibility	
	*HLA DRB1*03:01 PTPN22*	(17, 18)
	Childhood onset SLE susceptibility	
	XKR6 and *GLT1D1*	(19)
	Kawasaki disease	
	NEBL and *TUBA3C* (increased risk of coronary artery lesions)	(20)
	Henoch Schönlein Purpura (HSP) susceptibility	
	HLA class II region (including *HLA-DQA1/DQB1, HLA- DRB1*)	(21)
T-cell receptor (TCR) sequencing	JIA disease activity and treatment response markers	
	Circulating pathogenic-like lymphocytes (CPLs) and inflammation-associated Treg (iaTreg) – persistent disease activity and resistance to methotrexate and anti-TNFα therapy	(22, 23)
	TCR repertoire restoration – autoimmune disease remission after HSCT and sJIA remission	(24–26)

HLA, Human Leukocyte Antigen; JIA, Juvenile Idiopathic Arthritis; sJIA, systemic JIA; JDM, Juvenile Dermatomyositis; SLE, Systemic Lupus Erythematosus; TGF, Transforming growth factor; Treg, regulatory T cell; HSCT, Hematopoietic Stem Cell Transplantation.

to confer an increased risk of uveitis (OR 2.60) in female JIA patients (31) and 17 non-HLA variants were found to be statistically significant for a diverse range of clinical outcomes, such as actively inflamed joints and joints with limited range of motion, in a Nordic cohort of 193 patients of all subtypes excluding sJIA (15). In Kawasaki disease (KD), *NEBL* (OR 32.22) and *TUBA3C* (OR 21.03), both associated with cardiac muscle and tubulin respectively, were recently identified as risk factors for coronary artery lesions (20). While the current first line disease-modifying anti-rheumatic drug (DMARD) for all JIA subtypes remains as methotrexate (MTX), its limited efficacy necessitates the accurate prediction of MTX responders so that second-line therapy can be instituted in good time to those who do not to prevent disease progression. A 2014 study involving a cohort of 759 JIA patients from the United Kingdom, the Netherlands and Czech Republic surprisingly did not demonstrate significant association between the MTX pathway genes and treatment response, but instead identified other loci such as those related to TGF-β signaling as novel pathways for MTX response (16). Future targeted replication of these regions thus facilitates the optimization of genetic risk models for MTX response prediction.

Sequencing of the TCR Repertoire

T-cell receptor (TCR) sequencing is targeted toward the complementary determining region 3 (CDR3) loops, where most of the diversity in these heterodimeric cell-surface receptors is contained. The CDR3 regions are formed by random rearrangements between noncontiguous variables, diversity and joining (VDJ) gene segments in the β-chain locus, and between analogous variable and joining (VJ) gene segments in the α-chain locus (32). This process drives the generation of a diverse array of TCRs, with each T-cell clonotype possessing a specific TCR, which permits the adaptive immune system to recognize cognate antigens and mount an immune response. As pathogenic derangements in T-cell biology are highly implicated in the breakdown of immunologic self-tolerance integral to the development of pediatric rheumatic diseases such as JIA (33), characterization of the TCR repertoire thus provides an additional avenue on top of conventional immunophenotyping to understand disease pathogenesis, prognosis as well as response to treatment (**Table 1**). ImmunoSeq, a well-established technique that is developed by Adaptive Biotechnologies, uses a multiplex PCR and sequencing approach based on a synthetic immune receptor repertoire that minimizes amplification biases (34).

TCR sequencing has helped to reaffirm trafficking of CD4 subsets shared between the autoimmune synovial microenvironment and the systemic circulation in JIA patients (22, 23). Circulating pathogenic-like lymphocytes (CPLs), a subset of circulatory CD4 T effector (Teff) cells that mirror the pro-inflammatory phenotype of synovial CD4 T cells and expressing HLA-DR, were identified in significantly greater numbers in patients with active JIA who were resistant to methotrexate (MTX) and anti-TNF-α therapy (22). Notably, the TCR repertoire of these CPLs were highly enriched in synovial clonotypes, indicating the trafficking of these pathogenic cells to or from the synovial microenvironment. While it still remains unclear whether CPLs provide the autoimmune insult or have recirculated following activation in the inflamed synovium, a direct link between CPLs and disease activity has nevertheless been established with CPLs surfacing as a plausible marker for monitoring disease activity and treatment response. A similar dysregulation was also recognized in the regulatory T (Treg) compartment, whereby a subset of Treg cells defined by HLA-DR was enriched in active JIA patients (23). TCR sequencing indicates these inflammation-associated Treg (iaTreg) cells cosegregated with synovial Treg cells rather than with other blood Treg cells, and a small fraction of iaTreg clonotypes was found to demonstrate partial overlap in TCR repertoire with

arthritis-associated synovial Teff cells and blood CPLs. This hints at the importance of the inflammatory milieu which exerts an antigenic selection force in shaping systemic immunological processes. Therefore, TCR sequencing has pinpointed accessible diagnostic reservoirs of pathogenic cells that are likely to have recirculated into the bloodstream and correlated to disease activity. This paves the way to diagnostics that will prove to be a major improvement from current disease scoring systems (35), whose reliance on clinical signs and blood proxy inflammation parameters (e.g., ESR) are largely limited in accurately assessing disease progress and treatment response.

In JIA patients non-responsive to conventional DMARDs or biologics therapy, immune reconstitution through autologous hematopoietic stem cell transplantation (HSCT) may be one of the remaining options (36). Two illustrative studies have indicated TCR repertoire restriction in the Treg compartment (24, 25) of JIA or JDM patients prior to HSCT as compared to healthy controls. This points to a strong disease antigenic driving stimulus, and in particular patients who remain in remission with HSCT, had their TCR diversity restored as compared to relapse patients who retain a restricted oligoclonal profile (24). In a separate study, dominant TCR clones prior to transplantation were partially but not completely eliminated in remission sJIA patients, but rather restoration of TCR diversity suffices (26). Understanding on the mechanism of TCR diversity in relation to disease remission and its therapeutic implications has yet to be fully addressed.

TABLE 2 | Summary of recent immunomics applications and their impact on our understanding of pediatric rheumatic disease (II).

Immunomics techniques	Clinical application and discovery	References
Transcriptomics		
Microarrays	cSLE disease activity and realization of innate immunity as part of immunopathogenesis	
	Type I interferon signature and type I interferon-inducible gene expression	(38–40)
	JIA pathogenesis and treatment	
	Dysregulated interleukin-1 pathway in sJIA with active disease, anti-IL 1 therapies were introduced with good outcomes	(41–45)
	Differences in PBMC transcriptomics profiles – subtype-specific and/or disease state-specific in sJIA and non-sJIA	(39, 46–50)
	Neutrophil-specific transcriptional abnormalities persist in polyarticular JIA irrespective of disease state, suggesting aberrations in neutrophil metabolism	(51, 52)
	Kawasaki disease diagnosis	
	Whole blood gene expression signature – separates the disease from other childhood febrile illnesses	(53)
MicroRNA (miRNA)	JDM disease activity	
	Downregulation of miRNA-10a associated with increased expression of NF-$_k$B-controlled inflammatory mediators	(54)
RNA sequencing (RNA-seq)	sJIA disease activity	
	NK cell gene dysregulation (increased expression of innate genes *S100A9* and *TLR4*, decreased expression of immune-regulating genes *IL10RA* and *GZMK*) in active disease	(55)
	JIA pathogenesis	
	Increased autophagy with up regulation of two key genes, fatty acid synthase (*FASN*) and carnitine palmitoyltransferase 1A (*CPT1A*) within the fatty acid synthesis pathway	(56, 57)
	JIA treatment response	
	Monocyte gene expression profile may predict methotrexate non-responders	(58)

JIA, Juvenile Idiopathic Arthritis; sJIA, systemic JIA; JDM, Juvenile Dermatomyositis; PBMC, Peripheral Blood mononuclear Cells; SLE, Systemic Lupus Erythematosus; TLR, Toll-like receptor.

TRANSCRIPTOMICS

The transcriptome is the entire composite set of transcripts, both coding and non-coding, usually retrieved from a pre-selected subset of cells at a particular instance. This selective combination of transcripts, or the expression profile, gives another layer of biological insight pertaining to gene function, interaction and regulatory networks, which otherwise may not be apparent from the entire genetic sequence. From microarrays that capture limited ranges of known messenger RNAs (mRNAs) to the high-throughput next-generation sequencing (NGS) that can interrogate massive amounts of RNA in a genome-wide fashion, transcriptomics has greatly complemented genetic studies by identifying gene expression signatures for diagnostic discrimination or for shedding light on disease mechanisms (37), **Table 2**.

Microarrays

Microarrays quantitatively measure mRNA levels for thousands of genes in a biological sample, by relying on collections of oligonucleotide probes that capture cDNA or antisense RNA under high stringency conditions. Immobilized in defined positions on a solid matrix, labeled single-stranded nucleic acid fragments can be hybridized to these probes, and the amount of hybridization detected for a particular probe is proportional to the number of complementary fragments in the sample. Advances over the past decade have led to arrays for analysis of gene regulation (e.g., detecting microRNA), genome methylation signatures and even individual exons to assess alternative splicing. Due to their significantly greater dynamic range than reverse transcription polymerase chain reaction (RT-PCR) assays, microarrays are hence more adaptable to genome-wide high-throughput studies integral to decrypting the complex genetic networks in pediatric rheumatic disease (**Table 2**).

Since the 2000s, transcriptomic profiling of peripheral blood cells via microarrays has resulted in major discoveries in processes driving pediatric rheumatic diseases. In 2003, several groups independently identified the type I interferon signature in both pediatric and adult SLE patients (38–40). In particular,

the set of type I interferon-inducible genes was remarkably homogeneous amongst 28 out of 29 active pediatric SLE patients who were of different ethnicities and had exhibited varying degrees of disease activity (39). As such, these findings resulted in a paradigm shift to recognize the importance of innate immunity in pediatric SLE, which was contrary to the prevailing consensus that focused on adaptive immunity stemming from the disease's characteristic autoantibody production. This has subsequently encouraged similar studies in other rheumatic diseases such as dermatomyositis, systemic sclerosis and rheumatoid arthritis (59–61), with the partial overlap in interferon signatures suggesting commonalities in disease pathophysiology (62). Microarray analysis in sJIA patients also uncovered the role of the dysregulated interleukin-1 pathway in sJIA pathogenesis, whereby the interleukin-1 signature was most pronounced in patients with systemically active sJIA (41, 42). Such work has led to the development of therapies that specifically target the offending cytokines: several type I interferon therapeutics for use in SLE (e.g., anti-IFNα monoclonal antibodies [mAb] sifalimumab and rontalizumab, anti- IFNα/β receptor mAb anifrolumab) have undergone clinical trials over recent years with reasonable reduction in disease activity and normalization of cytokine signatures, albeit trial cohorts that consisted mainly of adult patients (63–65). Similarly, several IL-1 inhibitors (e.g., IL-1 receptor antagonist: anakinra, anti-IL-1 fusion protein: rilonacept, anti-IL-1beta mAb: canalikumab) have also proven to be considerably efficacious in clinical trials that recruited patients with long-lasting sJIA and poor response to DMARDs and biologics (43–45). In particular, anakinra has entered clinical practice with favorable outcomes noted in sJIA patients, especially when started early in the disease course with or without concomitant glucocorticoids (66–68).

The late 2000s saw several studies that sought to define disease-specific signatures as well as the biological basis behind various clinical phenotypes, especially active disease versus clinical remission. A 2007 study found 286 genes that were significantly up-regulated in peripheral blood mononuclear cells (PBMCs) isolated from active sJIA patients, and this signature was proposed to be disease-specific as most of the candidate genes did not overlap with those identified for other inflammatory diseases including RF-negative polyarticular JIA, KD and pediatric SLE (39, 46–48). Distinct gene expression profiles in PBMCs that segregate active and inactive sJIA were also identified, though results may be confounded by differences in treatment regimens (48). A separate analysis pinpointed subtype-specific transcriptomic profiles in PBMCs of treatment-naïve JIA patients, particularly between sJIA and non-sJIA subtypes (49), and a contemporary study on RF-negative polyarticular JIA revealed considerable heterogeneity between gene expression patterns of PBMCs at different disease states (active, clinical remission on/off medication) (50). Evidence for chronic neutrophil activation in RF-negative polyarticular JIA (51) led to a dedicated effort to characterize the gene expression profiles of neutrophils at different stages of the disease (52). Of note, neutrophils isolated from patients with inactive disease exhibited specific transcriptional abnormalities that fail to return to normal and were linked to aberrations in neutrophil metabolism (52).

Recent work has looked into whole blood gene expression profiles to determine diagnostic biomarkers as well as predictors of treatment response, in spite of the inherent "noise" from the composite signatures of multiple cellular subsets. The relative ease of collecting whole blood as opposed to fractionated cell subsets and the holistic examination of cross-talk between all innate and adaptive immune cells in disease pathogenesis make whole blood nevertheless an attractive candidate. Using whole blood microarray gene expression data obtained from the Trial of Early Aggressive Therapy in JIA (TREAT; ClinicalTrials.gov registry #NCT00443430), network approaches utilizing functional co-expressing gene modules unveiled extensive re-ordering of gene expression networks in polyarticular JIA patients following initiation of therapy. In particular, distinctions existed between responders and non-responders on how these networks evolved (69). A follow-up study compared whole blood gene expression data between TREAT subjects at baseline, a treatment-naïve independent cohort as well as healthy controls (70). One hundred and fifty-eight genes showed differential expression with at least a 1.4-fold difference (false discovery rate 0.05) when TREAT subjects were contrasted with healthy controls, with particular enrichment of genes regulating leukocyte adhesion and extravasation (especially interleukin-8) as well as CD3-TCR signaling. In the same study, a multi-omics approach combining GWAS and microarray expression data surprisingly found that none of the 158 genes were located within linkage disequilibrium blocks containing JIA-associated SNPs, which proposes the role of the non-coding genome in JIA pathogenesis (70). A 2018 study uncovered a 13-transcript whole blood gene expression signature (of which 7 were connected in a central hub of tumor necrosis factor and interleukin 6) that distinguished KD in the first week of illness from other febrile conditions (e.g. staphylococcal and streptococcal toxic shock syndromes, measles and other viral illnesses as well as childhood inflammatory diseases)(53). This signature displayed reasonably high specificity and sensitivity for early diagnosis (discovery: sensitivity 81.7%, specificity 92.1%; validation: sensitivity 85.9%, specificity 89.1%), with predictive performance in patients with definite, highly probable or possible KD in the validation set mirroring certainty of clinical diagnosis (area under curve [AUC] 98.1% 96.3% and 70.0% respectively).

There have also been contemporary microarray studies outlining the role of microRNAs (miRNAs) and individual exons in the pathophysiology of pediatric rheumatic diseases. miRNAs are short non-coding RNA molecules that downregulate specific mRNA transcripts either by translational repression or mRNA cleavage (71), and they have been shown to alter gene expression and signaling in immunological processes as well as autoimmunity (72–74). Based on evidence implicating several miRNA species in adult inflammatory myopathies (e.g., dermatomyositis and polymyositis) (75, 76), miRNA expression in muscle biopsies isolated from 15 children with active untreated confirmed or probable JDM was compared with that of 5 healthy controls (54). miRNA-10a was found to

be significantly downregulated by −2.27-fold, which was in turn associated with increased expression of NF-kB-controlled inflammatory mediators (e.g., IL-6, IL-8, TNF-alpha) as well as clinical and laboratory features of JDM (serum von Willebrand factor antigen level, Disease Activity Scores). Furthermore, miRNA and exon microarrays revealed distinct miRNA and gene isoform expression profiles in neutrophils from patients with active untreated RF-negative polyarticular JIA, though considerable overlap was noted in children with cystic fibrosis that is also characterized by chronic soft tissue inflammation (77). While the two phenotypes also shared several miRNAs and genes in their networks and annotated functions, hub miRNA networks remained unique to each disease. Future work of how the transcriptome and regulatory networks change in response to therapy may hence potentially unravel underlying disease pathogenesis to enable future rationalization of therapy.

RNA Sequencing

RNA sequencing (RNA-seq) with NGS is the direct ultra-high-throughput sequencing of cDNA derived from transcripts in the sample, and it has several considerable advantages over microarrays: (a) detection of transcripts is free from probe-specific hybridization thus avoiding the need for a priori knowledge of targets, (b) broader dynamic range, (c) lower background signal, (d) increased sensitivity and reproducibility. As such, RNA-seq is able to efficiently measure genome-wide RNA abundance, detect novel and/or allele-specific transcripts and pinpoint alternative splice variants associated with pediatric rheumatic disease in an unbiased fashion. With that, RNA-seq is better poised as a discovery platform for holistic deep expression analysis as compared with microarray systems which is typically customized for specific questions (**Table 2**).

Recent comprehensive RNA-seq transcriptome analyses, particularly in combination with fluorescence-activated cell sorting (FACS) or magnetic sorted cells have aided in the identification and characterization of dysregulated pathways in disease implicated cellular subsets. As sJIA involves prominent innate immune activation and lacks significant involvement of autoreactive T cells or autoantibodies (29), recent studies have used RNA-seq to define mechanistic, diagnostic, and predictive signatures in specific innate immune cells. Genome-wide RNA sequencing revealed 214 differentially expressed genes in magnetically sorted neutrophils from the blood of children with active sJIA disease compared with healthy controls (78). The most significantly upregulated gene pathway in active sJIA disease corresponded to "Immune System Process" including genes such as *AIM2*, *IL18RAP*, *NLRC4*, and IL-18 expression remains dysregulated at a lower intermediate level even in clinically inactive state as compared with healthy individuals. Another study sought to delineate the role of natural killer (NK) cells in sJIA by performing comparative RNA sequencing analysis of these FACS sorted NK cells from a cohort of 6 active sJIA patients and 6 healthy controls (55). Proinflammatory mediators IL-1β and IL-6 were identified to be major upstream drivers of NK cell gene dysregulation (e.g., increased expression of innate genes *S100A9* and *TLR4*, decreased expression of immune-regulating genes *IL10RA* and *GZMK*) in active disease. In conjunction with an altered plasma cytokine profile enriched in species that promote inflammation and NK cell survival, this thereby implicates the inflammatory milieu characteristic of sJIA in shaping the biologic behavior of NK cells and their consequent function in disease pathogenesis. Moving forward, future work can hence aim to better define RNA signatures in cells of innate immunity in sJIA patients that is stratified in relation to therapy response.

In non-systemic JIA subtypes, studies have focused on the adaptive immune system, whose role in disease pathogenesis has been well-documented. Transcriptomic analyses of sorted $CD4^+$ synovial T cells of patients with active disease (13 oligoarticular, 8 extended oligoarticular, 3 polyarticular) demonstrated enhanced expression of autophagy genes compared with PBMCs of patients and healthy controls (56). Interestingly, this was not accompanied by significant upregulation of autophagy in the presence of synovial fluid, yet the inflammatory phenotype of these cells was impaired on inhibition of autophagy with hydroxychloroquine. As autophagy is a cell-survival mechanism that permits energy and nutrient conservation (79), it was hence postulated that the increase in autophagy may have occurred to cope with the greater metabolic demand of inflammation, and targeting autophagy in dysregulated T cells may be a viable strategy to restore disrupted T cell homeostasis in JIA. Indeed, a separate study indicate that sorted $CD4^+$ memory T cells in RA/JIA patients exhibit higher autophagy, termed as "autophagic memory," that affords for better persistence through this metabolic advantage (57). This phenomenon was shown through transcription factor gene regulatory network analysis (TF-GRN) of the transcriptome (RNA-seq) of sorted JIA pathogenic T cells (CPLs), to be driven by the suppression of the *MYC* gene (57). Furthermore, RNA-seq data from CPLs indicate the up-regulation of two key genes, fatty acid synthase (*FASN*) and carnitine palmitoyltransferase 1A (*CPT1A*) within the fatty acid synthesis pathway (57), adding weight to the idea of metabolic advantage.

While the role of innate immunity in non-systemic JIA subtypes is less clear, emerging evidence has hypothesized the importance of neutrophils in linking both arms of the immune system in disease pathogenesis. Notably, prior microarray analyses reflected differences in neutrophil expression profile that correlated with disease phenotypes in RF-negative polyarticular JIA (52). The same authors sought to substantiate those findings by investigating the transcriptomes of neutrophils from 9 individuals (3 with active untreated RF-negative polyarticular JIA, 3 with the same disease that was inactive on medication, 3 children with cystic fibrosis) (80). One hundred and fifty nine genes were differentially expressed in children with active disease when compared to those with sustained inactive disease on medication (e.g., downregulation of type I interferon response genes and interferon-induced proteins in active disease), while 113 genes showed differential expression with at least 1.9-fold change ($p < 0.05$) when neutrophils from children with untreated RF-negative polyarticular JIA were compared with those from children with cystic fibrosis. Differential exon usage genes and long non-coding RNA (lncRNA) expression were also identified

between the disease phenotypes. Interestingly, the prior study on sJIA reported a dissimilar neutrophil gene expression signature that lacked significant upregulation of IL-8 and IFNγ. Though there is a need to evaluate these findings in larger cohorts, both studies further contribute to the promise of potential neutrophil biomarkers for diagnosis and prognosis across JIA subtypes, given the proposed adaptability in neutrophil transcriptomes under specific biological contexts.

There have been studies in non-systemic JIA subtypes that chose instead to work with unfractionated heterogeneous cell populations (e.g., PBMCs), though differing outcomes were noted in biomarker identification. Analysis of gene expression patterns in PBMCs of patients with polyarticular JIA at different treatment stages (active untreated disease, active on treatment or clinical remission on medication) as well as with healthy controls surprisingly failed to define molecular signatures that would assist in disease staging (active disease vs. clinical remission) or in diagnosis (untreated active disease vs. healthy controls) (81). In retrospect, the authors attributed this challenge to technical issues in RNA-seq and biological factors stemming from the heterogeneity within polyarticular JIA as well as PBMCs. On the other hand, examining the transcriptomic profile of PBMCs in oligoarticular and polyarticular JIA prior to MTX has yielded promising results (58). In this cohort that possessed an MTX response rate of 61.7% as defined by the ACR-Ped criteria, a signature predictive of eventual response was elucidated from 47 patients whose clinical outcomes were measured pre- and at least 2 months post-MTX treatment. The gene expression profile of MTX responders was distinct from, but more similar, to healthy controls than that of non-responders. There was also a strong correlation between the mean MTX non-responder signature with monocyte gene expression, which suggests the potential role of innate immunity in clinical response to MTX. While technical and bioinformatics noise remain as considerable issues especially in dealing with unfractionated cell populations in poorly-defined diseases, future work in improving library preparation and spike-in controls as well as developing appropriate computational approaches for data post-processing will hopefully augment our use of this powerful technology to understand disease mechanisms.

EPIGENOMICS

Epigenomics broadly entails the hereditary and phenotypic traits that can alter function at the genome level without a direct change in the genetic sequence (82). These epigenetic mechanisms allow for genetic and environmental factors to interact and contribute to particular phenotypes and diseases. There has been growing evidence to suggest that epigenetic modifications are implicated in several autoimmune diseases, e.g., modifications to DNA methylation has been detected in SLE, RA and Type 1 diabetes mellitus (83). Discovery of these epigenetic changes will provide another layer of dimension toward understanding how disease mechanisms operate holistically and ultimately allow for biomarker development for prognostic and diagnostic applications (**Table 3**).

TABLE 3 | Summary of recent immunomics applications and their impact on our understanding of pediatric rheumatic disease (III).

Immunomics techniques	Clinical application and discovery	References
Epigenomics		
CpG DNA Methylation	sJIA disease activity	
	CD4+ T cell DNA methylation was significantly decreased at the IL-32 gene as compared to healthy controls	(84)
	Certain CpG modules were statistically related to clinical fates and enriched on genes responsible for T cell activation in JIA patients with active disease before and after withdrawal of therapy	(23)
	Kawasaki disease pathogenesis and treatment	
	Hypomethylation within the promoters of TLR1, 2, 4, 6, 8, and 9 (whole blood), correlated with increase in mRNA expression of respective TLRs compared to healthy and other febrile controls, and reversed upon treatment with intravenous immunoglobulin (IVIG)	(85)
	DNA hypomethylation (whole blood) of *FCGR2A* was associated with resistance to intravenous immunoglobulin (IVIG) treatment	(86, 87)
Chromatin immunoprecipitation (ChIP) Assays	JIA pathogenesis	
	In JIA patients, neutrophils and CD4+ T cells exhibited H3K4me1 and/or H3K27ac marks in the non-coding areas of genetic risk, suggesting the crucial role of non-coding elements within leukocyte genomes	(88)

JIA, Juvenile Idiopathic Arthritis, TLR, Toll-like Receptor.

CpG DNA Methylation

DNA methylation of gene promoters, specifically at regions of CpG dinucleotides, is usually associated with reduced gene expression (89). Numerous studies conducted for adult rheumatological diseases have implicated aberrant DNA methylation (83). In RA, DNA methylation was examined specifically through bisulfite sequencing at a loci containing 22 CpG motifs upstream of the IL-6 gene (90). The reduction in DNA methylation in the−1099CpG motif was in tandem with an increased expression of IL-6; that is in line with the pathophysiology of RA, a chronic inflammatory disorder.

Technologies to examine DNA methylation have undergone an increase in their capacity to examine unique CpG sites upon the creation of arrays in the late 1990s. For instance, current DNA methylation array platforms such as the Illumina Infinium HumanMethylation450 (M450K) BeadChip are now able to target more than 450,000 methylation sites, giving us a genomic wide view of epigenetic disruptions. This epigenomic view through CpG arrays is illustrated in a study on how differential T-cell DNA methylation may impact JIA (91). Before this study, there were no prior studies about epigenetic disturbances in JIA. As epigenetic marks may be amenable to modification and thus

serve as candidate therapeutic targets (84), they sought to profile DNA methylation of purified $CD4^+$ T cells from healthy controls and JIA subjects. The Illumina platform was used to compare more than 25,000 CpGs sites, and analysis found significant decreased methylation at the IL-32 gene.

In a recent study, a genome-scale case-control analysis of $CD4^+$ T cell DNA methylation in oligoarticular JIA was conducted (92). The Illumina HumanMethylation 450 array was deployed to examine DNA methylation of >450,000 sites in sorted $CD4^+$ T cells from JIA patients. However, in contrast to the earlier JIA study as well as other adult-onset rheumatic diseases such as RA and SLE (93), the authors found no significant differences in the DNA methylation profiles between disease and controls. The authors attribute the differences between the studies to the targeted selection of $CD4^+$ T cells in one particular subgroup (oligoarticular) of JIA. However, independently in another study, the $CD4^+$ T cell DNA methylome of both polyarticular and extended oligoarticular JIA patients prior to and after withdrawal of antiTNFα therapy was investigated (23), to answer a pertinent clinical need in segregating patients who have either resolved disease or still require constant therapy. To allow for better noise reduction, CpG sites were analyzed with weighted gene co-expression network analysis (WGCNA), which clustered the CpG sites into statistically correlated CpG modules that are likely to be biologically correlated (23). In particular, this study revealed that certain CpG modules were statistically related to clinical fates, where JIA patients who are active prior/after withdrawal of therapy, were enriched for genes responsible for T cell activation.

Yet some studies have looked at a mixture of cell types to characterize biological differences with the progression of clinical treatment. One particular study on KD patients, examined the entire white blood population with the Illumina M450K beadchip, in an attempt to identify patterns of DNA methylation of all 10 human toll-like receptors (TLRs), typically known to be expressed across several cell types (85). The CpG sites within the promoters of TLR1, 2, 4, 6, 8, and 9 were hypomethylated in KD patients, and this was in line with the increase in mRNA expression of the respective TLRs. This was shown to be true when comparing the KD patients against the healthy or febrile non-KD controls, and the trend reversed upon treatment with intravenous immunoglobulin (IVIG) in KD patients. The reversal in CpG hypomethylation comes as a surprise, as epigenetic modifications tend to be stable, so this reversion could likely have resulted from a change in cellular frequency of certain immune subsets during the course of treatment. Nonetheless, studies have shown that TLRs 2, 3, 4, 6, and 9 may be the initial triggers for the immune response in KD patients (94), thus suggesting that epigenetic predisposition in TLRs (or dysregulation in specific immune subsets) may "sensitize" KD patients and play a crucial role in disease risk and pathogenesis. The same group also revealed a positive association between DNA hypomethylation of *FCGR2A* and resistance to IVIG treatment in KD patients (86, 87). The *FCGR2A* gene codes for the low-affinity immunoglobulin gamma Fc region receptor II-a protein, expressed on a variety of immune subsets and in particular phagocytes such as monocytes and macrophages. Pyrosequencing reconfirmed that patients who were IVIG-resistant had significantly lower *FCGR2A* methylation levels at all 5 CpG methylation sites studied than those who were IVIG-responsive (86). This significant hypomethylation was accompanied by significantly higher *FCGR2A* mRNA levels in KD patients compared to febrile controls. The clinical relevance was later determined (87): hypomethylation of the CpG marker cg24422489 at the *FCGR2A* gene promoter in KD patients was reversed after IVIG was administered, with a concomitant increase in *FCGR2A* mRNA expression. The authors suggest that *FCGR2A* likely play a pro-inflammatory role with increased susceptibility to KD and thus may provide a mechanistic rationale for the usage of IVIG in KD. These studies provide an additional layer of biological insight into how epigenetic mechanisms and their candidate target genes can influence disease pathology and treatment response.

Chromatin Immunoprecipitation (ChIP) Assays

ChIP is an immunoprecipitation technique that enables analysis of a spectrum of protein-DNA interactions, including transcription initiation factors on promoters or silencers on regulatory sites as well as the specific localization of defined histone modifications (95). This is performed with the intent to identify the DNA sequence to which a specified target protein complex binds either directly to or in a chromatin folded conformation. A variation of this technique is ChIP sequencing (ChIP-seq), which is able to identify DNA binding sites more precisely. In ChIP sequencing, oligonucleotide adaptors are added to the DNA bound to the target protein of interest and subsequently sequenced (95).

ChIP has been used in large-scale studies, namely the Encyclopedia of Functional DNA elements (ENCODE) and Roadmap Epigenomics projects. DNA-binding proteins such as enhancers and silencers cannot be predicted accurately *in-silico*, solely based on the DNA sequence (88). ChIP-seq plays a vital role in validating this physical interaction. The ENCODE and Roadmap Epigenomics projects showed that using ChIP-seq to direct to particular histone marks such as histone H3 mono-methylated at lysine 4 (H3K4me1) (96) can facilitate the identification of enhancers.

In pediatric rheumatic diseases, ChIP assays have been used in JIA, typically followed by sequencing (**Table 3**). Jiang et al. (88) used ChIP-seq to find out if there are specific epigenetic marks (H3K4me1and H3K27ac) associated with enhancer function in human neutrophils and $CD4^+$ cells (88). This was a follow-up from a GWAS study that showed 24 regions (or SNPs) of genetic risk for JIA, of which 22 were in noncoding genomic regions (14). The aim was to determine if there were functional elements situated in these non-coding areas of genetic risk. ChIP-seq was specifically used to check for enhancer-associated histone marks within the linkage disequilibrium blocks that comprises the 22 regions found via the GWAS. It was found that these linkage disequilibrium blocks are indeed rich in histone marks commonly associated with enhancers, adding further

weight on the disease susceptibility risk loci previously identified in GWAS.

Separately, Peeters et al. (97) used H3K27ac to identify a typical enhancer and super-enhancer signature in the $CD4^+$ memory and effector T cells derived from the synovial fluid of JIA patients (97). Use of the BET (bromodomain and extra-terminal domain) inhibitor JQ1 was found to inhibit super-enhancers that are related to immune response, in addition to reducing disease-associated gene expression. BET inhibitions have been previously shown to preferentially reduce super enhancer-associated gene expression (98). These results are specific to the synovial microenvironment and suggest that enhancer profiling could be used for the identification of disease mediators. BET inhibition can also be explored as a potential therapeutic for autoimmune disease treatment.

PROTEOMICS

Proteomics refers to the large-scale study of the entire complement of proteins and strives to understand the expression profiles, interactions, and functions of these proteins (99). What makes this landscape so complex is the enormous permutations to which proteins can be differentially expressed (splice forms) or modified, with their spatially and temporally distinct formats, culminating in a complex diversity of interactions. Proteins are deeply involved in the manifestation of cellular phenotypes, and the study of proteins can present succinct clues on immune cellular behavior and function.

Mass Spectrometry

Mass spectrometry (MS) became the predominant technique for examining proteins (100) at a proteome level with technological advances in particular to mass selection, detection, and analysis (101) gradually taking form. MS facilitates the acquisition of protein information, including protein identity (amino acid sequences), abundance and post translational modifications through accurate assessment of atomic mass spectra. There are three generic stages involved in the procurement of protein information by MS: sample preparation, sample ionization, and mass analysis (100, 101). Frequently, before a complex protein mixture can be analyzed by MS, it has to be resolved (e.g., trypsin digestion) and extracted using chromatographic means (e.g., reverse phase or pH). The resulting peptides have to be charged through soft ionization techniques (e.g., MALDI or ESI) and desolvated, prior to passing through mass filtering by designated quadrupoles and finally undergo mass analysis by detectors (e.g., orbitrap or time of flight). The acquired data (MS^1 and/or MS^2 spectra) is cross referenced against a mass spectra database through a software designed for the mass spectrometer configuration.

MS platforms are now adept at distilling candidate protein targets and increasingly being deployed to characterize proteomic profiles of pediatric rheumatic diseases (**Table 4**). One study found that different systemic autoimmune diseases (SAID), including JIA and JDM, share similar dysregulation in plasma protein expression and affected pathways (108). To reduce background noise from polymorphic genes, matched monozygotic twins that are discordant for disease development were studied, and plasma proteins found significantly different from the twins were further compared against other matched unrelated controls. Plasma protein levels were examined using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS). Pathway analysis revealed significant dysregulation in acute phase reactants, complement pathway, coagulation and retinoid receptor activation in SAID patients. With the aid of random forest modeling, 7 top proteins were identified, that were interconnected through paraoxonase 1 and a secondary link to IL-6, thus providing a candidate list of afflicted proteins and pathways present in SAID patients.

In JIA, MS has been employed to differentiate clinical subtypes. With the aid of MALDI-TOF-MS, Finnegan et al. (102) studied 15 treatment naive JIA patients and found distinct proteome profiles between the subgroups (oligoarthritis and polyarthritis) during early disease (102). The group found significant differences in expression levels of proteins involved in coagulation and platelet activation. Polyarticular JIA patients, who exhibit a more severe clinical presentation, expressed higher levels of fibrinogen-β/γ chains known to

TABLE 4 | Summary of recent immunomics applications and their impact on our understanding of pediatric rheumatic disease (IV).

Immunomics techniques	Clinical application and discovery	References
Proteomics		
Mass spectrometry	JIA classification	
	Distinct proteome profiles between the subgroups (oligoarticular and polyarticular) in early disease	(102)
	Polyarticular JIA patients expressed higher levels of platelet activation factors, including fibrinogen-β/γ chains	(103)
	Type VI collagen was found at higher levels in oligoarthritis patients	(104)
	Childhood-onset SLE with nephritis - biomarkers for disease activity	
	Eight stable urinary proteomic signatures present in patients with nephritis, displayed a strong correlation with renal disease and moderate correlation with renal damage	(105)
Multiplex enzyme-linked immunosorbent assay (ELISA)	JIA with methotrexate response	
	Predominant cytokine clusters during active/inactive disease were identified - several cytokines such as CCL2, CCL3 and CXCL9 were found to be significantly increased in the plasma of JIA patients, coinciding with inflammation	(106)
	JDM disease activity monitoring	
	CXCL10, TNF receptor Type II and galectin 9 showed significant increases in active JDM and strongly correlated to active disease and clinical JDM scores	(107)

JIA, Juvenile Idiopathic Arthritis; JDM, Juvenile Dermatomyositis; SLE, Systemic Lupus Erythematosus.

mediate polymerization of fibrin and binding to thrombin (103). Pathological changes in coagulation pathway proteins may contribute to the inflammatory spread across joints, which is observed in polyarticular JIA patients (102). In contrast, Type VI collagen was found at higher levels within oligoarticular JIA patients. Type VI collagen is known to be crucial for regulating normal synovial joint physiology where mice lacking collagen Type VI had a significant reduction in mechanical properties and experienced a myriad of musculoskeletal issues (104).

Apart from distinguishing disease subtypes, proteomics profiles have been exploited for biomarker discovery. Surface-enhanced laser desorption/ionization time-of flight (SELDI-TOF) MS was used in one study (105) of pediatric SLE patients, allowing for high-throughput profiling of urine samples and sensitive detection of low-molecular-weight biomarkers that may be missed by other conventional methods (109). A stable urinary proteomic signature encompassing eight proteins was indicative for pediatric SLE patients with nephritis. These markers displayed a strong correlation with renal disease and moderate correlation with renal damage. Identification of this urine proteomic signature may help in prediction of SLE renal disease prior to nephritis presentation.

Multiplex Enzyme-Linked Immunosorbent Assay (ELISA)

The enzyme-linked immunosorbent assay (ELISA) is commonly used for profiling of selected liquid analytes, in particular pertaining to immunological response. It uses an enzyme immunoassay (EIA), i.e., an enzyme reaction with its substrate, to detect the presence of a target antigen using specific antibodies. In pediatric rheumatic diseases, this technology has been actively used to profile cytokines or mediators involved in the disease process (**Table 4**). For example in JIA, decreased production of IL-10, a regulatory cytokine, has been found to be accompanied by increased pro-inflammatory cytokines (110). Conventional singleplex ELISA kits provide only a singular snapshot of the selected immune mediators, eventually increased in interrogation spectrum. With the development of beads or particle based multiplex immunoassays (MIAs). Current MIA kits (e.g., Luminex) allows the simultaneous detection of up to 65 unique mediators from samples in microliter volume. One MIA was developed for the detection of 30 inflammation-related human soluble mediators in plasma and synovial fluid, specifically in JIA (106). Using this assay, they were able to measure a diverse panel of chemokines, interleukins (ILs), and soluble adhesion molecule to create biochemical profiles for healthy controls and JIA patients. Cluster analysis of these results showed differences between active disease and remission. There was a predominant pro-inflammatory cytokine cluster during active disease, in contrast to an anti-inflammatory-related cytokine cluster during remission. Several cytokines such as CCL2, CCL3, and CXCL9 were found to be significantly increased in the plasma of JIA patients coinciding with active inflammation. MIAs have also been used in JDM to find markers for disease activity monitoring. This would allow for better personalization of therapeutic regimens. In one particular study that looked at 45 unique inflammation-related proteins in 25 JDM patients, 3 proteins were significantly elevated compared to the control group (107). CXCL10, tumor necrosis factor receptor Type II and galectin 9 displayed significant increases in active JDM. These were also strongly correlated to active disease and clinical JDM scores, that allows for tracking disease progression.

Cytokine profiles screened through MIA kits, could potentially be used to monitor disease activity, determine treatment response and play a role in the prediction of disease flares. Despite the relatively low-throughput in screening potential compared to mass spectrometry, the convenience and robustness in validating and deploying ELISA diagnostic kits in hospital labs, explains their utility and widespread usage.

CYTOMICS

Cytomics aims to understand complex cellular landscapes and systems at the single cell level by integrating molecular techniques (e.g., dyes and fluorophores) with digital spectra acquisition. Dissection of complex immune cellular phenotypes can augment our knowledge of how disease mechanisms operate. For instance, analysis of alterations in lymphoid and myeloid cells, allow for identification of immune cell subpopulations that are disease-specific (111) and may otherwise be buried within the bulk population, **Table 5**.

Multi-Parametric Flow Cytometry

Flow cytometry is the key platform utilized in the field of cytomics. Since its introduction more than half a century ago, fluorescence-based flow cytometry has been extensively used for functional analysis and characterization of immune cells subsets (111). Technological advancements have allowed for increasing numbers of measurable parameters per cell. The latest flow cytometers are able to detect $>$ 20 parameters. Accompanying this increase has been the extent of targets that can be assayed. Initial flow cytometry systems were limited only to cell surface marker analysis, that eventually expanded to intra-cellular markers with cell permeabilization techniques. Now, correlation of functional cell subsets with differential kinase states can be performed with the availability of kinase specific antibodies (117). Such *in vivo* kinase assays can provide better information on signaling pathways that are crucial to understanding cellular processes and responses to receptor triggering.

Multi-parametric flow cytometry has been actively deployed in the investigation of pediatric rheumatic diseases for immune phenotyping (**Table 5**). As autoimmune diseases can be partially attributed to the loss of self-tolerance, investigators examined PBMCs from pediatric SLE patients with a 12 color fluorescent based panel (112). Immune phenotyping indicated a decreased capacity to upregulate PD-L1 expression in monocytes and myeloid dendritic cells in active SLE patients as compared with healthy age-matched controls or SLE patient experiencing remission, suggesting a possible mechanism in loss of peripheral tolerance (112). Independently, Tarbox et al. (113) examined the presence of double negative T (DNT) cells in pediatric rheumatic diseases, which is known to increase in autoimmune lymphoproliferative syndrome due to defects in the Fas-apoptotic

TABLE 5 | Summary of recent immunomics applications and their impact on our understanding of pediatric rheumatic disease (V).

Immunomics techniques	Clinical application and discovery	References
Cytomics		
Multi-parametric flow cytometry	Childhood-onset SLE pathogenesis	
	Impaired upregulation of PD-1 expression in monocytes and myeloid dendritic cells in active SLE patients as compared to healthy controls or SLE patients in remission, suggesting a possible mechanism in loss of peripheral tolerance	(112)
	Double negative T cell elevation (> 2.5%), in children with SLE, MCTD and ANA-positive JIA	(113)
Mass cytometry (CyTOF)	JDM pathogenesis	
	Defective phosphorylation of PLCγ2 in natural killer (NK) cells compared to healthy controls	(114)
	JIA pathogenesis	
	Treatment-naïve polyarticular JIA patients displayed enhanced IFN-γ signaling in CD4 T cells and monocytes. Naïve CD4 T cells had more strongly phosphorylated STAT1 and STAT3 as compared to monocytes, which displayed increased phosphorylation of STAT3 compared with controls. This suggests that attenuation of IFN-γ signaling could be a novel alternative therapy for polyarticular JIA.	(115)
	Childhood-onset SLE pathogenesis	
	Monocyte cytokine signatures with high monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1β (MIP1β) and interleukin-1 receptor antagonist (IL-1RA) were found in treatment-naïve SLE children	(116)

JIA, Juvenile Idiopathic Arthritis; SLE, Systemic Lupus Erythematosus.

pathway (113). PBMCs were analyzed by a multi-parametric flow panel (>12) from pediatric patients with SLE, mixed connective tissue disorder (MCTD), JIA and elevated antinuclear antibody (ANA) without systemic disease (113). There was a significant increase in the number of patients with DNT cells raised ≥2.5% as compared with controls. It was found that 29.6% of patients displayed elevated DNT cells, as compared to 3.6% of controls and this was stable over ∼8 months, suggesting the role of DNTs/apoptosis in disease pathogenesis. Spreafico et al. (22) utilized a 12 color flow panel to allow for the sensitive detection of a circulating subset of pathogenic $CD4^+$ T cells that are phenotypically similar to $CD4^+$ T cells from the synovial micro-environment of JIA patients (22).These circulating pathogenic lymphocytes (CPLs) correlate significantly with disease activity and are increased in patients resistant to methotrexate and anti-TNFα therapy. As the blood serves as a convenient reservoir of cells that are easily accessible for diagnostic purposes, the authors strongly advocate the utility of tracking CPLs.

HIGH DIMENSIONAL SINGLE CELL RESOLUTION PROFILING

It is increasingly clear now that the immunological landscape is complex and heterogeneous. The inability to resolve high dimensional signals at the single cell layer with conventional technologies, irrevocably result in the concealment of unique cellular signatures in bulk data (118). The emergence of single cell technologies that permit high dimensional interrogation will provide unprecedented explosion of biological data that when interfaced with clinical perspective, can present new, exciting opportunities.

Single-Cell RNA Sequencing

Single-cell RNA sequencing (scRNA-seq) provides the transcriptome of individual cells (119), which better accounts for the stochasticity and heterogeneity in gene expression observed in populations previously thought to be similar, that now likely exist in an continuum of subsets. This is a marked improvement from traditional RNA-seq techniques that assess bulk populations and average signals from cellular populations, thereby now capturing important cell-to-cell variability that may be crucial for disease progression. In addition, scRNA-seq allows the sensitive identification of rare cell types that could have otherwise be overlooked in an analysis of pooled cells and facilitate the characterization of the spectrum of immune cell populations involved in the pathogenesis of pediatric rheumatic diseases.

Various scRNA-seq protocols have been published over the past few years, and they may be classified based on how single cells are captured and how RNA levels from a single cell is quantified. Flow-based and microfluidic technologies have been commonly used to isolate single cells: the former is ideal for selecting specific cell subsets using fluorescently-tagged monoclonal antibodies bound to specific surface markers, while the latter (e.g., Fluidigm C1) offers precise fluid control with an intricate system of valves and switches to isolate cells of interest. A modified version of conventional microfluidics technology, microdroplet-based microfluidics (e.g., 10x Genomics Chromium, Drop-seq, inDrop) allows a cell to be encapsulated in a droplet with a bead containing a unique barcode that will be attached to all downstream reads. As such, all droplets can be sequenced together in a high-throughput manner and reads accurately assigned to individual cells of origin. RNA quantification is achieved either by full-length or tag-based sequencing: while tag-based protocols only profile one end of each RNA and are hence thought to offer poorer read mappability; they are more amenable to highly parallel multiplexing and often incorporate the use of 4 to 10 bp long unique molecular identifiers that greatly reduce amplification biases (120).

The advances in scRNA-seq hardware have also spurred parallel advancements in computational handling of increasingly complex data output, which demands generic bioinformatics tools previously employed in bulk sequencing data analysis to be tailored to specific challenges in the single-cell setting. For instance, the intrinsic stochasticity amongst single cells

and technical variability from transcriptome sampling result in the violation of assumptions upon which most normalization methods are based (e.g., a stable relationship between transcript count and sequence depth), and instead introduce artifacts that bias downstream analyses (121). In response, novel regression-based and machine learning approaches that consider co-variance relationships between gene expression values have been developed to deconvolve gene expression signals for normalization and discovery purposes (121, 122).

The successes of scRNA-seq in cancer biology offer many lessons due to significant parallels with pediatric rheumatic diseases, including cell type heterogeneity, complex interactions between pathogenic cells and their microenvironment as well as immune dysregulation. For example, detailed modeling of transcriptional kinetics in individual tumor cells has facilitated the study of cancer evolution. In various cancers such as those of the intestinal and hematopoietic lineages, scRNA-seq has helped to characterize the layers of tumor hierarchies to uncover cell of origins as well as previously unknown populations that may be pathologically relevant (123). scRNA-seq has also augmented, especially in the context of pancreatic cancer, the direct detection of gene expression signatures of cancer cells separately from those of infiltrating stroma, thereby permitting better characterization of the function each component plays in tumorigenesis and unraveling more specific therapeutic targets (124, 125). Future applications for scRNA-seq in cancer are hence likely to be of considerable clinical utility in providing reliable measures for risk assessment, early stage detection and monitoring of treatment response. Relating back to pediatric rheumatic diseases, scRNA-seq technologies thus show great potential for clinical translation by enabling, across disease phenotypes, unbiased characterization of distinct immune cell subsets and their accompanying stochastic variability, discovery of unidentified cell types as well as reconstruction of lineage progression.

While current literature on pediatric rheumatic diseases has yet to showcase significant scRNA-seq analyses, early successes have already been reported in the study of adult rheumatic diseases, in particular rheumatoid arthritis (RA) and adult SLE. As synovial fibroblasts play important roles in initiating and driving RA by contributing to the proinflammatory milieu and promoting osteoclast function, scRNA-seq was used as part of a toolkit to define the molecular identity of the pathogenic fibroblasts (126). Comparing synovial fibroblasts from patients with chronic late-stage RA or osteoarthritis (OA), RA-specific transcriptomic changes were noted with 3 major subsets ($CD34^{-}THY1^{+}$, $CD34^{-}THY1^{+}$, $CD34^{+}$) identified after integrating bulk and single-cell transcriptomics. Following subsequent histological and functional assays, the $CD34^{-}THY1^{+}$ fibroblasts appeared to play the strongest role in promoting synovial swelling and inflammation. scRNA-seq has also helped to delineate SLE pathogenesis and disease complications, though studies were conducted on adult patients. For instance, transcriptomic analyses of human renal and skin biopsy samples from adult SLE patients derived a signature composed of interferon-inducible genes in renal tubular cells that correlated with clinical parameters of lupus nephritis (127). Interestingly, analysis of cumulative expression profiles of single cell keratinocytes derived from healthy non–sun-exposed skin of patients with lupus nephritis also demonstrated similar upregulation of those genes, thereby proposing the alternative use of accessible skin biopsies as a biomarker for renal disease. With concurrent advancements in sample handling ensuring reproducible downstream analysis, including a recently-published protocol verified in RA and OA for acquiring viable cells from cryopreserved synovial tissue with intact transcriptomes and cell surface phenotypes (128), tools are now in place for the profiling of human tissues for integrated analysis of immune repertoires and cell states. Moving forward, new technologies in single-cell profiling beyond transcriptomics puts forth the tantalizing prospect of multiplexing different measurements to derive a highly informative signature, thereby allowing us to better define biomarkers and therapeutic targets in pediatric rheumatic diseases.

Mass Cytometry

The mass cytometer or CyToF (cytometry time of flight) is essentially a mass spectrometer platform designed specifically to interrogate at the single cell resolution (129), examining in excess of 40 parameters. Cells are typically examined with target specific antibodies that are conjugated to rare heavy metals (lanthanides). These heavy metals are not found endogenously in the cells, which forms the basis for relative quantification of the target parameters. In traditional flow cytometry, the emission profiles of the fluorophores overlap. The spill over from the spectral emission across channels present difficulties in precise quantification. This is commonly rectified through spectral compensation by determining the ratio of spill over but eventually limits the parameters that can be resolved. On the other hand, mass cytometry detects discrete atomic masses, which avoids the need for any compensation. Current parameter limits are determined by the number of commercially available pure heavy metal isotopes, otherwise theoretical parameter limits exceed 100. Despite these advantages, mass cytometry has its constraints. Firstly, the analytical event rate is lower than that seen in flow cytometry (111), and the agitation due to nebulization causes about 30–50% of the input cells to be lost. These cells are eradicated during the process of detection, which disallows subsequent cell sorting (130). Nonetheless, mass cytometry is a promising technological development that is well-suited to unveil the complexity of biological details (**Table 5**).

Mass cytometry was performed on PBMCs from treatment-naive JDM patients and healthy controls in an attempt to understand cellular signaling (114). In combination with phospho-specific antibodies, the activation states of 14 signaling molecules were probed at baseline and after stimulation with cytokines and cross-linking antibodies. Defective phosphorylation of PLCγ2 in natural killer (NK) cells was the main signaling difference between patients and controls, whereby PLCγ2 hypophosphorylation was observed in patients. This PLCγ2 hypophosphorylation was correlated with reduced calcium flux via flow cytometry. Several studies implicate NK cells in JDM disease pathogenesis. NK cells are "lymphocytes" of the innate immune system and play roles in cancer surveillance

and antiviral defenses (131). Studies have suggested that human NK cell dysfunction may lead to the onset of autoimmunity, and the reduced calcium flux observed in Throm et al. (114) provide insights into the downstream functional consequences.

The same group also studied signaling abnormalities in polyarticular JIA and found that treatment-naïve patients displayed enhanced IFN-γ signaling in CD4 T cells and monocytes (115). Naïve CD4 T cells had more strongly phosphorylated STAT1 and STAT3 as compared to monocytes that displayed increased phosphorylation of STAT3 in patients than controls after 15 minutes of stimulation with IFN-γ. These results suggest that attenuation of IFN-γ signaling could be a possible alternative therapy for polyarticular JIA.

Pediatric SLE patients were also studied to evaluate the presence of immune dysregulation via mass cytometry. Different studies have offered conflicting information on the involvement of specific immune cell subsets in the pathogenesis of SLE. Some studies have showed that the circulating regulatory T cells are decreased while others have shown that numbers are the same while suppression of immune response is reduced (132, 133). This could possibly be attributed to the contextual nature of how studies have focused on specific aspects of the immune system rather than examining an integrated pool of information. One study tried to offer a single-cell system-level perspective of SLE by studying newly diagnosed and treatment naïve patients (116) via mass cytometry. They found that newly diagnosed, treatment naïve SLE patients had an association with distinct monocyte cytokine signatures with high monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein 1β (Mip1β) and interleukin-1 receptor antagonist (IL-1RA). Furthermore, these signatures were found to be inducible by plasma of active SLE subjects when the diseased plasma was incubated *ex vivo* with healthy donor's blood. This study shows the utility of mass cytometry in studying immune modifications in pediatric SLE, which may give us insights into disease pathogenesis.

CHALLENGES IN ANALYSIS AND SHARING OF HIGH DIMENSIONAL DATA

The advent of high dimensional data (e.g., in CyToF or scRNA-seq) presented unique challenges in deciphering and analysis; that saw the gradual acceptance of nonlinear dimensionality reduction algorithms such as *t*-distributed stochastic neighbor embedding algorithm (t-SNE) (134), uniform manifold approximation and projection (UMAP) (135) or refined variations of sorts (136). Application of these algorithms helps project the multi-dimensions onto a 2- or 3-dimensional space, allowing researchers to resolve and visualize high dimensional data. These studies also help provide unique insights to immune subset and pathway heterogeneity, in particular to pathological states.

Yet with the massive accumulation in high dimensional data across different platforms and experimental labs, the scientific field now faces the up-hill task of integrating diverse datasets and exploiting them for further data mining. One key initiative is ImmPort (http://www.immport.org/) (137) by the National Institute of Allergy and Infectious Diseases Division of Allergy, Immunology and Transplantation (NIAID-DAIT). As of 2018, ImmPort has amassed a depository exceeding 50,180 human/animal subjects from 1,369 experiments, spanning a variety of scientific data from CyToF, flow cytometry, serum and genetic markers or clinical variates. Uploading of data through this portal is performed through standardized templates with reproducible annotated descriptors. As clinical information is present, practices with regard to de-identification are strictly adhered to. Documentations such as case report forms or study protocols pertaining to clinical trials are annexed accordingly. Advance users could extract data from the portal through application programming interfaces (APIs) while immunologists equipped with basic computational skills could query the database through a graphical user interface (GUI) via ImmPort Galaxy. The authors have performed a proof of concept usage of previous clinical trial data, by identifying distinct granulocytes subsets as predictors for treatment response to rituximab in patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) (138).

Recently, the same authors demonstrated how the ImmPort data can be utilized in a massive framework through the implementation of the 10,000 Immunomes Project (10KIP) (139). The project filtered and drew 10,344 healthy individuals from the original ImmPort database, of which more than 1,000 are pediatric subjects below the age of 18. The 10KIP project serves to provide a healthy immunological control reference dataset ranging across 10 types of information including, CyToF, flow cytometry, multiplex ELISA, gene expression, and clinical variates. The healthy dataset in 10KIP was compiled through manual curation of the original ImmPort dataset through a defined list of inclusion/exclusion criteria, consisting of samples prior to experimental manipulations (e.g., stimulations). Data is provided as either (a) "formatted" which consists of data that are harmonized for their analyte nomenclature and units of measurement, or (b) "normalized" which is additionally computationally corrected for batch variations to facilitate cross study comparisons. The authors illustrated the utility and robustness of the dataset and batch corrections by reaffirming previously proven age, gender or ethnic related immunological parameter (e.g., serum cytokines, cellular subsets) perturbations shown by other groups.

The ImmPort and the spin-off 10KIP provide an exemplary demonstration how the challenges associated with integrating diverse immunomics data can be surmounted. Despite these efforts, the authors have cited several limitations that persisted (139). Firstly, the compilation of independent datasets from the original laboratories is inadvertently dependent on the accuracy of the annotations (data descriptors or labeling). The veracity of the descriptors is entirely contingent on users who upload the datasets. Next, a key issue is with regard to the heterogeneous nature of how different laboratories may collect and analyze samples and this will likely contribute to the variance in the analytes measured. Despite the demonstration of the utility of batch correction normalization, it is performed based on assumptions that may be invalid for certain studies, which

likely require further refinement. Lastly, datasets that are high in value but low in representation (e.g., numbers of RNAseq datasets were not sufficient) were omitted from inclusion in the 10KIP, a limitation dependent on user contribution or how well the platform has penetrated the community. The gradual implementation and uptake of such public databases which focus on viewing immunomics data as a whole will ultimately spur and allow tandem shifts in biological insights.

CONCLUSION

The era of immunomics provides unprecedented access to platforms that encompass a wide array of capabilities to interrogate the complexity of pediatric rheumatic diseases. We have shown how various groups have tapped on these technologies to peer into the elaborate networks of immune cell subsets and related pathways, which have in turn given us important clues to pathological mechanisms. The resulting explosion of biological data has further presented the challenge of how to best integrate and assimilate such large amounts of data into a coherent narrative.

Nevertheless, the need to improve stratification and personalization of existing therapeutic regimens as well as to provide new treatments necessitate continued in-depth research into the immune profile of pediatric rheumatic diseases. This would demand appreciation of each immunomics platform's strengths and limitations to design complementary approaches for addressing important questions. Starting from a biological sample (e.g., blood, synovial fluid), deep immune phenotyping can be first performed in an unsupervised manner (e.g., mass cytometry), so as to obtain immune signatures of diverse cell subsets. To streamline high dimensional biological information regarding the sampled cells, computational algorithms can be put in place for dimensionality reduction and functional annotation to derive relevant immune signatures. Subsequently, populations of interest can be sorted for targeted downstream analyses (e.g., RNAseq, pathway analyses, epigenetics) reiteratively and accumulated data may then be functionally validated against clinical correlates. This proposed framework permits initial unbiased interrogation of the biological sample at the single cell level that is not possible with conventional technologies, and target cell subsets can then be evaluated individually or in bulk at different levels of gene expression (e.g., genomics, epigenomics, transcriptomics, cytomics). All in all, judicious use of immunomics platforms will unequivocally identify unique cellular signatures which compose the key to unraveling the mysteries of autoimmune disease.

In addition, it is imperative to maintain close interaction among researchers, clinicians, bioinformaticians, and technologists alike for continued evolution within the immunomics field, which will definitely provide exciting opportunities for all.

DATA AVAILABILITY

No datasets were generated or analyzed for this study.

AUTHOR CONTRIBUTIONS

ST, KY, JL, JY, and TA contributed to the writing and conceptualization of the article. JL, TA, and SA helped in the revision of the manuscript.

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Translational Medicine in the Era of Social Media: A Survey of Scientific and Clinical Communities

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Background: The integration of new scientific discoveries into clinical practice costs considerable time and resources. With the increased use of social media for scientific communication, new opportunities arise to "bridge the gap" in translational medicine. The present study aimed to investigate how medical professionals access scientific information and understand their view on the role of social media in translational medicine.

Methods: A questionnaire regarding (i) the use of social media for scientific updates, (ii) the opportunities and challenges of social media for translational medicine, (iii) social media function *Chatbot*, and (iv) participant demographics was developed. The survey link was posted online from February, 2018, until April, 2018.

Results: A total of 555 professionals responded to the survey. Respondents identified themselves predominantly as researcher/scientists (27%) or medical/biomedical students (15%). The majority of participants was employed at a university or research institute (59%), and most practiced either in Europe (48%) or in Asia (37%). Seventy-eight percent of respondents reported receiving most of scientific news and updates via non-social media options, such as journal websites and newspapers. Fifty-one percent of respondents believed that social media could contribute to closing the gap between scientific discovery and translation to medical application. The most crucial opportunity created by social media was found to be "connecting the right scientist to the right clinician." Participants rated "the translation of scientific finding to clinical practice is too fast before the safety is properly demonstrated" as the most crucial challenge. Half of the respondents were aware of their institutions policy on the professional use of social media. Only 2% of respondents had previously used *Chatbot*.

Conclusions: Overall, medical professionals were positive about the idea that social media could contribute to the progress of translational medicine. However, it is clear that they are still being cautious about using social media for professional purposes. To fully harness the potential of social media on translational medicine, the medical community needs to be provided with educational programs, guidelines, and support infrastructure within social media.

Keywords: social media, translational medicine, *Chatbot*, facebook, twitter

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INTRODUCTION

The integration of new scientific discoveries, whether they be into clinical practice or into the pharmaceutical or nutritional industries, costs considerable time and resources. Most biomedical research institutions still excel in basic research. However, less effort is given to the dissemination of information to the general public. It is evident that a gap exists between the biomedical research community and patients in need of their discoveries (1). Although multiple organizations have dedicated efforts to reduce the time to implement new knowledge and research findings (2), the translation of progress made by basic, preclinical researchers into new therapies that benefit patients remains a long, difficult, and expensive process (3, 4).

Over the past decades, social media (SoMe) have aimed to connect people from all over the world, with popular SoMe forum Facebook's mission statement even being "to bring the world closer together" (5). The presence of medical journals on social media, sharing of their articles, and appearance of multiple entities that aim to explain the scientific findings to public could give rise to a new opportunity to "bridge the gap" in translational medicine. In addition to connecting medical professionals, patients and other individuals can share scientific information on SoMe as well, often adding their view on it. Moreover, large SoMe forums such as Facebook, Twitter, Instagram, and LinkedIn allow patients to organize themselves and raise both awareness and funds for topics for which they share a common interest (6, 7). SoMe also serve as a source of information for patients; thus, it is crucial for the medical community to be aware and influence the quality and assess the validity of the posted information (8). The measures to evaluate the effect of the social media in engagement of a population of interest are still being discussed and developed. Generally, the number of likes is used as the most frequent type of assessment of engagement (9); however, there are some concerns with such approach. There is a possibility that people like posts for various reasons and are not accessing or reading the content. Thus, various new measures need to be developed in order to improve the assessments of engagement by social media.

Several studies have assessed the use of social media by professionals. Mostly professionals use SoMe for personal rather than professional purposes (10, 11). There are efforts to call scientists into action to have a greater presence on SoMe as professionals (12). However, there are also skeptics that warn against potential pitfalls of social media (13, 14). Even though SoMe platforms have been around for decades, the medical society is late in embracing the use of them in a professional setting. However, SoMe are here to stay! Thus, education about the appropriate use of social media; implementation of policies from government, institutions, and professional societies; and full utilization of SoMe functions is crucial for bridging the gap between scientific discovery and clinical applications and involving the patients in all stages of translational research. Introduction of these new platforms and applications that could help to screen the information and interpret it could benefit translation of research and support clinicians and patients to find what they need in the enormous sea of facts and news.

Automated conversational tools, or *Chatbots*, have begun to receive interest in the healthcare and research spaces. *Chatbots* often accompany SoMe, however, can function as independent tools on any digital platform. A recent quick search on PubMed for the term "Chatbots" revealed 31 publications, starting from as early as 2011. While clearly a very new topic, the use of *Chatbots* is picking up in both medical practice and research studies. Such efforts are being made to create and use *Chatbots* in research and in practice, particularly in the field of psychiatry, such as mental health (15, 16); medication management (17); and behavioral interventions in obesity (18). Pereira et al. (19) conducted a search on the *Chatbots* in healthcare aiming at behavioral change. The study revealed 30 articles mainly focusing on nutritional and neurological disorders. Overall, there are multiple efforts to create *Chatbots* to support patients and healthcare professionals. However, there are no broadly used tools for this purpose. Thus, in addition to the questions regarding SoMe, this study aimed to create a better understanding about the awareness of the medical and research professionals about *Chatbots* and whether they have experience with this technology in their practice.

In order for translational medicine professionals to utilize social media to their best potential, it is necessary to better understand how participants in this field, which include both researchers and medical professionals, perceive and use SoMe and their tools. Therefore, the aim of the present study was to investigate how scientists and clinicians access scientific information and provide insights into their view on the role of social media in translational medicine.

METHODS

Survey Development

The survey was designed with the following research questions in mind: "Do professionals use SoMe for scientific updates?," "Do professionals think that SoMe can contribute to the progress of translational medicine?," "How do professionals rate potential opportunities and challenges that SoMe bring to translational medicine?," and "Do professionals use social media function *Chatbot*?" In the development of the survey, the authors aimed to include no more than 15 questions, so that it could be completed in <5 min and increase the likelihood of participation in the survey. Questions on profession, workplace, age group and geographic location were included in order to understand if professionals' attitude to SoMe is affected by any of these factors. A total of 11 questions regarding participant demographics and the research questions were developed based on consensus by all authors. An overview of the survey questions is provided in **Table 1**. The full survey including introductory text is presented in the **Supplementary Document 1**. In adherence to the guidelines of the SingHealth Centralized Institutional Review Board (CIRB), the nature of this study met with the criteria to be exempt from CIRB review.

Abbreviations: SoMe, social media.

TABLE 1 | Questions and answer options of the survey.

	Questions	Dropdown selection/Answer options
1	What best describes your position/profession?	a. Research assistant b. Researcher/scientist c. Professor d. Medical professional e. Clinician-scientist f. Medical/Biomedical student g. PhD student h. Management position (in industry, institution) i. Other (Please specify)
2	Where do you work/study?	a. University or research institute b. Academic hospital c. Non-academic hospital d. Industry (pharma, nutrition, medical device, etc.) e. Other (Please specify)
3	What is your age range?	a. Below 20 b. 20–30 c. 31–40 d. 41–50 e. Above 50
4	Where do you work?	a. Europe b. North America c. South America d. Africa e. Asia f. Australia
5	What sources do you use most to follow scientific news? (multiple answers possible)	a. Journal's websites b. Newspapers and/or news applications on mobile devices c. Update emails from journals d. Updates from your institution (website, newsletters, etc.) e. Facebook f. Linkedin g. Twitter h. Other (Please specify)
6	Do you think that social media can contribute to closing the gap between scientific discovery and its translation to medical application?	a. Yes b. No c. Maybe
7	If yes or maybe, which are the most crucial opportunities social media create? (rate 1–6)	a. Faster dissemination of scientific information b. Broader dissemination of scientific information c. Allowing open criticism of scientific discoveries d. Connecting the right scientist to the right clinician e. Facilitating the recruitment in clinical studies f. Facilitating surveys/online studies g. Other (Please specify)
8	If yes or maybe, which are the most crucial challenges social media create? (rate 1–4)	a. Distribution of fake news and incorrect conclusions b. Distribution of fraud c. Public over-reaction of un-confirmed findings d. The translation of scientific finding to clinical practice is too fast before the safety is properly demonstrated e. Other (Please specify)
9	Are you familiar with chatbot (Robot human-like conversational tool used on social media messaging platform)?	a. Never heard about it b. Yes, I've heard about it but I've never used it c. Yes, I use/have used this tool
10	Do you use chatbot (Robot human-like conversational tool used on social media messaging platform) for your work?	a. Yes b. No
11	Are you aware about your institutions policy on the professional use of social media?	a. Yes b. No

Survey Distribution

The survey was uploaded to online survey platform *SurveyMonkey* using the ADVANTAGE Team plan and was distributed via a number of forms of communication, represented in **Table 2** and **Supplementary Document 2**. In addition, the link could have been shared by respondents via

TABLE 2 | Survey distribution.

Source[a]	Estimated number of individuals reached
Singapore Women in Science	310
Eureka Institute alumni	241
Apollo Society chapters in Utrecht	30
Apollo Society chapters in Toronto	100
SingHealth	22,698
*Institute of Medical Biology A*Star*	300
Karolinska Institute facebook page	30,566
Utrecht University Medical students facebook pages and website	1,800
Utrecht Institute for Pharmaceutical Sciences	58
Personal *LinkedIn accounts, views*	763
Personal *Twitter accounts, views*	27
Personal *Facebook accounts, views*	81
Emails to personal professional connections	494
Total	57,468

[a] *The survey was distributed to personal contacts, social media forums, and through several scientific organizations. A brief description and the websites of these organizations are provided in* ***Supplementary Document 2****.*

their personal social networks and emails, which we would have been unable to track. Thus, the total number of approached professionals was estimated at 57,468.

The survey was launched on the 5th of February, 2018. The survey results were downloaded on the 25th of April, 2018.

Data Analyses

Prior to survey conduct the margin error was set to be below 5% with 95% confidence interval. We estimated that the medical and biomedical scientific community consists of 10^7 doctors and 10^7 biomedical scientists (20). As the survey outcomes are based on proportions and assuming the most conservative standard deviation when the proportion is 50%, a minimum of 385 respondents would be required based on an online calculator with a 5% margin of error (21, 22).

The analysis was performed using *SurveyMonkey* filtering and comparing tools and *Graphpad prism* (version 6). The number of respondents was converted into proportions and these were then compared. Subgroup analyses were performed for profession, workplace, age group and geographical location. The total number of individuals in the group was set as 100 percent and the responses for the respective question were compared. Bonferroni correction for multiple group comparison was applied.

RESULTS

In the 11 weeks that the survey link was online, the total number of respondents reached 555. As explained in the methods section, a minimum of 385 respondents was calculated to lead to a margin error <5%. The response rate in this study of 555 respondents led to a margin error of 4.16% (22).

TABLE 3 | Respondents characteristics.

Characteristics	*N* = 555
Profession, *n* (%)	
Researcher/scientist	150 (27)
Medical/biomedical student	82 (15)
Medical professional	72 (13)
Professor	56 (10)
Management position	53 (10)
Clinician-scientist	43 (8)
Ph.D. student	38 (7)
Research assistant	27 (5)
Other	32 (6)
Participant skipped question	2 (0)
Workplace, *n* (%)	
University or research institute	329 (59)
Academic hospital	111 (20)
Industry	68 (12)
Non-academic hospital	26 (5)
Other	21 (4)
Age group, *n* (%)	
Below 20	8 (1)
20–30	161 (29)
31–40	192 (35)
41–50	130 (23)
Above 50	64 (12)
Geographical location, *n* (%)	
Europe	268 (48)
Asia	203 (37)
North America	64 (12)
Australia	11 (2)
South America	7 (1)
Africa	0 (0)
Participant skipped question	2 (0)

Demographics of Survey Respondents

An overview of the demographic characteristics of the survey respondents is provided in **Table 3**. Of those individuals that participated in our study, the highest percentage identified themselves as researcher/scientist (27%), followed by medical/biomedical student (15%) and medical professional (13%). The majority of participants were employed at a university or research institute (59%). The age of survey participants was grouped into several categories. The highest proportion of participants were between the ages of 31–40 years (35%), followed by 20–30 year olds (29%). While surveys were distributed through contacts world-wide, most participants indicated that they worked in either Europe (48%) or Asia (37%). There were no respondents from Africa.

Sources of Scientific News

One of the possible functions of SoMe is information sharing. In survey question 5, participants shared their use of SoMe vs. other resources to update themselves on scientific news. A majority

of participants (77.6%) reported receiving most of scientific news and updates via non-social media options (**Figure 1A**). The most utilized non-social media outlets included journal websites, newspaper or news applications on mobile devices, update emails from journals and updates or newsletters from the professional's individual institution. Of the 22.4% of respondents that used social media as a means to receive scientific updates, participants relied on Facebook, Linkedin, and Twitter.

Social Media in Closing the Gap Between Scientific Discovery and Its Translation to Medical Application

When asked if social media could contribute to closing the gap between scientific discovery and translation to medical application, half of the respondents (50.5%) said "yes," while 41% answered "maybe" and 8.5% answered "no" (**Figure 1B**). When comparing these answers for subgroups, several differences were found to be statistically significant (i.e., had a P-value < 0.05). Based on profession, significantly more researchers/scientists said "yes" then did professors, clinician-scientists and students. Significantly more researchers/scientists indicated that they believe SoMe can contribute to translational medicine compared to those who said "no," while significantly more professors said "maybe" compared to those who said "yes" (**Supplementary Figure 1A**). Lastly, significantly more students said "no" compared to those who said "yes." Answers differed for age groups as well. The most optimistic age group was the 31–40 year olds, where significantly more respondents said "yes" compared to those who said "no" (**Supplementary Figure 1B**). No significant differences in responses to this question were found between respondents working in different geographic locations or types of workplaces (**Supplementary Figure 1C** and data not shown).

Opportunities and Challenges of Social Media in Translational Medicine

The respondents were asked to rate the most crucial opportunities that SoMe create, with a rating of 1 indicating the highest priority and 5 indicating the lowest priority. They scored "connecting the right scientist to the right clinician" as the most crucial with an average score of 2.85 (**Figure 2A**). "Facilitating the recruitment in clinical studies," "allowing open criticism of scientific discoveries," and "facilitating surveys/online studies" scored 3.01, 3.1, and 3.2, respectively. The potential opportunities found to be least crucial were "broader dissemination of scientific information" and "faster dissemination of scientific information," scoring 4.71 and 4.8, respectively.

The respondents scored "the translation of scientific finding to clinical practice is too fast before the safety is properly demonstrated" and the "distribution of fraud" as the most crucial challenges with average scores of 1.9 and 2.08, respectively (**Figure 2B**). "Public over-reaction of unconfirmed findings" and "distribution of fake news and incorrect conclusions" were believed to be less crucial at 2.95 and 3.34, respectively.

Institutional Policy on the Professional Use of Social Media

Of the 555 participants, responses were split ∼50 and 50% with those that were aware and those that were not aware of their specific institutions policy on the professional use of social media (**Figure 3A**). Those that were most aware were clinician-scientists and respondents in management positions (**Figure 3B**). Those that were the least aware were PhD students and researcher/scientists. Overall, those employed by industry or academic hospitals were more likely to be aware of the institutions policy on SoMe usage compared to those in non-academic hospitals and university/research institutes (**Figure 3C**). There was a similar level of understanding (∼50:50) among all age groups except in the under 20 group, which was the smallest age group; in the under 20 group only 1 out of 8 respondents was aware of the social media policy of their institution (**Figure 3D**).

Familiarity With and Usability of Chatbot

Participants were asked if they were familiar with *Chatbot*, a robot-like conversational tool used on social media messaging platforms. *Chatbot* is an example of functions within SoMe that can be used by professionals to search for information. Of the 550 participants that answered this question, 45% responded that they had "never heard about it (i.e., *Chatbot*);" while 43% answered "yes, I've heard of it but never used," and only 17% responded "yes, I use/have used this tool." Five hundred and fifty-two of the participants responded to the question "do you use *Chatbot* for your work?" A majority of 98% of respondents answered "no" to this question (**Figure 4** and **Supplementary Figure 2**).

DISCUSSION

The last decade has completely re-shaped the way in which we communicate. It has become clear that internet-based communication is growing and all fields of life have to adapt to its use, including the medical and research communities. Communication on SoMe forms a large part of internet-based communication and plays a crucial role in science information sharing, discussion and implementation of scientific discoveries. However, we are still learning how to properly use SoMe, while also assessing the associated risks and benefits. In order to utilize social media outlets to their best potential, while minimizing their disadvantages, it is important to first understand how social media are being perceived and utilized by members of the translational medicine community.

The survey respondents in this study—predominantly research scientists, medical professionals, and students—are still relying on conventional non-social media methods, albeit more often online, for reliable scientific news. Respondents speculated that the gap between discovery and translation could be bridged by SoMe, but at the same time feared that premature dissemination of results might be unsafe. Moreover, dissemination of fraud "fake" news was felt to be a problem. Tools such as *Chatbot,* which may help professionals fish for

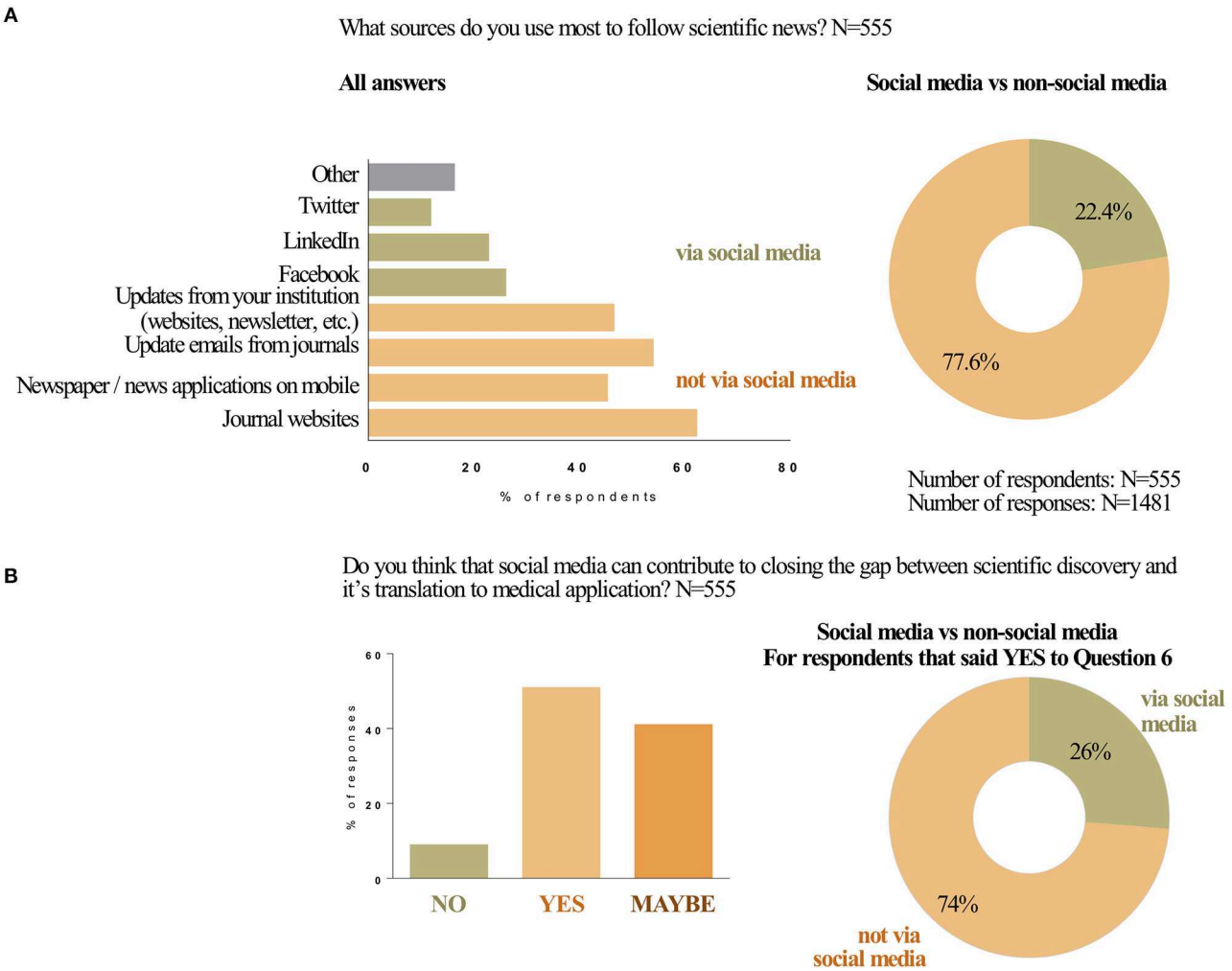

FIGURE 1 | Social media in translational medicine. Use of social media for scientific updates **(A)**. What sources do you use most to follow scientific news? Responses to Question 5 of the survey are plotted in the bar graph. For the doughnut graph the responses were combined for all social media (Twitter, Facebook, and Linkedin) and for non-social media sources (Journal's websites, Newspapers and/or news applications on mobile devices, Update emails from journals, Updates from your institution). Can social media contribute to closing the gap between scientific discovery and its translation to medical application **(B)**? Doughnut graph represents the use of social media (Question 5) by those who responded YES to Question 6.

information on SoMe, seem to be utilized only minimally amongst the survey respondents. This could be for several reasons: there are still too few *Chatbot* tools that exist for research and/or medical advice or professionals are less aware about opportunities that *Chatbot* presents (23, 24).

In this study population, less than one-third of the medical community utilized SoMe for scientific news. This may suggest two things: (1) the medical community has not changed its way of looking for reliable scientific information or (2) the scientific journals have just started utilizing the power of SoMe in transmitting scientific information to professionals. In this study, specialized scientific social networking sites such as *ResearchGate* and *Mendeley* were not included in the popular list. However, among the answer "others," only a few participants listed *ResearchGate, Medscape,* and *Google Scholar*.

Despite the smaller proportion of the scientific community relying on scientific news in SoMe more than half indicated that they "believed" that it has the potential to close the gap between scientific discovery and its translation to medical application. This may suggest that the society is in a transition phase between starting to explore the functions of SoMe and fully utilizing them professionally. Interestingly, the number of students in the survey that were optimistic in their belief that SoMe could close the gap between scientific discovery and translation to medical application was relatively small compared to researchers. We could not explain this phenomenon due to the small sample size and lack of additional data. If this finding is indeed true, it may be necessary to familiarize the student community with social media tools in translational aspects of medicine and consider adapting our education programs to include the use of SoMe training.

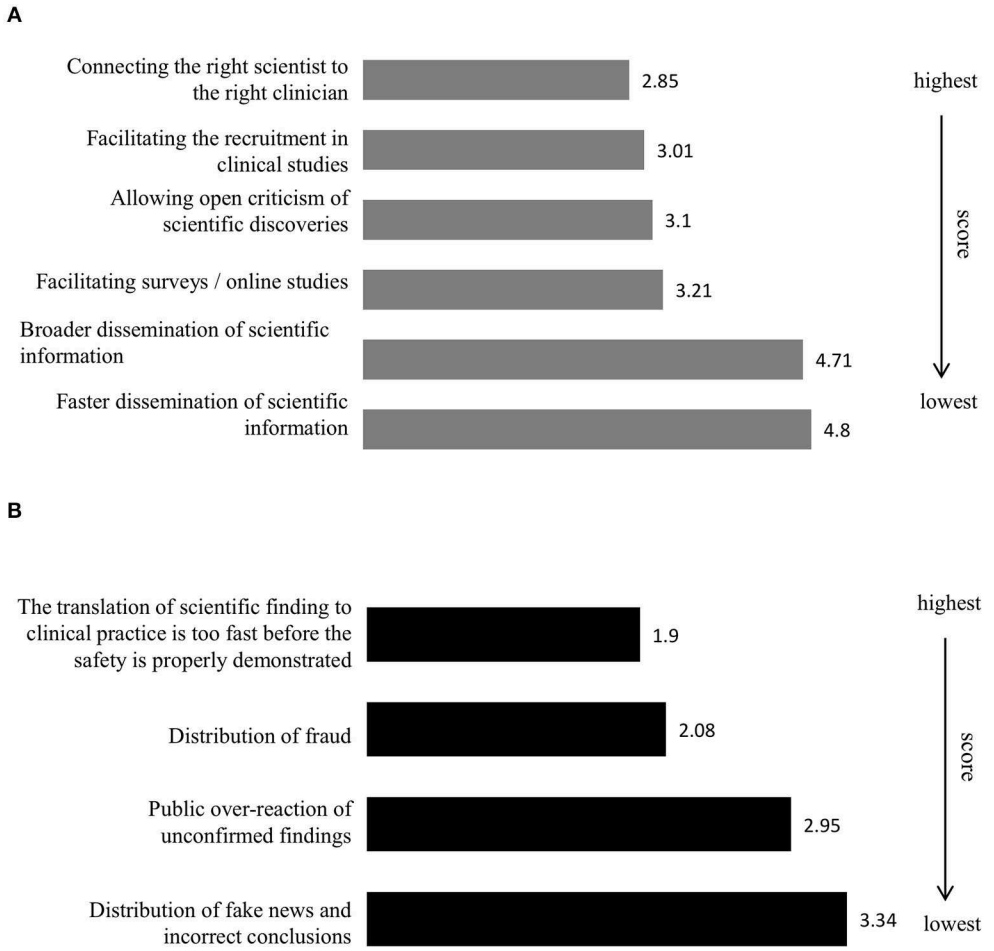

FIGURE 2 | Opportunities and challenges of social media in translational medicine. The most crucial opportunities social media create **(A)** (Q7) [If you answered yes or maybe to the previous question, which are the most crucial opportunities social media create (rate with 1 being the highest)]. The most crucial challenges social media create **(B)** (Q8) [If you answered yes or maybe to question 6, which are the most crucial challenges social media create (rate with 1 being the highest)]. Average score from all the respondents for each statement have been calculated and presented in the bar graph.

The favorite opportunity that the majority researcher/scientist respondents sought for social media to address was "to connect clinician and scientist," which is an important step in translational research. It may also be a challenge with only 8% clinician scientists responding in this survey. This can be noted by policy makers in bridging the communities through better usage of SoMe platforms within institutes, across scientific communities, and the public. Embracing SoMe in disseminating knowledge and research in public health seems to be adopted by many scientific (9, 25, 26) and patient forums already (27). Dissemination of internal policies to the students and researchers seems a priority in this respect, as they were least aware of the SoMe usage rules within their institutes.

There are tools available for professionals to utilize for "recruitment and clinical trials," such as *Chatbots* (12) and text mining approaches (28). However, the actual usage seems to be poor. While adaptation to such tools may be considered, caution should be exercised as these can also be subjected to trolling, privacy and other ethical issues (29). Any workshop or awareness program in this respect should engage ethical and technical experts to caution the "tech-naïve" medical professionals. It is no surprise that the "broader and faster dissemination of scientific knowledge" component of SoMe seems to be less appealing to a medical community. However, with more time spent on SoMe by the current and future generation, it may only be prudent for the scientific community to tap on this opportunity to disseminate new scientific information through SoMe in a reliable and realistic manner.

"Distribution of early clinical trials to patient community and false information" is undoubtedly the biggest challenge aspect surfacing in this survey, and it will prove to be a challenge that need to be tackled by the medical community in future (2, 13, 30). In this context, an active participation of the journals in disseminating such information, especially after subjecting the content to peer review before publication, may alleviate such issues.

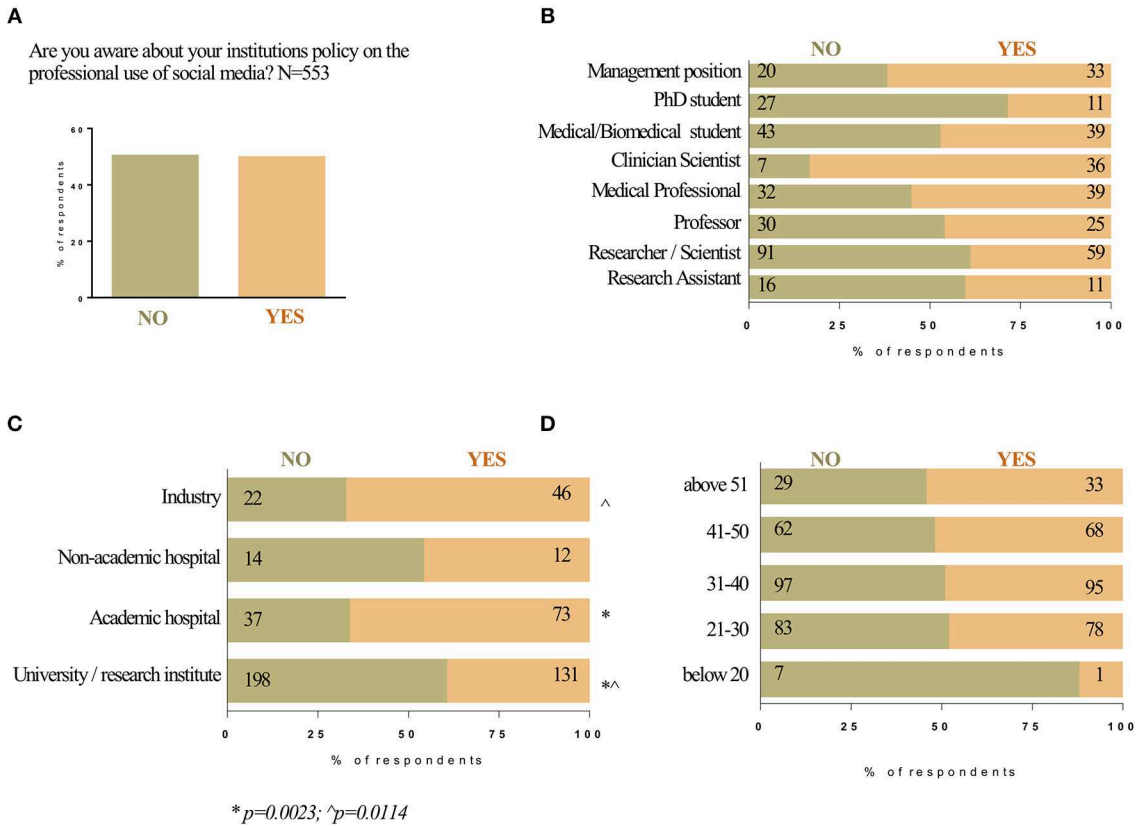

FIGURE 3 | Awareness about own institution's policy on use of social media. The responses to Question 11, "Are you aware about your institutions policy on the professional use of social media?" are shown on the column graph in percentages **(A)**. Institutions policy and occupation **(B)**. Institutions policy and workplace **(C)**. Institutions policy and age **(D)**. The bar graph illustrates the percent of each occupation/workplace/age group of the respondents that answered with NO (olive bar) and YES (light orange bar) to Question 11. The numbers at each side of the bar indicate the number of responses for NO/YES for each occupation/workplace/age group.

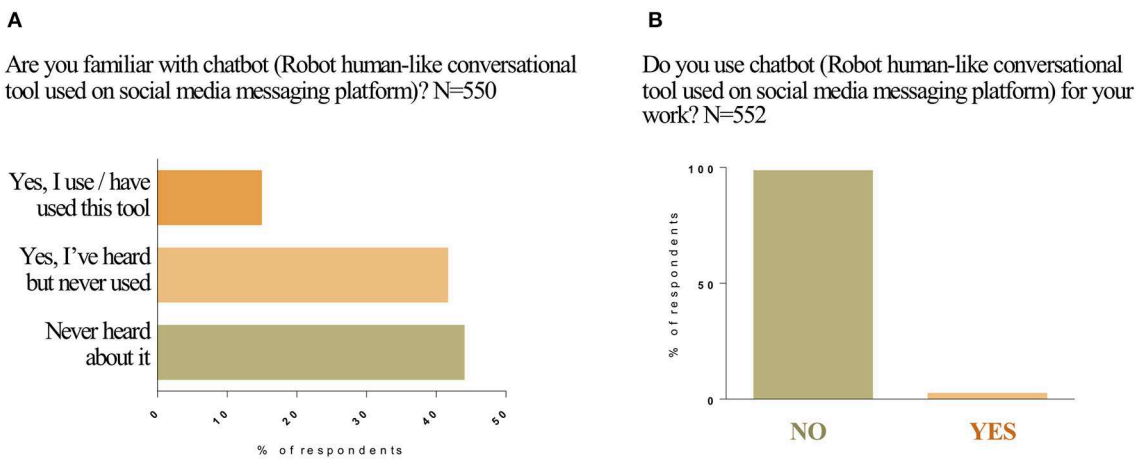

FIGURE 4 | Awareness and use of *Chatbot*. Are you familiar with Chatbot **(A)**? Do you use Chatbot for your work **(B)**? Responses to Question 10 were plotted on the column graph in percentages.

The growth of platforms for interactions of professionals, such as *Labspaces, Sermo, DailyRounds, Among Doctors*, and others might be beneficial for the purpose of interaction of within professional groups (31). However, they do not integrate other professions or members of the public. Another approach would be to create pages or groups

within bigger social media portals, mainly Twitter and Facebook (12, 32).

In the present survey study, the focus of the analysis was on the whole community of medical professionals and researchers. Some of the occupations might be under-represented, such as PhD students, clinician-scientists and research assistants (**Table 3**). Future studies should focus on these groups specifically to understand the use of SoMe. The present study was also limited by its low representation of professionals working in Africa and South America. It would be interesting to conduct a survey focusing on Africa in particular, as this is the continent with lowest internet and SoMe penetration, whereas North and South America have comparable internet and SoMe use (33, 34). The growing use of social media in Africa is an opportunity for dissemination of truthful information and engagement of the African community. Groups from trusted universities have the capacity of engaging new readers. Online educational programs for the use of social media would also be able to reach a bigger audience. Moreover, in this survey study, we focused on scientists and medical professionals. Clearly, there are other professions that contribute to translational medicine such as clinical study specialists, statisticians and data managers, patent attorneys, legal professionals who work with research and development, hospital and institutional administration, science communicators, patients, venture capitalists, and others. In order to complete the picture, future studies would need to assess the holistic relationship of all the people involved in the path of science creation and translation to medical applications, which will also include the end users' (i.e., patients) inputs.

The current study also puts social media to the test in conducting the actual research presented in this study. Only a small fraction of people whom the survey could potentially reach chose to participate (555 out of 57,468). Thus, future strategies for dissemination of such research which utilizes SoMe as the only outlet needs to consider the limitations for this method for dissemination. While common methods to bolster engagement include paid advertisement of the surveys, attracting influencers with significant followers and other innovative solutions, one must take into account that certain countries and age groups may not respond to such surveys on SoMe for a wide variety of unknown and unpredictable reasons.

Our study highlights that there is a clear need for specific educational programs and guidelines to be provided to the medical community in order for participants to harness the potential of SoMe on advancing discoveries and treatments in translational medicine. Such programs could include courses in universities dedicated to SoMe opportunities, pitfalls, and use. There should be courses with continual medical education (CME) credit points for educating the current workforce. In addition, SoMe could also be utilized for education purposes via scientific journals or university groups. Finally, encouraging more research in this area would also improve our understanding and help to grow the capable community to utilize SoMe to the full potential.

In conclusion, we found that the overall awareness of social media's role in translational medicine was realized by the medical community in this survey, but there seems to be lack of practical applications and utility. Educational programs and guidelines may provide the medical community with the tools to harness its potential.

ETHICS STATEMENT

In adherence to the guidelines of the SingHealth Centralized Institutional Review Board (CIRB), the nature of this study met with the criteria to be exempt from CIRB review.

AUTHOR CONTRIBUTIONS

ES created the online survey and performed the statistical analyses. SD edited the manuscript. ES, JL, MB, and SD contributed to the survey development, data acquisition, and writing of this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2019.00152/full#supplementary-material

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Building a Professional Identity and an Academic Career Track in Translational Medicine

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Biomedical scientists aim to contribute to further understanding of disease pathogenesis and to develop new diagnostic and therapeutic tools that relieve disease burden. Yet the majority of biomedical scientists do not develop their academic career or professional identity as "translational scientists," and are not actively involved in the continuum from scientific concept to development of new strategies that change medical practice. The collaborative nature of translational medicine and the lengthy process of bringing innovative findings from bench to bedside conflict with established pathways of building a career in academia. This collaborative approach also poses a problem for evaluating individual contributions and progress. The traditional evaluation of scientific success measured by the impact and number of publications and grants scientists achieve is inadequate when the product is a team effort that may take decades to complete. Further, where scientists are trained to be independent thinkers and to establish unique scientific niches, translational medicine depends on combining individual insights and strengths for the greater good. Training programs that are specifically geared to prepare scientists for a career in translational medicine are not widespread. In addition, the legal, regulatory, scientific and clinical infrastructure and support required for translational research is often underdeveloped in academic institutions and funding organizations, further discouraging the development and success of translational scientists in the academic setting. In this perspective we discuss challenges and potential solutions that could allow for physicians, physician scientists and basic scientists to develop a professional identity and a fruitful career in translational medicine.

Keywords: translational medicine, translational scientist, basic scientist, physician scientist, career track, biomedical sciences

BUILDING A BRIGHTER FUTURE FOR TRANSLATIONAL MEDICINE

Biological and medical research has greatly excelled during the last 50 years with huge advances in understanding disease pathogenesis. Despite these advances, a large "translational gap" exists in linking promising scientific discoveries to therapeutic interventions that improve the outcome of disease (1, 2). The United States National Institute of Health's National Center for Advancing Translational Sciences (NCATS) defined translational science as "the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and populations—from diagnostics and therapeutics to medical procedures and behavioral interventions." The possibilities for translational scientists, whether they are physician scientists or basic scientists, to bring observations from the laboratory to the patient and vice versa has never been greater. Yet, important barriers exist, that prevent the participation of biomedical scientists in the field of translational medicine (**Table 1**). While physicians have been traditionally considered as the most likely candidates to drive the translational scientific field from the bench to bedside because of their direct interactions with patients, the number of physicians engaged in research has steadily decreased by almost 50% between 1985 and 2012 (3). Their participation has been inhibited by a variety of previously identified factors including - but not limited to - a lengthy training pathway, difficulties establishing a career in science alongside practicing medicine, and accumulation of extensive debt during training (4, 5). In turn, basic scientists face their own specific obstacles when pursuing a career in translational science, such as having limited access to patients and clinical data, and poor alignment of the academic career and promotion track with the timeline of translational research. In addition, there are common challenges faced by both physicians and basic scientists due to the unique position of translational science bridging academic and clinical environments. The field of translational science meets a great need to better connect science and medicine. However, the unique requirements that come with interdisciplinary and long-term research projects are vastly different from the traditional way by which we currently approach biomedical research. In this perspective we discuss challenges and potential solutions that could allow for physicians, physician scientists, and basic scientists to develop a professional identity and a fruitful career in translational medicine. We hope that this perspective will increase awareness of existing limitations in biomedical sciences and spark discussion about the significant shifts needed to move biomedical sciences toward a future in which new knowledge is optimally translated into improved medical care.

TRAINING TRANSLATIONAL SCIENTISTS SHOULD BE INTERDISCIPLINARY AND COLLABORATIVE

Clinical practice and research are two separate disciplines, and training as a scientist alongside obtaining a medical degree is arduous. Medical training has historically been long and expensive, and has lengthened over time. In addition, trends in MD program curricula are shifting toward more specialization, increased focus on health care systems and delivery of care, and include less scientific knowledge that informs pathobiology and treatment of disease. In response to these forces, the American National Institute of Health (NIH) created the Medical Scientist Training Program (MSTP) to train physician scientists (https://www.nigms.nih.gov/training/instpredoc/Pages/PredocOverview-MSTP.aspx). MSTP trainees follow an integrated training in biomedical science and clinical practice, and receive a stipend and tuition allowance that helps reduce debt accumulation. However, the program is very competitive and currently supports merely ∼1,000 students. Programs with similar intent exist in Europe (e.g., AKO program, Maastricht University, The Netherlands), where a 4-years master program combines patient-oriented research and medical practice with the goal of translating the results of scientific research into the practice of patient care. However, like the MSTP, this program supports only a limited number of students.

Basic scientists receive highly specialized training, the nature of which is strongly influenced by their mentor and a small committee of professors with a similar research focus (6). As a result, graduate training is prone to have limited breadth and scope. Further, trainees are often discouraged to venture outside the scope of their thesis to explore independent projects as they are expected to work on a project of their mentor and to graduate within an acceptable time (**Table 1**). In contrast, success as a translational scientist requires training in collaborative and interdisciplinary environments (3). Not only is close collaboration within diverse teams of scientists and clinicians essential, translational medicine also involves participation from non-scientific stakeholders such as intellectual property officers, investors, patient advocacy groups, ethicists, and regulatory bodies. Although the strength of the team comes from the separate expertise of individuals, a common understanding of the entire process of translational medicine—including the diverse background, priorities and language of team members—is critical for successful teamwork. Diversity in a team increases creativity and likelihood of genuine innovation (7). Therefore, training in an interdisciplinary environment is essential for basic scientists to excel in translational research.

Considerable investment to develop and improve core programs supporting research career tracks in translational medicine has been made in the last two decades, and advanced degree programs in Translational Research have been established in many universities. Postdoctoral and pre-doctoral candidates participating in translational medicine programs are exposed to courses and research projects focusing on topics such as team building, translational science, clinical research, epidemiology, translational therapeutics, entrepreneurial sciences, and biomedical informatics. Interestingly, despite the fact that a large number of these academic programs are available to basic scientists and physicians alike, it seems that physician scientists are more likely to enroll in translational programs. For example, the large majority of registered students (∼68%) for the Master of Science in Translational Research at the University

TABLE 1 | Summary of major problem encountered by scientist pursuing a career in translational science and proposed solutions.

Problem	Proposed solution
The incentive and reward system within academia is poorly aligned with a career track in translational medicine	Academic institutions need to establish better evaluation processes for retention and promotion of their translational scientists: - Using metrics that recognize the wide range of potential contributions to translational medicine (clinical or social impact of the work, the degree of risk and innovation, the success in establishing multidisciplinary collaborations, reaching of specific milestones along the path of a project that could take long to complete, the successful launch of a product or clinical trial, and their involvement with and recognition by patient advocacy groups) - Clear guidelines on how individual contributions to large multidisciplinary efforts are evaluated and measured - Individualized or extended tenure clocks that are more proportional to the potential impact and better reflect the timelines of the work
The number of clinician scientists is declining due to longer training, high education costs and challenges combining clinical service and research	- Integrated training in biomedical science and clinical training, with a stipend and tuition allowance that helps reduce debt accumulation - Recognition that clinical care and research enrich each other, and clear expectations about the efforts made toward each appointment
The highly focused training of basic scientists with limited interdisciplinary or clinical exposure poorly prepares basic scientist for the collaborative nature of translational medicine	- Training in an interdisciplinary environment, including exposure to the clinic, will prepare basic scientists to excel in a collaborative translational research environment - Actively recruiting and encouragement of participation of basic scientists in existing advanced degree programs in Translational Research with courses and research projects focusing on team building, translational science, clinical research, epidemiology, translational therapeutics, entrepreneurial sciences, or biomedical informatics
The unique requirements of translational medicine, such as significant longer timelines, much larger number of lab members that can be funded with an average grant, larger overhead costs extending beyond the immediate duration and focus of the project, are not met by the current funding system	- Adjust time lines of grants, possibly by making funding for the next phase conditional on researching milestones - Divide increased costs, for example by requiring matching external funding from the research institution, an industry partner, or a patient advocacy group - Encourage young scientists to pursue a career in translational medicine by specifically providing funding for early-career scientists in their translational grants, and by removing restrictions such as a "time-since-PhD limit" on all personal fellowships in recognition that research does not always follow the anticipated timescale
Building an infrastructure to promote education and research in translational medicine is a resource-intensive enterprise	- Creation of and funding for centralized "hubs" or "cores" that are characterized by shared, multidisciplinary use of expensive laboratory equipment, data power and complex professional skills (e.g., genomics, imaging, flow cytometry, animal facilities, data, and biobanking) that are necessary to support large translational research projects - Create a collaborative and interdisciplinary environment where basic scientists and physician scientists, clinical personnel, patients and intellectual property officers interact regularly to support new thinking and to promote translational research

of Pennsylvania were participants in an MD or an MD/PhD program, while PhD candidates formed only 7% of the student pool (As of August 2018, http://www.itmat.upenn.edu/mstr-alumni.html). Research institutes have an incredible opportunity to improve their translational medicine programs by actively recruiting more basic scientists to help create a more diverse population of researchers needed for a well-rounded translational medicine program.

CAREER EVALUATION AND ADVANCEMENT OF TRANSLATIONAL SCIENTISTS

Practicing physician scientists reported major challenges that limit the ability to engage in both clinical practice and research, with difficulty of balancing time between clinical, research, and teaching responsibilities as leading obstacle (5). Physician scientists are often affiliated with multiple clinical and research departments, each having different objectives and interests. Such shared appointments can easily lead to under appreciation of the efforts of the physician scientist when individual departments regard time spent in the other department as "lost time," preventing the physician scientist from making a full contribution to their mission. Instead, clinical and research contributions should be evaluated in concert and departments should value the unique insights and experience a dual appointment can bring.

Performance and progress of basic scientists is mainly evaluated by the number of publications and authorship rankings, and by the amount of funding secured. The current review system and associated metrics result in pressure to publish promptly and frequently. These dynamics are important contributors to the increasingly recognized problems such as lack of reproducibility, invalidated data, avoidance of risky or team-oriented projects, and ultimately research waste (8–12). Furthermore, publication impact is quantified using parameters such as journal impact factor or H index, numbers that do not correlate with the quality or the social impact of the published work (13). Another limitation of this publication-driven environment is that

individual contributions are impossible to discern and only first and last authors are fully recognized—although multiple journals now require a thorough description of individual contributions of each author in an attempt to give credit where due.

A large part of the solution resides in establishing evaluation and promotion processes that are more consistent with the goal of translational medicine: to improve human health. Because the nature of translational medicine is vastly different from current academic customs, academic leadership will first have to actively promote and reward a collaborative and translational scientific culture. Only when the value of translational science is well-embedded in the culture of universities, can evaluation criteria be developed that are better aligned with the requirements of translational science. Appraisal metrics should no longer rely primarily on number of publications and grants, but also recognize the wide range of potential contributions to translational medicine. A portfolio of "productivity" should be considered where not just the number of publications is included but also the potential clinical or social impact of the work, the degree of risk and innovation, successfully establishing multidisciplinary collaborations, reaching of predefined milestones within a continuing project, the launch of a product or clinical trial, and involvement with and recognition by patient advocacy groups. Institutions need to create clear guidelines that are well-disseminated on how individual contributions to large multidisciplinary efforts are evaluated and measured. These might include specific metrics for the different domains of the project: design, execution, and analysis in the basic science and clinical realm as evaluated by reviewers who can assess those individual contributions. Such a renewed evaluation process also requires a different composition of review committees, including interdisciplinary expertise from researchers, clinicians, and other healthcare professionals. Consideration should be given to individualized or extended tenure clocks that are more proportional to the potential impact of the research and better reflect the timelines of the work.

TRANSLATIONAL SCIENCE REQUIRES A DIFFERENT FUNDING SYSTEM

A challenge faced by all translational scientists is that the unique requirements of translational medicine are not met by the current funding system. For example, the timeline of translational science is significantly longer than the duration of most funding cycles. In addition, a multidisciplinary translational team is much larger than the average number of lab members that can be funded with a grant. Lastly, the overhead costs in translational science are large and often extend beyond the immediate duration and focus of the project. An example is the development and maintenance of a biobank. Collecting well-preserved patient material over extended periods of time can be of crucial value to multiple translational research groups and projects, but in the current funding climate it is difficult to secure sufficient and long-term funding for such an endeavor. Research institutions could play a key role by creating an infrastructure that would allow long-term coverage of such shared resources, for example by creating a Translational Science Institute with a leadership that actively pursues funding for core facilities, e.g., through donors or collaborations with industry.

Securing independent funding has become more challenging, particularly for young scientists (14). The hypercompetitive funding situation has led to an academic environment that discourages collaboration, sharing of resources and open science practices, and the risk of pursuing projects that are either long, novel or difficult (15). The strict criteria and timescales for eligibility and outputs of early-career grants further encourage the pursuit of readily publishable research. In the UK, the Medical Research Council, Cancer Research UK and the Wellcome Trust have now removed their time-since-PhD limit on all personal fellowships in recognition that research does not always follow the anticipated timescale. Funding agencies could further encourage young scientists to pursue a career in translational medicine by specifically providing funding for early-career scientists within larger translational grants. Most beginning scientists have not built a large network yet, which makes it difficult to serve as the principal investigator and form a translational team needed to secure funding and make large project succeed.

Translational research is a long-term endeavor with uncertain outcome, and it is understandable that funding agencies have reservations committing large sums of money to such risky projects. A solution could be to make funding conditional. Continued funding could depend on performance and intermediate results, such as the milestone-driven disbursement program of the California's Stem Cell Agency (https://www.cirm.ca.gov/researchers/managing-your-grant#payment). For example, the funding agency could fund the patent and a dose-response study only if animal toxicity studies proved successful. Another model of conditional funding is to require the additional funding from a different source. A funding agency could provide 80% of funding for a project on the condition that the other 20% is covered by a third party. This would be another example of how having an overarching Translational Science Institute could facilitate connections between promising projects and potential funding opportunities. By dividing costs and incorporating intermediate milestones, the risks for funding agencies are kept to a minimum. In addition, translational research, in and of itself, reduces the risk associated with large, long-term projects by internal peer review. Because translational research teams are composed of experts with different backgrounds and skill sets, they can create innovative ideas while simultaneously the individual group members serve as peer-reviewers of their team members and as such many pitfalls will be obviated.

Many private and public funders are now seeking to promote collaboration and network building between academia and industry, incentivizing scientists to "think big" and connect to experts that can help translate their findings (e.g., funding

for translational medicine by the NCATS, the Collaborative science award of the American Heart Association, and the private-public-consortium subsidy "Health-Holland"). This new recognition of necessity to actively facilitate translational research pathways has come about through funders' deeper knowledge of their own funding successes and failures, and pressure to be more transparent and accountable to stakeholders and beneficiaries. Taken together, funding agencies are in a position to take the lead to reform the scientific climate and promote translational research and its benefits to society. By developing a grant system specifically for translational research, large funding agencies can promote interdisciplinary research while accommodating long-term timelines inherent to translational research. By staying in dialogue with the scientific community and adjusting funding structure to the current needs, funding agencies will ultimately see a larger return for their investments and a greater impact in improving human health.

TRANSLATIONAL SCIENTISTS REQUIRE A MULTIDISCIPLINARY INFRASTRUCTURE TO SUCCEED

Building an infrastructure to promote education and research in translational medicine is a resource-intensive enterprise. Data suggest that it can show a return on investment (16–18), however such an infrastructure requires a substantial and long-lasting investment of money and time in trainees, mentors and core research facilities. Development and maintenance of adequate shared infrastructures is also considered a major goal for academic centers promoting translational research programs (19, 20). Centralized "hubs" or "cores" that are characterized by shared, multidisciplinary use of expensive laboratory equipment, data power and complex professional skills (e.g., genomics, imaging, flow cytometry, animal facilities, data, and biobanking) are a necessity to maintain institutional competitiveness among universities and research centers around the world. As an example, a central hub named EATRIS (European Research Infrastructure Consortium) was created across Europe to create a proper infrastructure for translational research and it currently includes over 80 top-tier academic institutes (https://eatris.eu). In addition, many universities have started to developed their own infrastructure to support translational research. Examples are valorization offices—tasked with putting academic knowledge to practical use, through offering advice on collaboration with third parties, intellectual property and support for licensing, patenting and entrepreneurship—and a wide variety of incentives for researchers to engage in knowledge transfer activities and focused on the importance of shared biobanking (e.g., BBMRI-ERIC, http://www.bbmri-eric.eu/) and data sharing (e.g., ELIXIR, https://www.elixir-europe.org/) (21).

In similar fashion, hospitals and healthcare providers, tempted by the highly interactive research and clinical care aspects of translational medicine, have started to bring biomedical research and healthcare delivery together inside one highly collaborative space. Case in point, The Shirley Ryan AbilityLab, a rehabilitation hospital born in 2017 from the ashes of the Rehabilitation Institute of Chicago (RIC) is an example where clinical and research laboratories have become the heart of the institution and are both horizontally and vertically integrated and connected to patient care. Another example is the recently opened Princess Maxima Center for Pediatric Oncology in the Netherlands, where an environment is created where research scientists and physicians, clinical personnel, patients and intellectual property officers interact regularly to support new thinking and to promote translational research. The hope is that this milieu, where research is brought to the patient and not the other way around, will lead to the transformation of care with the intent of leveraging the convergence of science, engineering and technology to rapidly advance outcomes.

Financial support for building academic infrastructure and collaborative programs that support translational medicine is traditionally provided through competitive funding programs from public national Agencies. In the US, NIH-sponsored NCATS' Clinical Translational Science Awards (CTSA, https://ncats.nih.gov/ctsa) have provided substantial support for the development of clinical and translational research enterprises through the establishment of research hubs that provide core resources, essential mentoring and training in translational medicine. Examples of such CTSAs are the Institute for Translational Medicine (ITM, https://chicagoitm.org/) and Northwestern University Clinical and Translational Sciences Institute (NUCATS, https://www.nucats.northwestern.edu/). During the formative years of the CTSA program, several sites also forged collaborations by creating regional consortia based on geographic proximity to enable sharing of local resources and meetings of trainees, including the Chicago Consortium for Community Engagement (C3)—a collaboration among Chicago CTSAs—and the Sharing Partnership for Innovative Research in Translation (SPIRiT) Consortium, a model for collaboration across CTSA Sites (22).

THE WAY FORWARD TO TRANSLATIONAL SCIENCE

In summary, to create the translational science discipline necessary to rapidly bridge the gap between bench and bedside, highly trained physician scientists and basic scientists that focus on patient-oriented research outcomes are equally needed. To allow talented scientists to develop an identity and career as a translational scientist the current academic system needs to be reformed. Advances in training and recruiting translational scientists in academia will ultimately depend on the research and funding priorities that are set at a national level. For both physician and basic scientists, early exposure to clinically-relevant research and educational programs in a communal interdisciplinary environment that stimulates opportunities for clinical and biological ideas to "cross-pollinate" is absolutely necessary. Having a supportive and well-organized institutional framework, including a dedicated graduate or postgraduate program

for translational medicine with accessible mentors suitably trained in translational medicine is crucial. Importantly, career evaluation and promotions, and funding opportunities that are designed to match the unique and complex infrastructure of translational science are indispensable for translational scientists to succeed.

AUTHOR CONTRIBUTIONS

SvD, AD, NG-O, PH, CL, VM, AvR, and NR developed the concept and outline of the manuscript and contributed to the preparation of the manuscript. SvD and NR with significant help of AD, did the final editing of the manuscript.

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OPINION
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The Value of Creativity for Enhancing Translational Ecologies, Insights, and Discoveries

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INTRODUCTION

The conventional scientific approach dictates use of higher-order analytical and systematic thinking to generate original solutions to problems. The act of originality however implies a departure from normality and the constraints of conventional boundaries. Creativity—the most complex and abstract higher order cognitive skill—likely lies at the core of innovative, solution-based thought by scientists (DeHann, 2011). Yet there is little if any formal teaching of creativity in the sciences, and "art" and "science" continue to mistakenly be portrayed on opposing ends of a spectrum of innate cognitive function.

As the research landscape continues to shift toward increasing complex interprofessional and multidisciplinary initiatives, scientists more than ever need to draw on creative thought processes not just to fuel discovery but to assemble and manage larger and more complicated collaborative relationships. It will be essential to incorporate scientific creativity in education and training programs for the next generation of scientists (DeHaan, 2009; Ness, 2011; Spoelstra et al., 2014; Foster and Lemus, 2015).

While applicable to all realms of science, in this article we use an example from translational medical research to illustrate the diversity of players that can be involved in scientific discovery. Consistent with the theme of originality, our article will take the unconventional form of a fable. Our aims are to (i) emphasize the importance of incorporating creativity into existing research programs, (ii) encourage readers to explore their own creative style, and (iii) provide a first step to educate trainees in the use of creative thought (see "Call to Action" insert) to enable convergent and divergent thinking within science's rule-bound system.

CASE STUDY: THE VALLEY CROSSING

How endlessly long the valley was. Far more hot and dry than our travelers could have imagined.

"Oh no!" Fox froze.

Horse bumped into Fox. "Excuse me," he mumbled.

Parrot, who had been catching a ride on Horse's back, flapped his wings, and squawked. "Eek! A mouse! A dead mouse!"

Fox howled. Mouse looked up with fright. Goose One and Goose Two divided themselves: one at the front and one at the back of the group. Together they formed a protective wall.

"A dead mouse! A dead mouse!" This was Parrot again—who else—given to repeating everything he saw and heard.

The group was used to seeing skeletons. In fact, the trail was paved with them. But this was the first carcass they encountered on their journey, and it was startling. They had been plodding along for what seemed like an eternity. Dehydration, heat stroke, and exhaustion were exacerbated by insurmountable rocks, never-ending hills, and crisscrossing paths.

"What will it be this time? Left or right?" Horse asked jokingly. "Straight on! For sure!" Fox seethed.

"Squeak, squeak," said Mouse but no one heard.

The truth was, they had no idea. They had lost their way long ago. With each step, each wrong turn, they were getting too tired to continue. But they had to keep going. They had come from afar, this brave group of six, and were determined to reach their destination on the other side of the valley. Time was running out though—they had to get there before they would be enveloped by the pitch dark and the freezing cold of night.

At home the wanderers were pillars in their community. But here, in this inhospitable environment, their skills were useless. All they could think to do was stay as optimistic as possible, but the stress was getting to them.

"I'm drenched in sweat," said Horse, noting the irony of wading through the cracked dry mud of a riverbed that in wintertime would flood the valley with its wild and dangerous torrents. But now, in the middle of a long hot summer, there wasn't a drop of water in sight, apart from the beads of sweat that rolled from Horse's dusty coat. Like Horse, salty drops dripped into Fox's eyes. Horse, being a real workhorse, was used to this. But Fox wasn't. She could barely see her own paw. Both her vision and mind were becoming clouded. She craved a juicy chicken (she simply loved bird meat) and it took all her strength to not lick her lips around Goose One and Goose Two. She couldn't, they were partners after all and they had to work together. Furthermore: one doesn't (usually) eat colleagues.

As they walked on, the broken skeletons of mice became mere crackles beneath their feet. Suddenly, though, they stumbled over a skeleton that made them pause in horror.

"It's a goose!" Parrot shrieked. "Oh my! A dead goose! A dead goose!" Parrot's cries sounded more excited than horrified. "A dead goose!" Parrot couldn't stop himself.

Goose One and Goose Two refused to let themselves be disturbed. "Hold on," they honked. "Hold on, we're good." We won't end like this, they thought. Stay focused. "Straight on we go."

But doubt had crept into the group miles ago.

"Squeak, squeak," said Mouse but once again, no one listened.

"How can you be so sure?" Fox inquired of Goose One and Goose Two. "Didn't we get lost 100 times already?" "100 times! 200 times! 300!" Of course this was Parrot again.

"Oh come on, you. Get off my back," Horse said to Parrot. He hated to waste time and just wanted to press on. Moreover, he was getting annoyed with Parrot's constant nattering.

"How can you two be so sure of this direction? I don't see any evidence here," Fox persisted.

Goose One and Goose Two ignored them all and shrieked in a reassuring tone, "Hey guys, don't waste your energy, just follow us." Though their air was full of self-confidence, the journey was getting to them too. Their neutral gray feathers were covered with a layer of filth that made them feel like grotesque crows. They craved a cool water bath in which they would clean their feathers with joyful splashing and playful hollering. With this in mind, they led their colleagues down a narrow path toward what looked to be a very promising vibrant green space with a luxurious pool. But they were fooled. There was no oasis.

"Wow! A mirage!" cheered Parrot. "A real mirage! Number one on my wish list!"

The other animals did not share Parrot's enthusiasm. Horse was especially fed up and aggressively shook his coat, flinging Parrot into the air. Mouse was increasingly weary; she had unsuccessfully been down this path before with other groups. They carried on, all six of them, despite their hardships, still focused on their collaborative mission.

Goose One was the first to see a bright white figure slowly moving in the distance. A mirage again? No. It actually looked like a living creature on its back. Sleeping? No. Napping? No. Sunbathing with a book! How could that be? The group was approaching a state of delirium. Sunburned and dehydrated as they were, no one wanted to admit what they saw. But the closer they got the more they believed, until all six froze in mid-step.

"QUACK!"

The whole group jumped, frightened by a high-pitched noise that came from the reclining figure.

"Well, my word!" said Fox, "It looks like a…"

"And it talks like a…" joined Horse.

"But then we still have to prove…" shrieked both geese in unison, though they were interrupted in mid sentence.

"Good afternoon!" said a ducky voice. "I'm Duck. Pleased to meet you. Don't be scared. It looks like you could use some help."

A collective sigh of relief swept through the group as Duck inquired about the purpose of their journey. They all started talking at once. They just rattled away in a delirious state of exhaustion and excitement. "Help! Yes! That's what we need. We are done here! Do something! Anything!"

In the midst of the commotion, Duck waited patiently until the group was ready for her. She sat on a rock, wings folded behind her head, facing the burning sun. If she wouldn't have had a duck's beak, it would almost look like she was smiling. Her Zen-like ease calmed the group.

"Hey, come on, guys!" Goose Two said. "Let's stop for a moment."

"Yeah," Horse added, "Why not listen to what this duck has to say."

"Might be bloody helpful," said Parrot, actually expressing an original thought.

"But wait! This is a *duck*!" said Fox, while Duck calmly cleaned her white feathers with her beak. "Doesn't a duck need water?"

"Yeah, I would say so too," neighed Horse. Goose One and Goose Two agreed.

Duck, who brought light to the group and not only because her feathers shone like the brightest sunbeams, stood up and started to walk. "Come on guys." she said, "Let's walk and talk. And with her clumsy webbed feet she started to march so firmly and sure of herself that the group couldn't help but follow in awe. "I'm

Duck," Duck said, "and that's a good thing. I love a good problem. What's up?"

"Well listen," they said. "We have a goal that's out of sight."

"Then focus on me and not the goal," Duck said.

From this moment on, Duck took the lead. The others followed her, eyes fixed on her white feathers and orange webbed feet, and ears tuned to her alarm-like quacks, which didn't seem so alarming anymore. During their walk, Duck did most of the talking. She explained to the group how important it was to reach the valley's end before dark, how they would turn into frozen statues if they didn't make it. But she didn't frighten the group with this rather unpleasant perspective. On the contrary: she taught her new acquaintances special survival tools.

"First of all," Duck explained: "you might think you're a team, but you're not acting like one." The group was too tired to argue, apart from some vague grumbling. "Let's work on your collective skills."

Duck settled on the parched ground, convincing the pack to join her. Leaning against a formation of rocks, the group circled around her. Duck took stock of each member, pointing her beak at the animals, one at a time. First to both geese, whose protecting attitude had become too rigid during their travels. Then to Fox, who seemed to have lost his cunning entirely. Horse himself pointed out that his hard work didn't always amount to much. And Parrot, he was admonished for his constant jibber-jabbering. Lastly, Duck scolded the whole lot for not listening to Mouse.

"Squeak, squeak!" said Mouse, and suddenly the others heard "Speak, hear me speak!" And this time, for the very first time since entering the valley, they listened.

"Look at it this way," Duck said reassuringly. "Parrot is a talker, so put him in a position to share his observations with the group. But Parrot, you need to use your wings to offer those observations. Fox, be shrewd about how you use your brute strength to overcome obstacles. Recognize when to use your nose, paws and teeth. Goose One and Two, use your eyes like I do."

Yes, Duck mentioned the geese's eyes for a reason, as it pointed to her own strength: her vision. Duck's eyes were located at either side of her head, and capable of a 340-degree field of vision. She had a clear view of possible solutions, both nearby and on the periphery.

After some more exposition followed by a brainstorming session on how to use the desert to its full potential, they continued on their way. The valley, dry and hot as it was, happened to be Duck's habitat, which meant there was nothing to fear. Duck's way of guiding the group through the hostile landscape was quite extraordinary. What seemed like harsh terrain for the group was a playground for her, in which obstacles were toys. Duck showed the group that they could use barren trees as monkey bars, hilly paths as slides and sloped rocks as launch pads. Before long, the group joined Duck in whimsically reimagining their environment. They too started to jump, clamber, slide, and play with their surroundings. Parrot flew in front, narrating his birds-eye-view of upcoming hazards. Fox shrewdly dug holes around obstacles, set her teeth in roots in order to clear the path and create escape routes. Goose One and Goose Two took turns sharing their lead role with the others. Suddenly they found themselves more at ease in the middle, proudly helping Duck scan the desert with their bird's eyes, while making it a point to converse with Mouse about their direction. And Horse couldn't stop himself from being a workhorse: he carried each and every animal that needed a short rest on his back. That is, apart from Parrot, who was already sufficiently relaxed, and so pleased with his new role up in the air that he didn't even think of descending onto Horse's back anymore.

In the end, all hazards were warded off with the help of this lowland inhabitant who was so naturally at ease here in the arid valley. As the crimson-gold sky dissolved into the cold blue of evening, the group arrived at the valley's edge. They were bursting with curiosity, and now, with their goal in sight, they simply had to know.

"Duck, what about you? How can you possibly live here? How come you survive? How can you thrive here, in this valley of death?"

"It's your valley of death, not mine," said Duck, while nodding to the horizon. High on a hilltop, a pasture green stretched out in front of Goose One and Goose Two, Fox, Horse, Mouse and Parrot, all ready to climb up. "I see it differently. I treat it differently. Like water off a duck's back." Thus, spoke Duck, whose beak appeared, once again, to be smiling.

DISCUSSION

Through this fable we use animal symbolism to portray different stakeholders that may be present when crossing the so-called valley of death; this is an allegory for one of the many difficult paths of translating scientific discoveries into medicine practice reforms that in this fable is represented by the harsh landscape and physical barriers (Guilford, 1959; Gardner, 1983; Csikszentmihalyi, 1996; Robinson, 2009). The character of Duck is an applied metaphor for creativity that, when applied, unites and helps the group of basic scientists (Goose One and Goose Two), physicians (Horse), attorneys (Fox), journalists (Parrot), and patients (Mouse) overcome obstacles and reach their goal. We recognize that the characters and backdrop may differ depending on the actual nature of the stakeholders and goal. Yet regardless of context, different creative processes illustrated throughout the fable can augment the traditional knowledge and skills of translational science stakeholders:

Divergent Thinking

In contrast to classical convergent thinking, which is primarily concerned with solving well-defined problems in order to arrive at the best, right, or conventional answer, a person uses divergent thinking to move from one known idea to imagining many possible solutions to a problem. The fluent, flexible and original spontaneous, non-linear manner in which divergent thinking is employed (Csikszentmihalyi, 1996) is exemplified in the fable through Duck's (and later, the Geese's) unique field of vision and the way it affected her understanding of the landscape (Guilford, 1959).

BOX 1 | Call to action.

An exercise to introduce creativity in the sciences. The intention of this fable is to provoke discussion among scientists regarding the role of creativity in scientific endeavor and science education. We encourage readers to use the fable as a focal point for such discussions and/or an example for trainees to craft their own creative work to explain complex scientific concepts.

Multiple Intelligences

Individuals have multiple forms of intelligence but often utilize only one or a few [dominant form(s)]; other forms are often dormant as opposed to being non-existent or weak (Gardner, 1983; Robinson, 2009). In our fable, the characters hold tight to skills they utilize in their day-to-day profession, failing to see the ineffectiveness of those skills in the desert, for e.g., Parrot's talkative nature and Fox's legal intelligence, while essential for their respective professions, are virtually useless in the valley (Butler, 2008). Eventually, Fox and Parrot collaborate and draw on innate skills (flying and digging) that were previously dormant in order to find nourishment for the group that in this context is representative of the process of findings investors for financial sustainability of research projects.

Play and Flow

By far the easiest way into creative problem solving is to organize a team in which diverse skill sets are encouraged to freely collaborate and explore the sorts of unbiased and abstract ideas needed to solve "wicked" problems, and in which the experience is so enjoyable for all participants that they continue to do it even at great cost (Csikszentmihalyi, 2008). If the challenge the group is attempting to solve completely engages its collective skill set, the group will often find itself in a "flow" state, which in turn creates new skills to tackle more difficult challenges. In the fable, Duck reminds the group of their common purpose (Csikszentmihalyi, 1997; Butler, 2008; Fernandez-Moure, 2016) and eventually we see the animals losing themselves in the playground they once saw as a hostile environment, and taking turns sharing the load (Horse carrying different characters) and the lead. Leadership is negotiated, as when Goose One and Goose Two learned *when* to resist the temptation to venture down every fork in the road that, while appealing to their scientific curiosity and not technically a "wrong turn," was exhaustive for the other team members.

We encourage the reader to consider and practice some of the mentioned creative processes; deliberate use of creativity in science communication (for example through the creation of a fable) is a laudable first step for scientists wishing to incorporate or enhance creativity in their program of research (see **Box 1**). In doing so, it may expedite scientific discovery, but most importantly, cognizant creative practice should allow scientists and non-scientists to maximize enjoyment that comes from collaborative discovery.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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