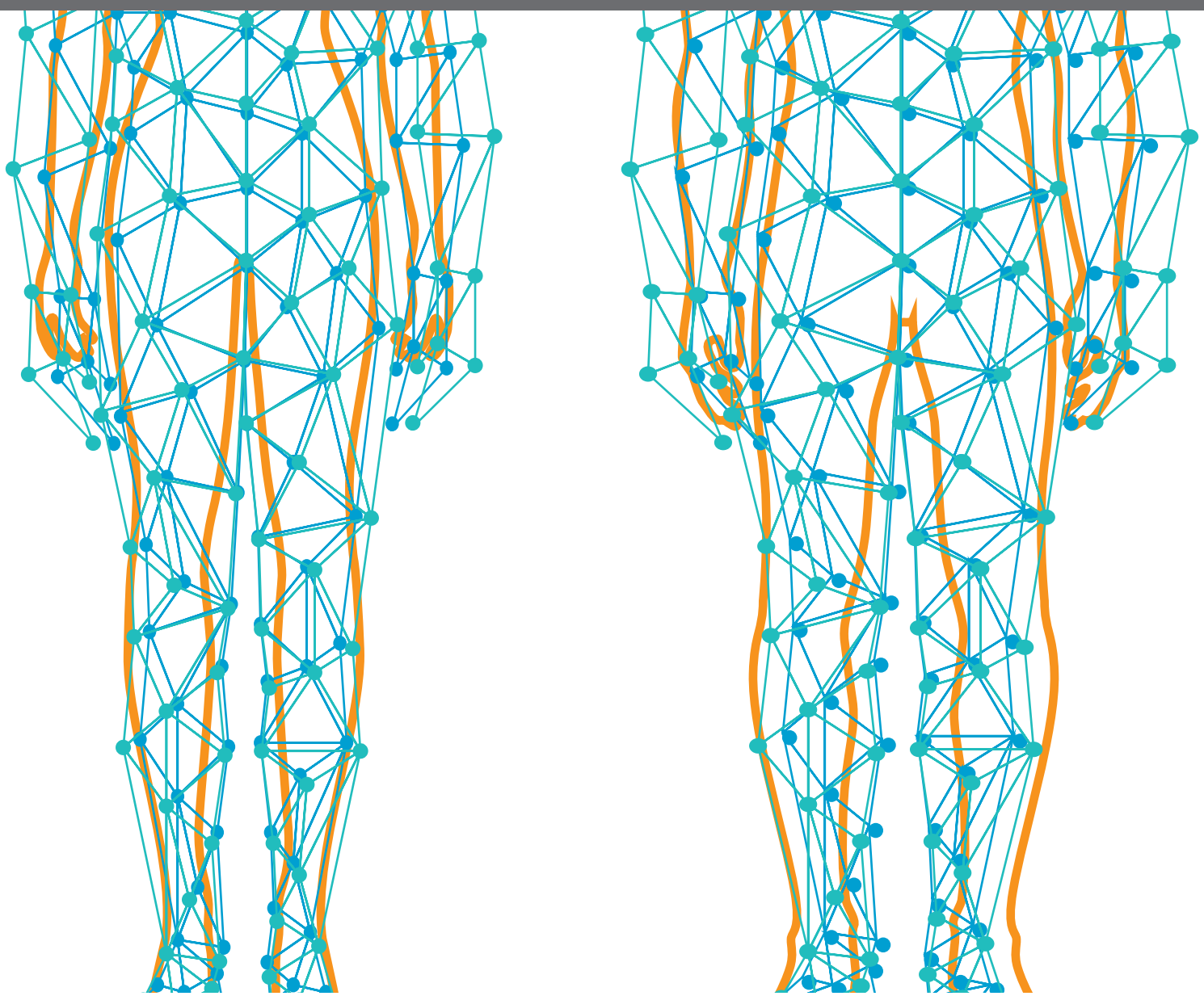
PUBLIC-PRIVATE PARTNERSHIPS AS DRIVERS OF INNOVATION IN HEALTHCARE,
2nd Edition

EDITED BY: Hilde Stevens and Michel Goldman
PUBLISHED IN: Frontiers in Medicine



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ISSN 1664-8714
ISBN 978-2-88963-945-8
DOI 10.3389/978-2-88963-945-8

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PUBLIC-PRIVATE PARTNERSHIPS AS DRIVERS OF INNOVATION IN HEALTHCARE,
2nd Edition

Topic Editors:
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Multi-stakeholder collaborations involving partners from public and private sectors are essential to address global health challenges and to move precision medicine forward. This eBook assembles a collection of papers which either illustrate recent achievements or discuss new perspectives offered by public-private partnerships in healthcare.

Publisher's note: In this 2nd edition, the following article has been added: Laverty H and Meulien P (2019) The Innovative Medicines Initiative –10 Years of Public-Private Collaboration. Front. Med. 6:275. doi: 10.3389/fmed.2019.00275

Citation: Stevens, H., Goldman, M., eds. (2020). Public-Private Partnerships as Drivers of Innovation in Healthcare, 2nd Edition. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88963-945-8

Table of Contents

frontiers in Medicine

EDITORIAL
published: 31 May 2019
doi: 10.3389/fmed.2019.00114

Editorial: Public-Private Partnerships as Drivers of Innovation in Healthcare

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Keywords: editorial, public-private parternships, healthcare, innovation, medicine

Editorial on the Research Topic

Public-Private Partnerships as drivers of innovation in healthcare

THE FORMAT: FROM BILATERAL TO MULTILATERAL

Around the turn of the century, a rather simple classification of public-private-partnerships (PPPs) in the world of medicine development sufficed. These PPPs consisted primarily of bilateral collaborations between pharmaceutical companies and academic institutes. Since then, these "simple" bilateral PPPs have been complemented by different and more diverse types of PPPs. On the one hand, PPPs emerged such as the Medicines for Malaria Venture (MMV) or the Drugs for Neglected Diseases Initiative (DNDI) with as major drivers charities, country donors, industry, and academic groups. These so-called product development partnerships (PDPs) focus on developing products for specific communicable diseases impacting health of patients in less affluent countries. On the other hand, Pharma-PPPs, such as the Innovative Medicines Initiative (IMI), emerged that focused on jointly tackling specific -precompetitive- issues in medicine development. The major players in the last category consisted of the pharmaceutical industry (large pharma), small, and medium sized enterprises (SMEs), academic institutes and–again- governmental funding programs (1, 2). Since then the background of participating stakeholders of PPPs has greatly diversified. Important new stakeholders joined the PPP consortia, including patient organizations, regulatory bodies, health technology assessment agencies, insurance companies, and IT-companies (see articles in this special issue, e.g., Aartsen et al.) All have their unique incentives to join, which makes the PPP concept more difficult to define and to evaluate in terms of its benefits. Nowadays, many PPP-flavors exist and the number and diversity continues to grow. Contributions to this special issue exemplify this current development in the PPP-world.

ADDED VALUE: IN THE EYE OF THE BEHOLDER OR MORE CONCRETE IMPACT MEASURES?

Early on, questions were raised about the assessment of performance and success-failure of PPPs (1–3). Performance indicators to look at were identified as: the input, the process, the output, the short-term outcome, and impact. See **Figure 1** for details. The basis for this methodology was already developed and tested in other fields. What makes the Pharma-PPP case so special are the long timelines–years- to measure "impact." The classical PPP projects have a typical running time of 4–6 years. The long-term outcome-and impact e.g., in terms of concrete new medicines can only be measured many years after finishing the project and on top of that there are many "diluting" contributing factors in the post-PPP years. Moreover, simply looking at the number of medicines

OPEN ACCESS

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *02 May 2019*
Accepted: *07 May 2019*
Published: *31 May 2019*

Citation:
de Vrueh RLA, de Vlieger JSB and Crommelin DJA (2019) Editorial: Public-Private Partnerships as Drivers of Innovation in Healthcare. Front. Med. 6:114. doi: 10.3389/fmed.2019.00114

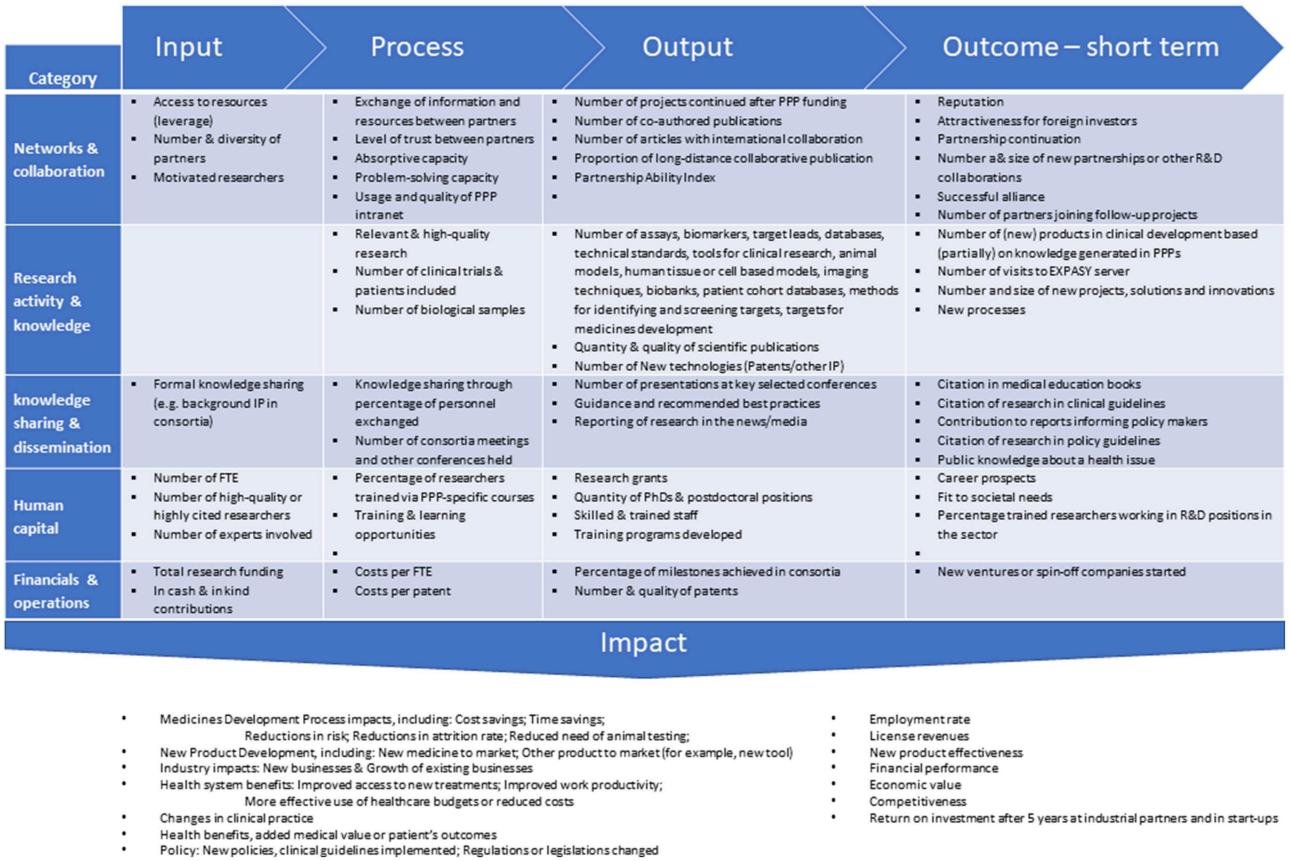

FIGURE 1 | Reported performance indicators to be considered in a research PPP performance measurement system, classified into 5 categories. Figure adapted from (2).

developed based on the activities of a PPP significantly underappreciates the additional impact from knowledge transfer, ongoing collaborations, patents, spin-off companies formed, and last but not least the educational aspect PPP initiatives offer (See **Figure 1**). The true impact of the first generation of PPPs now becomes visible and we can review that according to the key performance indicators set out from the start [cf. (4, 5)].

In that light, there is one question that was often raised in the early days and that can now be answered, i.e., the concern about the quality of the research output -read publications- of PPPs. Several studies made it clear (3, 4) that the impact of publications measured in terms of impact factor of scientific journals and number of citations of IMI and TI Pharma consortia was comparable–if not higher- than of articles published through "regular" academic groups efforts.

SUSTAINABILITY: TO STAY OR TO PERISH?

What is the chance for a consortium to survive after finishing the first funding round? Before answering this question it should be clear whether the project, topic-wise, is supposed to be continued at all? Some projects simply do not have a horizon beyond their running time. They are set up to solve a particular -often concrete- problem. However, what if a prolonged existence is foreseen? Experience teaches us that then already in an early stage the question of sustainability should be addressed. For instance, in case infrastructure has been built up, such as databanks or test facilities, further strategies to continue activities after the first funding round should be subject of discussion early on. The article by Aartsen et al. in this special issue discusses various sustainability strategies developed for IMI projects in detail and lists "lessons learned."

EVOLUTION: PPP QUO VADIS?

The adoption of the "open innovation model" by the pharmaceutical industry has given the PPP concept a big push. Originally, the public partners were mainly academic and national or international public funding organizations. The large pharmaceutical industry with or without SMEs took care of the private side. Over time, the background of stakeholders in PPP consortia has diversified. Patient organizations and health insurance companies joined the consortia. Regulatory

bodies such as EMA and FDA are becoming partners as well, although these institutions are very cautious to safeguard their independence from large pharma and other private stakeholders. Big IT organizations such as Google and Amazon (cloud-computing services) expanded the spectrum on the private side (Moreno et al.) as did medical device-diagnostics companies such as Siemens, Agilent, and Philips in the context of IMI. This expanding source of partners will change the character of PPP consortia. Also, the scope of activities evolved. As partners in first PPPs were jointly exploring science and collaboration in a truly pre-competitive field, a shift toward projects where partners share their strategic assets is now observed. E.g., in the IMI—European Lead Factory (see this issue: Karawajczyk et al.) industry decided to share some proprietary assets allowing competitors and public partners to boost their drug discovery programs. It demonstrates that the PPP concept has become a trusted way of working and partners now seem comfortable to evolve the model with activities closer to their core business.

These recent developments raise the question whether the original, rather narrow definitions of a PPP as mentioned at the beginning of this editorial will properly describe the PPPs in medicine development in the future. Partners outside pharma now join the game and change the dynamics and "culture." The walls between the classical "silos" disappear rapidly.

The remaining question is then. PPP concept in the world of medicine development: Quo Vadis?

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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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 19 January 2017
doi: 10.3389/fmed.2016.00075

The European Lead Factory: A Blueprint for Public–Private Partnerships in Early Drug Discovery

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The European Lead Factory (ELF) is a public–private partnership (PPP) that provides researchers in Europe with a unique platform for translation of innovative biology and chemistry into high-quality starting points for drug discovery. It combines an exceptional collection of small molecules, high-throughput screening (HTS) infrastructure, and hit follow-up capabilities to advance research projects from both private companies and publicly funded researchers. By active interactions with the wider European life science community, ELF connects and unites bright ideas, talent, and experience from several disciplines. As a result, ELF is a unique, collaborative lead generation engine that has so far resulted in >4,500 hit compounds with a defined biological activity from 83 successfully completed HTS and hit evaluation campaigns. The PPP has also produced more than 120,000 novel innovative library compounds that complement the 327,000 compounds contributed by the participating pharmaceutical companies. Intrinsic to its setup, ELF enables breakthroughs in areas with unmet medical and societal needs, where no individual entity would be able to create a comparable impact in such a short time.

Keywords: European Lead Factory, Joint European Compound Library, high-throughput screening, collaborative research, drug discovery, translational research, Innovative Medicines Initiative, public–private partnership

OPEN ACCESS

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *29 October 2016*
Accepted: *23 December 2016*
Published: *19 January 2017*

Citation:
Karawajczyk A, Orrling KM, de Vlieger JSB, Rijnders T and Tzalis D (2017) The European Lead Factory: A Blueprint for Public–Private Partnerships in Early Drug Discovery. Front. Med. 3:75. doi: 10.3389/fmed.2016.00075

INTRODUCTION

While we continuously obtain a better understanding of disease-causing mechanisms, we still face a number of challenges when translating these findings into therapeutic products that reach patients' needs (1, 2).

Innovation and discoveries derived from academic research institutes have great potential to be developed into clinically meaningful products; however, it is clear that these parties often lack the resources and experience to fully progress their findings toward the clinic. Traditional pharmaceutical

Abbreviations: DD, drug discovery; ELF, European Lead Factory; ESC, European Screening Center; FDA, Food and Drug Administration; HDB, honest data broker; HTS, high-throughput screening; IMI, Innovative Medicines Initiative; IP, intellectual property; IT, information technology; JECL, Joint European Compound Library; NTDs, neglected tropical diseases; PPP, public–private partnership; SME, small- to medium-sized enterprise.

companies can build on decades of experience in bringing drug candidates successfully to patients. However, due to several well-reported reasons (1–3), the traditional business model faces a gap between early discoveries and product development.

Despite large investments and advances in basic and applied pharmaceutical research in recent years, the success rate in drug discovery (DD) and development of innovative therapies in most disease areas has been low as a result of this translational gap (2, 3). Consequently, the substantial need for new drugs remains and poses a serious threat not only to patients but also to the welfare of modern society (4).

In response to this necessity for new solutions, the DD landscape is continuously adjusting itself to pursue a sustainable and more productive research and discovery model (5, 6). Currently, the precompetitive space in pharmaceutical research is being redefined, and more transparent and collaborative innovation approaches are increasingly being embarked upon. The objectives are not only to share investment risks but also to minimize attrition rates of DD, pool complementary talents and resources, provide sustainable infrastructure platforms where different players have access to the brightest ideas and are able to interact liberally, and exchange collective solutions to problems arising in the DD process (7). Public–private partnerships (PPPs) are the tool of choice for bridging this gap (8, 9).

Small molecule therapy remains one of the cornerstones of modern medicine. Approximately 90% of all the therapeutics sold are based on small molecule drugs. The Food and Drug Administration's Centre for Drug evaluation and research, which oversees the approval of new drugs, approved 45 new drugs in 2015. This marks a 19-year high after hitting a low of 18 new approved drugs in 2007 (10). Out of the new drugs approved in 2015, two-thirds are derived from small molecular entities. This exemplifies the fact that a significant number of new medicines introduced are derived from chemical compound collections.

High-throughput screening (HTS) is an effective and well-established methodology to assess the biological effect of large collections of chemical compounds. This methodology has matured over the years at large pharmaceutical companies and has generated more new active pharmaceutical ingredients than any other rational DD approach (11). However, the success of an HTS campaign highly depends on the quality of the compound collection, the infrastructure, the assays, i.e., how to read out the biological response of the screening compounds, and the data interpretation skills (12). Hence, expertise and experience from a broad range of specific life sciences must be collected and amalgamated.

With this in mind, the Innovative Medicines Initiative's (IMI) European Lead Factory (ELF) project was launched, with an aim to create a collaborative PPP DD platform to seed and execute early-stage projects more effectively (13). By combining an industry-standard HTS infrastructure (European Screening Centre), a state-of-the-art Joint European Compound Library (JECL) and newly developed information technology (IT) solutions, ELF enables any European biotech company or research institute to access, free of charge, tools, resources, and know-how that were once available exclusively in the large pharmaceutical companies (14).

ELF: A COLLABORATIVE EARLY DD EFFORT

European Lead Factory is unique in its reach, with interaction points for organizations of all sizes: from single individuals who can submit chemical library ideas and/or disease-related targets, up to the participating multinational pharmaceutical companies (**Figure 1**). This heterogeneity is also reflected in the core team of the ELF: it comprises 7 established pharmaceutical companies, 10 small- to medium-sized enterprises (SMEs), and 13 academic partners, who collaborate in a precompetitive mode (14). Crowdsourcing of innovative chemistry and biology allows the project to be at the forefront of these respective fields, while equipping the DD community with high-quality starting points. ELF operates as a translational hub, to which scientists from SMEs and academia, from all over Europe, can submit their ideas and have those translated into tangible assets that can be developed internally or in collaboration with partners (**Figure 1**). In addition, by combining innovative ideas in chemistry and biology, it opens up new areas that have yet not been explored by those currently working on DD projects.

SMEs AS AN IMPORTANT DRIVER FOR SUCCESS IN PPPs

Public–private partnerships are, at the onset, often accused of a certain degree of inertia that results from a complex partner mix, opposing interests, democratic decision-making, and high demand of transparency. ELF has circumvented this and managed to be highly effective and fully operational within a year through a clear governance structure, intellectual property (IP) regulation, IT software solutions, in combination with the drive of the ELF partners to deliver valuable output for the benefit of the wider community. This partnership works much beyond the objectives of any single partner.

Certainly, the high ratio of SME involvement in ELF has had a pivotal role in accelerating many processes. SMEs have over the past decade worked closely with and for the larger pharmaceutical industry, as well as with public research institutes in early DD projects. ELF has provided the SMEs with a showground to further prove their abilities. The participating SMEs are instrumental in implementing the production and management of the compound library and performing the screening. Their agility and emphasis on producing results has had a professional influence on the ELF machinery, making it the well-oiled initiative it is today.

While academia and SMEs inject innovation and execution power to the PPP, the established pharmaceutical companies provide the means and experience to develop the scientific discovery of biologically active molecules into medical therapies. The extensive drug development expertise available in pharmaceutical companies provides opportunities to academics and biotechs to valorize the results either in downstream alliances along the pharmaceutical value chain, through license agreements around generated IP, or through the generation of spin-outs based on assets generated within their ELF participation.

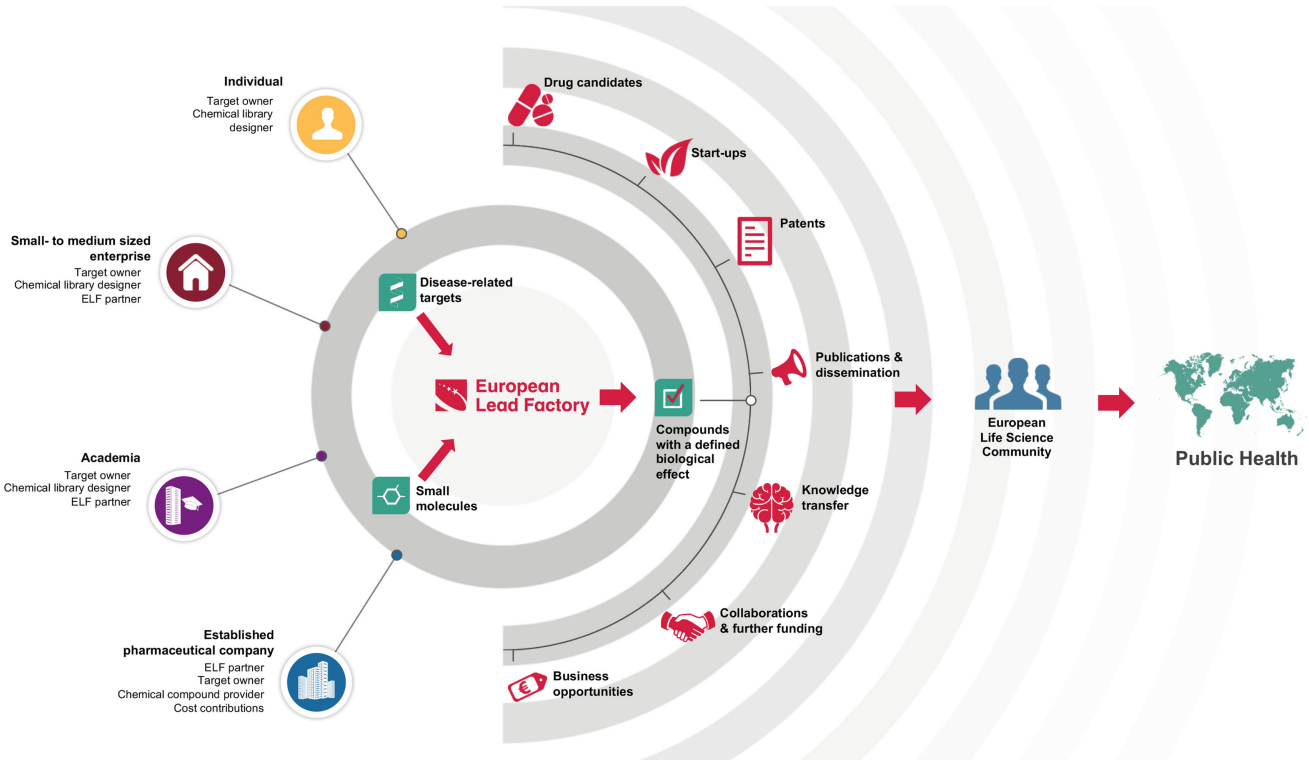

FIGURE 1 | **European Lead Factory is a translational hub**. It uses the collective intelligence in the European life science community to connect disease-related targets (provided by target owners) with high-quality small molecules (based on library design ideas or provided by established pharmaceutical companies) resulting in compounds with a defined biological activity. Many types of outcomes are fed back to the community with the ultimate aim of benefiting public health.

THE ELF MODE OF ACTION

Now fully operational, the ELF provides a unique platform for translation of innovative biology and chemistry into high-quality starting points for DD. This cohesive PPP contains three essential assets for bridging the innovation gap of early DD: (i) access to a state-of-the-art chemical compound collection (15, 16), (ii) access to screening facilities of industrial standards, and (iii) access to the expertise required to convert the obtained results and data into potential drug candidates.

JOINT EUROPEAN COMPOUND LIBRARY

The quality and diversity of the compound collection is of upmost importance in DD. The JECL is one of the strongest assets of the consortium. It constitutes a collection of starting points for new therapies and consists of two parts: the pharmaceutical industry compound collection and the public compound collection. At the onset of the project, over 327,000 high-quality compounds were contributed by the seven pharmaceutical industry partners within the consortium according to exacting selection criteria agreed upon by the participating partners. Within the time frame of ELF, these compounds are being complemented with up to 200,000 newly synthesized compounds (15).

In return for their compound contributions, the participating pharmaceutical companies have access to the entire compound collection for screening a limited number of internal targets. In this way, ELF provides a neutral platform that allows different companies to access their competitors' compound libraries. By combining screening compounds from different sources, more target classes are being addressed than by anyone single source, opening up for the revitalization of discovery projects at the participating pharmaceutical industry partner, which have failed to produce attractive hits in in-house campaigns. Consequently, the available chemical space is being utilized more efficaciously. To date, an impressive one-third of the finished ELF industry projects have triggered additional drug development efforts at the respective company. Activating such projects will eventually benefit the patients, who have an increased chance for new therapies.

Out of the 200,000 novel compounds targeted, over 100,000, based on more than 220 scaffolds (molecular frameworks), are already synthesized and available to the European Research Community midway through the project (16). More than 500 library ideas have been selected and evaluated to be processed within ELF. This new compound collection is based on proposals that are submitted by chemists—from either within or outside the consortium—using a step-by-step procedure *via* a web-based

tool (17). The compound collection is unique and diverse compared to commercial sources and typical chemical compound repositories.

When submitting library proposals to ELF, external contributors retain the right to continue doing research on the chemical entities and to publish their own research and findings. Only an exclusive set of compounds that is being synthesized within ELF is being kept proprietary. In order to ensure the quality of the produced library, submitted library proposals are being assessed by a Library Selection Committee. It consists of eight members from the pharmaceutical industry, SMEs, and academia, all bound by confidentiality, in order to provide broad and complementary chemistry and DD expertise, thereby ensuring a high-quality library. The data and information provided at a library proposal stage are used to assess the original proposals against six specific drug relevant selection criteria: novelty, molecular properties, synthetic tractability, diversity potential, structural features, and innovative library design. Furthermore, molecular properties and structural features should be preferably aligned to contemporary hit- and lead-like properties (15).

Given the size and heterogeneity of the chemistry partners within the ELF consortium (23 out of the 30 partners are involved in the chemistry activities), chemistry project management is critical to its success. Real-time monitoring, data storage, and decision-making are enabled by TarosGate 2, a secure informatics platform, which seamlessly connects the chemistry laboratories of the academic and SME partners. Since the software covers three important aspects of the decentralized collaborative work: (i) work documentation as an electronical lab journal, (ii) management of the project, and (iii) communication, it has a noticeable impact on the operational speed of the chemistry consortium.

EUROPEAN SCREENING CENTER (ESC)

One of the greatest challenges in the postgenomic era is how to translate the host of genetic knowledge into drug targets, i.e., proteins or biological structures, which can be modulated to give a desired biological effect. The number of available targets is greater than ever. To dissect which ones are worth pursuing has proven difficult and associated with a great need of highly interdisciplinary collaborations. A researcher at any European SME or academic institute is welcome to submit a proposal to ELF for screening his or her drug target. The proposals are reviewed based on scientific value and technical maturity. The last is defined by the requirements for the screening assay, which has to be compatible with HTS and executable in well plates, together with the availability of complementary assays to further refine the hit compound selection.

The drug targets selected from the European life science community are being screened at the ESC. Once the assay is transferred, the work begins by optimizing it further. After a first screen against all available compounds in the collection (currently over 400,000), the so-called primary hits (typically a few thousands) are further evaluated to confirm engagement with the defined drug target and to establish activity levels of desired and undesired biological effects. At this point, three to five different types of assays have been applied and the number of interesting compounds is narrowed down to typically a few hundreds. The ELF medicinal chemists make the final selection of the best ≤50 compounds, based on information provided by the researcher who proposed the target and the purpose of the research (drugs vs. tool compounds) (12).

As of end of August 2016, 72 public target projects have been selected by ELF. In order to extract the most interesting compounds for these projects, more than a total of 150 biochemical, cellular, and biophysical assays have been developed, 49 HTS have been completed and over 1,000 compounds have been granted to owners of public target projects that can serve as potential new starting points for DD projects. Further work to validate the selected compounds have been performed for 23 of the 30 projects. In this process, >1,500 bespoke compounds have been synthesized by the ELF medicinal chemists and provided to their target owners.

From the very start, ELF aimed for non-discriminating crowdsourcing activity with a special focus on innovation. As a consequence, the current drug target project portfolio is complementary and clearly different from the industry (13, 18). It includes many targets considered as highly challenging, such as protein–protein or protein–DNA/RNA interactions (15% of the projects), and very few of the most pursued target types, e.g., kinases (7%) and proteases (4%) (**Figure 2A**). Interestingly, the stringent requirement for an HTS-compatible assay format does not seem to have affected the innovative aspect on target level. Although the projects are spread over a wide range of disease areas, illustrated in **Figure 2B**, there is a high proportion of oncology projects (42%). This might be a reflection of the relatively abundant funding opportunities for cancer research, leading to a higher chance of accessing the infrastructure needed to develop an HTS-compatible assay. The aspiration for societal benefit is illustrated by the number of projects in infectious diseases (18% in total). In fact, ELF recently lowered the hurdles for non-profit DD projects in the area of neglected tropical diseases, freeing charities, and other organizations from financial obligations in their pursuit of new therapies for patients in the least developed countries (18).

It is important to emphasize that the control and IP rights of the biology drug target projects remain with the original proposer. This secures the involvement of the biology experts within the ELF to efficiently use the collective intelligence in translating the findings into clinically relevant small molecules. A fit-for-purpose IP framework allows successful projects to be further progressed to clinical studies, while research use of results is facilitated. ELF projects derived from academia and SMEs choosing to look for a commercial partner have to provide the ELF pharmaceutical industry partners with a right of first option, which the target owner have the right to refuse. For the participating industry partners, this provides an additional opportunity to have insight into novel innovative drug targets that these pharmaceutical companies would not have access to. The Honest Data Broker is a consortium software developed specifically for ELF to balance the scientific and IP requirements of all the involved parties. It ensures that all the partners work together in a productive, and where required, transparent

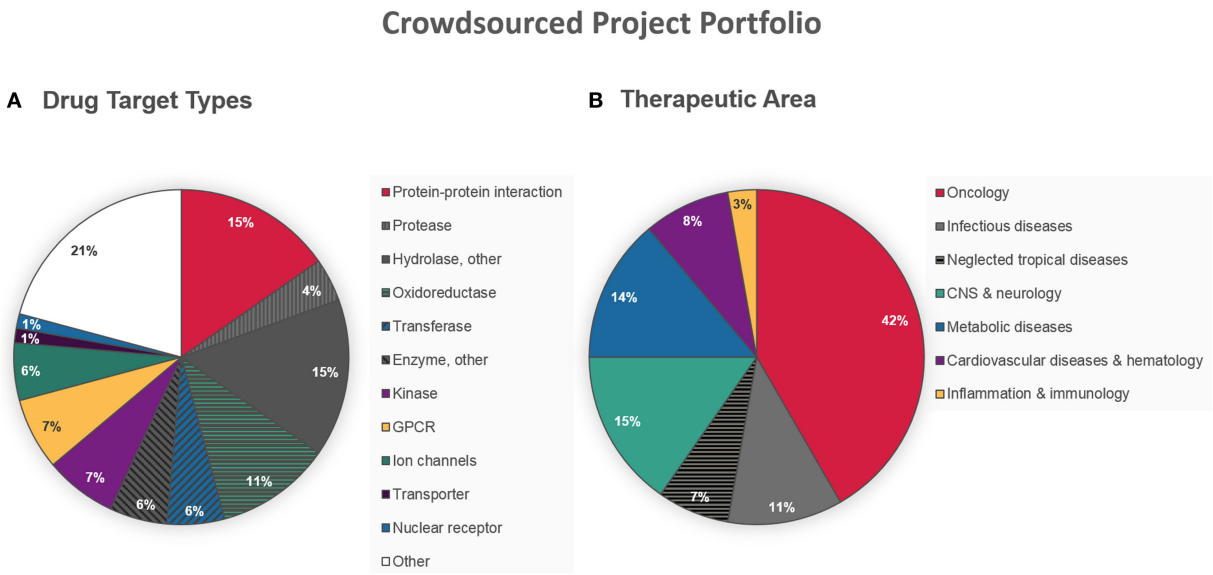

FIGURE 2 | Character of crowdsourced disease-related target projects accepted by European Lead Factory (ELF) as of August 31, 2016. **(A)** Nature of molecular drug target. **(B)** Main therapeutic area addressed by the projects.

environment, as one single unit, despite the different nature and interests of the various participating stakeholders (academia—SME—pharmaceutical industry) (19).

CONCLUSION

Three years after the start of the project, ELF has matured from a start-up initiative to a well-organized group of over 150 scientists. Experts from all essential areas of early DD—industry, academia, and SMEs—now jointly produce high-quality output for the wider public benefit. In this time, the PPP has published >30 articles and the results from the first crowdsourced ideas gradually disseminate in the public domain for everyone to assess (6, 12, 13, 15, 19–48).

At the time of writing this paper, researchers from 13 countries are involved, one spin-out company has been established, and patents have been filed by academic research groups based on the screening results of their submitted screening proposals to the ELF. Over 120,000 new compounds have been synthesized and added to the screening library. So far, 72 screening programs have been accepted from European academic groups and biotechs and are currently being processed.

The resulting biologically active compounds are used by biotechs to further progress their DD programs, by universities to be optimized toward potential therapies, or used as chemical tools to support groundbreaking basic research. For the pharmaceutical industry partners, currently 17 out of 49 screening campaigns with the ELF compound library have triggered further work within the companies.

A less tangible, but just as important, outcome of this PPP is the impact it has on the human capital involved. The constant flow of knowledge exchange between scientists in different disciplines and organizations inside and outside ELF allows to fully capitalize on the collective intelligence.

OUTLOOK

Unmet medical needs still prevail in nearly all indication areas. Although several initiatives have been launched in the past few years on a regional, national, or international scale (49–53), ELF is the first effectively operating pan-European initiative embracing both the public and private sectors.

European Lead Factory provides a unique platform for connecting innovative biology and novel chemistry into high-quality starting points for DD. Intrinsic to its setup, ELF enables breakthroughs in areas with unmet medical needs, where no individual entity would be able to create a comparable impact in such a short time.

With an active life science community in Europe, the results will be absorbed and further developed into clinically meaningful drug candidates. While having bridged a major gap in developing innovation in chemistry and biology toward an interesting DD project, it is already clear that the next translational gap is already emerging. Valuable compounds derived from JECL have now been extensively tested *in vitro* and have seen some preclinical *in vivo* models, but the subsequent development of those compounds into drug candidates needs the next push. Currently, some of the DD projects flow into other initiatives within the IMI portfolio, or are under evaluation by other funding organizations such as the Wellcome Trust or pharmaceutical companies to be further developed. Facilitating such a subsequent step will be an important driver to increase the long-term impact of ELF on the European community. Together with the essential stakeholders for the next phase, these types of PPPs can jointly shape the future

of medicine. In fact, ELF could serve as a blueprint of how future PPPs might operate in order to efficiently find cures that could reach patients in dire need of new treatments.

AUTHOR CONTRIBUTIONS

AK, KO, JV, TR, and DT contributed equally to the writing and the editing of the manuscript.

FUNDING

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115489, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind contribution.

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Disclaimer: All the authors are members of the European Lead Factory consortium.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

REVIEW
published: 09 March 2018
doi: 10.3389/fmed.2018.00065

Getting Digital Assets from Public–Private Partnership Research Projects through "The Valley of Death," and Making Them Sustainable

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Projects in public–private partnerships, such as the Innovative Medicines Initiative (IMI), produce data services and platforms (digital assets) to help support the use of medical research data and IT tools. Maintaining these assets beyond the funding period of a project can be a challenge. The reason for that is the need to develop a business model that integrates the perspectives of all different stakeholders involved in the project, and these digital assets might not necessarily be addressing a problem for which there is an addressable market of paying customers. In this manuscript, we review four IMI projects and the digital assets they produced as a means of illustrating the challenges in making digital assets sustainable and the lessons learned. To progress digital assets beyond proof-of-concept into widely adopted tools, there is a need for continuation of multi-stakeholder support tailored to these assets. This would be best done by implementing a structure similar to the accelerators that are in place to help transform startup businesses into growing and thriving businesses. The aim of this article is to highlight the risk of digital asset loss and to provoke discussion on the concept of developing an "accelerator" for digital assets from public–private partnership research projects to increase the chance that digital assets will be sustained and continue to add value long after a project has ended.

Keywords: precompetitive research, digital assets, innovative medicines initiative, translational research, infrastructure

OPEN ACCESS

Edited by:
Michel Goldman, Université libre de Bruxelles, Belgium

Reviewed by:
Rolf Bass, Retired, Basel, Switzerland
Dimitrios Tzalis, Taros Chemicals GmbH & Co. KG, Germany

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *28 June 2017*
Accepted: *20 February 2018*
Published: *09 March 2018*

Citation:
Aartsen W, Peeters P, Wagers S and Williams-Jones B (2018) Getting Digital Assets from Public–Private Partnership Research Projects through "The Valley of Death," and Making Them Sustainable. Front. Med. 5:65. doi: 10.3389/fmed.2018.00065

The Innovative Medicines Initiative (IMI) is the world's largest biomedical research public private partnership. IMI projects are generating large amounts of medical research data. With the advent of big data approaches, any pretense that medical research is not a digital business has finally been exposed as the myth it has long been.

Accordingly, the IMI has funded numerous e-infrastructure and knowledge management projects (1). Each of these is targeted at the development of digital assets, enabling data services and platforms, which fill key gaps in the drug discovery value chain. Like any new product or service, enabling digital assets face a Valley of Death (2, 3). Often in a funded project, they are developed to proof-of-concept and a working prototype. But once project funding ends, the generated digital assets are at great risk of never being developed to the point where they achieve sustainable traction.

The real risk is that the medical research data, generated by IMI projects and dependent on their co-developed digital assets, may become less accessible to the scientific community. It is, therefore, important to secure long-term sustainability and availability of project generated digital assets, as well as their integration within current ecosystems.

By its very nature, a public–private partnership includes different types of stakeholder who have varying perspectives and aspirations. The interest of pharmaceutical companies in projects that produce digital assets is mostly driven by the desire to enable research at a wide scale, which would be challenging for anyone company to achieve on their own. So, from perspective of the pharmaceutical industry, IMI projects are a means to work pre-competitively to address key gaps in the pharma value chain (4) [e.g., Drug Disease Model Resources consortium (DDMoRe),[1] U-BIOPRED,[2] European Translational Information and Knowledge Services (eTRIKS),[3] and Open PHACTS[4]].

For smaller companies, with limited access to data specialists, public–private partnerships provide an opportunity to develop and access digital assets that are otherwise out of reach. For even smaller companies who are engaged in the development of data services and platforms, public–private partnerships provide the opportunity to participate in co-development. The assumption is that their core capabilities will be integral to the outputs of a project.

From the academic perspective, the interest lies in the production of innovative data services and platforms. The developed digital assets do have a potential impact on the ability of the wider scientific community to drive understanding of diseases (U-BIOPRED profiling data). Such an impact is also important to patient organizations, and regulators involved in these projects.

Regardless of the stakeholder, sustainability of the produced digital assets is essential for achieving the impact they are most interested in. However, achieving sustainability for digital assets is not straightforward. Our intent is to provoke a discussion to highlight the risk of losing digital assets after project funding ends and to propose a concept that will help to mitigate that risk.

CHALLENGES IN ACHIEVING SUSTAINABILITY OF PROJECT OUTCOMES

There are no guidelines or financial regulations, no core agreement template or best-practice strategy, for sustaining a public–private partnership or its digital assets. It is not unlike a startup business. A startup is usually formed to solve a particular problem for which there is a large enough market of customers who will pay for that solution. At the end of the funding period of public–private partnerships, stakeholders have already paid for a solution, and there is usually no *a priori* consideration as to the size of the potential market.

Startup Funding

A steady cash flow is needed to host, maintain, or even develop digital assets. Adequate and sustainable funding can be generated through offering services for a fee, sponsorship fees for membership in foundation or charity taking on the development of the digital assets, or both. Providing services requires an underlying organizational structure for which there will be costs to be covered. A particular challenge is that in order to obtain funding from other revenue sources such as a follow-on grant, there needs to be a legal structure, which requires funding to establish.

Conflicting Business Models (Academia vs. Industry vs. Non-Profit)

To become financially viable, there has to be a clear understanding of the added value of the offered digital asset. Academic digital assets are often sustained by rolling components of tangible value into new projects such that these digital assets slowly evolve into core capabilities and community assets. In industry, there is a balance that has to be struck between leveraging digital assets from the public domain, integrating data and services with internal data and capabilities, and procuring proprietary services from commercial providers. This creates a large integration overhead. The non-profit business model is to make digital assets open and widely available. This is a promising solution, but even non-profits have to provide value in order to generate sufficient revenue to operate. While making access more open is necessary, this has to be achieved in a way that covers the cost of maintaining and developing that asset in the future. There is no such thing as a free lunch, and as digital assets become both increasingly important and vital to drug discovery, they also become increasingly complex and expensive to provide.

OPTIONS FOR SUSTAINING DIGITAL ASSETS

Developing a Sustainable Business Model

Good business models are developed in a dynamic fashion as illustrated by a quote by Eric Ries from Lean Startup: "*Startups that succeed are those that manage to iterate enough times before running out of resources*" (5). Just providing a business model/strategy to a team of domain experts is only a start of a journey toward sustainability.

Collaborative Business Model Generation

One of the biggest challenges in developing a sustainability model is communication. The academic mindset differs from the business mindset resulting in a communication gap. Sharing information, reaching consensus, open exchange of ideas and building upon each other's work is part of the *modus operandi* in public–private partnership. To arrive at a sustainability model for digital assets this gap has to be bridged. It is also important to retain the engagement and commitment of the community which built the digital assets while simultaneously engaging other stakeholders. This is particularly the case with open source assets, and those

[1] http://www.ddmore.eu.
[2] http://www.europeanlung.org/projects-and-research/projects/u-biopred/home.
[3] https://www.etriks.org.
[4] http://www.openphactsfoundation.org.

which require engagement and adoption of the wider scientific community beyond those originally in an asset's development.

The use of a business model canvas (6) or a derivative thereof to structure an iterative discussion is an effective approach for building a common understanding and integrating the perspectives of multiple stakeholders. In the eTRIKS project, an "asset maintenance canvas" was used to work with project partners to discuss and develop plans for sustainability, while DDMoRe and Open PHACTS used an approach more similar to a business model canvas. This is a very flexible approach, which allows a complete understanding of the sustainability requirements for any given asset that is understandable to all stakeholders and helps to facilitate the process.

Sustainable Solutions

The role of providing further maintenance and development of digital assets developed in project can be carried forward by: (1) project partners, (2) an established commercial/nonprofit organizations, and/or (3) a newly formed external commercial/nonprofit organization. The biggest challenge lies in arranging for covering the costs of maintenance and further development. Depending on the nature of the digital assets, one option might be preferred over the other especially when considering intellectual property rights and obligations. Here, we present four different solutions, which illustrate real practical experience of sustaining digital assets, together with the inherent risks.

EXAMPLES OF SUSTAINABILITY IN IMI PROJECTS

U-BIOPRED

The project Unbiased BIOmarkers in the Prediction of REspiratory Disease (U-BIOPRED) was one of the first IMI projects to develop a plan to create the necessary infrastructure to support data integration, exploration, and preservation. Asthma is a diverse disease, and it is thought that many different phenotypes of asthma are not properly understood. U-BIOPRED created "handprints" that identify sub-phenotypes of asthma from large-scale phenotypic characterization of 1,025 patients. The effort involved the integration of multiple types of data including various high dimensional data types such as proteomics, metabolomics, genomics, and even a newly coined "breathomics."

The size of the dataset, while large, was not large enough to consider it "big data." It was, however, rich in terms of its complexity and the number of research questions it could address. In total, U-BIOPRED developed 12 analysis workflows, which were taken forward by separate teams. Over 100 publications have been planned. The complexity and richness of the dataset resulted in a number of challenges including managing the access for all the different parties, integration of different data types, and handling all the different analyses and teams that were engaged in analyzing the data. From the start, it was recognized that U-BIOPRED needed a platform to manage the data and knowledge that was being generated in the project.

During the early phase of the project, Janssen Pharmaceuticals, which was not an original partner, joined and brought their internal knowledge management (tranSMART) system into the project. The tranSMART platform allows for the parsing and exploration of translational research datasets curated into a common data model. Such a platform helps to solve the challenge of having multiple parties working on the same dataset as it provides a common repository that can be used to select out relevant subsets of the larger dataset. It is also being used to "explore" the dataset even to assist internal decision making within some of the U-BIOPRED pharmaceutical company partners. Such a use highlights the real value and the potential of a digital asset to improve the efficiency of research and new therapy development.

The U-BIOPRED collaboration is being maintained as part of the effort to develop a research agency within the European Respiratory Society (ERS) (7). "Data" is one of the main strategic activities of the ERS research agency and the support of the ERS has been essential to maintain the digital and other assets that were developed in U-BIOPRED. As was recently highlighted in the New England Journal of Medicine collaborations where nonprofits and patients have a central role are having a significant impact and may be the way to conduct translational research in the future (8). Nonprofits can act as a "backbone organization" (9) in translational research projects such as the Movember Foundations Global Action Plan (10). For U-BIOPRED, the ERS has been the "backbone organization" that is assuring that the maximal value is derived from the assets generated in the project. This could be a particularly important strategy for digital assets as non-profit organizations are able to take a long-term view and often see the value in making the most out of the assets we have and increasing the efficiency of medical research and development.

The inherent risk in this model is that it is dependent upon one organization and is a generalized model for sustaining all assets not just digital assets. Digital assets cannot be static like a biobank or even a dataset, they have to maintain a continued development trajectory if they are to remain relevant and gain traction.

European Translational Information and Knowledge Services

The adoption of the tranSMART platform by U-BIOPRED stimulated further development of an IMI call topic focused on supporting IMI projects in their knowledge management needs—eTRIKS. As the project eTRIKS was being formed, Janssen Pharmaceuticals was working with the Pistoia Alliance to develop a nonprofit foundation to further develop tranSMART as open source software. The eTRIKS project was premised on using the tranSMART platform for supporting projects.

The initial remit for eTRIKS was to support 40 projects over the course of 5 years. At the end of 5 years, eTRIKS has supported 61 projects to varying degrees. A large part of that support has comprised substantial contributions to the tranSMART open source development effort. It has also included the development of a number of analytical tools through a collective effort termed eTRIKS Labs. As such, eTRIKS has produced a number of digital assets, which are in various stages of development.

The know-how developed over the course of the eTRIKS project will be sustained beyond the eTRIKS funding period as an eTRIKS Data Science Network that will be a consortium

of providers that offer advice, support, development, curation across the data value chain. The digital assets will be maintained by the individual partners who had a major role in their development. eTRIKS has gone through a process of developing asset maintenance plans for each digital asset that include information on where it will be maintained as well as the provision of the necessary documentation.

The decision to sustain digital assets in a distributed network in eTRIKS was premised on two factors. Through the close relationship with the TranSMART Foundation, it was recognized that bundling the assets into a separate entity would create the risk that they may not be sustained if that entity did not achieve sustainable funding. Second, the lack of a stable structure or model that the assets could be transferred to, except for those that are being incorporated into the tranSMART platform. Another factor that played a role in this decision is that the individual partners contributed to the development of these assets and have a stake in seeing them sustained and gaining future value through further development.

There is, however, a risk with this model in that organizations with a primary education and research mission, are not focused on producing digital assets that attain the same degree of rigor as commercial products. Thus, these assets may never move through the digital asset "valley of death" to become more widely adopted or used beyond an academic research setting.

Open PHACTS

The integration and application of diverse data for applied idea generation is a key step in early drug discovery research. Data from multiple sources both from the public domain and private sources are essential to understand the potential for new ideas, particularly relating to the relationship between potential drugs and targets. To lower the barriers to drug discovery, and power early precompetitive research, Open PHACTS built the first large-scale semantic drug discovery platform focused on answering key questions in early drug research (11). Through leveraging the experience of pharma companies, academics, and SMEs, Open PHACTS has been able to build a powerful open resource for drug discovery (12), which both simplifies data access and enables value-added research-focused workflows. Provisioning of fit-for-purpose research data services requires a stable, secure infrastructure, which has established the semantic data standards needed through close engagement of the wider academic community. Importantly, the Open PHACTS project recognized the need for digital assets sustainability early on, and has established the Open PHACTS Foundation (see text footnote 4) as a UK-registered non-profit charity, which maintains and develops the data services and infrastructure beyond the timeframe of the IMI project, which was completed in April 2016. The Open PHACTS Foundation is open to membership for any researcher or organization who share an interest in the applied use of research data for exploring biology, and who are willing to contribute to the running and maintenance of the Open PHACTS infrastructure and services.

Early in the process of establishing the Open PHACTS Foundation as the sustaining entity for the Open PHACTS IMI project output, several industrial partners (GSK, Janssen, Lilly, Roche, and Novartis) and academic partners (University of Vienna, University of Maastricht) joined the Foundation as partners. To ensure continued sustainability, a wide membership of private and public users is necessary to both maintain the current infrastructure and to develop and grow for the future. The Open PHACTS Foundation is a funded partner in H2020 projects, and a key pillar of sustainability remains leveraging the public–private opportunities to bring researchers together and better understand how to use data to better discover new drugs.

The risk in this model is having to fund the operating costs of the Foundation from sponsorships. There are any number of public/private partnerships that have come to the end of their funding period and look to subscribe to sponsors for further funding. This can lead to what has been informally expressed as "foundation fatigue."

Drug Disease Model Resources consortium

The Drug Disease Model Resources consortium set off to harmonize and standardize the way mathematical and statistical models are used and integrated in Pharmacometrics (PMX) to improve the quality, efficiency, and cost effectiveness of decision-making in Model-Informed Drug Discovery and Development (13). PMX model encoding is performed with a very heterogeneous set of software languages. Different notation and vocabulary as well as formats and file types are limiting the exchange of information. In order to make it easier to share and integrate models of compound, mechanism, and disease level data, DDMoRe faced the challenge of finding common ground to develop standards as a backbone for one platform to store and exchange models. DDMoRe succeeded in delivering a range of open-source exchange standards; a unified Model Description Language, the XML-based Pharmacometrics Markup Language a new exchange format for encoding of models, associated tasks, and their annotation (14), The Standard Output,[5] a tool-independent standard exchange XML-based format for storing results. Systems like a repository to store models (Model Repository) and an Interoperability Framework as a tool to integrate software languages have been developed on top of the standards to demonstrate the possibility of sharing models and expertise within and between companies, regulatory authorities, and academic institutions.

Setting a standard is a collective piece of work, but a standard only becomes the standard if used by many. Additionally, further development and coordination of the standard requires industry and academic institutions to work together. The DDMoRe Foundation[6] has been established as a Dutch-registered non-profit foundation to maintain and grow both standards and infrastructure for the benefit of the global community, pharmacometric experts, and the users of their model output alike. Early in the process of fundraising, two industrial partners (Servier and Pfizer) and two academic partners (Uppsala University and the University of Pavia) have joined the Foundation as partners. Recently, three more partners (GSK, Merck KGaA, and Leiden University) joined; however, to cross the "valley of death," more partners

[5] http://ddmore.eu/projects/so-standard-output.

[6] http://www.ddmore.foundation

need to be onboarded also representing SMEs and CROs. To assure that the digit assets become more widely adopted, ongoing negotiations with stakeholders like health authorities (e.g., EMA and FDA) have to materialize in concrete plans and actions for future alignment and development supporting the implementation of a sharing platform based on the DDMoRe standards.

Such a model carries the risk that the rate of adoption of standards does not achieve a large enough critical mass to provide sufficient funding for its continued development.

LEARNING FROM THE STARTUP COMMUNITY

The challenge of having to sustain and further develop a digital asset after it has garnered some degree of proof-of-concept is not unlike the challenge faced by startups. Startups face what has been described as a "valley of death" where proof-of-concept has been achieved and early adopters are using the product. But, the process of gaining an increased market share and improving the product such that it can be scaled to meet a larger demand and satisfy customers is an enormous risk and requires funding. The startup community has addressed this at least in part by forming "incubators" or "accelerators" to help bring startups together, provide them some basic infrastructure and coaching, and provide a means for assessing which ones are most viable thereby reducing the risk to investors. These structures also help to reduce redundancy for standard activities such as contracts, accounting, and administrative staff.

A similar type of structure could be developed for the digital assets of IMI or other publicly funded digital assets. This could provide a common pool of knowledge about transforming digital assets into more sustainable products as well as provide a degree of flexibility in the type of support offered. Most importantly, it could provide a platform for those interested in the various digital assets that are being produced to assess which ones are worthy of further investment. It would also serve as a means of reducing the fragmentation that happens when assets are resolved back into the remit of the individual partners and help to protect the integrity of digital assets so that their progress can continue in a linear manner. There would be an additional advantage in that in such a structure one could find various digital assets that would be of use for a new project or even a new commercial project.

CHANGE IN PARADIGM

Through IMI, stakeholders have shown a clear commitment to drug discovery bottlenecks and enabling precompetitive research. For newly generated digital assets to become sustainable, they cannot be dependent on industrial funding alone. Similar to the model of the IMI, there needs to be continued public/private support to move these digital assets through the "valley of death" and support their continued development into more robust software and resources. This is not a unique challenge to IMI-generated digital assets, as digital science is becoming increasingly prevalent, this issue is relevant to the medical research community as a whole. For the most part, the funding streams for the translation of medical research are not the same as those which funded the research (13). Grant funding agencies are focused on research outputs such as new therapeutic targets and new technology. The risk is that there will be a lot of redundant efforts as new projects re-capitulate development and proof-of-concept efforts of preceding projects. There is too much to be done to waste resources in redundant efforts. IMI has lead the way in showing the potential of funding the development of tools and infrastructure that will enable the medical research community to capitalize on the potential of digital science. Now is the time for the whole community to embrace this change and deliver on that promise together in the future.

There are ongoing efforts to maintain digital assets. The IMI implemented a call topic on exploitation and sustainability of IMI project results where projects could place their assets into the call and different consortia could apply to have funding for maintaining those assets.[7] The Pistoia Alliance is a nonprofit alliance that works on precompetitive projects to lower barriers to R&D innovation. They have successfully shepherded digital assets such as the tranSMART platform (15). ELIXIR is a European program that is focused on developing a European informatics infrastructure including bioinformatics.[8] Grant funding agencies, industry, and other stakeholders such as disease foundations, regulators, and government bodies need to invest more into the refinement and maturation of digital assets. This would be best achieved by establishing digital asset accelerators that select the most promising digital assets and support their continued development under a common umbrella. This would bring the benefit of building know-how and experience, sharing best practices in making digital assets more robust and ultimately bringing them into a sustainable future. Experience in Silicon Valley is that accelerators do not need large amounts of funding to have substantial impact (16). Our hope is that this article can help to provoke a discussion that can lead to the support of more investment in sustaining the best digital assets so that the research outputs of projects remain accessible future projects do not have waste effort building digital assets anew.

AUTHOR CONTRIBUTIONS

WA, PP, SW, and BW-J contributed equally to this work.

[7] http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call11_CallText.pdf.

[8] https://www.elixir-europe.org/about-us accessed 16/01/2018

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Conflict of Interest Statement: The author SW is the CEO of a company that provides consulting services to help manage projects and provide recommendations on sustainability solutions for projects and their digital assets. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

REVIEW
published: 20 January 2017
doi: 10.3389/fmed.2017.00003

Public–Private Partnerships in Cloud-Computing Services in the Context of Genomic Research

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Public–private partnerships (PPPs) have been increasingly used to spur and facilitate innovation in a number of fields. In healthcare, the purpose of using a PPP is commonly to develop and/or provide vaccines and drugs against communicable diseases, mainly in developing or underdeveloped countries. With the advancement of technology and of the area of genomics, these partnerships also focus on large-scale genomic research projects that aim to advance the understanding of diseases that have a genetic component and to develop personalized treatments. This new focus has created new forms of PPPs that involve information technology companies, which provide computing infrastructure and services to store, analyze, and share the massive amounts of data genomic-related projects produce. In this article, we explore models of PPPs proposed to handle, protect, and share the genomic data collected and to further develop genomic-based medical products. We also identify the reasons that make these models suitable and the challenges they have yet to overcome. To achieve this, we describe the details and complexities of MSSNG, International Cancer Genome Consortium, and 100,000 Genomes Project, the three PPPs that focus on large-scale genomic research to better understand the genetic components of autism, cancer, rare diseases, and infectious diseases with the intention to find appropriate treatments. Organized as PPP and employing cloud-computing services, the three projects have advanced quickly and are likely to be important sources of research and development for future personalized medicine. However, there still are unresolved matters relating to conflicts of interest, commercialization, and data control. Learning from the challenges encountered by past PPPs allowed us to establish that developing guidelines to adequately manage personal health information stored in clouds and ensuring the protection of data integrity and privacy would be critical steps in the development of future PPPs.

Keywords: public–private partnerships, cloud computing, genomic research, large-scale projects, MSSNG, ICGC, 1000 Genomes Project

OPEN ACCESS

Edited by:
Michel Goldman,
Université libre de Bruxelles, Belgium

Reviewed by:
Adamantios Koumpis,
University of Passau, Germany
Jan Klimas,
Comenius University, Slovakia

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *15 November 2016*
Accepted: *06 January 2017*
Published: *20 January 2017*

Citation:
Granados Moreno P, Joly Y and Knoppers BM (2017) Public–Private Partnerships in Cloud-Computing Services in the Context of Genomic Research. Front. Med. 4:3. doi: 10.3389/fmed.2017.00003

INTRODUCTION

Public–private partnerships (PPPs) have been increasingly used to spur and facilitate innovation in a number of fields. Healthcare is one of them. Some examples include the PATH Malaria Vaccine Initiative, the Drugs for Neglected Diseases Initiative, the TB Alliance, and the International AIDS Vaccine Initiative. These partnerships usually involve a health authority, public hospitals or research

centers, and private companies, usually pharmaceuticals. The purpose is commonly to develop and/or provide vaccines and drugs against communicable diseases, mainly in developing or underdeveloped countries (1). With the advancement of technology and of the area of genomics, these partnerships started focusing on genomic research projects that aim to advance the understanding of diseases that have a genetic component and to develop personalized treatments. This new focus has brought about other forms of PPPs. These new forms of PPPs involve information technology (IT) companies, which provide computing infrastructure and services to store, analyze, and share the massive amounts of data genomic-related projects produce.

This article explores models of PPPs proposed to handle, protect, and share the genomic data collected and to further develop genomic-based medical products. It also identifies the reasons that make the model suitable for these purposes and the challenges it has yet to overcome. To achieve this, the article describes the details and complexities of MSSNG, International Cancer Genome Consortium (ICGC), and 100,000 Genomes Project (100,000 GP), the three PPPs that focus on large-scale genomic research to better understand the genetic components of autism, cancer, rare diseases, and infectious diseases with the intention to find appropriate treatments. All the three projects require cloud-computing services (CCSs) to store, process, and share the massive amounts of genomic and health data that they collect. Both MSSNG and ICGC partnered with a commercial IT company that provides public CCSs. The 100,000 GP has a private cloud and partnered with private companies that do the sequencing of the DNA samples and that will develop diagnostic tools and treatments.

Our analysis compares these three genomic research projects, two of which (MSSNG and ICGC) include a well-established private IT company for the provision of CCSs as partners. We identify core elements about their organization, their goals, and current status and progress. The 100,000 GP has in-house (private) CCSs and partnered with private companies for other purposes [sequencing and interpretation assistance and translational research and development (R&D)]. This variation allows us to determine whether there is a difference between having a private specialized company handling the storage and sharing of genomic data or having in-house CCSs.

The sources we used for the description and analysis of the projects were the projects' websites, documentation, and press releases without including internal private agreements with the companies that were not made public. Relying only on public documents, however, prevents us from learning about undisclosed challenges that the projects may encounter, their approaches to solve them, as well as private negotiations between the public and the private parties, all of which may limit our analysis. The sources we used for the context were peer-reviewed articles obtained from Google scholar using key terms such as "cloud-computing" and "public-private partnerships" alone and "cloud-computing" or "public-private partnerships" AND "health research," "genomic research" or "medical genetics." We also consulted Canadian, American, and British governmental websites and policies.

The article is organized into three sections. The first section presents the basic concepts of PPPs in the area of healthcare. This section intends to provide a general context on the characteristics, uses, stakeholders, benefits, and challenges of PPPs. The second section focuses on the three large-scale genomic research projects that use a model of PPPs and CCSs to reach their goals. It starts with basic concepts of cloud computing including characteristics, models of service, deployment models, and stakeholders and uses in healthcare. It then focuses on each of the three genomic research projects. For each project, we describe the purpose, current status, parties involved and roles, data location, conditions of elasticity in terms of costs and space, extent of control that the leading organizations of the project have over the data stored, access conditions, and confidentiality and privacy mechanisms. The third section discusses the lessons learned from all the three projects including the benefits that the projects have found in using a PPP model as well as the challenges that they still face.

CONTEXT

PPPs in Health-Related and Genomic Research

In medical research (e.g., genomic, pharmaceutical, clinical, etc.), the development of innovative results and products requires a constant targeting of new diseases or conditions to better understand the causes or factors associated with the disease, find and optimize new drugs and treatments, and address current safety, efficacy, and validation concerns. This challenging, complex, and constantly changing environment has encouraged parties from the public and the private sectors to intensify their collaboration (2). One common model of collaboration is that of a PPP with technological features that involves the use of CCSs.

A PPP is an agreement between the public and the private sectors to collaborate with each other by sharing objectives, resources, risks, and responsibilities (3). The partnership can be national or international, depending on its partners. The purpose of a PPP in the context of innovation is to jointly tackle the difficulties of the different stages of the innovation and translation processes and to make those processes more efficient. This purpose is based on the acknowledgment that the innovation and translation processes are too diverse, burdensome, and lengthy for either to take on alone (2–4).

Public–private partnerships have become a very important and prolific model to spur innovation, strengthen businesses, and more efficiently build and maintain public infrastructure. For instance, they have been used in projects to build and maintain roads, bridges, tunnels, railroads, airports, schools, and hospitals. They have also been used to build and operate prisons and to provide the infrastructure to solve water supply problems (3–6). Research in many fields, including health, has also used PPPs (7). Particularly in the context of healthcare and health-related research, many PPPs are created to make the process of R&D of drugs, vaccines, diagnostic tests, and medical devices more efficient and effective, as well as to improve patients' access to medical innovative products (2, 4, 8, 9).

Different types of partnering may take place. Some include strategic innovation partnerships, consortia, joint research, crowdsourcing, outsourcing, licensing, incubator, and venture capital investments. The most common partners in PPPs in health-related research include public and private hospitals; public and private universities; non-for-profit organizations; patient organizations; small-, medium-, and big-size pharmaceutical and biotechnology companies; and governmental agencies. Technological advances in IT (e.g., the power of hardware, software, and mobility of devices), biomedicine, the different types of *omics* (e.g., genomics, proteomics, metabolimics, etc.), and the production of big data[1] have attracted a new essential partner: IT companies (10).

Public–private partnerships are useful to improve access to health-care services as well as to spur R&D in the field (3). Since multiple partners will be able to combine their resources, infrastructure, and responsibilities, they may have the possibility to allocate their resources more efficiently and thereby use some of these resources to provide health-care services in a larger area. Furthermore, by combining resources, infrastructure, and skills from members of the public sector, PPPs may also help to focus on a specific condition that is endemic to a particular region where, because of the poor socio-economic conditions of its population, there is not a very profitable market and therefore potentially no interest from pharmaceutical companies. This focus may help to overcome situations of market failure and address diseases that would otherwise be neglected (3, 13). With respect to R&D, these partnerships could satisfy different needs, such as enabling access to new ideas or providing the perspectives of a broader community, overcoming complicated or extensive challenges such as regulatory approvals, transferring of knowledge or expertise, and establishing an earlier involvement with entrepreneurs (2).

Public–private partnerships allow the different partners to share resources that include economic funds, knowledge, expertise, information (e.g., data and samples and patient base), and infrastructure. They also enable partners to share risks, responsibilities, and networks of experts while accessing new ideas from a broader community. Sharing economic resources, risks, and responsibilities can alleviate the burdens inherent in the innovation process making it less costly and faster. For instance, it can avoid or decrease the need for costly initial capital investments. Sharing expertise, ideas, information, and infrastructure can make the process more efficient, more fluid, and more interconnected. Overall, these benefits increase the value of the investment and infrastructure of all the partners as well as the value of the project the PPP was set for (2–4).

Public–private partnerships can also democratize the innovation process, as more agents, and not only those with all the initial necessary resources, can participate. For instance, small- and medium-size companies could enter a PPP and participate in large-scale projects, which they would not be able to do, if they depended entirely on their own means and resources. This democratization could also benefit developing countries, as the governments and companies of these countries could be able to participate in projects that, because of the costly resources that they require, are more technologically and scientifically advanced and usually take place in developed countries. This could ultimately promote the economic, scientific, and technological growth of these countries, as employment would be created, distribution of goods would be increased, and technological and scientific advancements would be transferred (14).

However, despite the abovementioned advantages of PPPs, there are certain difficulties that need to be considered and overcome. First, the parties entering the partnership may have unrealistic expectations about what the partnership is supposed to create. Second, the parties from the public sector tend to have objectives and interests that differ from those of the parties of the private sector. Third, the negotiation process to achieve these partnerships is complicated. This is even more serious in partnerships whose projects are caught in the middle of political debates or public opposition because of their focus or the subject matter of those projects. Fourth, there may be inadequate legal or regulatory frameworks, which could make the partnership more difficult to set or to maintain. Fifth, these partnerships need to be maintained, particularly in health-related research, as the processes of R&D in this field tend to be lengthy. These difficulties make the coordination and management of partnerships challenging (2–4, 7).

In order to address and even overcome some of the abovementioned difficulties, certain reforms have been suggested. For instance, it has been proposed that those who have the authority to make decisions in the project be involved in the R&D process from its inception. This would allow them to act in a timely manner. Additionally, the coordination and decision-making process needs to be mindful of the specific field(s) associated with the project. Progress and deliverables need to be continuously monitored in order to increase the chances of detecting any hurdle or setback that may arise. Work methods and agreements should be clarified. It is also recommended that political, legal, commercial, operational, environmental, and economic risks and responsibilities be distributed among all the partners in a timely fashion. For this, they should be identified and distributed among the partners in accordance with the partners' financial and technical capabilities for management. In addition to all these recommendations, maintaining mutual confidence and trustworthiness throughout the project is one of the most important suggestions to ensure that the PPP succeeds (3, 7, 15).

Cloud Computing in Genomic Research

In health-related research, and particularly regarding genomic research, the involvement of IT companies in PPPs is essential. The development of devices to continuously collect data from patients created massive amounts of data. Furthermore, the advent of genomics and other *omics* fields and of technologies that accelerate the collection of data have also contributed to the production of massive, complex, and potentially helpful data (10, 12, 16). These data need to be stored, organized, analyzed, and made accessible to researchers and developers in order for them to discern patterns, associations, and trends for the better

[1]Big data can be defined as vast amounts of data with significant variety or heterogeneity that can be accessed and analyzed to reveal patterns, trends, and correlations [Dimitrov (10), p. 159; Costa (11), p. 433; Jordan (12), p. 5].

understanding of diseases in order to create improved and customized diagnostic tests, drugs, vaccines, and treatments (10, 11). These needs often create problems of interoperability among the different sources of the aforesaid data and platforms, high costs of infrastructures, and other necessary technological tools. Hence, trained personnel are required to manage, operate, and maintain the infrastructure as well as to be capable to analyze, process, and share the data (12, 17). In order to address these problems, CCS providers are desirable partners in genomic research partnerships (14–18).

Cloud computing is defined "as a model for enabling ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g., networks, servers, storage, applications, and services) that can be rapidly provisioned and released with minimal management effort or service provider interaction" (19, 20). Based on this definition of the National Institute of Standards and Technology, CCSs are provided on demand (server time or storage), accessible through the use of standard mechanisms over a broad network, immersed in a resource pool serving multiple consumers, and elastic. The elasticity allows multi-tenancy (i.e., one single application can serve multiple users) (16, 20, 21).

Cloud-computing services can be deployed in a private cloud, a community cloud, a public (commercial) cloud, or in a hybrid cloud. A private cloud provides exclusive services to one single organization, and the infrastructure (data center) is owned, managed, and operated either by that same organization that uses it or by a third party. A community cloud provides services to a specific group with a common interest, and the infrastructure may be owned, managed, and operated by one or more organizations in the group or a third party. A public cloud provides services to the general public, and the infrastructure is owned, managed, and operated by a company, an academic or governmental organization, or a combination of both. A hybrid cloud is composed of two or more clouds that can be private, public, or community (15, 16, 18, 20, 22).

Cloud-computing services are offered in three models: infrastructure-as-a-service,[2] platform-as-a-service,[3] and software-as-a-service[4] (15, 16, 20, 22). Some authors also include mobile backend-as-a-service[5] (21, 23). Four types of stakeholders are associated with CCSs in health-care fields. The first ones are end-users (also called consumers). They use the services on demand based on their own specific needs. End-users include physicians, medical staff, patients, medical researchers, and IT experts. Patients use CCSs for purposes of personal health-care management. Medical researchers and staff use them for medical and genomic research. Finally, IT staff employs CCSs for the creation and implementation of cloud-based solutions (16). The second type of stakeholders refers to service providers (companies and organizations). They own, operate, maintain, and update the system and provide the service to the end-users. The enablers are the third type of stakeholders. Even though not essential, they sell products and services to facilitate the delivery and use of the CCSs. Finally, the regulators are in charge of providing guidelines, standards, and rules regarding the proper and ethical use of CCSs. These regulators can be national or international. Regulations can focus on privacy, security, liability, intellectual property, cross-border issues, access and transfer, governmental extent of monitoring and access, and forensics (21).

Cloud-computing services bring a number of benefits. For example, they allow companies and organizations to use computing resources (e.g., storage and analytical computing) as a utility on a pay-per-use basis. This condition results in costs reduction, as the infrastructure needed is "rented," rather than having to invest in building and maintaining the infrastructure. These reduced costs allow any company or organization, including those that are small and medium sizes, to enter the research field, potentially also benefiting companies, organizations, and entities in developing countries. The latter could avoid costly investments while using and exploiting state-of-the-art computing processes. CCSs can rapidly and easily scale-up or scale-down on a need-to basis. This situation gives customers flexibility to add, expand, reduce, eliminate, or re-distribute their resources and services. Moreover, companies and organizations can hire on-demand self-services and decide the location of the server where their data will be stored. IT experts are responsible for maintaining the infrastructure, thus making the upkeep of the cloud easier. Customers can share resources and costs among themselves, allowing a more efficient use of resources and reduced costs and timelines. The use of CCSs can also increase productivity in the development of the projects undertaken by customers, given that multiple users can work simultaneously on the same data and collaborate without the need for constant software upgrades. Along with this efficient use of resources, CCSs also reduce the time that clinical and genomic research takes. Usually, these processes require researchers to download or upload data to their local computers in order to process, analyze, and obtain results. These results then need to be uploaded to repositories for publishing and sharing. Since cloud computing eliminates the need to download the data, the whole process is shortened. In addition, given that there is no need to build and maintain individual infrastructure each time a project requires computing services, the use of CCSs could be considered more environmentally friendly. Finally, even though there are still concerns about losing control over certain data, the centralization of the data,

[2]The IaaS provides storage, networks, and analytical/processing computing services for application program interfaces (APIs) to migrate workloads and data to a virtual machine. In this case, users have a determined storage capacity, processing capability, and other resources that they can use to start, stop, access, and configure the virtual machine they have been assigned. They are allowed to install their own operating systems and applications on the infrastructure provided [Mell and Grace (20), p. 3; Dove et al. (15), p. 1272; Kuo (22), p. 2; Marston et al. (21), p. 178].

[3]The PaaS hosts development tools that are made available *via* APIs, browsers, or software to develop and deploy software applications onto a cloud infrastructure [Mell and Grace (20), p. 2 and 3; Dove et al. (15), p. 1272; Kuo (22), p. 2; Marston et al. (21), p. 178].

[4]The SaaS allows users to deliver software applications and run them on a cloud infrastructure. The applications are accessible from the users' devices through the use of a web browser or a program interface, without the need to install the application in a particular computer [Mell and Grace (20), p. 2; Dove et al. (15), p. 1273; Kuo (22), p. 2; Marston et al. (21), p. 178].

[5]The MBaaS provides a way to link web applications and mobile applications to a cloud infrastructure.

the increased security-focused resources (e.g., encryption tools and techniques, firewalls, auditing capabilities, etc.), and the specialization of IT personnel that focuses on these matters are ways to increase the level of security (15, 21, 22, 24).

The most serious challenge with CCSs in healthcare is the perceived risk of possible loss of control of health data, jeopardizing the safety and security of data and patients' privacy and confidentiality. A proposed solution is the use of controlled access, audit control, authentication, authorization mechanisms, as well as transmission and storage security. Some of these tools include secure transmission protocols, special security certificates, access control lists, electronic keys, and digital signatures. However, these measures may be inconvenient, particularly in emergency situations. The use of tools that allow the anonymity of data has also been suggested,[6] but anonymization prevents the return of health results. Data integrity may also be at stake due to hacker attacks, network failures, or poor management. Again, the use of controlled access, authentication, authorization, and transmission and storage security measures can also help to preserve data integrity. Ensuring that CCS providers have appropriate backups and retrieval measures in place can be also helpful. Another concern regarding the use of CCSs is reliability. Cloud-computing providers can suffer outages (e.g., Amazon's outages in 2008, 2011, and 2012). They may also suspend certain services either temporarily or permanently (e.g., Google Health). CCS providers also have to ensure compliance with data privacy laws of the specific locations of the data centers where data are stored and transferred. Getting end-users to trust CCSs and providers, particularly with respect to data security and privacy, is perhaps the greatest challenge (15, 16, 22, 24).

Irrespective of these challenges, CCSs have been used in several areas of healthcare: telemedicine/teleconsultation,[7] medical imaging,[8] public health and patient self-management,[9] hospital management and information systems,[10] therapy,[11] and secondary use of data (16). Genomic research in particular benefits from the secondary use of data. Since CCSs enable the storage of massive amounts of data and the use of complex computing processes at reduced costs, it is possible to simultaneously do clinical and genomic data analysis, text mining, and ongoing clinical research (16).

By enabling global access to clinical and genomic data and other resources, CCS providers unlock the value of big data, and particularly of genomic data. Global access to such data allows scientists, researchers, and developers to use data generated in different regions, from different patients, and with different techniques. It also allows researchers and developers from different backgrounds and multiple disciplines to work together simultaneously. This diversity enables them to better identify and understand patterns, variants, and correlations among the multitude of factors that cause or prompt a disease so as to innovate and eventually provide accessible health-care services (14, 15). These advantages constitute the rationale for the involvement and uptake by research centers, academic institutions, and governmental agencies in PPPs. Private companies have reasons as well for getting involved in CCSs and in PPPs in the area of genomic and medical research. The first reason is economic. Given the advantages posed to end-users, the demand for these services has greatly increased in the past and is expected to grow even more within the next few years. In 2014, the value of the cloud-computing industry was expected to be $150 billion. Furthermore, companies providing public, community, and hybrid clouds are able to avoid the underutilization of their infrastructure and of their other resources. The third reason is that some companies are increasingly interested in contributing to improving the population's health (21).

Governmental policies and regulatory frameworks can help to create favorable conditions for the success of PPPs and the use of CCSs (3). The "Cloud First" policy in the U.S. is an example of a governmental policy that supports and encourages partnerships with new technology.[12] Laws and policies that address issues of consent, privacy, and personal data applicable in the context of cloud computing can also facilitate the use of CCSs, as they can increase the trust of the general public, research institutions, and funding agencies on projects involving cloud-computing technology (3, 15, 27).

[6] An example of anonymity tools is the use of a biological PIN code that allows a donor to provide a sample without any identity data. In this case, the registration of the sample includes only the individual's unique biological characteristics without enabling any link back to the donor [Dove et al. (15), p. 1271].

[7] Cloud-computing services in telecommunication/teleconsultation allow actors in the area of healthcare (e.g., medical practitioners, specialists, clinicians, nurses, paramedics, etc.) to communicate and share data. An example of this case would be collecting, accessing, sharing, and analyzing the data of a particular patient from different hospitals or health-care providers (e.g., patient records and medical history). For instance, the Cloud Cardiology enables medical professionals to share ECGs simultaneously with members of the hospital and with other practitioners outside the hospital [Griebel et al. (16), p. 4].

[8] Cloud-computing services are used in the area of medical imaging to store, share, and process images. An example of this type of images would be X-rays. For instance, Accenture Medical Imaging Solution is built to review X-rays, MRI, and CT scans [Griebel et al. (16), p. 7; Ahuja et al. (24), p. 15].

[9] Cloud-computing services enable broad access to health data concerned with disease prevention, health promotion, and improvement of the population's health. For instance, they may be used to store personal health and lifestyle data collected by mobile devices and extract patterns that would help prevent epidemics and improve the population's health. They can also be used to monitor the progress of conditions such as post-traumatic disorder syndrome (Tele-PTSD Monitor) or to provide specialized training routines after receiving physiological data (iFit) [Griebel et al. (16), p. 8].

[10] Cloud-computing services allow hospitals to digitalize health records, update clinical processes, and give access to medical staff at anytime and from anywhere. They can also provide faster and more accurate billing [Kuo (22), p. 4].

[11] Cloud-computing services help to host and operate applications for planning, managing, and assessing therapeutic interventions. For instance, VirtuaLinac is a web application used to model radiation treatment components. iSMART is a cloud-computing web server that provides access to information on over 20,000 compounds of traditional Chinese medicine that focuses on identifying compatible and derivative compounds that could be useful for drug research [Griebel et al. (16), p. 9; Chang et al. (25)].

[12] The U.S. Cloud First policy was launched in February 2011. Its purpose was to encourage the governmental agencies to evaluate the possibility of implementing safe and secure cloud-computing options before making any investments in IT infrastructure. With this policy, the U.S. government was aiming to be more efficient, agile, and innovative (26).

For example, in general terms, consent rules usually require that any use or disclosure of health information is previously authorized in writing by the individual to whom the information belongs. However, recent consent policies and projects have changed so as to adapt to and benefit from recent practices of democratization of access of data, by which many researchers from different centers share and analyze data. MSSNG is an example (14, 28, 29).

In the U.S., the Health Insurance Portability and Accountability Act (HIPAA) provides national standards for the protection of certain health/medical information (privacy rule) and for the protection of this information when it is held or transferred in electronic form (security rule). The main purpose of HIPAA is to allow covered entities[13] to adopt new technologies in order to improve patients' health while still protecting the privacy of individuals' health information. The health information protected is "all individually identifiable health information[14] held or transmitted by a covered entity or its business associate,[15] in any form or media, whether electronic, paper or oral." CCS providers can be considered business associates. HIPAA can encourage the use of CCSs, as it allows the donors of genomic data to trust that risks to the safety of their data or to their privacy will be minimized[16] (15, 22, 28, 29). In addition to HIPAA, the U.S. has the NIH security best practices for controlled access data. This document states the minimum standards of National Institutes of Health (NIH) regarding the management and protection of controlled access to data transferred to and maintained by institutions either in their own data centers or in CCSs. The use of encryption and firewalls, as well as access control procedures, is suggested as protection mechanisms (14, 30).

Canada's Personal Information Protection and Electronic Documents Act (PIPEDA) regulates the way in which members of the private sector collect, use, and disclose personal information[17] in commercial activities. This includes information collected and/or stored online. According to PIPEDA, organizations or companies are only allowed to use or disclose the information they collect on the terms agreed at the time of collection, unless a new expressed consent of the individual who provided that information is obtained (22, 31–33). Similar to HIPAA, PIPEDA and the NIH's best practices can encourage the use of CCSs by obligating CCSs providers to adopt measures that protect the safety of health data and the donors' privacy.

SELECTED PROJECTS

The advancement of DNA sequencing techniques has facilitated and accelerated the generation of genomic data. The costs of sequencing have also decreased. These new conditions have prompted the launch of large-scale projects that involve members of the public and private sectors playing different roles (14). Some examples of PPPs that involve CCSs for genomic research include (1) the Collaborative Cancer Cloud that partners Intel, the Knight Cancer Institute at Oregon Health and Science University, the Dana-Faber Cancer Institute, and the Ontario Institute for Cancer Research; (2) the Cancer Genome Collaboratory (CGC), whose partners are the Open Cloud Consortium, the Ontario Institute for Cancer Research, and the Bionimbus Protected Data Cloud; (3) MSSNG that partners Autism Speaks and Google; (4) 100,000 GP which joins Genomics England (GE) with AbbVie, Alexion Pharmaceuticals, AstraZeneca, Berg Health, Biogen, Dimension Therapeutics, GCK, Helomics, NGM Biopharmaceuticals, Roche, and Takeda; and (5) the ICGC that partnered with Amazon Web Services (AWS). We focus on the last three (**Table 1**).[18]

[13] The term "covered entities" refers to any health plans, health-care clearinghouses, and any health-care provider who transmits health information in electronic form in connection with transactions for which the Secretary of HHS has adopted standard under HIPAA [US Department of Health and Human Services (28), p. 2].

[14] Individually identifiable health information refers to "information that relates to the individual's past, present, or future physical or mental health or condition, the provision of health care to the individual or the past, present or future payment for the provision of healthcare to the individual, and that identifies the individual or for which there is a reasonable basis to believe can be used to identify the individual." [US Department of Health and Human Services (28), p. 4].

[15] Business associate is defined as a person or organization, different from a member of a covered entity's workforce that performs certain functions or activities or that provides certain services to a covered entity involving the use or disclosure of individually identifiable health information. Some of these activities include claims processing, data analysis, utilization review, and billing. The services are legal, actuarial, accounting, consulting, data aggregation, management, administrative, accreditation, or financial [US Department of Health and Human Services (28), p. 3].

[16] Some of the rules stated by HIPAA to protect health information are the following. (1) That covered entities must have policies and procedures to maintain their workforce's access and use of protected health information to the minimum amount reasonably necessary and in accordance with their specific roles. (2) That they must also have privacy practices. (3) That companies and organizations are prohibited from sharing personal health data to non-affiliated parties. (4) That the use or disclosure of an individual's protected health information by a covered entity requires the written consent of such an individual or that such use or disclosure falls within the allowed or required uses or disclosures stated by the privacy rule. Required disclosures are those that have to be made to the individuals when they request access to their information and to HHS when an investigation, review, or enforcement action orders it. The allowed uses and disclosures are those made to the individual, those in association with treatment, payment and healthcare operations, those that serve as an opportunity to agree or object, as an incident, those based on public interest and benefit activities, and those made regarding limited data for purposes of research, public health, or health-care operation. (5) That the use or disclosure of limited data set (protected health information from which specific direct identifiers have been removed) for purposes of research, public health (i.e. to avoid a serious threat to health or safety) or health-care operation is among the permitted uses or disclosures without the need of the individual's consent. (6) That genomic data stripped of identifiers may not be considered protected health information, and therefore, the use or disclosure of de-identified health information is not restricted [US Department of Health and Human Services (28), p. 4, 9, and 20].

[17] Name, age, ethnic origin, and medical records are just few of the forms of information considered personal.

[18] For more information on the first two examples, see for (1) Collaborative Cancer Cloud: Dana-Farber Cancer Institute and Ontario Institute for Cancer Research Join Collaborative Cancer Cloud | Ontario Institute for Cancer Research," *Ontario Institute for Cancer Research*, March 31, 2016, http://oicr.on.ca/news/news-releases/dana-farber-cancer-institute-and-ontario-institute-cancer-research-join-collaborative-cancer-cloud; "Dana-Farber Cancer Institute and Ontario Institute for Cancer Research Join Collaborative Cancer Clo," *Oregon Health & Science University*, March 31, 2016, https://news.ohsu.edu/2016/03/31/dana-farber-cancer-institute-and-ontario-institute-for-cancer-research-join-collaborative-cancer-cloud and for (2) Cancer Genome Collaboratory: The Cancer Genome Collaboratory | Genome Canada," *Genome Canada*, accessed September 7, 2016, http://www.genomecanada.ca/en/cancer-genome-collaboratory and "Main—Bionimbus Protected Data Cloud," accessed September 7, 2016, https://bionimbus-pdc.opensciencedatacloud.org/.

TABLE 1 | Summary of the selected cases.

	MSSNG	International Cancer Genome Consortium (ICGC)	100,000 Genomes Project
Launch date	2014	2008	2012
Focus	Autism	Cancer	Rare disorders, infectious diseases, and common cancers
Goals	To collect and sequence DNA from 10,000 families to understand causes of the autism condition across its wide spectrum, identify its different subtypes, and help in the development of more personalized and accurate treatments	To collect and sequence 50,000 genomes. To coordinate and generate current and future large-scale cancer genome studies in tumors from 50 different types and subtypes of cancer in order to identify common patterns of mutation and understand the biology of cancer	To collect and sequence 100,000 genomes from 75,000 patients. To enable new scientific discovery and medical insights regarding the selected rare disorders, infectious diseases, and common cancers for the creation of better tests, better drugs, more accurate and timely diagnoses and treatments, and more personalized care
Public and private partners	Public sector: Autism Speaks-Autism Genetic Resource Exchange and Toronto's Hospital for Sick Children Private sector: Google	Public sector: 25 research centers from around the world, the TCGC, and Cancer Genome Collaboratory (CGC) Private sector: Amazon Web Services (AWS)	Public sector: Genomics England (GE), National Institute for Health Research, Public Health England, Health Education England, 13 National Health Services (NHS) Genomic Medicine Centres, GE Clinical Interpretation Partnership (GeCIP) partnership, and 85 NHS trusts and hospitals Private sector: Illumina, Congenica, WuXi NextCODE, Omicia, Cypher Genomics, Nanthealth, Genomics Expert Network for Enterprises (GENE) Consortium, and GeCIP partnership
CCS provider/type	Google—private company offering public cloud-computing services (CCSs)	AWS (Amazon)—private company offering public CCSs and CGC—public academic resource offering private CCSs	GE—company owned by the U.K. Department of Health offering private CCSs
Status/progress	7,000 whole genomes sequenced. The project has provided access to more than 100 investigators from 9 countries	10,000 whole genomes sequenced and 89 cancer genome projects. ICGC Data Access Compliance Office (DACO) has approved access to 734 projects (including renewals) over the years	16,171 whole genomes sequenced. No mention of projects/researchers approved to access to the data
Characteristics of services	Scalable, elastic, on-demand, and accessible through a broad network. Specialized service for big genomic data	On-demand, elastic, and scalable. Specialized for massive data	Scalable and elastic. Members are encouraged to nominate new diseases
Security and safety	Encryption, online backup, and disaster recovery. ISO 27001, SSAE-16, SOC1, SOC2, and SOC3 certifications	Encryption. ISO 9001, ISO 27018, SOC1, SOC2, SOC3, FISMA, PCI DSS, ITAR. FIPS 140-2 certifications. The AWS Data Processing Agreement is approved by Art. 29 Working Group. Access approved by ICGC DACO	Encryption. BS7799 and ISO27001 certifications. No raw data can be downloaded or withdrawn. Access Review Committee assesses access requests. GENE members pay a fee for access
Benefits of the specific public–private partnership for CCSs	1. Access to Google's massive infrastructure, capabilities, geographical presence, and experience handling sensitive and personal data. 2. Compliance with the laws of several jurisdictions. 3. No special application or program needed. 4. Enabling of global and multidisciplinary collaboration and accelerated research and development (R&D). 5. No initial investment for cloud-computing capability needed. 6. Potential trust on the project because of Google's involvement. 7. Diverse and enriched analysis due to possibility to download data.	1. Access to AWS' massive infrastructure, capabilities, geographical presence, and experience handling sensitive and personal data. 2. Compliance with the laws of several jurisdictions. 3. No special application or program needed. 4. Enabling of global and multidisciplinary collaboration and accelerated R&D. 5. No initial investment for cloud-computing capability needed. 6. Potential trust on the project because of Amazon's involvement. 7. Diverse and enriched analysis due to possibility to download data.	1. Private companies' involvement in the data's sequencing and the translational process is expected to accelerate the R&D process. 2. Specially tailored for the project's needs, circumstances, and UK regulations. 3. GE maintains exclusive control over the stored data. Data cannot be downloaded, and they never leave the data center, which grants GE higher control over the data. 4. Given GE's nature (owned by U.K. Department of Health as opposed to being owned by a private company), participants may trust the project more.

(*Continued*)

TABLE 1 | **Continued**

	MSSNG	International Cancer Genome Consortium (ICGC)	100,000 Genomes Project
Challenges	1. Potential distrust on the project because of Google's involvement. 2. Even MSSNG having control over the access to the stored data, Google is in charge of the data's security, safety, and integrity. 3. Less control over the data, as they can be downloaded. 4. Confidentiality and privacy are still unresolved: re-identification of participants is possible. 5. Reconciliation of different expectations and goals of public/private sectors.	1. Potential distrust on the project because of AWS' involvement. 2. Even ICGC having control over the access to the stored data, AWS is in charge of the data's security, safety, and integrity. 3. Less control over the data, as they can be downloaded. 4. Confidentiality and privacy are still unresolved: re-identification of participants is possible. 5. Reconciliation of different expectations and goals of public/private sectors.	1. Geographical expansion requires ensuring compliance with new jurisdictions. 2. Large investment needed to start and maintain the CCS. 3. Reduced GE's experience handling massive amounts of data in comparison with Google's or AWS' and potential less trust on GE's capacities to secure the data. 4. Open access/open science vs. no download policy. 5. Confidentiality and privacy are still unresolved: re-identification of participants is possible. 6. Reconciliation of different expectations and goals of public/private sectors.

MSSNG

The project, which was launched in December 2014, is sequencing and analyzing the DNA of 10,000 families affected by autism. The aim of this project is to help to understand the causes of the condition across its wide spectrum, identify its different subtypes, and help in the development of more personalized and accurate treatments. It seeks to promote and enable open science research and lead to a better understanding of autism. The name of the project has the vowels of the word "missing" deliberately omitted symbolizing the missing pieces of the autism project. The project is a collaborative effort of Autism Speaks, Toronto's Hospital for Sick Children (Centre for Applied Genomics), and Google. It also has funding contributions from KRG Children Charitable Foundation, the Canadian federal government and the province of Ontario, Gordon and Llura Gund Foundation, Mel Karmazin Foundation, and the Allerton Foundation. MSSNG's key leaders are David Glazer (Google), Mat Pletcher (Autism Speaks), and Stephen Scherer (Toronto's Hospital for Sick Children and University of Toronto) (34, 35).

In April 2016, the project released more than 5,000 whole genome sequences. In August 2016, this number rose to 7,000. MSSNG includes 3,000 genome sequences from participants in the Autism Genetic Resource Exchange (AGRE) (35, 36). Until now, MSSNG has granted access to its database to more than 100 investigators from 9 countries. Access to this database has enabled research projects on several aspects associated with autism. For instance, in August 2016, researchers from the Toronto's Hospital for Sick Children published a study in the *npj Genomic Medicine* journal on the genome-wide characteristics of the novo mutation in autism and on the epigenetic risk factors for autism[19] (38).

[19]This is study is found as Yuen et al., "Genome-wide characteristics of the novo mutations in autism" (37), *npj Genomic Medicine*.

MSSNG has several partners. Autism Speaks is a non-for-profit organization and advocacy group located in New York, U.S. Its involvement in MSSNG is associated with the awareness, fund raising, and support of basic, translational, and clinical research and projects such as AGRE. AGRE is a DNA repository and family registry of genotypic and phenotypic information funded by Autism Speaks. The Toronto's Sick Children Hospital is a public hospital located in Toronto, ON, Canada, with governmental funding specializing in children and affiliated to the University of Toronto. Its involvement in the project is on the scientific research area. Both parties—Autism Speaks-AGRE and Toronto's Sick Children's Hospital—represent the public sector and provide the genomic data, health information, and the scientific/medical analysis.

Google represents the private sector in MSSNG. The partnership with Google outsources CCSs to store, process, and share the genomic data collected by Autism Speaks and Toronto's Sick Children's Hospital with researchers around the world. Google is a multinational company focused on Internet and computer-related services and products whose objective is to "organize the world's information and make it universally accessible and useful" (39). As such, it has created tools that help to organize almost all kind of information and fulfill its objective. For instance, Google's Search, Maps, and YouTube allow users to access documents, images, information, videos, and roads and make that information useful to satisfy their individual needs. Google Cloud Platform supports the aforesaid services and helps users to do something similar with their own information. It also helps to store, organize, analyze, process, and make accessible complete medical/health records, including genomic data. Google Genomics was conceived to specialize on big genomic data (12, 14). Furthermore, Google has long-supported the open source philosophy and has implemented philanthropic programs in areas such as climate change, public health, and poverty. In view of this, it would be safe to assert that one of the reasons

for which Google entered this PPP with Autism Speaks and Toronto's Sick Children Hospital could be its genuine interest in maintaining its involvement in the efficient management of big data and contributing to a deep understanding of autism and the development of personalized medicine that will help to manage this condition (14, 40–42).

The MSSNG database contains research data,[20] whole genome sequencing (WGS) data, and researchers provided data (43). This information is stored, processed, and made available through Google's infrastructure. First, the data are uploaded to Cloud Storage and then imported to Google Genomics. The latter allows researchers to access the data using Genomics APIs, explore it with Google BigQuery, and analyze it with Google Compute Engine (44).

Google's CCSs are scalable, elastic, provided on-demand, and accessible through a broad network. They offer predefined or custom machines with persistent disks or local SSD,[21] support for Linux and Windows, and encryption for the data on the fly before being transmitted. These conditions allow MSSNG to scale-up or scale-down as needed. Furthermore, Google's storage service is highly durable with online backup and disaster recovery (45, 46). This, along with Google's long-term experience in IT, makes it the most suitable party in the PPP to be responsible for the CCSs of the project and for the integrity of the data. Moreover, the project's nature makes its success dependent on the existence of a large network of researchers that contribute to the advancement in the understanding of autism and on the reliability and stability of the cloud-computing infrastructure and services. Given Google's global and powerful infrastructure, partnering with it to obtain cloud computing can enable the large global network of researchers that the project needs and can support a long-term project.

In terms of security and safety, MSSNG also seems to maintain a reasonable level of control over the data stored. Google's Data Processing and Security Terms state that while Google processes the data submitted by the customer (in this case, Autism Speaks and Toronto's Sick Children Hospital), it is the latter who controls the data. Google's processing is only performed in accordance with the customer's instructions (46, 47). Access is provided by Data Access Compliance Office (DACO) to anyone complying with the project's access and privacy policies, which include the use of encrypting tools (48, 49). To ensure this, Google has "technical and organizational measures to protect the data against accidental or unlawful destruction or accidental loss or alteration, or unauthorized disclosure or access" in place, including several layers of encryption to protect the data. This includes ensuring that its staff complies with these measures. Google will promptly notify the customer of any security breach and will immediately take the reasonable steps to minimize the harm. Google's security and privacy measures comply with the ISO 27001, SSAE-16, SOC 1, SOC 2, and SOC 3 standards (46, 50). The project's data will be stored where MSSNG chooses between the U.S. or Europe or another location setting offered by Google (46, 51). Either Autism Speaks and Toronto's Sick Children Hospital or whoever collects the data is responsible for obtaining the necessary consent for the data to be stored and processed by Google (47). Finally, all changes to Google's Data Processing and Security Terms or to the services will be posted online (47).

ICGC and the Cancer Genome Atlas (TCGA)

The project was launched in 2008 with the intention of coordinating and generating current and future large-scale cancer genomes studies in tumors from 50 different types and subtypes of cancer (52, 53). For this, genomes of at least 50 types of cancer will be collected, mapped, and shared. The objective of coordinating and generating numerous large-scale cancer genomes studies rises from the potential to identify common patterns of mutation and understand the biology of cancer found in using systematic genome-wide screens (54).

The headquarters of the project are located in the Ontario Institute of Cancer Research in Toronto, ON, Canada. The list of current ICGC members include over 25 research centers from Australia, Canada, China, Europe, France, Germany, India, Japan, Mexico, Singapore, Saudi Arabia, South Korea, Spain, the U.K., and U.S.[22] All entities are allowed to become members, provided that they comply with the ICGC's principles and guidelines (55). There are different types of scientific partnerships/collaborations. ICGC funding members of large-scale projects are expected to have approximately 500 patients per sample and an estimated contribution of USD $20 million. Those who contribute with less than 500 samples (at least 100) and less than USD $10 million are members with affiliate status. Research members are centers that acquire and analyze samples for one or more cancer genomes and that are nominated as such by a funding member, who will provide the necessary funds for them (52, 55).

TCGA is a collaboration between the National Cancer Institute and the Human Genome Research Institute to create comprehensive and multidimensional maps of genomic changes in 33 types of cancer. TCGA is one of the world's largest collections of cancer genome data available from more than 11,000 donors. TCGA created a pipeline to collect, select, and analyze human tissues on a very large scale. Its funding is federal from the National Cancer Institute, the NIH, and the Department of Health and Human Services. The project is scheduled to end in 2017 (56, 57).

There are currently 89 cancer genome projects examining different types of tumors. The tumors being examined are from the biliary tract, bladder, blood, bone, brain, breast, cervix, colon, eye, head and neck, kidney, liver, lung, nasopharynx, oral cavity, ovary, pancreas, prostate, rectum, skin, soft tissues, stomach,

[20] Research data include information concerning the participants such as family configuration, age at time of testing, sex psychopathology, diagnosis, cognitive functioning, family and medical history, and other relevant clinical information, without including any personal identifying information.

[21] A persistent disk can be attached to different virtual machines retaining the data; so if a virtual machine is terminated, the disk can be attached to a new one. On the other hand, local SSD is physically attached to the server hosting the virtual machine.

[22] The NHS includes 27 institutes all of which are part of the U.S. Department of Health and Human Services [NIH Press (55)].

thyroid, and uterus (55). The datasets of TCGA are also stored and released through AWS. The ICGC and TCGA have collected, stored, analyzed, and released data from 10,000 genomes. By 2018, the ICGC project intends to have over 50,000 genomes (15, 53, 56).

In addition to the scientific partners mentioned above, the project has academic and commercial partners that provide CCSs. The CGC is the academic partner, and AWS is the commercial partner in this hybrid cloud. The CGC was built and is led by the Ontario Institute for Cancer Research. This cloud stores data that are restricted to a small group of beta testers approved by ICGC DACO. The data stored in the CGC are provided by 25 projects and 14 primary sites. There are two data centers: SciNet (Toronto) and Bionimbus (Chicago) (58, 59). AWS hosts data obtained from 20 projects and 12 primary sites. The datasets are hosted at the U.S. East (Northern Virginia) EC2 facility and are accessible in 190 countries (54, 58–60).

Amazon is one of the world's largest providers of CCSs. The services operate from several geographical regions: U.S. East (Northern Virginia), U.S. West (Northern California and Oregon), Brazil (Sao Paulo), Europe (Ireland and Frankfort), South Asia (Mumbai), Southeast Asia (Singapore), East Asia (Tokyo, Seoul, and Beijing), Australia (Sydney), and GovCloud (Northwestern U.S.). Canada, China, India, Ohio, and the U.K. have been announced for 2017. All of the data and services stay in their designated region. Each region has multiple separated data centers to prevent outages from spreading. In December 2014, AWS was operating 1.4 million servers. The customer chooses the region in which its data will be stored. ICGC chose U.S. East (Northern Virginia) (61–63).

The CCSs provided by AWS are on-demand, low-cost, pay-as-you-go, and scalable. The services run in Mac, Linux, and Windows. Like Google, AWS has services specially tailored for scientific computing that adapt to the needs of massive datasets (60, 64, 65). AWS will notify its customers of any change to the services provided (63). ICGC is responsible for ensuring that the data comply with the respective applicable laws (66). Some of the AWS resources may be replaced or terminated. In these cases, AWS will not be held responsible for any damages, liabilities, or losses resulting from those replacements or terminations (66).

Amazon Web Services offers strong security measures and tools that have been certified and accredited, data encryption at rest, and in transit to manage the data. For instance, AWS security measures and tools have the SOC1, SOC2, SOC3, FISMA, PCI DSS, ISO 27018, ISO 9001, ITAR, and FIPS 140-2 certifications. Furthermore, the AWS Data Processing Agreement, approved by the Article 29 Working Group, meets the standard provisions of the European Commission with respect to data protection when data is transferred between clouds and regions. In accordance with the AWS privacy terms, AWS will only disclose the content stored in its cloud if it is mandated by law or a binding order of a governmental or regulatory body. AWS also offers reliable backup services. However, the customer, in this case ICGC, is responsible for the operation, maintenance, use, security, protection, and backup of the data. Finally, given the specialization on genomics/health-related data, AWS expressly states that they comply with HIPAA (60, 62–65, 67–71).

The ICGC member nations agree to core bioethics principles and elements for informed consent, privacy, and access. These requirements include that the data and samples will be used for cancer research, that they will be made available to the international research community through an open or controlled access database, and that this availability will be done under terms and conditions that will maximize the participant's confidentiality (55). The data are made rapidly and freely available to the global research community through the ICGC data portal. Researchers have access to open and controlled portions of the data and to a number of user interfaces that address simple gene-oriented queries as well as those involving genomic, clinical, and functional information (15, 72).

The access to the ICGC data stored and processed in the AWS cloud is approved by ICGC DACO, which utilizes user authentication and authorization (e.g., decryption keys) to ensure safe access. Until today, 734 projects (including renewals) have been approved to have access to the ICGC data. Access to TCGA data is approved and done through the Cancer Genomics Cloud being Seven Bridges Genomics, the entity responsible for authorizing access to the data. This access and collaboration are expected to help researchers to identify commonalities and differences among different types of cancer. Other AWS customers/projects in the area of healthcare include NASA NEX, 1000 Genomes Project, TCGA, GenomeNext, and the Human Microbiome Project (56, 64, 67, 73, 74).

Amazon's official motive for entering such a partnership is its interest in helping to "achieve major healthcare breakthroughs and unlock the mysteries of the human body" through the use of bioinformatics. This is also one of the main reasons for them to develop open source tools (73). The ICGC project definitely benefits from the AWS' massive infrastructure, capabilities, geographical presence, and experience in safely and efficiently handling these amount of sensitive and personal data. It also benefits from the flexibility and adaptability of the services to the project's specific needs. The cloud-computing partnerships with AWS and CGC allow scientists to access, search, and analyze ICGC without the need to install any special application or program or to download any of the datasets. This enhances collaboration and accelerates the R&D of tools and treatments for cancer patients (58, 60).

100,000 GP

The project, launched in late 2012, aims to "enable new scientific discovery and medical insights" and to "kickstart the development of a U.K. genomics industry." It intends to create better tests, better drugs, more accurate and timely diagnoses and treatments, and more personalized care to save lives. The project focuses on rare disorders, infectious diseases, and common cancers. In order to achieve this, the project created 13 National Health Services (NHS) Genomic Medicine Centres to recruit approximately 75,000 patients to provide DNA samples and clinical information for the collection and analysis of 100,000 genomes between 2015 and 2017 (75–80).

In March of 2015, patients were already being diagnosed under the 100,000 GP. By December 20, 2016, the project had sequenced 16,171 genomes (81, 82).

Genomics England is in charge of the 100,000 GP. It is a company funded in 2013 by the Department of Health. It manages the contracts with U.K.-based companies, universities, and hospitals regarding the supply of services of sequencing, data linkage, and analysis. GE is also responsible for the secure storage of personal data as per NHS rules (75).

The project's main scientific partners are the National Institute for Health Research, NHS England, Public Health England, Health Education England, and 85 NHS trusts and hospitals across England (75). While GE funds the WGS for patients of the NHS England Genomic Medicine Centres, the Northern Ireland Executive and the Medical Research Council funds the Northern Ireland Genomic Medicine Centre. Scotland and Wales have recently joined the project. The company Illumina is the private partner responsible for sequencing the DNA in the Wellcome Trust Genome Campus in Hinxton, U.K. Illumina will also develop a platform to improve and automate genome interpretation (77–79, 83). The project also partnered with other four companies to help with clinical interpretation: Congenica, WuXi NextCODE, Omicia, Cypher Genomics, and Nanthealth (79, 84).

In addition to these partnerships, the project has also partnered with the Genomics Expert Network for Enterprises (GENE) Consortium, composed of private companies, and the GE Clinical Interpretation Partnership (GeCIP), composed of researchers and clinicians from academia and the NHS researchers. There are currently 10 members in the GENE. Their goal is to accelerate the development of new diagnostics and treatments. On the other hand, members of the GeCIP help to interpret genomic data in a clinical context. Any individual, student, or staff member affiliated with a university or academic research institution, NHS trusts or authorities, charitable organization related to the 100,000 GP, U.K. and foreign governmental departments that carry significant research activity, or foreign health-care organizations (public or private) that undertake significant research activity can apply to become a member of GeCIP. Exceptionally, individuals affiliated with private U.K. health-care institutions, commercial companies, or self-employed can become members of GeCIP (85–88).

The raw data collected and stored by the 100,000 GPs are kept in GE's data centers. In contrast to our two previous cases, no raw genome data can be downloaded and withdrawn from GE's data center. Doctors, nurses, and health-care professionals in the NHS Genomic Medicine Centres have access to the data of their patients for health-care purposes. Researchers and companies need to apply to have access, but the computational analysis is done within its confines. The Access Review Committee assesses access requests by each company or researcher. Access to the data can only be for health research purposes, limited to the data they need in accordance with their application and research protocol, only allowed through a secure login, and as mentioned above, without downloading any data. Members of the GENE have to pay a fee for becoming members and having access to the GE data services. The fee for large companies (i.e., USD $1 billion market capitalization) is USD $320,000. The fee for smaller companies is USD $32,000. These fees cover part of the costs of storage, security, and analytic services. They also commit to having a specific number of employees devoted to the activities relevant to the project. GENE members can have a controlled access to up to 5,000 genomes and corresponding health information (78, 80, 89–91).

An independent Ethics Advisory Committee advises the GE board on participants' consent, privacy, and confidentiality and on how to best ensure data's security. GE will take all the measures necessary to maintain the security of the data. Some of these measures include removing identifying information from the raw data and encryption tools. The GE data center complies with the BS7799 and the ISO27001 security standards. Because the project is focused on England's (and extending to Ireland's, Scotland's, and Wales') population and the data remain in the GE's data center, the project only commits to comply with U.K. legislation (e.g., Data Protection Act of 1998 and Access to Health Records Act of 1990) (77, 80, 89, 91).

The type of cloud provided by GE in this project is private, unlike the cloud in the MSSNG and the ICGC projects. The PPP differs in organization and in dynamics as well. Whereas in MSSNG and ICGC, the private sector was represented by the CCS providers, in the 100,000 GP, the CCSs are provided by the public sector in partnership with some private companies helping with the DNA sequencing and interpretation of data. Similar to the services provided by Google and AWS, the CCSs are scalable and elastic, as members can and are even encouraged to nominate new rare diseases and tumor types to be included in the project (92).

The companies' early involvement in the research and their collaboration with researchers may accelerate the translation of basic research into concrete clinical innovative products, but the impact of restrictions on data downloading remain to be seen. Patients may have access to a better, timely, and more accurate diagnosis and treatment, given that any relevant information resulting from the sequencing and analysis of the participants' samples will be returned to their doctors. Furthermore, health-care staff is trained with new skills and practices (78, 80, 90).

The expressed intention of the parties involved in this project is to achieve a better understanding of the involvement of genomics in cancer, rare disorders, and infectious diseases and the development of new diagnostic tools and personalized treatment that advances the field and the industry and improves patients' health. This is mentioned in the project's documents, description, and policies. However, their access and use model remain contentious. The reason for involving members of the public and the private sector and for assigning them the respective roles they have is based on two recognitions: that the private sector has always had an important role in the development of innovative medical products and that an early involvement of all its parties may help to employ resources more efficiently and to accelerate the R&D process (77, 78, 86).

LOOKING FORWARD: LESSONS LEARNED

The three case studies presented have benefited from being PPPs. Google's and AWS' private cloud-computing infrastructure and services have considerably empowered the MSSNG and the ICGC research projects by enhancing the value of the genomic

and health data they have collected in the following manner. First, the IT companies' infrastructure and services enable a global and multidisciplinary network of researchers that can collaborate and share their ideas, knowledge, experience, skills, and resources. Collaboration and sharing enhances the value of that genomic and health data, as more R&D can result from that data. Second, the global aspect of Google's and AWS' services (e.g., the servers located in different regions) requires them to comply with laws of several jurisdictions. This increases the possibility of expanding the projects to larger geographical areas. Third, MSSNG and ICGC are able to use this infrastructure and these services without having to put up large capital investments for their setup and maintenance. This helps to democratize the innovation process, as it allows small- and medium-sized research centers and companies from developed and developing countries to get involved in such large research projects. Fourth, having Google and AWS as the companies responsible for providing CCS can add reliability and trust in the minds of the participants and the other partners of the projects. The reason for this potential increase in reliability and trust is that both companies have a long, well-established experience in handling big data. This experience may translate into having the necessary resources and skills to have strong security measures. Furthermore, having these companies not only as CCS providers but also as partners in these projects can result in more specially tailored and better suited terms of service, as the companies have an invested interest in the success of the projects. When customers simply hire CCSs as opposed to forming a PPP with the companies that provide them, they usually have to adapt to the terms under which they generally provide their services. This is problematic given that most of these terms of use state limited responsibility for the integrity and mobility of the data. These limits are handled differently when the CCS providers have a larger interest invested in the project, as in the case of MSSNG and ICGC.

Some of the benefits found in these two cases are also observed in the 100,000 GP, including, above all, links to health-care data in a network of researchers and innovators who share their ideas, knowledge, experience, skills, and resources, thereby increasing the value of the genomic data and the potential of a more efficient R&D process. However, given that in this case, the CCSs are provided by a private in-house data center, there are certain differences. For instance, the 100,000 GP only complies with the laws of the U.K. This makes it difficult to expand the project to other regions. Second, this project had to make a considerable initial capital investment to set up the data center and the cloud-computing infrastructure. Third, contrary to MSSNG and ICGC, the 100,000 GP maintains exclusive control over the data. This could increase the trust that users and participants may have on the protection of their privacy but decrease access and use for research and downstream benefits for patients. Moreover, given the limited experience that GE has in comparison with Google or AWS in handling massive amounts of data, some participants may in fact doubt GE's capacity to effectively protect the donors' data. Yet, the participation of the private sector in the sequencing and translational process in this project is expected to accelerate the R&D process, as they bring in their infrastructure and their scientific, technological, and budgetary experience into the process. Furthermore, having such an early involvement of private companies in the research process allows all parties to share their expectations and to contribute their opinions and their interests (e.g., nominating new rare diseases) to the general coordination and management of the partnerships challenges.

Overall, it could be said that while being organized as PPPs and employing CCSs, the three projects have advanced quickly and are organizing themselves to be important sources of future personalized medicine. Nevertheless, the benefits and achievements that the three projects have had, there still are unresolved matters. The first is the protection of confidentiality and privacy. The three projects implement, to the best of their abilities, security measures (e.g., encryption, removal of identifying information, controlled access, privacy and data sharing policies, etc.) that aim to maintain the confidentiality and privacy of the participants. The 100,000 GP even provides that the data will never leave their data center, which may undermine further research and innovation. In all the three, however, the re-identification of the participants remains a possibility due to the necessary linkage with health records. The second concern is the differences in expectations and goals that the different partners may have while joining and participating in a project. In the MSSNG and the ICGC projects, the stated reasons for Google and AWS to become partners do not seem to contradict the incentives of the partners of the public sector, namely, to advance the understanding of genetic diseases and to improve patients' health with better diagnostics and personalized treatments. However, there may be other untold goals. For example, advertising is the source of the majority of Google's revenues (93). Furthermore, Google is deeply involved in the development of artificial intelligence (94, 95). Given Google's other possible interests, it is important that projects develop robust and transparent governance structures and conflict of interest policies to secure public trust. On the other hand, in the 100,000 GP, its private partners have a strong economic expectation/incentive that may run contrary to the scientific/medical goals. It should be stated, however, that this may also occur later on in the MSSNG and ICGC projects when the projects enter the translational phase. The third issue is the possible loss of control of the data, particularly in the case of the MSSNG and the ICGC projects that allow downloading of data for more diverse and enriched analysis. While the data are stored and analyzed in data centers with strong security measures and while they grant MSSNG and ICGC control over their data, neither of the leading institutions in these projects is in charge of the management, implementation, and decision-making regarding the security measures. Finally, as regards the 100,000 GP and its private data center, the fact that the data never leave the data center causes underutilization of the project's data. This characteristic may also be perceived as in conflict with some of the common principles of open science (e.g., open data sharing, fast dissemination of knowledge, cumulative R&D, etc.) (96), as any data sharing will be very limited.

An important issue in our analysis of all the three cases is that we could not confirm whether some of the suggestions to overcome challenges found in PPPs that we mentioned earlier are actually being implemented, as our sources of information were mute in this respect.

CONCLUSION

Public–private partnership is a useful and effective collaborative R&D model. It is particularly relevant for projects where the R&D process cannot be fully taken on by the public or the private sector alone. PPPs enable members of both sectors to come together and increase the availability of multiple resources and diverse knowledge and expertise that can make the innovation process less burdensome and costly, more efficient, effective, shorter, and with a wider reach. It also makes the R&D process more efficient, as it allows objectives and needs of the parties involved in the different stages of the R&D process to be known and addressed. In this respect, particularly in genomic research, the model of PPP facilitates the translation of basic to clinical research and it enables the use of CCSs.

Cloud-computing services increase the usefulness of genomic data for understanding disorders with a genetic component and developing improved and more personalized diagnostic tools, drugs, and treatments. They achieve this by enlarging the data users' network in two ways. They can extend the geographical availability of the genomic data they store. They make it easier and cheaper for all users to access, analyze, and store their own and others' data, regardless of whether they are or belong to small- and medium-sized centers from developed or developing countries. As a result, there has been an increase in the use of CCSs in health-care services and health-care research.

The three projects we discussed in this article benefit from the PPP model as well as from the use of CCSs, despite the differences in the way they are organized. However, there are two important matters that should be kept in mind. First, protection of data and privacy is essential for cloud computing to fully benefit and spur medical and genomic research. End-users are likely to have more trust in CCSs when they perceive that their data and privacy are properly protected. The more trust end-users have in the cloud, the bigger the network of users and projects using the data in the cloud will be. The larger the network of contributors, the faster the progression in genomic and medical research could happen and the more chances that patients will have to benefit from personalized healthcare (22). Second, even though the benefits of PPPs are palpable, this collaborative model still presents certain challenges. Large-scale genomic projects can be of long duration and cover a sizable geographical area. They can include a variety of partners and contributors with different and potentially conflicting objectives, resources, expectations, and viewpoints. Early integration of all parties, timely and appropriate distribution of functions and responsibilities, frequent monitoring of results, constant communication and trust among the partners, and adequate governance frameworks are helpful in managing those complications and increasing the chances of a successful PPP, provided also that the public is kept involved and informed about the project (3, 4).

Learning from the experience of past PPPs is critical in order to avoid making the same mistakes in the future. Therefore, research on those past PPPs to document the projects' achievements and failures as well as to provide information on the development and outputs of such partnerships would provide helpful guidance for future PPPs (3, 7). In addition, we propose that guidelines on best practices to adequately manage personal information stored in clouds and transferred online for research purposes be established to foster the protection of data integrity and privacy. These guidelines should enable research institutions to maintain control over the use of the data during and after research projects conclude and encourage data transfer in accordance with open science principles.

AUTHOR CONTRIBUTIONS

PG drafted the article. PG, YJ, and BK contributed to the design of the article, interpretation of the data, critical revision of the paper contributing to its intellectual content, and approved the final version. They all agreed to be accountable for all aspects of the article.

FUNDING

This work was supported by Fonds de Recherche du Québec - Santé (Chercheur Boursier Junior 2 # 30719), Exactis Innovation (BL-NCE) ethical and legal framework (Tri-Council/Exactis Innovation-NCE), Canada Research Chair in Law and Medicine (950-217983), and the Cancer Genome Collaboratory NSERC/ Toronto (448167-13).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 29 January 2018
doi: 10.3389/fmed.2018.00006

Toward a Tiered Model to Share Clinical Trial Data and Samples in Precision Oncology

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The recent revolution in science and technology applied to medical research has left in its wake a trial of biomedical data and human samples; however, its opportunities remain largely unfulfilled due to a number of legal, ethical, financial, strategic, and technical barriers. Precision oncology has been at the vanguard to leverage this potential of "Big data" and samples into meaningful solutions for patients, considering the need for new drug development approaches in this area (due to high costs, late-stage failures, and the molecular diversity of cancer). To harness the potential of the vast quantities of data and samples currently fragmented across databases and biobanks, it is critical to engage all stakeholders and share data and samples across research institutes. Here, we identified two general types of sharing strategies. First, open access models, characterized by the absence of any review panel or decision maker, and second controlled access model where some form of control is exercised by either the donor (i.e., patient), the data provider (i.e., initial organization), or an independent party. Further, we theoretically describe and provide examples of nine different strategies focused on greater sharing of patient data and material. These models provide varying levels of control, access to various data and/or samples, and different types of relationship between the donor, data provider, and data requester. We propose a tiered model to share clinical data and samples that takes into account privacy issues and respects sponsors' legitimate interests. Its implementation would contribute to maximize the value of existing datasets, enabling unraveling the complexity of tumor biology, identify novel biomarkers, and re-direct treatment strategies better, ultimately to help patients with cancer.

Keywords: data sharing, precision medicine, oncology, clinical research, biobanking

OPEN ACCESS

Edited by:
Sandor Kerpel-Fronius, Semmelweis University, Hungary

Reviewed by:
Katsura Tsukamoto, Gifu Pharmaceutical University, Japan
Segundo Mariz, European Medicines Agency, United Kingdom

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *04 October 2017*
Accepted: *11 January 2018*
Published: *29 January 2018*

Citation:
Broes S, Lacombe D, Verlinden M and Huys I (2018) Toward a Tiered Model to Share Clinical Trial Data and Samples in Precision Oncology. Front. Med. 5:6. doi: 10.3389/fmed.2018.00006

INTRODUCTION

Cancer still figures among the leading cause of death and diseases worldwide with approximately 14 million new cases diagnosed in 2012 (1). Historically, the hallmark of cancer treatment consisted of nonspecific cytotoxic agents alone or in combination with radiotherapy and/or surgery. In the past few years, clinical cancer research has seen a remarkable evolution, whereby many new and promising, specific or targeted treatment options including precision medicines and immune-oncology drugs complement the more traditional therapeutic arsenal (2, 3). Precision oncology makes use of the presence of predictive biomarkers that identify patient subpopulations that are likely to show a

response to a therapy (4). Oncology, with its genetically driven disease etiology, has typically been at the forefront of this precision medicine revolution.

The oncology market may well be expanding (5, 6); however, stakeholders are confronted with an increasing number of challenges as a consequence of the shift toward precision oncology. Drug developers for instance, acknowledge that research and development (R&D) of precision oncology therapeutics puts the more conventional drug development models under stress (7). The gold standard to generate evidence to change clinical practice comes from randomized controlled trials (RCTs). Such models start from a tumor's location in the body or histopathology rather than its underlying molecular makeup. Consequently, the generation of clinical evidence of predictive biomarkers or treatments targeting specific subgroups becomes a more daunting task. In addition, testing targeted therapies in clinical trials is challenging in view of the establishment of statistical significant effects, or recruitment of sufficient numbers of patients (8). Statistical significance may still occur in case the treatment has a large effect size and the incidence of the targeted group is sufficiently high in the total treatment population, or in case trials are designed to include a larger number of trial participants. However, the latter would increase costs, at times when drug developers are looking for savings. The decline in healthcare budgets coupled with escalating R&D costs and complexities has convinced stakeholders that the traditional models for drug development applied to precision oncology are unsustainable and may no longer be suitable to tackle coming challenges (9, 10).

The life science industry witnesses a history of huge challenges, whereby stakeholders adapted or evolved accordingly. For instance, the everlasting call for more effective therapeutics along the pharmaceutical crisis led to the emergence of alternative models for working together (11, 12). Likewise, the current complexities brought about by data-intensive precision oncology research outweigh the efforts possible within the walls of single organizations. The generation of clinical evidence in genomic diverse and geographically dispersed groups of patients requires access and linkage of massive amounts of data, including various types of "-omics" data extracted from biological samples, combined with lifestyle and clinical information, but also long-term side effects and survivorship issues, often referred to as "Big Data" (13). Yet, these are stored in distinct formats, originate from varying data sources, and are held by different stakeholders, complicating their integration. Present-day, data and samples generated from RCTs are not maximally leveraged by the cancer research community to achieve advances in precision oncology (14–18).

By pooling data from completed studies, researchers have access to large cohorts of patients, providing more statistical power to draw meaningful conclusions for patients. For example, data can be mined to allow *post hoc* subgroup analysis and thereby increase the precision of estimates of treatment efficacy, validate gene signatures, detect safety problems undetectable in smaller populations, generate new biological insights and increase the efficiency of R&D for instance, both in terms of time and costs, by avoiding duplicating trials and coming to better trial designs (19, 20). Volume enables greater understanding of the complexity of tumors, and the same holds true for samples: to create a comprehensive catalog of genes that acquire driver mutations in 2% or more of patients with cancer, Lawrence et al. suggests that more than 100,000 cancer samples need to be analyzed (21). Consequently, besides health information technology advances, it is critical to engage all stakeholders and share data and samples across research institutes to harness the potential of vast quantities of patient data that are currently locked away. It is against this backdrop that several groups and organizations have initiated collaborations to innovate the clinical research paradigm in oncology research.

With human samples being estimated worth more than diamonds, and data being handled as a new type of currency, appropriately managing these valuable patient resources is of utmost importance (22). In this paper, we theoretically describe different strategies for increased sharing of patient data and material that have been installed over the past decade. In parallel, a number of examples of these models are described. We zoom in on an emerging type of collaborative data sharing models in precision oncology that aims to combine omics and clinical data to address the current clinical research challenges: omics screening platforms. Finally, we introduce a tiered model to share patient data and samples, with appropriate consideration for patient and commercial confidentiality.

MATERIALS AND METHODS

This study is based on a scoping literature review. A search in the PubMed database using a combination of medical subject headings and text-words was performed from September 2016 to March 2017. The following key words and synonyms were used: data sharing, big data, biobanks, clinical research, clinical trial, precision oncology, and precision medicine. After removing duplicates, the remaining papers were screened in a stepwise manner based on title, abstract, and full texts. Included were papers where the content was clearly linked to the key words. Excluded were non-English papers. Key publications were selected in agreement with experts. Further, the reference list of the articles was checked to include additional articles. Besides examples from the literature, additional examples were included upon recommendation of experts being academics involved in clinical oncology research [e.g., omics screenings platforms and the Aide et Recherche en Cancérologie Diggestive (ARCAD) database]. Additionally, selected initiatives were discussed in a semi-structured way with multiple experts (oncologist, academics, and industry representatives) and websites of official organizations were screened to acquire in-depth knowledge. Not all models are specifically geared to clinical (oncology) research data, for instance general models for genomic data sharing [e.g., European Genome-phenome Archive (EGA) or database of Genotypes and Phenotypes (dbGaP)]. For cancer, however, being a genetically driven disease, genomic data sharing is of high importance to unravel the genomics underlying the disease, illustrated by the fact that these models are frequently being deployed in this context. Therefore, models that are—or could potentially be—of relevance for precision oncology research were also included.

RESULTS

In total, 374 articles were found through the search strategy. After applying the inclusion and exclusion criteria 38 articles relating to data sharing were withheld. Another 50 articles, reports and/or websites from institutions complemented these, which were recommended by experts or found through the reference method. Of these, 19 key articles provided insights on DSMs (**Table 1**). Similar to the studies by Wilhelm et al., Sydes et al., and Green et al., we classify two main strategies: "open access" models characterized by absence of a decision maker, and "controlled access" models (17, 23, 24). Where the former enables scientific peers to replicate or conduct new research without barriers, the latter imposes some form of control, as we will see sometimes for good reasons. Using this framework, examples were grouped in appropriate categories depending on their access strategy (i.e., open versus closed), deciding body (i.e., donor, provider, independent body, provider, and requester), and if possible location of database or biobank (centralized or federated). Our proposed sub-classification builds further on the four models proposed by Mello et al. combined with the other literature (25).

All stakeholders involved in clinical research have different roles/responsibilities in the process of data and sample sharing toward the common goal of improving patient benefits. In general, the sharing process (**Figure 1**) can be defined in a number of iterative steps; donors providing data or samples to the collector; the collector providing the samples and/or data to the sponsor, who stores them in a database and/or biobank; data providers (sponsors of clinical study or database or biobank); data provider

TABLE 1 | Examples of different data sharing models with respective benefits and drawbacks.

Model	Advantage	Disadvantage	Reference
	Open access strategy		
Open access	No selective access, enables research without barriers; data sharing at relatively low costs and little administrative burden	No benefit-risk balancing; magnified risks in terms of misuse of data (no assurance that sound scientific methods are used); requires tools and resources for freely downloadable large, heterogeneous and complex datasets; no direct contact between data provider and requester impeding to provide information on the dataset; less suitable for datasets with high privacy risks	(17, 23, 25–28)
	Controlled access strategy		
Provider	Pre-specified set of criteria should ensure a transparent system; possibility to appeal to an independent board	Lack of full transparency or assurance of impartiality; difficult to identify data holders	(25)
Catalog	Clear overview of types of data held by different study teams; allows data generators to maintain autonomy	Datasets obtained on different consent forms complicated reuse	(29–31)
Partnership	Conduct of research in accordance with requirements of both parties; benefit-sharing strategies	Complex negotiations; increased timelines before project start	(11, 14, 32, 33)
Gatekeeper	Data provider cannot veto a request; transparent procedure; full assessment of scientific request and requester; apply benefit-risk balance test data sharing and share minimum data necessary for the request; communication portal between data provider and data requester	Costly (infrastructure, administration, maintenance; curation costs; human resources; opportunity costs); potentially time-consuming procedure	(23, 25, 26, 34–36)
Database query	No direct data sharing, thus can be applied for (personal or commercially) sensitive data; analyses are conducted by original study team who are most familiar with the nuances of the dataset; not limited by particular formats	Little control and transparency on executed queries; resource-intensive for data holders; potentially considerable wait times for requesters.	(25, 27, 30)
Donor controlled	Patient engagement and empowerment; effective reuse of data with explicit consent of the donor	Additional burden (increased resources for health literacy; infrastructures to manage patient preferences…)	(37, 38)

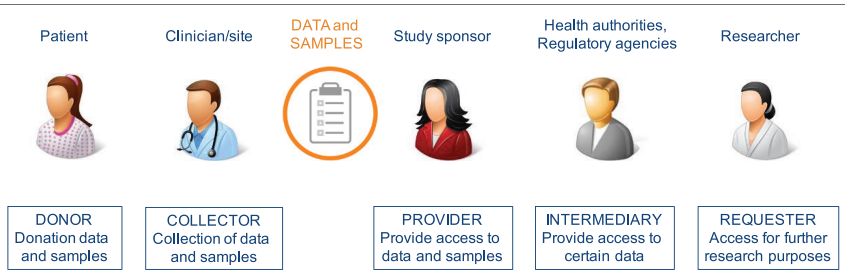

FIGURE 1 | Chain of stakeholders involved in the process of sharing of clinical patient data and samples.

making data or samples upfront available, or requesters finding the data or material, requesting access *via* intermediary or directly to provider, negotiating, and—upon agreement—receiving the requested data or material by the requester. **Figure 2** shows a schematic overview of nine types of DSMs, representing numerous data sharing initiatives as identified in literature, which aim to facilitate the sharing process for clinical research data. Some of these models are also used in practice to provide access to patient material. **Table 1** provides an overview of all discussed models with the respective benefits and drawbacks.

These models provide varying levels of control, access to data and/or samples (**Table 2**), and different types of relationship between the donor, the data provider, i.e., the primary study team or sponsor, and the data requester, i.e., the researcher of the secondary project (**Figure 1**). Different types of data can contain or occur in all levels of identifiability; however, it is generally accepted that human material and genomic information consider identifiable data since they entail all of one's individual characteristics, and in addition, also personal information of relatives. Whether genetic and omics (genomes, transcriptomes, proteomes, exomes, epigenomes, and other types of similar information) data are classified as "primary" or "inferred" data depends on the level of investment the researchers made to generate, analyze, and report the data.

Open Access Models

Open access models are characterized by the absence of any review panel or decision maker. Researchers submit data which are available for download either directly or after a simple registration procedure. The fields of genomics have paved the way for fully open access databases, with the publicly funded Human Genome Project, characterized by the immediate and proactive publication of the human genome sequence, at the forefront (48). In general, only data accompanied with a consent for open sharing for research uses can be deposited in publicly available databases, such as the National Human Genome Research Institute and the European Bioinformatics Institute (EMBL-EBI) publicly funded Catalog of Published Genome-Wide Association Studies (GWAS Catalogue) (49), or the publicly funded Ensembl (50) database specifically tailored to store genomic, transcriptomic, proteomic, or sample data. In the Personal Genome Project (PGP), initiated more than a decade ago at the Harvard Medical School, genomic

TABLE 2 | Categorization of data and material according to (A) level of identifiability or encryption to safeguard the protection of an individuals' identity, and (B) nature of the data and material.

	Category	Explanation
A	Identifiable data	Data that can be attributed to a specific data subject without the use of additional information
	Coded/pseudonymized data	Data processed in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information
	De-identified/anonymized data	Data that cannot be attributed to a specific data subject
B	Material	Blood, saliva, tumor tissue…
	Primary patient data	The raw data underlying the results that enable reproducing the research
	Inferred, derived patient data	Data created by an (intellectual or financial) investment on the part of the primary research team
	Report of results	Summary of research data

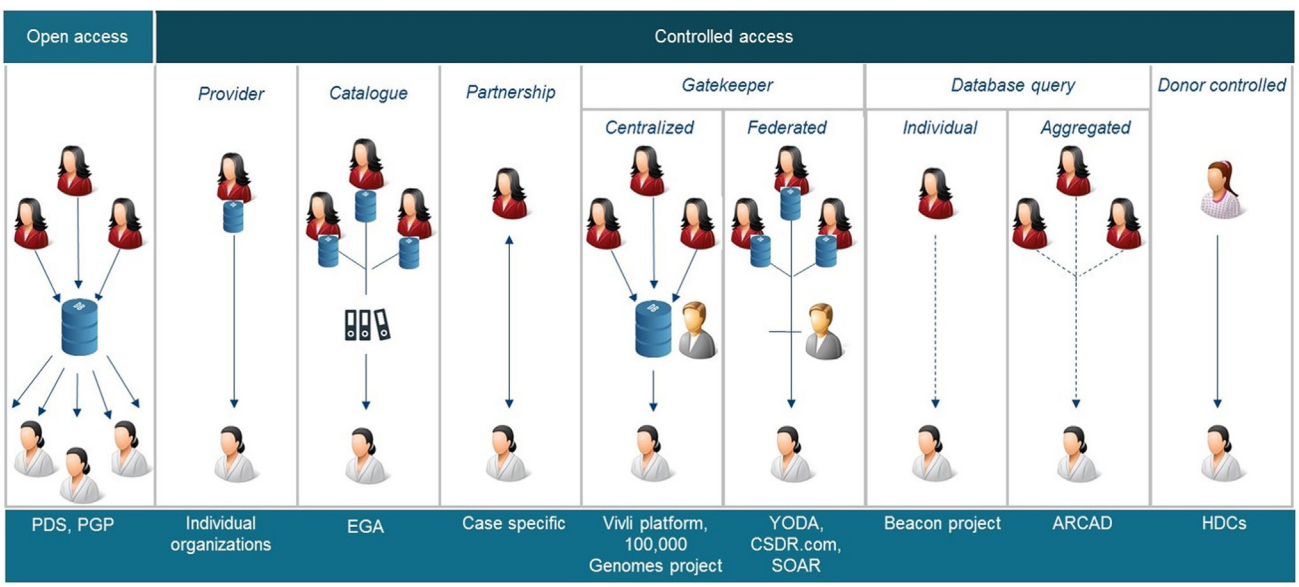

FIGURE 2 | Schematic overviews of nine different data sharing models identified. PDS, project data sphere, PGP, Personal Genome Project, EGA European Genome-phenome Archive, YODA Yale University Open Data Access, CSDR.com ClinicalStudyDataRequest.com, SOAR, Supporting Open Access Research, ARCAD Aide et Recherche en Cancérologie Diggestive, HDC health data cooperatives. Some of these models are also applicable to share samples.

data from volunteers are openly shared, with the explicitly acknowledgment that it is impossible to guarantee privacy or anonymity. Therefore, the PGP appeals only to participants willing to waive any privacy expectations, through its so-called "open consent" (51). To further accomplish its goal of developing a publicly accessible dataset, the PGP makes use of creative commons licenses to share participants' data and samples with minimal access restrictions (52).

Similar open access regimes are being deployed to share clinical trial data. The Project Data Sphere (PDS), a nonprofit initiative launched in 2014 and funded by the CEO Roundtable on Cancer, allows researchers to share, integrate, and analyze individual patient data (IPD) on a simple web-based platform (26). Many of these datasets can be downloaded onto researchers own computing environments, allowing much flexibility. To do so, users must register and accept a responsible use agreement. Besides data access, authorized users have access to SAS analytical tools to assist with data analysis and are provided access to templates of legal agreements. Data are submitted mostly after publication of trials to protect commercial interests, and to protect trial participants' privacy, only after de-identification of any personal information. PDS proposes a de-identification strategy that satisfies legal requirements (the expert determination method of the HIPAA Privacy Rule is the preferred method (53)); however, final responsibility resides within the data provider (54). Additionally, other clever de-identification strategies for clinical trial data are proposed (55). By renouncing any form of control by an organization, the platform minimizes barriers to access and share data, and hopes to maximize potential benefits. Concerns have been expressed however, that unrestricted access to clinical trial data would lead to unskilled analysis and thus to flawed results. Such papers containing fallacious insights could be the basis of (pressured) misleading regulatory actions potentially harming patients (25, 27, 28). However, it is recognized that this model may be less suited for disclosing data of trials for rare disease or sensitive data where identification risks may be higher, i.e., genomic data from clinical trials (17). At present, the PDS contains data from almost 100,000 research participants from 116 trials provided by academia, government and industry sponsors. Just recently, PDS initiated alliances with Merck KGaA to jointly lead the Global Oncology Big Data Alliance (GOBDA) (56). GOBDA will enrich PDS by including data from rare tumor trials, experimental arm data and real-world patient data and leverages its potential by application of big data analytics.

A similar open access model has been introduced by the EU regulator in its flagship policy 0070. Here, the European Medicines Agency (EMA) commits to proactively publish clinical reports of all initial marketing authorization applications submitted after 1st of January 2015 on the publicly available website https://clinicaldata.ema.europa.eu/web/cdp/home (57). Besides this user-friendly tool to get access to clinical reports, their use is further governed by two different terms of use (ToU) attestations. The applicable ToU depends on the intended use and information contained in the reports, which can be for on-screen view only when it considers general information purposes, or for a full download for academic and non-commercial research purposes (58). In order not to interfere with the Agencies' decision-making process, documents will be published once the decision about a market authorization is made. Further, to anonymize published data from the clinical reports, personal data are redacted. Also, companies' commercially confidential information (CCI) can be redacted, although in general, the Agency does not consider clinical data (i.e., clinical reports and IPD) as CCI. The EMA is committed to also share (whenever possible anonymized or otherwise pseudonymized) IPD in a later phase via this website.

To the best of the author's knowledge, no open access regimes for clinical samples were found. One of the potential reasons might be captured in the following quote from a biostatistician in an academic research organization: *"If you talk about sharing samples, this is an action that cannot be repeated forever considering their perishable nature. You need to have more governance on deciding what the best purpose and the best timing is to re-use samples."*

Controlled Access Models

Besides a pure open access model, a more restrictive approach is applied in the controlled access models. Here, some form of control is exercised by either the donor (i.e., patient), the data provider (i.e., initial organization), or an independent party. This control allows for balancing the benefits and the risks of the data sharing: does the value gained from providing the data and executing the research outweigh the risks in terms of potential privacy breaches or competitive concerns? Six different controlled access models can be differentiated.

The Data or Sample Provider in the Driver Seat

While advances in precision oncology research depend among other things on the appropriate integration and retrospective analysis of patient data, it also often depends on the willingness of the providers (i.e., the custodians) to share "their" data or samples. Although it is generally accepted that sponsors or research teams can from an intellectual property (IP) point of view not *own* these resources, whoever possesses the data or samples physically, *controls* them and may determine whether and by whom its benefits can be tapped.

Under the traditional regime, third parties' access to and use of clinical trial data is subject to the original trial sponsors' authorization and can be granted to individual datasets on a case-by-case basis, mainly according to some formal mechanism laid down in the organizations' policy. There is only little transparency, however impartiality (i.e., avoidance of selective access) is guaranteed as far as possible by having a mechanism for approval that is bound by a set of clearly defined criteria. In addition, the conditions for access in case of a positive decision should be declared in advance. In case of a negative decision, the rationale should be documented and publicized, which may in some organizations be appealed to a Data Access Committee (DAC) that takes a final decision. As such, the model aims to prevent data providers to impede data sharing for non-legitimate reasons.

For a long time, sharing of patient-level clinical trial data happened too often through informal processes, with the study sponsor in control of the decision of whether to share or not. The molecular disease classification of colorectal cancers is a case in point. When the first anti-epidermal growth factor receptor

(EGFR) antibody therapies for colorectal cancers were brought to the market by industry, there were no subpopulations identified (59). It was only shortly after, through re-analysis of the industry-driven trials by academic investigators, that the association was made between activating mutations in the K-RAS gene and a lack of response to anti-EFGR inhibitors. This lead to a subdivision in responders (wild-type K-RAS) and non-responders (K-RAS mutations), and ultimately to a repurposing of the drug restricted to the responders accounting for approximately 60% of the total previous population (60). Later, other academics bundled forces to investigate the effects of other downstream mutations (PIK3CA, B-RAF, and N-RAS) on the efficacy of an EGFR inhibitor, cetuximab (erbitux, Merck KGaA), and, once again, confirmed low response rates demonstrating these to be negative predictive biomarkers (61). Today, taking all subpopulations together, the number of patients not benefiting from treatment was increased to almost 60% of the initial population, 60% that could otherwise be exposed to serious side effects when treated with anti-EFGR therapies. However it took more than 3 years before these new findings were picked up by the industry, to re-analyze the original trial data, and to confirm the result (62). This illustrates that in silo approaches, insufficient data sharing, and poor academia-industry interactions result in sub-optimal or delayed introduction of the latest scientific results into clinical practice.

The same seems to be true when it comes to clinical trial samples, as explained by an academic researcher often involved in clinical trials with oncologists and pharmaceutical companies: *"oncologists think, even from 20 years ago, 'these samples were collected by me 20 years ago, I can decide who can do what with them', and it is the same what the company will say: 'I collected this, I paid for this, so I can decide who accesses it', (…) I think that after a certain amount of time, you should take (this decision) away from these parties."*

Catalogue

Catalogues, for instance public databases like the EU EudraCT database or the US ClinicalTrials.gov, containing metadata on organizations' individual datasets, can help to identify the holders of clinical trial data and samples as a starting point for the access approval process. However, control still resides with the initial provider. Information found in catalogs is often only limited and the functionalities of the navigation interfaces can be improved, as said by a biostatistician from an academic research organization: *"The current trial registration tools are insufficient; individuals have a hard time to extract the correct information from the data as they are being entered now."*

Besides these non-detailed databases, also metadata of more detailed datasets, including genomic or genetic datasets, can be found on public websites. Such data may be distributed across databases and computers around the world, virtually connected through software interfaces that allow seamless, controlled access. The EGA, launched in 2008 by the EMBL-EBI, goes further than merely cataloging data by also archiving and brokering data from data submitting organizations (29). The EGA provides an overview of studies for which participants have consented to their data being shared for research uses—but not for full, open public release. Access to individual-level biomolecular and phenotypic data can be requested, after which the data access decisions are made by the DACs of the submitting institution, not by the EGA (29). Consequently, the model allows data submitting institutions to maintain autonomy. The International Cancer Genome Consortium for instance, launched in 2008 to generate comprehensive catalogs of genomic abnormalities, uses the EGA to make its data available to the entire research community as rapidly as possible under particular access conditions (63). The EGA has similarities with its US variant, the dbGaP provided by NCBI (64). However, the dbGaP does not work with a de-centralized access-granting system since access decision are made by the National Institutes of Health.

When it comes to samples, biobank networks like the publicly funded pan-European BBMRI-ERIC initiative, aim to improve the accessibility and interoperability of existing sample collections (65). After registration on a public website, a web-based query tool provides an overview on available samples and associated medical data in the BBMRI catalog. Submitted research requests undergo ethical and scientific review by the BBMRI-ERIC Ethical and Scientific Review Board, respectively, after which the final access decision is made by the local biobank's access committee.

Partnership

When a research project with a request for data is of sufficient scientific value for the data provider (e.g., the sponsor), he may decide to enter into collaboration with the requester rather than merely providing the data, and the same is true when it comes to sharing clinical samples. The Vice President Global medical affairs of a large pharmaceutical company explains: *"If an external researcher or co-operative group has an idea involving retained samples and they submit it to the company, we could potentially enter into a collaboration."*

When initiating a collaborative project with existing data or samples (i.e., "retrospective model"), both parties must come to mutual agreements on the use of and access rights to pre-existing and newly generated data, publication of research results, and—sometimes the most complex—on pre-existing and resulting IP. However, the associated iterative negotiation processes are time consuming, resource, and labor intensive. To aid these discussions, partnership toolkits and standardized agreements have been developed (66). Still, the lack of formal mechanisms to make partners work together is regretted by a general manager oncology from a large pharmaceutical company: "*I hope that, by some (intervention) from the authorities, these discussions or negotiations could be taken more under an umbrella, making it easier for everybody, because now many researchers and companies don't understand this anymore; it starts to be a legal department at the hospital and a legal department here, and there is no science involved anymore."* Collaborations span a range of models and can occur in the form of interdisciplinary academic initiatives, academia-industry (11, 67), industry–industry, or more complex multi-stakeholder partnerships (5, 68). Specific collaborations with a high public interest [e.g., biomarker research in oncology (69)] could be incentivized through financial, legal, or organizational support, or in the form of private–private partnerships (PPPs) which have their own IP and data sharing specifications (70).

The retrospective nature of most conventional data sharing models limits the data to be used rather exploratory or for hypothesis generating research. In another approach, partners seek each other and establish a new database/biobank with the aim to be widely accessible for multiple research purposes (i.e., "prospective model"). Especially in precision oncology, a number of collaborative initiatives has been set up to develop in a prospective fashion sustainable, high-quality, and integrated patient data collections, leveraging linked clinical and -omics data to accelerate research, facilitate patient-centered clinical trials and/or provide clinical insights that can be fed back to patients. A member of an independent review board (IRB) from a renowned, large data sharing model stated the following in this respect: "*We are seeing more of 'pre-competitive collaborative research' because the blockbuster days are gone and everybody needs the same basic data so why not just work together in a public-private consortium to move everything forward and when you get enough data and samples then you can go back to your competition and see who gets the product out first.*"

Performing clinical trials in smaller treatment populations increasingly pivots around operational challenges, namely how to perform large-scale sample characterization for patient screening. Collaborative platforms propose to jointly organize such screening in a precompetitive setting, for instance in Europe the European Organisation for Research and Treatment of Cancer (EORTC) Screening Patients for Efficient Clinical Trial Access initiative (32) or the US National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH), or the for-profit, multi-institutional oncology research information exchange network (42) (**Table 3**). The opinion of a medical doctor illustrates this: *"A consequence of precision medicine is that pharmaceutical companies will need to compromise; they might need to enter into collaboration agreements with these types of screening platforms because it will be too difficult to have access to certain patients, otherwise their business is finished."*

Gatekeeper Model

Under this regime, access to data is not at the data providers' discretion but may be granted by a distinct entity. Often, an IRB acts as a neutral intermediary that decides on the access to specific data sets. It does so, based on the scientific soundness of the research proposal submitted by researchers, on the expertise of the team and taken into account to benefit-risk balance of providing the data for that specific purpose. In this model, a central entity can act as a repository to collect and house existing clinical trial data ("centralized model"), or as a web-based search system providing general information about available data sets, however the data themselves are stored by the data providers ("federated model"). Such approaches support procedural transparency since they obligate to motivate decisions for non-disclosure. Industry representatives on their side, favor this approach compared to an open access model, because it allows initiating a dialog with requesters to explain questions on datasets, certain findings, or rationales for trial adaptations.

The industry's commitment to data sharing builds on the gatekeeper model (71) and is implemented by single organizations

TABLE 3 | Non-exhaustive overview of prospective, collaborative -omics screening platforms to facilitate clinical research in precision oncology.

Platform	Organization(s)	Location	Omics analysis	Tumor	Reference
AURORA	BIG	Belgium	NGS for a panel of 411 cancer-related genes	Breast	(39, 40)
Exactis	PMT	Canada	No information publicly available	Breast, lung, colorectal, ovarian, melanoma, prostate	(41)
ORIEN	Moffitt Cancer Center, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Richard J. Solove Research Institute in Columbus	US	No information publicly available	All malignancies	(42)
NCI-MATCH	NCI	US	NGS	Solid tumors	(43)
PMT initiative	Exactis Innovation	Canada	-omics platforms	Colorectal, lung, melanoma, breast	(41)
SPECTA	EORTC	Europe	-omics platforms	Colorectal, lung, brain, melanoma, rare, prostate	(32)
Stratified Medicine Platform 2	Cancer Research UK	The UK	No information publicly available	NCSLC	(44)
The CPCT	Nederlands Kanker Instituut-Antoni van Leeuwenhoek Ziekenhuis, Erasmus MC Kanker Instituut, UMC Utrecht	The Netherlands	HiSeq Xten Illumina (WGS) (45)	All malignancies	(46)
U-can	Uppsala University	Sweden	WGS, SNP analyses, RNA Seq	Colorectal, leukemia, lymphoma, prostate, brain, gynecological, neuroendocrine, breast	(47)

CGH, comparative genomic hybridization; EORTC, European Organisation for Research and Treatment of Cancer; NCI-MATCH, National Cancer Institute-Molecular Analysis for Therapy Choice; NGS, next generation sequencing; NCSLC, non-small cell lung cancer; ORIEN, oncology research information exchange network; PMT, personalize my treatment; RNA, ribonucleic acid, SNP, single nucleotide polymorphism, SPECTA, screening patients for efficient clinical trial access; The CPCT, the center for personalized cancer treatment; WGS, whole genome sequencing.

(i.e., the public–private funded Yale University Open Access (YODA) project of Johnson & Johnson (72), or the publicly funded Supporting Open access Research (SOAR) initiative (73)) and by collaborative platforms such as the ClinicalStudyDataRequest.com platform (74). These platforms provide access to data through a password-protected secure internet connection; however, data are not downloadable. Costs of the platform are born by the data providers, according to Rockhold F. et al *"An investment of about $30,000 to $50,000 per year is needed for an academic sponsor to list up to 20 studies on the request site and for up to 10 research projects to be undertaken using data in the secure access site,"* consequently "*The overall costs can seem disproportionately high for sponsors or investigators with few trials.* ," deferring other organizations from joining the platform (34).

The Vivli platform, sponsored by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard University (MRCT Center), aims to create a singly portal, merging the myriad of existing platforms of sponsors enabling analysis of multiple datasets (35). Vivli is flexible for data providers since its secure computing environment enables aggregation of both centrally as well as federally hosted dataset. The platform will curate data from existing platforms into structured, computable metadata to allow for more accurate searches. On top of clinical trial data, ViVli aims to develop over time, the capacity to also share other data such as real-world data and omics data (35). Data shared through such secure platforms is free of charge, however, some have voiced concerns about the costs and resources required to secure and sustain this model (34). A drawback is that these platforms often do not allow access to individual genomic data or samples.

The gatekeeper model is advised by international recommendations for biobanks to share human material (75). Consequently, many local biobanks operate with an appointed IRB. However, it is seen that access arrangements of many biobanks lack completeness, not at least when it comes to the establishment of independent access mechanisms to maximize the value of clinical sample collections (76).

Some initiatives, like the (public and privately funded) 100,000 Genomes Project, are focused on enabling access to genomic data linked with continually updated clinical data of cancer patients (77). External scientists must apply for membership of the 100,000 Genomes Project research community. Upon approval of a research project by an IRB (so-called "Access Review Committee', ARC) and an internal Ethics and a DAC, members can access the data for free on the project's secure servers, pharmaceutical companies on their part have to pay a substantial fee (78). This project is set up by Genomics England, a company owned by the Department of Health. Both the whole genome sequencing data, clinical data and any IP generated during the project are owned by Genomics England, who proclaims to license this to third parties under favorable terms. Any profits made ought to be reinvested into genomics medicine (78).

Database Query

In an alternative, more restrictive model, data are not shared directly and custody is retained, rather the research questions or a copy of an analytical computer program is sent to the data provider, who runs the query and sends back the computed results to the requester. This so-called "database query" model is believed to be more secure since fewer copies of data—that can be attacked or stolen—are made (30). This model is useful to access sensitive data (e.g., for genome analysis) by requesting results from queries on personal identifiable data, since the latter fall out when the analytical results are presented to the requester. Datasets can be queried individually, or at the aggregate level. A possible limitation of the model may include its lack of transparency, precluding requesters from verifying that the results they receive are valid.

In 2012, a group of gastrointestinal oncologists bundled forces to launch the ARCAD Advanced Colorectal Cancer Database Project (79). This project, supported by public and private grants from industry, aims to bring together in one single database de-identified IPD from most of the recent prospective clinical trials in advanced colorectal cancer ("aggregated model"), including both industry and academic trials across all lines of therapy. Currently, IPD from almost 40 randomized trials comprising >35,000 patients are incorporated into the database. Data include baseline demographics, clinical and laboratory assessments (including relevant biomarkers), treatments, tumor measurements over time, and outcomes. Both ARCAD and non-ARCAD members are invited to propose further studies with a view to collaborative projects; however, the database will be analyzed by ARCAD statisticians and trialists (80). Research proposals will be examined by ARCAD review committee, and to respect the interest of data providers, all data providers are consulted before every analysis and have the freedom to withhold their trial data from any analysis.

BBMRI-ERIC suggest the use of the database query model in case industrial users want to access samples. Human samples can legally and ethically not be sold; however, industrial users may access and use specimens for the R&D of commercial products (65). BBMRI's so-called "Expert Centers" are not-for-profit intermediate infrastructures set up as PPPs that will perform analysis of human samples at the request of industry, and subsequently make the data available that may be used in product development. The same model is suggested to be of use in a situation where researchers from different countries want to collaborate, but when country-specific legal restrictions on export of human material complicate international research. In such situation, expert centers act as "highways" for transnational research collaborations, meaning that samples will be analyzed in the country of origin, and only research data are shared (65).

The Beacon Project of the (public and private funded) Global Alliance for Genomics and Health (GA4GH) and ELIXIR, the on EU grants based infrastructure for life science data, is a more technology-savvy example of this model (81). The project aims to improve the discoverability of genomic data by making use of "beacons." Beacons are online web services, tiny search functions added to databases, which allow users to query institutions' databases to get specific allele-presence information. For instance, it allows questions in the form of "Do you have any genome with a 'nucleotide x' at position 'y' on chromosome 'z'?" to which the beacon responds with either "yes" or "no." The result of this query efficiently informs the user as to whether the variant of interest exists, and thus whether an access request for more detailed data

would be deemed useful. As such, beacons are a first step toward greater openness and data sharing. By its federated approach—one single space allows querying across beacons set up by the member organizations—data providers maintain control.

Donor Controlled

In line with the European Commissions PerMed consortium recommendations and the revised EU data protection framework, both underlining the importance to enhance patients' control over their own data (82), trial participants are advocating for more control over their own medical data (83). In this respect, privacy-enhancing techniques such as e-consent have been proposed to allow for a more dynamic interface where trial participants can manage their own data sharing preferences (84).

Health data cooperatives try to circumvent the inaccessibility resulting from data silos, by prospectively creating a trusted entity where individuals can safely store, control, manage, and share their own data. In this hypothetical model, participants themselves can thus decide to open up their data, and to whom they disclose it (37). In support of genomics research, similar programs have been proposed where individuals' can donate their DNA and health records, analogous to organ-donor systems (38).

The growing interest of public and patient engagement in research is also reflected in the establishment of a number of patient-led biobanks, for instance the German Patients' Tumor Bank of Hope (PATH) (85) which collects blood and tumor tissue with associated data from breast cancer patients over time. Decision to grant requesters access to the samples and data are made by its board which consists out of three breast cancer survivors (86). Such models, where donors control access, are considered ethically correct by a legal advisor from a clinical research center: *"Samples belong to the patient, and organizations get access to them through a study or a trial, (…) but they remain the property of the patient; the person who can decide what happens with the samples should be the person from whom the sample was collected."*

Toward a Sustainable Biomedical Sharing Ecosystem

The recent revolution in science and technology applied to medical research has left in its wake a trial of biomedical data and human samples; however, the opportunities remain largely unfulfilled. To harness these opportunities biomedical research organizations' and pharmaceutical companies' collaboration and innovation models should appropriately adapt. Not surprisingly, the debate is largely focused on the precision oncology research arena considering its high potential to leverage "Big data" and samples into meaningful solutions for patients.

Sharing such data is critical to scientific and medical progress, but is has been hampered because of legal, ethical, financial, strategic, and technical barriers. Fulfilling the legal/ethical requirements to protect participants' privacy, or organizations' confidentiality while guaranteeing incentives for investment in research, seems to conflict with an approach of openly sharing personal data and human material to advance scientific knowledge and achieve patient benefits.

From a policy perspective, the question is whether patients and society are better off under a regime that favors open data sharing over a regime of more controlled or very restricted data sharing. Further, should the sharing of clinical trial data and samples (openly or controlled) be mandated, and if so, how and to what extend should this be organized in a legal, ethical, and innovation-friendly way? To resolve this dilemma, a better understanding of different sharing models and their characteristics was deemed useful. Based on pre-existing literature and practical examples as well as expert opinions, we conceptualized a number of models.

While the primary goal of all models is to enable further research, it seems obvious that the open access approach mirrors this goal perfectly. Examples demonstrate that the open access model has been proven feasible, traditionally in the field of genomic research but now also for clinical trial data. Sharing genomic data from clinical research participants through this model remains more difficult, and this might be due to differences in applicable consent restrictions between non-clinical versus clinical trial genomic research projects. The impressive amount of trials submitted in PDS demonstrates that providers are willing to submit their data, underlining the success of the model. While guaranteeing the protection of privacy might be impossible when sharing genomic information, the PDS provides guidance about methodologies that can be applied to de-identify clinical trial data in compliance with legally prescribed standards (53).

Having appropriate safekeeping mechanisms in place to control sharing, by providing access only after fulfillment of certain conditions, for instance for privacy-sensitive data or data restricted by IP protection, remains a good alternative for keeping both patients' and organizations' interests safe. The traditional controlled access models have led to an emergence of numerous data and sample silos, undoubtedly at the expense of scientific advances. Comprehensive catalogs with different types of data and samples would provide a useful tool to identify the custodians of data and samples collections and determine whether access is of interest. However, current legally mandated trial data catalogs seem insufficient, especially to track down biomarker data or samples. Voluntary catalogs such as the BBMRI-ERIC model are to be applauded but it remains unclear to what extent this biobank catalog will contain information on sample collections held under the auspices of for instance for-profit trial sponsors, complicating the access to these valuable resources.

Partnerships remain a vital strategy in biomedical (oncology) research to maximize the value of resources that would otherwise remain untouched. Despite the willingness to collaborate, both academia as industry representatives indicated to regret the lack of systematic and coordinated approaches to enter into partnerships. Still too often, research projects are initiated based on personal contacts. The scale and opportunities brought forward by Big data, together with the complexities afforded by the level of precision we are aiming for in oncology, may be an inflection point: the need to study rare variants, the combinatorial complexity of treatments and the increasing number of stratified trials have led to the setup of prospective and precompetitive -omics screening platforms. It may not be practical in the future to work without collaborating with such models in order to conduct

patient-centric trials to validate certain precision oncology treatments. For sure, the setup and maintenance of these platforms have their own difficulties, not at least high costs and resources to recruit and characterize a critical mass of patients, which is in turn essential to attract downstream research projects of which the revenues could again be invested. Another complexity centers on the quality of information. Where retrospective data from federated models can be informative, it can be questioned whether these data will meet regulatory standards to support and change clinical decision-making. This does not mean that such data should not be used; rather the results should be interpreted cautiously. Alternatively, to generate sufficient large collections of regulatory-grade patient data in a prospective fashion demands logistical solutions for instance for biobanking; however, at costs that might make it unaffordable.

An emerging trend to share clinical trial data is the use of the gatekeeper model. One of the reasons for this might be that it secures neutrality on the decision, and at the same time ensures some form of interaction between data generator and data requester. Each study has its limitations, who are best known by the researchers involved in the project. Not knowing these might introduce important confounding in secondary analysis. For instance, a good understanding of the conditions under which the data and samples were collected, the complex datasets, and specific statistical tests in biomarker studies in oncology is essential to ensure appropriate analysis. Through this model, the primary research team can provide this necessary guidance, or can be invited to join the secondary study. The huge costs of this model, however, renders it less attractive. Since sharing clinical samples is impossible through an open access model considering their physical nature, further encouraging the use of gatekeeper models to share clinical samples is useful. The relevant IRBs will need to make some additional decision relating to for instance prioritization of scientific projects on the basis of evaluation criteria (76).

Lastly, also federated models in which queries are sent to the original data or sample providers, thereby not necessitating an act of sharing sensitive information, are being adopted. Depending on the level of detail that can be queried, such models can be considered more secure. Consequently, these models are especially useful to address data protection issues or concerns about IP and competitiveness. Several important precedents have been set here by the oncology research community such as the Beacon Project where uncovered genetic variants from one institution can be linked to similar variants of other databases, increasing evidence on their clinical relevance and utility.

Data and sample sharing models have evolved over the past decades, now spanning a continuum from traditionally closed models up to full open access models. Different strategies will continue to exist and it is highly unlikely that completely open models will dominate future practices. However, in an era where data is driving future innovations, but the data sources are fragmented, finding appropriate models to share and collaborate on projects are quintessential. Several models are mapped here, describing various levels of control over the data, and different relationships between data providers and users. We believe that there is no universal or one-size-fits-all solution that should be mandated by policy makers. However, we would like to propose a tiered model for sharing that takes into account the characteristics attached to certain types of data and samples (**Figure 3**). The proposed model is tiered, as it offers a strategy depending on the legal, ethical, and strategic issues attached to the shared resources.

A first tier would be for everyone to share de-identified raw, IPD from clinical trials—indispensable information for verification of studies—by use of an open access model such as proposed by PDS. This approach requires in parallel solid processes for de-identification, exclusions to openly share datasets with high risk for re-identification, and the implementation of commonly agreed responsible use attestations. Additional tiers offer more detailed information made available upon request through controlled access mechanisms. For accessing samples or genomic information, it may be impossible to use an open access model

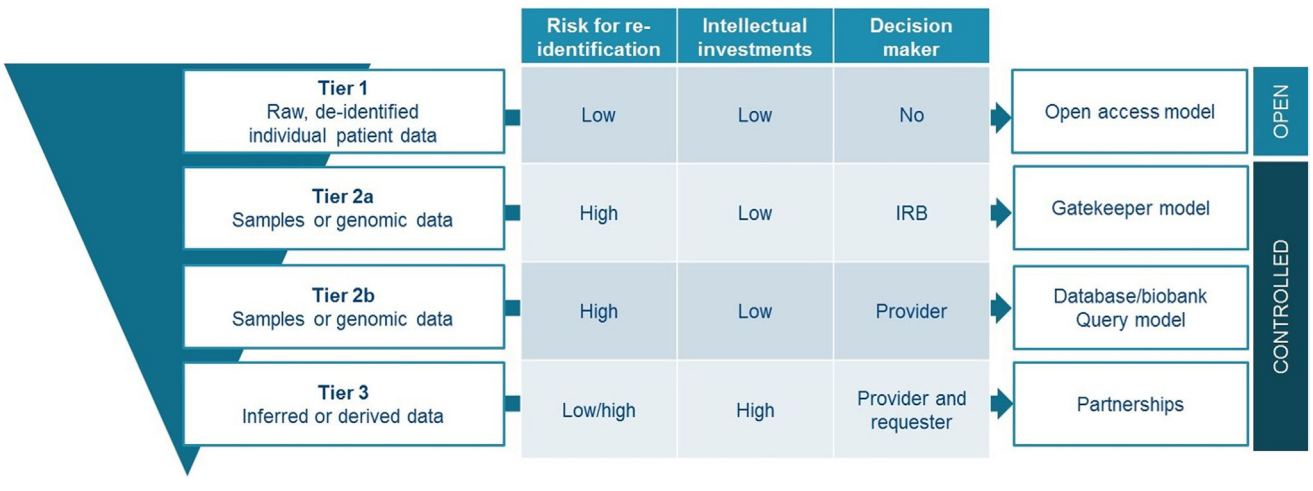

FIGURE 3 | Proposed tiered-layered model to share and access clinical data and samples.

considering their sensitive nature, unless patient would provide open consent which is highly questionable in the context of clinical research projects. We believe that gatekeeper models with independent oversight, would be most suited to organize data sharing for these types of patient resources (tier 2a). If for some reason, more control from the data and/or sample providing organization would be necessary; the database query model represents a good alternative (tier 2b). As a third tier, the setting up of partnerships should be promoted. These partnerships should aim to maximize the use of inferred or derived data, while addressing competitive concerns related to them. Promotion of partnership can be done for instance through the provision of structured contractual agreements of which a substantial part should be attributed to IP and benefit-sharing agreements. Similarly, both academia and industry engaging in precision oncology clinical research could benefit from such structured agreements for collaboration with an -omics screening platform.

Overarching all tiers, the further development of a standardized cancer ontology combined with catalogs or other search tools for metadata to make the providers of data or samples more findable is considered useful, in line with the first of four FAIR principles (87). Further, we support as a rule that all reporting of results based on research with shared data and samples should contain appropriate co-authorship, or at least attributions, to recognize and acknowledge the original data or samples holders (i.e., provider) (88). Finally, to increase donor's control over their data and sample management, and to increase overall transparency—two key principles embedded in the upcoming EU General Data Protection Regulation (89)—the use of modern privacy-enhancing tools such as dynamic forms of e-consent should be further explored (83, 90).

Through the latter measure, patients would have an opportunity to become more actively engaged in the whole data sharing process. More generally, our proposed model aims to increase transparency and thus trust in the use and subsequent reuse of clinical trial data and samples, while maximizing benefits. As such, this model aims to respect patients who put themselves at risk by participating in a trial, and meets the obligation delineated in informant consents that the results from trials lead to the greatest possible benefits not necessarily for the participating patients but for future patients.

This study suffers from a number of limitations. First, the results are based on the author's interpretation of the literature. Although in line with other articles, others might come to a different classification of the models. Second, we restricted our search to general data (and sometimes sample) sharing models and models specifically deployable in oncology, imposing a selection bias. Yet, other examples (fitting within this categorization) in other disease areas exist. Third, certain of these models relate to sharing genomic research datasets and not specifically to clinical oncology research data. Although useful, since the boundaries between both types of research are increasingly blurred in data-intensive precision oncology research, genomic data sharing has typically followed a liberal model, characterized by an open approach to freely share and exchange data (e.g., Bermuda Principles 1996).

Further unveiling the molecular architecture of cancer necessitates the inclusion of data resulting from multiple omic methods applied to patient samples. Hence, it is necessary to enlarge the current focus on clinical trial data sharing to include sharing of samples of which new information can still be extracted. Currently, efforts to encourage sample sharing are limited when compared to data sharing. To conclude, we propose a tiered-staged model for sharing of clinical trial data and samples that takes into account the legal, ethical, and strategic concerns. Such model can help spark the debate to come to commonly agreed solutions that aim to facilitate precision oncology research, an area that will maximally benefit from increased sharing. According to the Clinical Cancer Genome Task Team of the GA4GH: *"If we don't concentrate our efforts (and dedicate substantial resources) to robustly improve data sharing, we risk undermining precision oncology's capacity to deliver substantive advances for people with cancer."* We believe our proposed model can increase these efforts and contributes to maximally achieve this aim. Organizations active in oncology drug development should think about an effective tiered-sharing strategy to maximize the value of the resources donated by patients, while not diminished the incentives to invest in research. Research shows that the drug development model has reached its innovation capacity, and this is especially true for precision oncology (7, 12, 91–93). The adopted open innovation practices by the research community—of which data sharing being one of the most pronounced ones—beholds the power to shift the current paradigm of siloed and fragmented clinical research toward scientific collaborations based on pooling of expertise, ideas and resources. Over time, this will contribute to a more efficient drug development model, advance science and aid in the fight against cancer.

AUTHOR CONTRIBUTIONS

SB wrote the original manuscript. All authors read, contributed, and approved the final manuscript.

FUNDING

The PhD project of SB is supported by the EORTC.

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Conflict of Interest Statement: SB received a PhD scholarship of the EORTC. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

REVIEW
published: 16 August 2017
doi: 10.3389/fmed.2017.00134

More Haste, Less Speed: Could Public–Private Partnerships Advance Cellular Immunotherapies?

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Cellular immunotherapies promise to transform cancer care. However, they must overcome serious challenges, including: (1) the need to identify and characterize novel cancer antigens to expand the range of therapeutic targets; (2) the need to develop strategies to minimize serious adverse events, such as cytokine release syndrome and treatment-related toxicities; and (3) the need to develop efficient production/manufacturing processes to reduce costs. Here, we discuss whether these challenges might better be addressed through forms of public–private research collaborations, including public–private partnerships (PPPs), or whether these challenges are best addressed by way of standard market transactions. We reviewed 14 public–private relationships and 25 underlying agreements for the clinical development of cancer cellular immunotherapies in the US. Most were based on bilateral research agreements and pure market transactions in the form of service contracts and technology licenses, which is representative of the commercialization focus of the field. We make the strategic case that multiparty PPPs may better advance cancer antigen discovery and characterization and improved cell processing/manufacturing and related activities. In the rush toward the competitive end of the translational continuum for cancer cellular immunotherapy and the attendant focus on commercialization, many gaps have appeared in our understanding of cellular biology, immunology, and bioengineering. We conclude that the model of bilateral agreements between leading research institutions and the private sector may be inadequate to efficiently harness the interdisciplinary skills and knowledge of the public and private sectors to bring these promising therapies to the clinic for the benefit of cancer patients.

Keywords: cellular immunotherapy, cancer, adoptive cellular transfer, CAR-T cell, public–private partnerships, Collaborative Research and Development Agreements, technology licensing

OPEN ACCESS

Edited by:
Michel Goldman, Free University of Brussels, Belgium

Reviewed by:
Bruno Laugel, Cardiff University, United Kingdom
Dimitrios Tzalis, Taros Chemicals GmbH CoKG, Germany

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *22 December 2016*
Accepted: *25 July 2017*
Published: *16 August 2017*

Citation:
Bubela T, Bonter K, Lachance S, Delisle J-S and Gold ER (2017) More Haste, Less Speed: Could Public–Private Partnerships Advance Cellular Immunotherapies? Front. Med. 4:134. doi: 10.3389/fmed.2017.00134

INTRODUCTION

Public–private partnerships (PPPs) are collaborative efforts to achieve mutually agreed objectives (1). They draw on the respective strengths and resources of the parties involved. In therapeutic product development, PPPs are based on complementary skills, materials, and knowledge along a translational continuum of research and development (R&D) by public/non-profit sector

researchers and those in the biotechnology and/or pharmaceutical sectors. While considerable attention has been paid to PPPs engaged in the development of drugs and diagnostics or other devices, this perspective considers the role that PPPs might play in overcoming the clinical development and implementation challenges for cancer cellular immunotherapies. It first identifies the challenges, then takes a case-based approach to review public–private collaborative relationships in the US, and finally expands on the potential for multiparty PPPs to advance this promising field for the benefit of cancer patients.

CLINICAL DEVELOPMENT AND IMPLEMENTATION CHALLENGES FOR CANCER CELLULAR IMMUNOTHERAPIES

Cellular immunotherapies have been hailed as transformational for cancer care. In 2013, *Science Magazine* declared immunotherapy (cellular and checkpoint inhibitors) as its breakthrough of the year (2), and financial markets have generally concurred—2015 was a record year for investment in life sciences companies, with the greatest investment (1,496.49 Mill USD) in the category of immunotherapy/vaccines (3). The excitement stems, in part, from advances in adoptive cellular transfer (ACT), which uses chimeric antigen receptor (CAR-T) cells, tumor-infiltrating lymphocytes (TILs), or T cell receptor (TCR) engineered cells to recognize and target cancer cells (4). ACT promises to improve on the 2.5-month overall gain in survival time reported for cancer drugs approved between 2002 and 2014 (5). For example, clinical trials of CAR-T cells have reported positive results in acute lymphoblastic leukemia (ALL) (6), acute, relapsed refractory chronic lymphocytic leukemia (7), refractory multiple myeloma (8), and pediatric relapsed and refractory B-cell acute lymphocytic leukemia (B-ALL) (9). Similarly, TILs have shown great promise for metastatic melanoma (10–12).

Cellular therapies, in general, and cellular immunotherapies, in particular, face multiple challenges in clinical development and implementation. With respect to clinical development, leading cellular immunotherapy researcher, Dr. Steven A. Rosenberg, has identified lack of suitable targets as a major obstacle for cellular immunotherapies (13). If cellular immunotherapies are to be effective for solid tumors and for hematological malignancies, they must target cancer cells without causing off-target toxicities (14–16). Such toxicities, especially if unpredictable, will be a serious limiting factor for the clinical adoption of cellular immunotherapies. The identification of such cancer-specific antigens is therefore paramount for the future development of the field because most normal tissues, if destroyed by the cellular immunotherapy, cannot be replaced. Clinical trials have reported deaths from cardiopulmonary and neurological toxicities (14–16). Furthermore, cellular immunotherapy for B-cell leukemias that target CD19 may destroy normal B-cells. This can be palliated with immunoglobulin replacement (17). Hematological stem cell transplantation, often performed after these therapies, can also restore normal levels of immune cell subsets. Both, however, are delivered with Intensive Care Unit support, thereby increasing the cost of the therapies.

Cellular immunotherapies must also overcome their potential for other serious adverse events, primarily cytokine release syndrome. There appears to be a correlation between the efficacy of the immunotherapy in destroying cancer cells, and its adverse side effects—high efficacy in killing cancer cells may lead to a cytokine storm, especially in patients with a high disease burden (18). Neurotoxicity poses an additional risk. For example, in November 2016 leading cellular immunotherapy biotechnology company, Juno Therapeutics (Seattle, WA, USA), announced that it is placing a voluntary hold on the Phase II clinical trial of its leading CAR-T cell product, JCAR015, following the death of two participants with relapsed or refractory B cell ALL (19, 20). This voluntary hold for acute irreversible cerebral edema followed a hold placed on the same trial in July 2016 by the US Food and Drug Administration (FDA) due the deaths of three participants also from cerebral edema (21). At the time, Juno Therapeutics blamed the deaths on the addition of the chemotherapy, fludarabine, to eliminate the patient's existing T-cells, making way for the CAR-T cells. The FDA lifted the hold only 1 week later (22). Not unexpectedly, the new November 2016 (without fludarabine) hold has had a dramatic effect on Juno Therapeutics shares; its stock price plummeted by 44% before trading was halted, and the impact of the deaths has spilled over to negatively impact other CAR-T cell companies (19, 20).

Even if cellular immunotherapy toxicities can be overcome, clinical implementation will be limited by the expected high cost of the therapies ($150,000–$500,000 per dose) that is, in part, determined by the emerging service-based autologous business model for cellular immunotherapies (23). ACT therapies currently derive from the cancer patient's own circulating lymphocytes. Such autologous therapies incur substantial logistical challenges for scale-up. The circulating lymphocytes must be extracted from the patient, genetically manipulated (CAR or TCR transgenic T cells) or selected for antitumor effect (TILs), expanded, and then reinfused into the patient (12). Current business models suggest processing will occur in a centralized current Good Manufacturing Practice (cGMP) facility, while extraction and infusion will occur at a cancer center. Leading cellular immunotherapy companies, such as Juno Therapeutics and Kite Pharma (Santa Monica, CA, USA), are investing in cGMP infrastructure. The global pharmaceutical giant, Novartis (Basel, Switzerland), initially signaled its intent in the field by opening a Cell and Gene Therapies Unit and purchasing a New Jersey cGMP facility that was originally developed for bankrupt cancer vaccine company, Dendreon (Seattle, WA, USA). However, in February 2016, it closed the Unit to focus on its non-cellular cancer immunotherapy pipeline (24). This shift of Novartis toward its traditional business model cancer therapies, such as checkpoint inhibitors, may indicate continued skepticism in a viable business model for cellular therapies (25). To the detriment of the field, autologous therapies have so far demonstrated greater efficacy than generic allogeneic products. Nevertheless, Cellectis (Paris, France) has advanced an allogeneic CAR-T immunotherapy derived from T cell precursors manipulated using TALEN® technology into

Phase I clinical trials (2015-004293-15). The product has been developed in collaboration with Pfizer and Servier and therefore does not represent a PPP. However, Cellectis has entered into a research and development alliance with researchers at MD Anderson Cancer Center (TX, USA), discussed below. The development of allogeneic cellular immunotherapies will be a fruitful area for future PPPs. Advances in all aspects of the service pipeline are therefore central to the clinical success of cellular immunotherapy.

ANALYSIS OF CURRENT PUBLIC–PRIVATE RELATIONSHIPS FOR CANCER CELLULAR IMMUNOTHERAPY

Public–private partnerships are one form of research collaboration based on shared decision making by the public and private sector parties involved with respect to goals, membership, ongoing management, potential expansion of the collaboration, and distribution of benefits (26). Such partnerships harness the complementary skills of the parties along the translational continuum from research laboratory to clinical trials, recognizing that the pathway for most therapies is neither certain nor linear, especially for novel treatment paradigms such as cellular immunotherapy. Rather, the pathway involves iterative research and development as successive challenges in safety and efficacy are identified and sometimes addressed.

Many biomedical PPPs are supportive of the precompetitive portion of the translational continuum wherein they facilitate the sharing of tacit knowledge (27), data, and materials, without limiting the ability of specific actors to appropriate knowledge that is closer to practical application (28–30). As such, PPPs stand in contrast to pure market transactions based on service contracts and technology licensing that more clearly delineate the rights and responsibilities of parties in a competitive environment (26). For example, a research-intensive, precompetitive PPP may be based on a consortium agreement between multiple members that sets out a shared governance structure. In contrast, relationships based on market transactions rarely establish the shared governance models that characterize PPPs. An intermediate form is a hub and spoke model whereby a central party enters into bilateral research agreements with multiple parties to advance its centralized goal. The ordering of research relationships from shared governance structures and collaborative research agreements to service contracts and technology licenses mirrors the translational continuum, from precompetitive to competitive research. The constellation of agreements will depend on the maturity of the technology in question and the state of certainty about its efficacy and market.

The preceding section identified four challenges that might be better addressed by PPPs, given the nascent stage of the field of cellular immunotherapy: (1) the need to identify novel cancer antigens to expand the range of therapeutic targets and minimize both off-target effects and on-target but off-cancer effects; (2) the need to develop strategies to minimize serious adverse events, such as cytokine release syndrome; (3) the need to develop allogeneic therapies; and (4) the need to develop efficient production/manufacturing processes to reduce costs. The issue is whether these challenges might be better addressed through forms of public–private research collaborations, including PPPs, or whether these challenges are best addressed by way of standard market transactions. In this section, we review public–private research relationships in the US. In the next section, we discuss how PPPs might improve the clinical translation of cellular immunotherapies.

The focus of our review was on PPPs that had developed products in clinical trials up to December 2015. For our review, we selected 14 US public–private relationships for the clinical development of cancer cellular immunotherapies based on a comprehensive analysis of 1,579 interventional clinical trials from global registries, of which 329 were industry sponsored (31). Of these, 35 companies had products in clinical development beyond Phase I, with verified status as of September 2016. Of these 35 companies, 34 were biotechnology companies operating in Western Europe ($n = 16$) and North America ($n = 17$), and one was the pharmaceutical company, Novartis. We reviewed the history of the public–private relationships of Novartis and the 11 North American companies whose clinical trial registry entry indicated that their product was still in clinical development (i.e., not terminated or withdrawn) and listed at least one collaboration with a research institute (**Table 1**). This is a limitation of our review—we only identified collaborations from the clinical trial record; we did not contact companies or interview investigators associated with all the industry-sponsored clinical trials and may therefore have missed some collaborations with academic centers.

We identified 23 separate agreements. In addition, our review of the academic literature and biotechnology news coverage by STAT News and FierceBiotech of cancer cellular immunotherapy identified four additional agreements by US companies of interest, whose product or technology development fills a gap to an identified challenge: Bellicum Pharmaceuticals (Houston, TX, USA), bluebirdbio (Cambridge, MA, USA), Cellectis (Paris, France), and Adaptimmune Therapeutics (Abington, UK). We further reviewed the history and nature of the research relationships based on documents identified in biotechnology and pharmaceutical trade publications (Factiva database), company websites and SEC filings, and contracts—10 of which had a full-text version available on the Recap database (confidential details redacted).

Our review of the 25 agreements identified a mixture of collaborative research agreements and pure market transactions in the form of service contracts and technology licensing (**Table 2**). The research agreements for collaborations between companies and research institutions (including universities and hospitals) were based on a hub and spoke model. In other words, when a company listed multiple collaborators on its sponsored clinical trial, all of the research agreements were bilateral between the company and the research institute. Our search only identified two relationships that clearly articulated a shared governance structure (likely an underestimate based on publicly available data we accessed rather than interviews with the parties). Cell Medica's (London, UK) separate agreements with Baylor College of Medicine and the University College London both stated that

TABLE 1 | Public–private collaborative efforts in the US of cancer cellular immunotherapy in Phase II and III clinical trials.

Company sponsor	Collaborators	Public/ private	IPO year/ founding year	Product	Cell type[a]	Cell source	Target[b]	Condition	Clinical trial phase in September 2016 and identifiers
Argos Therapeutics	Rockefeller University; Duke University	Public: NASDAQ: ARGS	2014	Rocapuldencel-T	DC	Auto	TERT, OFA, G250 + CD40L	Renal cell carcinoma	3 (started 2012, active) NCT01582672
Asterias Biotherapeutics	Cancer Research UK; Cell Therapy Catapult	Public: NASDAQ: AST	2016	GRNVAC1	DC	Auto	hTERT	Acute myeloid leukemia	2 (completed 2011) NCT00510133
Atara Biotherapeutics	Memorial Sloan Kettering; Amgen; Celgene	Public: NASDAQ: ATRA	2014	EBV-CTL	T	Allo	EBV	Non-Hodgkin's lymphoma	2 (started 2011, still recruiting) NCT01498484
Cell Medica	Baylor College of Medicine; University College London	Private	2006	CMD-003	T	Auto	EBV	Non-Hodgkin's lymphoma	2 (started 2014, recruiting) NCT01948180
ImmunoCellular Therapeutics	Cedars-Sinai Medical Center	Public: NASDAQ: IMUC	2006	ICT-107	DC	Auto	AIM-2, MAGE-1, TRP-2, gp100, HER-2, IL-13Ra2	Glioblastoma	3 (started 2015, recruiting) NCT02546102
Juno Therapeutics	Fred Hutchinson Cancer Research Center; St. Jude Children's Research Hospital; Memorial Sloan Kettering Cancer Center; Seattle Children's Research Institute	Public: NASDAQ: JUNO	2014	JCAR015	CAR-T	Auto	CD19	Acute lymphoblastic leukemia (ALL)	2 (started 2015, recruiting) NCT02535364
Kite Pharma	National Cancer Institute; UCLA David Geffen School of Medicine; Tel-Aviv Sourasky Medical Center; Leiden University Medical Center; Alpine Immune Science	Public: NASDAQ: KITE	2014	KTE-C19	CAR-T	Auto	CD19	Mantle cell lymphoma	2 (started 2015, recruiting) NCT02601313
Lion Biotechnologies	National Cancer Institute	Public: NASDAQ: LBIO	2010	Contego (LN-144)	TIL	Auto	TS	Melanoma	2 (started 2015, recruiting) NCT02360579
Northwest Biotherapeutics	King's College London	Public: NASDAQ: NWBO	2001	DCVax-L	DC	Auto	TS	Glioblastoma	3 (started 2006, ongoing) NCT00045968
TVAX Biomedical	National Cancer Institute; University of Kansas Medical Center	Private Spin off from University of Kansas	2004	TVI-Brain-01	CTL	Auto	TS	Grade IV glioma	2 (started 2011, recruitment status not verified) NCT01290692
Novartis Pharmaceuticals (Switzerland)	National Cancer Institute, University of Pennsylvania	Public: VTX: NOVN	1996	Tisagenlecleucel-T (CTL019, CART19)	CAR-T	Auto	CD19	ALL	2 (started 2015, recruiting) 2 (started 2014, recruiting) NCT02445248 NCT02435849 NCT02228096

[a]*Cell type: (+), multiple agents per product; DC, dendritic cell; CTL, cytotoxic T-cells (CD8+); CAR-T, chimeric antigen receptor T cell; T, T cell; TIL, tumor-infiltrating lymphocyte.*
[b]*Target: EBV, Epstein–Barr virus; TS, patient tumor sample; TCL, tumor cell line; CTA, cancer testis antigens.*

the research would be conducted under the guidance of a Joint Steering Committee, with representatives from each party to the respective agreement. In the agreement with University College London, either party could bring novel targets or platform technologies to the collaboration. Note that these agreements specifically stated their stage of research as preclinical and early clinical,

TABLE 2 | Nature of the relationship between companies and research institutions in the development of cancer immunotherapies.

Company sponsor[a]	Collaborators	Collaborative research relationship[a]	Technology licensing/service agreements[a]
Argos Therapeutics	Rockefeller University and Duke University		Cofounders of company were researchers the two universities who discovered role of dendritic cells in the immune system and developed a method to generate dendritic cells (Rockefeller) and developed a unique RNA-based dendritic cell technology (Duke)
Asterias Biotherapeutics	Cancer Research UK; Cell Therapy Catapult	2015: The collaboration with the Cell Therapy Catapult will trigger the initiation of an Asterias subsidiary in the UK to more effectively collaborate with Cancer Research UK and the Cell Therapy Catapult[a]	2014: Service agreement between Cancer Research Technology and Asterias for product manufacturing of cancer biotherapeutics 2015: Service contract to develop scaled production procedures with Cell Therapy Catapult. The program will utilize the know-how and resources assembled at the Cell Therapy Catapult along with expertise in pluripotent stem cells at Asterias to industrialize production of pluripotent stem cell-based therapeutics[a]
Atara Biotherapeutics	Memorial Sloan Kettering (MSK); Amgen; Celgene	2014: Parties agreed to collaborate on further research to develop additional cellular therapies, including against other antigens or CAR-T cells	2014: Worldwide exclusive option agreement from MSK for the development and commercialization of T-cells activated against: EBV, CMV, and WT1 in exchange for cash and Atara common. If Atara exercises its option, MSK will receive an upfront license payment and be eligible to receive additional payments based on achievement of development, regulatory and sales-related milestones, as well as royalty payments 2015: Atara exercised its exclusive option for the three programs to expand its pipeline after EBV target received Food and Drug Administration breakthrough-therapy designation
Adaptimmune Therapeutics	MD Anderson Cancer Center	2016: Announced a multiyear strategic alliance to expedite the development of novel adoptive T-cell therapies for multiple types of cancer, targeting	2016: The alliance pairs preclinical and clinical teams from the MD Anderson with Adaptimmune Therapeutics' Specific Peptide Enhanced Affinity Receptor (SPEAR®) T-cell technology platform that enables the identification of targets (e.g., MAGE-A10 and MAGE-A4) expressed on solid and hematological cancers and to develop affinity-enhanced TCRs with optimal potency and specificity against them
Cellectis	MD Anderson Cancer Center	2015: Cellectis and MD Anderson have entered into a research and development alliance that aims to develop novel allogeneic cellular immunotherapies	2015: The Alliance aims to build on MD Anderson's preclinical and clinical expertise in leukemia and myeloma coupled with Cellectis' first-in-class allogeneic CAR T-cell therapeutic approach and manufacturing capabilities
Cell Medica	Baylor College of Medicine (Dr. Leonid Metelitsa)	2016: Codevelopment partnership with Baylor College of Medicine (Baylor) to develop next-generation technologies (CAR, NKT, and TCR) for engineering immune cells with enhanced functions for the treatment of solid tumors. Within the codevelopment structure, Baylor will conduct the preclinical and Phase I clinical research under the guidance of the Joint Steering Committee. Cell Medica will work in parallel to support early product development and will use its substantial experience in manufacturing clinical-grade cell therapies to establish robust production processes suitable for industrial scale-up	2016: License and Option Agreement for two platform patents related to engineered NKT cells, three target cancer antigens for CAR-modified NKT cells, and a TCR technology. Cell Medica has paid an upfront fee for the exclusive licensing arrangements and will make additional payments to exercise its exclusive option to license future products
Cell Medica	University College London (Profs. Hans Stauss and Emma Morris)	2016: Research collaboration to utilize UCL's novel TCR technology to generate TCR products for cancer treatment. UCL will conduct the preclinical and early clinical research under the guidance of a Joint Steering Committee. As part of this agreement, both parties can bring targets or platform technologies to the collaboration, aiming to generate leading edge modified TCR products. Cell Medica will support product development with expertise in manufacturing clinical-grade cell therapies and establishing robust production processes suitable for industrial scale-up	2016: Exclusive license and option agreement with UCL Business for TCR platform patent and two target antigens. Cell Medica has paid an upfront fee and will make additional payments to exercise its exclusive option to license future products. UCL is eligible to receive further payments related to clinical, regulatory and sales milestones, as well as single digit royalties

(*Continued*)

TABLE 2 | Continued

Company sponsor[a]	Collaborators	Collaborative research relationship[a]	Technology licensing/service agreements[a]
ImmunoCellular Therapeutics	Cedars-Sinai Medical Center, Los Angeles		2015: Company was founded following the acquisition of cellular-based technology from Cedar Sinai ImmunoCellular Therapeutics that was established in 2006 with cellular-based technology licensed from the Cedar-Sinai Medical Center. Technology included dendritic cell-based vaccines for brain tumors and other cancers and neurodegenerative disorders. In 2012, the company also exclusively licensed related technologies for specific cancers from the University of Pennsylvania
Juno Therapeutics	St. Jude Children's Research Hospital		2013: Exclusive license for IP related to JCAR014 and JCAR017, genetically engineered autologous T lymphocytes for cancer. Royalty payments based on clinical and development milestones[a]
Juno Therapeutics	Seattle Children's Research Institute		2013: Exclusive license for IP related to the development and commercialization of lead cancer immunotherapy CAR-T products: JCAR014 and JCAR017[a]
Juno Therapeutics	Fred Hutchinson Cancer Research Center		2013: Exclusive license for IP related to JCAR014 and JCAR017, genetically engineered autologous T lymphocytes for cancer[a]
Kite Pharma	National Cancer Institute (Dr. Steven A. Rosenberg)	2012: CRADA for the development and commercialization of novel engineered peripheral blood autologous T cell therapeutics for the treatment of multiple cancer indications 2015: Amended CRADA for expanded tumor neo-antigens and CAR-T products for solid tumors[a]	
Kite Pharma	National Cancer Institute (Dr. James N. Kochenderfer)	2012: CRADA for engineered peripheral blood autologous T cell therapeutics (eACT) for hematological and solid cancers[a] 2013/5: Research collaboration for engineered peripheral blood autologous T cell therapeutics (eACT) for hematological and solid cancers[a] 2012/5: Research collaboration for engineered peripheral blood autologous T cell therapeutics (eACT) for hematological and solid cancers[a] 2016: CRADA for fully human anti-CD19 CAR product for B-cell lymphomas and leukemias	2012/3 and 2012/5: Options for exclusive license for engineered peripheral blood autologous T cell therapeutics (eACT) for hematological and solid cancers[a] 2014: Exclusive license for IP related to TCR-based products against HPV-16 E6 and E7 oncoproteins for cancers associated with HPV infection
Kite Pharma	National Cancer Institute	2014: CRADA for research and clinical development of TCR product candidates directed against HPV-16 E6 and E7 oncoproteins[a]	2014: Exclusive license for IP related to TCR-based products against HPV-16 E6 and E7 oncoproteins for cancers associated with HPV infection
Kite Pharma	University of California, Los Angeles (UCLA)		Exclusive, worldwide license agreement for technology to advance the development of off-the-shelf allogeneic T-cell therapies from renewable pluripotent stem cells
Kite Pharma	Tel-Aviv Sourasky Medical Centre (Prof. Zelig Eshhar: 2013 appointed to Scientific Advisory Board Kite Pharma)	2015: Research agreement for collaboration on peripheral autologous T-cell therapeutics on CAR or TCR platforms	
Kite Pharma	Leiden University Medical Centre (LUMC)	2016: Research agreement to identify and develop TCR product candidates targeting solid tumors associated with the HPV type 16 infection	Option to license multiple TCR gene sequences for the development and commercialization of product candidates
Genesis Biopharma (GB) founded in 2007 with SAB member Rosenberg merged with Lion Biotechnologies in 2013[a] (Dr. Steven A. Rosenberg)	National Cancer Institute	2011: CRADA with GB to develop TILs designed to destroy metastatic melanoma cells using a patient's tumor infiltrating lymphocytes[a] 2015: LB amended CRADA to include 4 new tumor indications for TIL therapy[a] 2016: extended CRADA for another 5-year term to 2021. Includes development of TIL therapy for treatment of metastatic melanoma, bladder, lung, breast, and HPV-associated cancers[a]	

(*Continued*)

TABLE 2 | Continued

Company sponsor[a]	Collaborators	Collaborative research relationship[a]	Technology licensing/service agreements[a]
Northwest Biotherapeutics (NW Bio)	Kings College, London Cognate BioServices Inc. is NW Bio's contract manufacturer for DCVax®	2001: Manufacturing and clinical trials partnership whereby trials for DCVAx for GBM conducted at King's College Hospital with expanded access program, and Cognate BioServices, Inc. provides technology transfer and training in proprietary DCVax production processes, adding manufacturing capacity and flexibility without need for further investment by NW Bio	
NW Bio	Fraunhofer Institute for Cell Therapy and Immunology	In addition to same terms as above. The partnership makes NW Bio eligible for certain grants through the German government, which, if approved, could amount to as much as 2–3 million Euro	
TVAX Biomedical	National Cancer Institute; University of Kansas Medical Center		Start-up company from the University of Kansas Medical Center formed to commercialize TVAX immunotherapy for personalized cancer treatment
Novartis Pharmaceuticals (Switzerland)	National Cancer Institute, University of Pennsylvania	2012: 5-year global collaboration to research, develop and commercialize targeted CAR immunotherapies for cancer treatment and to build a first-of-its-kind Center for Advanced Cellular Therapies on the Penn campus in Philadelphia at a cost of $20 Mill USD	2012: Penn grants Novartis an exclusive worldwide license to the technologies used in an ongoing trial of patients with CLL with CTL019 as well as future CAR-based therapies developed through the collaborations. Milestone and royalty payments to Penn
Bellicum Pharmaceuticals	LUMC		2015: Research agreement under which Bellicum will provide LUMC with funding for research to discover and validate high-affinity TCR product candidates targeting several cancer-associated antigens. Bellicum receives option to obtain an exclusive, worldwide license to practice and exploit the inventions
Bluebirdbio and Celgene	Center for Cell and Gene Therapy at Baylor College of Medicine, Texas Children's Hospital and The Methodist Hospital, Houston (Dr. Malcolm Brenner)	2013: bluebirdbio, Celgene, and Dr. Brenner will work collaboratively to advance and develop existing and new products and programs in the CAR T-cell field. Financial terms include upfront payment and up to $225 Mill USD per product in potential option fees and clinical and regulatory milestones	bluebird bio has the right to participate in the development and commercialization of any licensed products resulting from the collaboration through a 50/50 codevelopment and profit share in the US in exchange for a reduction of milestones

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CRADA, Collaborative Research and Development Agreement; DC, dendritic cell; EBV, Epstein–Barr virus; GBM, glioblastoma multiforme (brain cancer); HPV, human papillomavirus; IP, intellectual property; NKT, natural killer T cells; TCR, T cell receptor; TIL, tumor infiltrating lymphocyte; WT1, Wilms tumor 1.

[a]*Contract(s) available for review from Recap database.*

after which, Cell Medica had an exclusive license and option agreement to move forward with the codeveloped technologies. Indeed, the majority of the collaborative research agreements we identified additionally provided for options or licenses to the technologies developed.

One benefit of PPPs may be in the efficient transfer of tacit knowledge (know-how) through collaborative interactions. However, our review demonstrated that market transactions in cellular immunotherapy may also account for such knowledge transfer (**Table 2**). For example, the agreement between Asterias Biotherapeutics (Fremont, CA, USA) and Cancer Research UK provided for negotiations to adapt the technology transfer plan associated with a joint development project to use the company's expertise in cell-manufacturing and industrial scale-up to improve manufacturing/production of the research institute's cellular immunotherapy candidates. The company committed to the transfer of manufacturing/production know how, including in the form of training of research institute staff. Similarly, the agreement between Northwest Biotherapeutics (NW Bio) (Bethesda, MD, USA) and Kings College London provided for technology transfer and training *via* its manufacturing service provider, Cognate BioServices (Memphis, TN, USA).

Another stated benefit of the collaborative agreements (especially with UK/European research institutes) was access to public funding, for example access to German funding in the agreements between the Fraunhofer Institute for Cell Therapy and Immunology and NW Bio, and between Asterias Biotherapeutics and Cancer Research UK.

In the US, the preferred model for research agreements between the National Institutes of Health (NIH) and companies is the Collaborative Research and Development Agreement (CRADA). CRADAs provide the legal framework for investigators from these two sectors to conduct research in pursuit of common goals, while leveraging their own research resources: "The purpose of a CRADA is to make Government facilities, intellectual property, and expertise available for collaborative interactions to further the development of scientific and technological knowledge into

useful, marketable products" (32). All collaborators must make significant intellectual contributions to the research project or contribute materials and resources not available at the NIH. CRADAs are distinct from sponsored research. CRADAs are not a general funding mechanism, but are specific in their support of the collaborative project. Their terms ensure research freedom and may not unreasonably restrict or constrain the dissemination of research information. Nevertheless, they do support the protection of proprietary materials and intellectual property rights and may grant the industry partner an option to exclusively license intellectual property.

The seven CRADAs we identified also were bilateral in form (**Table 2**). However, they notably covered the identification of new cancer antigens for targeted cellular immunotherapy. This result is representative of a traditional role of research institutes in target identification for drug discovery. Target identification may be based on review of the peer-reviewed literature followed by early-phase trials to demonstrate safety and proof-of-concept in humans (33). Since most targets will prove neither safe nor efficacious, the public sector plays an important role in de-risking these for later stage development, including through research to enhance understanding of the molecular biology and possible mechanisms of action. Indeed, eight of the research agreements and six of the license agreements we identified explicitly mentioned new antigens/products as a goal.

Finally, we added Bellicum Pharmaceuticals and bluebirdbio to our list of companies because they are explicitly developing technologies that derive from university-based research to mitigate adverse events. These companies are developing molecular switch technologies for programmed cell death of CAR-T or similar cells or to mute CAR-T cell therapy associated adverse events, respectively. We also added Adaptimmune Therapeutics because it is an example of a strategic alliance for target identification. The company has entered into a strategic alliance that combines the companies T-cell technology platform that enables the identification of targets expressed in solid and hematological cancers with MD Anderson Cancer Center's expertise in preclinical and clinical research (**Table 2**). Finally, we added Cellectis, which has entered into a research and development alliance, also with MD Anderson Cancer Center, to use the company's CAR-T cell therapeutic approach and manufacturing technology and MD Anderson Cancer Center's research expertise to develop allogeneic CAR-T cells. The latter technology has the potential to simplify the business models for manufacture and delivery of CAR-T therapies, thereby reducing costs.

COULD PPPs ADVANCE CANCER CELLULAR IMMUNOTHERAPY?

Our review focused on collaborations for clinical development beyond Phase I, which may, in part explain, why we found limited evidence that the products in development resulted from precompetitive PPPs. The public–private relationships we identified were based on bilateral collaborative agreements between companies and research institutions for research based on a common goal. They rarely identified shared governance mechanisms, but rather relied on a hub and spoke model for research relationships. This focus on bilateral agreements and pure market transactions in the form of service contracts and technology licenses is representative of the commercialization focus of the field. The rapid advancement of cellular therapeutics comes with attendant hype with respect to potential efficacy and market size, as evidenced by media and other coverage and a rapid increase in the number of clinical trials and investment in private-sector companies (34).

The market enthusiasm for cellular therapeutics exists in spite of serious concerns about adverse events, business models, and the complexity of cells as therapies (34, 35). Indeed, the latest deaths in Juno Therapeutics' clinical trial have brought criticism that therapies are being tested in terminal cancer patients without adequate understanding of their biological mechanisms and potential for adverse events (19, 20). This lack of mechanistic understanding presages an expanded role for pre- and early-stage clinical research in the province of research institutions. It may be summed up by the saying "more haste, less speed," which is defined by the Cambridge English Dictionary as meaning that if you try to do things too quickly, it will take you longer in the end.

In addition to an enhanced role for academic-industry collaborations in overcoming adverse events, we identified one case—Asterias Biotherapeutics—that exemplified the role of PPPs in the development of production/manufacturing (**Table 2**). This implies a greater role for not only the clinical research community, but also for bioengineers that specialize in cell processing, manipulation, sorting, and expansion to clinical dosage levels (25, 36). The research agreements we identified were focused on clinical partnerships and therefore raise opportunities for an expanded set of interdisciplinary partners. At this juncture, there is an important role for industry expertise, as evidenced by some agreements for cGMP scale-up for clinical application.

Finally, there is a clear convergence of interests between research institutions and industry in the identification and preclinical characterization of novel cancer antigens, both to expand the types of tumors that may be targeted by cellular immunotherapies and reduce on-target, off-cancer adverse effects. As stated above, the de-risking of novel targets falls within the purview of research institutions and target identification has been the subject of successful PPPs. The best known of these is the Structural Genomics Consortium (SGC) that creates an open collaborative network of scientists across sectors to identify druggable protein targets and develop chemical probes for drug discovery (29, 37). The differences between the SGC and the research collaborations we identified are the large number of partners within the SGC and its commitment to open science (38). Its open science model and common governance structure stands in contrast to a proprietary model based on options to license codeveloped intellectual property. PPPs such as the SGC bring the added benefit of enabling systematic, high-throughput research that avoids duplication of effort and reduces costs.

While the SGC is built on an open science model, other PPPs enable commercialization based on formal intellectual property

rights within an open innovation platform. Such a model may be more palatable in the context of cellular immunotherapy, given the rapid advance to clinical translation in the field and the fact that the field is dominated by biotechnology rather than larger pharmaceutical companies. One example is the European Lead Factory, a pan-European drug discovery project of 30 partners established in 2013, which has received E196 million in funding from the Innovative Medicines Initiative and other sources (39). The European Lead Factory supports the generation of a compound library and an industry-standard screening center, providing free access to around 500,000 novel compounds. Any researcher from a European academic center or a small- and medium-sized enterprise (SME) can apply to screen a drug target of interest and to which the researcher/SME has intellectual property rights. If a screening application is accepted by the European Lead Factory, the parties enter into a standard contract that ensures confidentiality of the screening program and resulting data. Researchers/SMEs receiving the results are able to manage them as they see fit, but are given the option to partner with one of the participating pharmaceutical companies. Researchers are free to make results public, following the PPP's publication guidelines. However, if the screening program results in patent rights, there is an obligation to share benefits with the European Lead Factory. The researcher/SME can pay the PPP a fixed amount while filing the patent, a higher amount 2 years following filing, or a percentage of royalties generated by the patent.

Given that cellular immunotherapies are highly personalized, autologous therapies, it is expected that there might be an additional convergence in the discovery of cancer targets for cellular immunotherapies and precision medicine initiatives. The latter are building PPPs focused on the identification and development clinical protein-based biomarkers. For example, the Personalized Medicine Partnership for Cancer is a public–private consortium, in part funded by the Government of Québec, Canada (http://pmpc-org.com/en/). It partners a Quebec-based multidisciplinary network of clinicians, academic scientists and other members of the translational research community with private-sector partners: Caprion, a Montreal-based biotechnology company, Oncozyme Pharma (Montreal, QC, Canada), Pfizer Canada (Kirkland, QC, Canada), and Sanofi Canada (Laval, QC, Canada). Exemplifying the convergence between biomarker and cancer antigen discovery, in 2016, Caprion presented results on the use of its platform to identify neo-epitopes for cancer vaccines and adoptive T-cell therapies (40). Similarly, in 2012, the German Ministry for Education and Research granted 1.2 Mill Euro over 3 years to a public–private Consortium of Individualized Vaccines for Cancer (41).

In conclusion, a strategic case may be made to establish multi-party PPPs with governance structures to advance two areas that are crucial to the safe and effective translation of cellular immunotherapies for cancer: cancer antigen discovery and characterization and improved cell processing/manufacturing and related activities. This conclusion is supported in the Recommendations of the Blue Ribbon Panel on *Research Opportunities for the Vice President's Cancer "Moonshot,"* which may still proceed in some form under the new US administration, identified a strategic need for better coordination for data and tumor samples from cancer patients that may benefit from a series of PPPs (42). To advance immunotherapies, it recommended the integration of methods and sequencing data, especially with respect to proteins that are uniquely expressed in pediatric cancers, supported by the integration of PPPs "to develop the right immunotherapeutic tools (drugs) to exploit these targets" (42).

In the rush toward the competitive end of the translational continuum for cancer cellular immunotherapy and the attendant focus on commercialization of research, many gaps have appeared in our understanding of cellular biology, immunology, and bioengineering. In the US, the model of bilateral agreements between leading research institutions and the private sector may be inadequate to efficiently harness the interdisciplinary skills and knowledge of the public and private sectors to bring these promising therapies to the clinic for the benefit of cancer patients.

AUTHOR CONTRIBUTIONS

TB designed the review, drafted, edited, and submitted manuscript; KB, SL, J-SD, and EG contributed to the review, commented on draft manuscript, and approved submission.

ACKNOWLEDGMENTS

TB and EG's contributions were supported by a grant from the BioCanRx NCE: Clinical, Social and Economic Impact Program (PI: TB); a Stem Cell Network Strategic Core Grant: Public Policy & ELSI Research in the Stem Cell Field (PI: TB); and the PACEOMICS project (co-lead investigators: C. McCabe and TB) funded by Genome Canada, Genome Alberta, the Canadian Institutes for Health Research, and Alberta Innovates-Health Solutions. KB, SL, and J-SD's contributions were supported by Genome Canada's Personalized Cancer ImmunoTherapy Program (www.pcitp.org) and its partners Génome Québec and the Canadian Institutes for Health Research. The authors wish to thank Dr. Marc Lussier (PCITP) for helpful feedback and Zackariah Breckenridge, Katherine Fu, Jaclyn Hutchinson, and Yael Mansour for research assistance.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

MINI REVIEW
published: 07 December 2017
doi: 10.3389/fmed.2017.00218

Innovative Approaches to Increase Access to Medicines in Developing Countries

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Access to essential medicines is problematic for one third of all persons worldwide. The price of many medicines (i.e., drugs, vaccines, and diagnostics) is unaffordable to the majority of the population in need, especially in least-developed countries, but also increasingly in middle-income countries. Several innovative approaches, based on partnerships, intellectual property, and pricing, are used to stimulate innovation, promote healthcare delivery, and reduce global health disparities. No single approach suffices, and therefore stakeholders need to further engage in partnerships promoting knowledge and technology transfer in assuring essential medicines to be manufactured, authorized, and distributed in low- and middle-income countries (LMICs) in an effort of making them available at affordable and acceptable conditions.

Keywords: public–private partnership, product development partnership, intellectual property, pricing mechanism, access to healthcare

OPEN ACCESS

Edited by:
Sandor Kerpel-Fronius, Semmelweis University, Hungary

Reviewed by:
Sarah Galbraith-Emami, World Health Organization, United States
M. Rashad Massoud, University Research Co, United States

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *06 October 2017*
Accepted: *20 November 2017*
Published: *07 December 2017*

Citation:
Stevens H and Huys I (2017) Innovative Approaches to Increase Access to Medicines in Developing Countries. Front. Med. 4:218. doi: 10.3389/fmed.2017.00218

INTRODUCTION

Today's healthcare systems, both in developed and developing countries, face serious challenges. And time is pressing; in the years to come, we will face a dramatic shift in health problems resulting from epidemiological transition (1, 2). The poorest countries in developing regions carry the highest burden of disease: communicable diseases (CDs), non-communicable diseases (NCDs) (3), and the risk of new diseases related to changes in the social and physical environment, the socio-behavioral illness (4).

Access to essential medicines is problematic for one third of all persons worldwide (5). The price of many medicines (i.e., drugs, vaccines, and diagnostics) is unaffordable to the population in need,

Abbreviations: APOC, African Programme for Onchocerciasis Control; BMGF, Bill & Melinda Gates Foundation; CD, communicable diseases; DNDi, drugs for neglected diseases initiative; EC, European Commission; EFPIA, European Federation of Pharmaceutical Industries and Associations; ELF, European Lead Factory; GAVI, global alliance for vaccines and immunizations; GCP, good clinical practice; GSK, GlaxoSmithKline; IMI, innovative medicines initiative; IP, intellectual property; IGO, international governmental organizations; IPRs, IP rights; IPTK bank, intellectual property, technology and know-how bank; LMIC, low- and middle-income countries; MA, market authorization; mHealth, mobile health application; MMV, medicines for malaria venture; MPP, medicines patent pool; NCD, non-communicable diseases; NGO, non-governmental organizations; NTD, neglected tropical diseases; OWH, Institute for One World Health; PDP, product development partnership; PPP, public–private partnership; R&D, research and development; TPP, Trans-Pacific Partnership; TRIPS, agreement on trade-related aspects of intellectual property rights; TTIP, Transatlantic Trade and Investment Partnership; UN, United Nations; WHO, World Health Organization; WIPO, World Intellectual Property Organization; WTO, World Trade Organization.

especially in the least-developed countries, but also increasingly in middle-income countries. The latter category comprises 105 countries, accounting for 70% of the world population, 75% of the poor, and a majority of the global disease burden (6, 7). Prices may decrease when multiple companies need to share market, in which context overcoming intellectual property (IP) obstacles is essential (8).

Stakeholders bundle forces in assuring essential medicines are manufactured, authorized, and distributed in low- and middle-income countries (LMICs) at affordable conditions. But challenges remain, i.e., guaranteeing high distribution coverage, ensuring affordability, and adoption of essential medicines, both at provider level and end-user level (9). Developing countries lack infrastructure needed to increase access to medicines. Most diagnostics are not designed for implementation in non-optimal laboratory conditions present in developing countries, with lack of air conditioning, stable electrical power, or refrigerators to store samples and chemicals (10, 11). Through microfluidic systems, high-tech technologies could find their way to the developing world laboratories. But the need for faster and more accurate diagnostics remains (10).

This article provides an overview of innovative approaches by stakeholders to address health challenges in developing countries, shedding light on business models for healthcare delivery. We look at the role of partnerships, IP, and specific pricing models for promoting innovation by providing incentives to invest in (collaborative) research and development (R&D), as well as to increase access to medicines.

METHOD

A comprehensive review of literature was performed. Relevant articles were identified by searching databases, such as PubMed, Google Scholar, and documents like Official Journal of the European Union (EUR-Lex) up to March 2016, with an update in September 2017. Websites of relevant organizations, including public-private partnerships (PPPs) such as the innovative medicines initiative (IMI) and the medicines for malaria venture (MMV), pharmaceutical organizations' websites, such as GlaxoSmithKline (GSK) and European Federation of Pharmaceutical Industries and Associations (EFPIA), and non-governmental organizations' websites and private foundations' websites, such as World Health Organization (WHO), World Intellectual Property Organization (WIPO), World Trade Organization (WTO), and Bill & Melinda Gates Foundation (BMGF), were explored.

PARTNERSHIPS AS A MODEL TO FACILITATE ACCESS TO MEDICINES

Pharmaceutical companies no longer stick to traditional drug development models to tackle the enormous health challenges ahead of us. Being the key player in the drug development process, the pharmaceutical industry is partially responsible for finding solutions. During the last decades, the majority of the 20 largest research-based pharmaceutical companies have increased efforts to provide access to essential medicines in developing countries (12), e.g., by supporting or participating in product development partnerships (PDPs) (9).

Historically, PDPs directed toward neglected tropical diseases (NTDs) were the first collaborative efforts to tackle inequities in the health sector. In 1987, Merck & Co. donated ivermectin (Mectizan®) to treat onchocerciasis or river blindness, first distributed by the African Programme for Onchocerciasis Control (APOC), a partnership between the World Bank, the WHO, and non-governmental organizations (NGOs) in West-Africa, and expanded later to Africa and America (13, 14).

Product development partnerships, such as the MMV, have served as a source of inspiration for the pharmaceutical industry to apply the PPP model to disease areas other than NTDs, such as NCDs. The IMI, driven by EFPIA and supported by the European Commission (EC), has been a flagship early-phase research PPP (15). Initially, IMI focused on NCDs, but as the PPP matures, it aims at tackling NTDs (14). The European Lead Factory (ELF), for example, explicitly waives certain fees related to non-profit drug discovery programs for NTDs (16).

Public–private partnerships, and PDPs in particular, are vehicles suitable for delivering healthcare and strengthening healthcare systems. Such multi-stakeholder efforts are able to ensure product registration, increase local production and distribution capacity, and ensure governance for global health, e.g., adoption of new health technologies in national treatment policies in disease-endemic countries. In this way, PDPs such as the MMV, Drugs for Neglected Diseases Initiative (DNDi), and Institute for One World Health (OWH), advance public health (17, 18). PDPs strengthen research capacity in LMICs by building infrastructures at trial sites, providing equipment and setting up training in good clinical practice (GCP) and dedicated disease-specific research platforms in endemic countries. To achieve its objectives, PDPs partner with different stakeholders, such as high-income country pharmaceutical companies, local manufacturers, national disease-specific control programs and platforms, national governments and philanthropic organizations (9).

Public–private partnerships leverage knowledge and technology transfer of new medical technologies to both developed and developing countries. For example, the mobile health application (mHealth) Text4Baby, providing free health information to expectant mothers by means of text messages, is a PPP that, through a network of hundreds of partners, scales up its services (19). Partnerships could improve the scale of knowledge and technology transfer capacity of African Institutions that prove to be leaders in their area of focus (20). PPPs can improve both health products and services delivery by scaling their programs to a national level, involving health workers and communities (21). mHealth strategies are linked to improved data collection and reporting, planning and decision-support, training, and overall improved communication (22).

Moreover, knowledge and technology transfer should happen in both directions. Completely rethinking business models or applying reverse innovation requires adequate examination of models applied in developing countries in the context of developed countries. The technology applied in low-resource programs can stimulate innovation in developed countries, for example, by using text messages and interactive voice recognition systems

instead of smartphone applications or by targeting the markets of the underserved such as elderly or immigrant communities (19). In this way, an innovation continuum can exist.

IP AS A TOOL TO FACILITATE ACCESS TO MEDICINES

A robust IP framework is perceived by most right holders as essential to guarantee contribution to the state of the art while maintaining control over how creations, protected by IP rights (IPRs), are used. As such, IPRs have a facilitating role for improved healthcare in developing countries and should not be perceived as a hindrance. In pharma, patents are considered as the most important IP protection tools, providing the owner exclusive rights to prevent use of the patented product or process without the consent of the owner for 20 years in a particular territory. Data protection and market exclusivity rights are IPRs granted to the market authorization (MA) holder for a period of 8, 10 (or 11) years, respectively, after MA. Generic or biosimilar products are not allowed to enter the market as long as such IPRs are in force.

In many cases, at the time of product launch on the market, at least half of the patent term may have expired. Accordingly, industry claims to prolong the period of protection for their medical inventions (23). In theory, an increase of the period for patent and data or market exclusivity can increase profits, which may lead to innovation if appropriately re-invested in R&D. However, there is no any evidence that innovation thrives when extending exclusivity terms. In addition, generics are relied upon by most developing countries. Potential consequences of implementing prolonged exclusivity periods in developing countries could be enormous. Some propose that revenues from extended patent terms could be considered as a source of funding for drug donations to the least-developed countries (24).

One major issue is to guarantee that patent protection for pharmaceutical products creates incentives for R&D and does not hinder patient access in developing countries. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of the WTO, implemented in 2005, created on the one hand incentives for R&D by introducing minimum standards for protection of IP. On the other hand, it introduces some flexibility such as compulsory licenses whereby access to IP protected technologies is granted *via* licenses imposed by governments, based on specific criteria, for instance, public health reasons. The members at the Doha Ministerial Conference in November 2001 agreed upon exemptions to patent protection in least-developed countries till 2016, with a potential extension to 2033 (25, 26).

With respect to compulsory licensing, some LMICs, not able to produce new drugs, could invoke such licensing and hence rely on capabilities of a developed country. Some state that compulsory licensing may cause consequences on other markets, as lower pricing of a compulsory licensed drug may trigger parallel export of the cheaper drug into more expensive markets.

The issuing of compulsory licenses gives a certain level of autonomy to Southern countries, but implies a certain legal, administrative, and reputational cost. In addition, some firms believe that compulsory licensing diminishes their incentives for innovation (11). Nonetheless, the overall impact of compulsory licensing seems beneficial (27). The TRIPS Agreement created an environment legitimizing innovators and generic companies, stimulating cross-border alliances, increasing numbers of R&D alliances, patent filings, and R&D investment. The main issue remains the impact of TRIPS on drug pricing and on biopharmaceutical companies' willingness to invest in health problems at the local level (28).

Measures included in trade and investment agreements, e.g., the much debated Transatlantic Trade and Investment Partnership (TTIP) or the Trans-Pacific Partnership (TPP) agreements, impose far-reaching IP standards favoring the monopoly of large drug producers: extending patent terms, lowering patentability criteria, data/market exclusivity preventing generic and biosimilar drugs to enter the market, data protection obligations for biologics enabling high prices of e.g., cancer biologic drugs to remain longer on the market and routes to block generic drugs from entering the country. These provisions, called the TRIPS-Plus provisions, can, when translated effectively into domestic law, disproportionately affect developing countries by leading to high prices for essential medicines. To this end, policy makers have a crucial role in negotiation of policies and regulations (29, 30).

Other IP mechanisms relevant in the access debate are patent pools. The medicines patent pool (MPP) aims to enable affordable production of HIV drugs still under patent protection by obtaining voluntary licenses from patent holders and making these licenses available to generic companies in LMICs. Royalties will be paid to patent holders, and licenses to generic companies will be offered only in LMICs (8).

Another initiative in this line is an intellectual property, technology and know-how (IPTK) bank, a single platform licensed as a package with associated training modules. The IPTK bank could offer assistance in navigating vaccine registration with national regulatory authorities. The licensing approach covers patented technology to be disseminated to multiple developing-countries vaccine makers and royalties paid to the patent holder. IPTK banks would require an initial period of funding until provision of affordable vaccines would render them to be self-sustainable (8). Currently, the main source of external funding for vaccines in low-income countries is the global alliance for vaccines and immunizations (GAVI) (11). The subsidies provided by GAVI to finance new vaccines in a response to the 2012 World Health Assembly Global Vaccine Action Plan are intended to be limited to a 5-year period, with the expectation that, over that time, prices will fall, allowing donors and national governments to continue vaccine financing. Unfortunately, to date, this expectation has not been realized. There remains a need to establish mechanisms ensuring sustainable vaccine pricing once the initial period of support has ended (8).

The WHO report "Research and Development to Meet Health Needs in Developing Countries" considered several policies/models for access to medicines. The first model is a global framework on R&D, supporting priority medical R&D aimed at addressing neglected diseases. This model is not meant to replace the current IPR system, but is an additional instrument to meet the R&D needs of developing countries (31). The second model is a proposal that deals with open approaches to R&D, such as open innovation, open source, open access publishing, precompetitive R&D platforms, and equitable licensing (32).

In both proposed models, there is a need for flexible application of IPRs to reduce IP hurdles for innovation, which may reduce duplication in research and contribute to capacity-building, knowledge, and technology transfer (32). The WHO also covers the ethical dimension and the myriad of economic, commercial, technological, and regulatory factors related to providing healthcare, particularly to the poor (33).

Several types of IP strategies can be adopted in these two models, depending on the type of partnership. In partnerships focused on CDs, a partnership-focused strategy is adopted whereby IP is preserved for project partners. In partnerships focused on developing diagnostic devices or on NCDs, often an open collaboration strategy is used, whereby IP is shared with a broad research community. There might also be a hybrid strategy, wherein the IP framework applied is negotiated on a case-by-case basis. In any case, much ambiguity remains about the type of IP strategy most suitable, calling for transparency and explicitness in IP policies (34) (**Figure 1**). Ideally, public and private partners complement each other in many ways. Both the public partner, such as NGOs or international governmental organizations (IGOs), and industry deploy IP, trade, and rules of competition. However, there is a difference in their market, mission, and strategy. The public partner serves as balancing force for the competitive advantages of industry (35).

PRICING MODELS TO FACILITATE ACCESS TO MEDICINES

Increased access to essential medicines can be established by prolonging patent terms whereby the revenues are reinvested for drug donations (24). However, the donor model (e.g., the Mectizan Donation Program) has also encountered criticism. Long-term drug donations are unsustainable due to a lack of infrastructure for technical, economic, and political support (35).

Especially the production of low-cost medicines and distribution thereof is challenging. Specific financing mechanisms stimulate price reductions of essential medicines leading to rapid uptake. The Global Fund's Affordable Medicines Facility for Malaria, for example, is set up to provide significant subsidies to the private sector, as a large portion of people access medicines primarily through private markets (9). Furthermore, generic competitors and trade regulations are key to driving prices down, requiring involvement of multi-sectoral global governance agencies, such as the WTO.

Differential or tiered pricing means selling essential medicines in LMICs at prices below those in industrialized countries (36). In order to avoid parallel trade (export) of low-priced drugs to high-income countries, contracts including confidential rebates are used. This concept gained attention in the profit as well as non-profit sector since setting a product price to consumers' willingness or ability to pay seems to be a profit maximizing strategy. At the same time, tiered pricing can increase consumers' welfare by creating access to medicines. Yet tiered pricing does not guarantee a price that is equitable or affordable (37). In addition, generic prices are generally lower than tiered prices. Furthermore, tiered prices will unlikely be reduced in case of absence of competition, on the contrary, tiered prices may increase when competition does arise.

Off-patent competition results in prices below those in a tiered pricing setting. But tiered pricing may lead to anticompetitive effects when a very low tiered price discourages market entry by potential competitors. It is in situations of low demand and

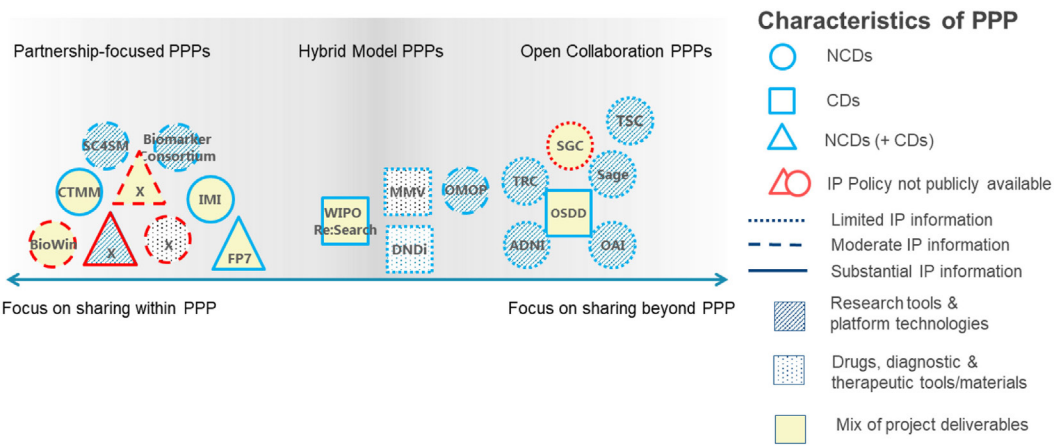

FIGURE 1 | Link between intellectual property (IP) frameworks as defined in the IP policies of the public–private partnership (PPPs) analyzed, the information provided in the IP policies, project focus, and project deliverables. PPPs are categorized by research focus [non-communicable diseases (NCDs, circles), communicable diseases (CDs, squares), or a mix (triangles)]; availability of IP information [unavailable (gray outlines) and limited, partial, or substantial availability (black outlines)]; and deliverables [research tools and platform technologies (striped shading), drugs, diagnostic, and therapeutic tools or materials (dotted shading) or a mix (no shading)]. ADNI, Alzheimer's Disease Neuroimaging Initiative; BioWin, Biotechnologies Wallonie Innovation; CTMM, Center for Translational Molecular Medicine; DNDi, Drugs for Neglected Diseases Initiative; FP7, European Framework Programmes; IMI, innovative medicines initiative; MMV, medicines for malaria venture; ND, not disclosed by PPP request; OAI, Osteoarthritis Initiative; OMOP, Observational Medical Outcomes Partnership; OSDD, Open Source Drug Discovery; SC4SM, Stem Cells for Safer Medicines; TSC, the SNP Consortium; TRC, the RNAi Consortium; SGC, Structural Genomics Consortium. [Figure adapted from Stevens et al. (34) with permission from the authors.]

production capacity that tiered pricing by a single producer in developing countries may result in the widest access. Some difficulties remain with tiered pricing: what is the "lowest price possible," what is a "fair price," and how to negotiate if own production capacity is not favorable. In this sense, market segmentation needs to be considered both across and even within national markets (38).

However, income-related price discrimination and competition alone may not lead to affordable prices in low-income countries (39). Because of skewed income distributions in LMICs, drug prices with respect to mean per capita income are the highest in the poorest countries. Generic prices are below originator prices but because of lack of regulatory requirements for generic quality in LMIC, the latter is heterogeneous and uncertain to consumers. The optimal pricing strategy of a manufacturer is based on the type of product and on consumer' perceptions and willingness to pay for that product with a particular quality. Procurement procedures rely on minimum quality standards. They also introduce originator and generic prices compared with the counterpart retail pharmacy prices and may reduce uncertainty related to quality, hence focusing competition on price (39).

CONCLUSION

Several mechanisms, based on partnerships, IP, and pricing, are used to promote healthcare delivery and reduction of global health disparities. The mechanisms applied involve mostly existing drugs and devices that have lost their economic value in developed countries. Besides investigating how access mechanisms currently used could be enhanced, there is obviously a need to increase research for NTDs. Supported by strong leadership and actions at national or regional level, the United Nations (UN) commitments on the "25 by 25 goal," i.e., a 25% reduction in premature NCDs mortality by 2025, can be achieved (40). Organizations such as WHO, WIPO, and WTO have a leading role in designing policies applicable to the various stakeholders. A critical mass of strong leaders in science, policy making, financing, and education are pivotal in building an innovation continuum.

AUTHOR CONTRIBUTIONS

HS and IH contributed to the design of the manuscript, performed the research, and wrote the manuscript.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Fonds Baillet Latour for supporting HS with the Chair in Translational Medicine, the Brocher Foundation for hosting HS as a visiting researcher (April 2017). The authors also wish to thank K Debackere, M Goldman, and the students from course Evidence in Clinical Practice [(E0C30A), Master in Medicine, KU Leuven] for their assistance with the literature review and data collection.

FUNDING

HS holds the Chair in Translational Medicine, funded by Fonds Baillet Latour.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

REVIEW
published: 29 May 2017
doi: 10.3389/fmed.2017.00056

Adaptation through Collaboration: Developing Novel Platforms to Advance the Delivery of Advanced Therapies to Patients

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For the nascent field of advanced therapies, collaboration will be a game-changer, turning scientific progress that was once unimaginable into transformative medical practice. Despite promise for lifelong management and even cure of disease, skepticism remains about the feasibility of their delivery to patients, fueling investment risks. With the potential for long-term effectiveness in need of frequent reassessment, current approaches to predict real-life drug performance bear little relevance, necessitating novel and iterative schemes to monitoring the benefit–risk profiles throughout the life span of advanced therapies. This work explains that reinventing an adoption route for Advanced Therapy Medicinal Products is as much about the scientific and clinical components, as it is about the organizational structures, requiring an unprecedented level of interactions between stakeholders not traditionally connected; from developers and regulators, to payers, patients, and funders. By reflecting on the successes and lessons learned from the growing space of global precompetitive consortia and public–private partnerships, as well as a number of emerging accelerated development pathways, this work aims to inform the foundations for a future roadmap that can smooth the path to approval, reimbursement, and access, while delivering value to all stakeholders. Echoing the growing demands to bring these transformative products to patients, it provides critical insights to enhance our capacity in three fundamental domains: deploying the operational flexibilities offered by the growing space of collaborations, utilizing emerging flexible and accelerated pathways to tackle challenges in quantifying long-term effectiveness, and building the necessary digital and clinical infrastructure for knowledge development.

Keywords: gene therapy, cell therapy, ATMP, open innovation, precompetitive collaboration, accelerated pathways

Advanced Therapy Medicinal Products (ATMPs), including cell/gene therapies and tissue engineered products (1), offer unprecedented promise for long-term management and even cure of disease, especially in areas of high-unmet medical need, from terminal forms of cancer to vision loss.

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *22 January 2017*
Accepted: *27 April 2017*
Published: *29 May 2017*

Citation:
Papadaki M (2017) Adaptation through Collaboration: Developing Novel Platforms to Advance the Delivery of Advanced Therapies to Patients. Front. Med. 4:56. doi: 10.3389/fmed.2017.00056

Abbreviations: ATMP, Advanced Therapy Medicinal Products; IMI, Innovative Medicines Initiative; C-Path, Critical Path Institute; PPPs, public–private partnerships; CAMD, Coalition Against Major Diseases; CDISC, Clinical Data Interchange Standards consortium; CFAST, Coalition For Accelerating Standards and Therapies; ADNI, AD Neuroimaging Initiative; BC, Biomarkers Consortium; FNIH, Foundation for the National Institutes of Health; AMP, Accelerating Medicines Partnership; CMOs, Contract Manufacturing Organizations; ADA-SCID, Adenosine Deaminase Severe Combined Immunodeficiency; PSTC, Predictive Safety and Toxicology Consortium; HipSCi, Human-Induced Pluripotent Stem Cells Initiative; EMA, European Medicines Agency; HTA, Health Technology Assessment.

The socioeconomic and patient benefits of building an ATMP enterprise could be immense, reflected by the recent volume of investment, and mushrooming number of clinical trials in gene therapies for rare diseases and immuno-oncology. However, skepticism remains about the feasibility of their commercialization and delivery to patients, especially as the durability of their effect can only be determined in the long haul (2).

Notwithstanding a number of technical and development challenges, generating sufficient clinical and cost-effectiveness data, achieving reimbursement, and embedding them to existing medical practice remain opaque. In addition, ATMPs are tested by the broader inefficiencies of the current system, which remains expensive and slow in getting affordable new therapies to the right patients at the right time, fueling the need for a paradigm shift.

The common denominator for traditional drugs and ATMPs involves achieving a trade-off between the need for timely access and robust evidence of clinical and economic outcomes. In contrast to the current binary, pre/post-market model of clinical and commercial assessment, removing the uncertainty around the real-world value and effectiveness of new approaches, for many, necessitates an iterative approach to monitoring a product's benefit–risk profile throughout its life span. Global policy makers have been launching a number of coordinated strategies to drug development, licensing, and reimbursement, exemplified by UK's Accelerated Access Review, the EU Adaptive Pathways pilot, and Japan's Sakigake legislation.

Although there are no proven methods or established frameworks to reinvent a pathway for adoption of ATMPs, this level of system change will rest on new avenues, founded on continuous dialog and interactions between stakeholders not traditionally connected, from developers and regulators, to payers, patients, and funders. The growing space of global precompetitive consortia and public–private partnerships (PPPs) can illuminate some of the critical enablers needed for this level of engagement and coordination.

By deconstructing challenges that exceed the capacity of single organizations, national and global consortia linking government, academia, and industry, such as the EU Innovative Medicines Initiative (IMI) or the FDA Critical Path Institute (C-Path), have covered significant ground during a remarkably small window of time toward the development of new knowledge, translational tools, and infrastructure that advance the biomedical space. However, as we move toward higher complexity measures of progress, like the development and delivery of transformative therapies, these interactions have to transcend the scientific space, to devise new organizational and policy frameworks, build the infrastructure needed by health systems, and ultimately reduce the financial uncertainty in this space.

Against a backdrop of growing demands to drive meaningful patient outcomes from ATMPs, we have to become better in three critical areas: deploy the operational flexibilities offered by the variety of collaborations, upholding novel flexible policies and pathways to address the inherent gaps in quantifying long-term effectiveness, and building infrastructure and test-bed environments for knowledge development.

By reflecting on the successes and lessons learned from collaborations over the past two decades, this work aims to inform the foundations for a future roadmap that ensures ATMPs and important new treatments can reach patients, while delivering value to all stakeholders. This paper refers to various global examples of vehicles for cross-stakeholder dialog, as well as emerging accelerated development pathways, all of which will be paramount to maintain momentum and smooth the path to approval, reimbursement, and access, for ATMPs that are following on behind.

SETTING SAIL: ENTERING THE ERA OF ATMPs

After 30 suspenseful years, the field of ATMPs is finally coming of age, with clinical successes already emerging across diverse areas of unmet need, from oncology and cardiology, to vision repair and skin/tissue regeneration. In 2016 the first gene therapy in the EU was approved, GSK's Strimvelis for Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID), and is presently only reimbursed in Italy, whereas ChondroCelect, the first EU approved cell therapy, is still only covered in Spain, Belgium and the Netherlands. Although over 650 clinical trials have been conducted to date, only 8 ATMPs are granted a marketing authorization in the EU, with 2 withdrawn from commercial activities due to lack of uptake (3).

Upholding and replicating the successful stride of an effective treatment for a clinically challenging condition, like Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID), would provide a much-needed technical, clinical, and commercial proof for the larger scale adoption of ATMPs, just like rituximab became the undercurrent for the advent of monoclonals. However, with the last three decades focused primarily on advancing our scientific understanding of ATMPs, a number of unique challenges remain as clinical knowledge, policies, skills, and services are still co-evolving with the technology in real time.

UNCHARTED WATERS: CANVASSING UNIQUE AND PERSISTING BOTTLENECKS

Production of ATMPs involves the manipulation of living, cell-based materials (and viral vectors for gene therapies), all thus underpinned by distinctive variability. The sensitivity of these materials requires novel processes, complex development systems, and sophisticated quality control streams, calling for skills and infrastructure unlike anything used for traditional pharmaceuticals. Although vector gene therapies and products from standardized tissues are less time sensitive and can leverage more traditional supply models, for autologous products or where product shelf-life is limited, there is need for specialized centers for access and treatment, which can accommodate "bedside" closed systems and decentralized supply chains (4).

It is key to understand that in this space, the "process *is* the product", as any change in manufacturing could affect a treatment's efficacy and safety. This is a paradigm change in regulation, posing new riddles around Good Manufacturing Practice (GMP), requiring new standards for quality, potency and safety, as well

as process design and assurance strategies (5). With individual batches essentially corresponding to a different product, ATMPs also face unique challenges in product standardization, including inspection and release testing (6).

These challenges are ever more important for production scaling-up from early phase 1 and 2 trials, currently done within small academic or hospital GMP facilities, to Phase 3 trials and commercial supply, to ensure product equivalence and cost control (7). Clinical development of ATMPs is also met with an inefficient assessment framework, failing to provide clear go/no-go decision criteria (8). ATMP trials are highly type and disease dependent, tailored to much smaller patient populations. Traditional algorithms are not adequate to capture the potential lifetime effects, calling for new endpoints and designs (i.e., for single-arm trials), which becomes more perplexing under the light of evolving knowledge around ATMPs (9).

With a number of scientific challenges yet to be resolved, the costs of ATMPs remain high. Moreover, the promise for lifelong effectiveness raises regulation and reimbursement challenges around the limited availability of evidence at the point of approval and pricing negotiations (6), as well as budget impact and affordability issues that shift influence from Health Technology Assessment (HTAs) to payers. Uncertainties around data availability and maturity question how ATMPs can meet cost-effectiveness thresholds in the existing HTA methodologies, which could disproportionally disadvantage them (10). Outstanding issues also include the discrepancy between evidence for regulatory approval and for HTAs, as well as harmonization of HTA requirements and methodologies across Europe and globally.

Despite the ongoing progress, ATMP development timelines are still long and winding and in addition to dealing with the regulatory complexity, developers, mostly SMEs, face huge risks in accessing capital, while meeting HTA requirements and negotiating coverage. Maintaining current momentum and investment in this nascent space will require funders to have increased clarity on a product's journey to market and the views of regulators and payers (11). With established supply chains and assessment paths limited to traditional small molecules and large biologics, ATMP's call for a reinvention of the entire pathway from production, to assessment and adoption (12).

CHANGING COURSE: REINVENTING THE WAY WE DEVELOP TREATMENTS

Because of their promise for sustained effect and an individual–patient focus, ATMP discovery, development, manufacturing, and licensing/coverage assessment steps become less linear and predictive than traditional drug discovery and more co-located than established supply chains. Given the patient-targeting nature of the majority of ATMPs, manufacturing and quality aspects are also embedded from discovery through to development, while clinical assessment and adoption are seamlessly linked. Securing patients' access to these therapies, thus, requires a more coordinated approach across product development and enhanced capacity for stakeholder collaboration (13).

Although ATMPs lend themselves naturally to a greater level of coordination, not all of these challenges are uncommon to other breakthrough areas (14). Despite the high investment in R&D during the past decades, or perhaps as a direct consequence, a striking gap remains in innovation reaching patients, as breakthrough science is outpacing the current assessment system in a number of ways (15). Growing patient demand for timely access to better treatments, new science leading to segregation of disease subtypes, and patient-tailored, precision medicines, as well as growing pressures for measures of budget impact and the value of new products, are common drivers of change that force new business incentives to keep innovation alive and sustainable. Simply securing regulatory approval for a new product is no longer an adequate marker of success. The yardsticks have moved, requiring novels ways to deliver new, better, affordable therapeutics to the right patients faster and do this reliably and sustainably.

The biggest challenge involves getting earlier/timely patient access, while equipping decision makers with adequate information on the benefit/risk thresholds. Without any prior clinical experience for ATMPs, where stability of the effect needs frequent reassessment, current systems focusing on upfront evidence to predict real-life drug performance, bear little relevance. Against this backdrop, acceptance of higher uncertainty can only be balanced by the real-time monitoring and continuous generation of development and treatment outcomes evidence, throughout the lifecycle of ATMPs. Arguably, the only sustainable access route to market and the patients involves re-engineering a transparent and coordinated approach to clinical assessment, licensing, and coverage, including monitoring of clinical use.

It is clear that the time has come to improve our innovation strategy. Progressing the ATMP space beyond early examples of clinical efficacy and toward adoption on a larger scale will require a set of important adaptations, predicated on early and continued efforts to remove barriers to collaboration. Practical solutions have to be developed within three key domains:

1. Maximizing use of emerging flexible tools on licensing and reimbursement.
2. Deploy the flexibilities offered by collaborations and develop new platforms for convergence.
3. Establish infrastructure and "test-bed" environments for capacity and knowledge building.

Increasing Systemic Flexibilities for ATMP Adoption

Regulators were the first to step up to the challenge of balancing access under limited evidence by devising new ways to manage this uncertainty. In recent years, a number of flexible licensing pathways were introduced across the world to allow for accelerated access, provided that patient benefits outweigh the need for additional data (16). Notable examples include the MHRA Early Access to Medicines Scheme and the NHS Accelerated Access Review in the UK, the Adaptive Pathways pilot and the 2016 PRIME scheme in the EU, and the FDA Breakthrough Treatment Designation in the US (17) (**Table 1**).

TABLE 1 | Key examples of the existing and emerging pathways of relevance to Advanced Therapy Medicinal Products (ATMPs), covering regulatory, reimbursement, and access and new stakeholder dialog platforms in EU, US, and the UK as example of a national jurisdiction.

	Existing tools	New and emerging schemes	Platforms to facilitate adoption
EU	• ATMP regulation • Emergency use, exceptional circumstances • Orphan designation • ATMP hospital exception • Scientific Advice, Protocol Assistance • Compassionate use for unlicensed drugs • Conditional Marketing Approval	• Accelerated assessment • Adaptive pathways pilot (lifecycle approach) • EU PRIME scheme on priority medicines **Reimbursement:** • Managed entry/patient access agreements	• European Medicines Agency (EMA) Innovation Taskforce: for academics and SMEs • STAMP from EC Expert Group • Parallel reviews: – EMA/HTA scientific advice – EMA/FDA review • Registries and other PHV tools; EMA Registries pilot
US	• Fast Track • Accelerated approval (with surrogates) • Priority review **Reimbursement** • Coverage with evidence development	• SMU; Special Medical Use for disease subsets • Breakthrough Therapy designation • Regenerative Medicine Advanced Therapy designation (RMAT) **Reimbursement** • Managed access for private payers	• FDA Critical Path Innovation Meeting • Parallel Scientific advice between EMA/FDA
UK	• Early Access to Medicines Scheme (EAMS) • UK Specials • NICE Scientific Advice mechanism	• Accelerated Access Review (AAR) • NHS Commissioning through evaluation • NHS Executive Specialized Commissioning schemes	MHRA Innovation Office Regenerative Medicine one stop shop[a] Innovation Partnership: NHS, MHRA, NICE, NIHR NICE Office for Market Access NICE "mock" technology appraisal on CD-19 CAR-T

The list is not exhaustive. ATMP regulation: (EC) No. 1394/2007.

[a]The UK's One Stop Shop: includes MHRA, the Human Tissue Authority, The Human Fertilisation and Embryology Authority (HFEA), and Health Research Authority (HRA). For a detailed analysis or comparison of these schemes, please see Ref. (16, 18–20).

In the same spirit, the reimbursement space saw the advent of more iterative approaches that allow the gradual buildup of evidence, including managed entry agreements and coverage with evidence development (21). These also mark a shift from an one-off view on payment assessments to progressive schemes to measure product value and reduce uncertainty around cost-effectiveness at the time of negotiation (18). ATMP affordability discussions have also led to proposals for risk-sharing schemes (i.e., lifetime leasing or annuity-based models) that would allow a more adaptive way to gain evidence on anticipated value (19).

For ATMPs, whereby long-term effectiveness is difficult to quantify at the outset, schemes that balance acceptance of uncertainty with a preagreed and clear plan for progressive knowledge accumulation can be truly transformative. Built on the premise of early and continued stakeholder cooperation, in 2014 the European Medicines Agency (EMA) launched a pilot on the Adaptive Pathways scheme, setting the foundations for novel coordinated pathways from clinical assessment to HTA (20). The scheme poses an iterative development program that allows early approval and coverage for a benefit/risk optimized population through ongoing evidence gathering, often exploring the use of smaller trials and surrogate endpoints (22).

By allowing earlier clinical use, such adaptive approaches for development would press forward the confirmation of a product's real-world performance and provide much-needed clarity on downstream coverage criteria, urgently sought by ATMP investors and manufacturers. They also provide a key opportunity to align and address the evidence requirements for licensure and reimbursement, subject to stakeholder connectivity around post-authorization commitments and the continued collaboration between manufacturers, regulators, HTAs, and payers, as well as patients.

Advancing Collaboration for Advanced Therapies

The Common Language of Innovation: Deploying the Tools of Open Innovation

The challenges in reinventing an adoption route for ATMPs are as much about the scientific and clinical components, as they are about the organizational structures. Early and sustained interactions between academics and manufacturers, regulators, HTA assessors, and patients will be critical to start aligning, at least some, aspects of the decision-making process and leverage the progressive accumulation of new knowledge on benefit/risk that emerging translational tools and digital infrastructure allow. As pressure to deliver transformative treatments increases, many seek to understand how to establish the environments necessary for stakeholders to share resources and risk and achieve goals as complex as the emergence of a sustainable ATMP sector.

Over the last 20 years, collaboration models, such as "public–private partnerships" (PPPs) and "precompetitive consortia," have grown in popularity in the global pharmaceutical industry in response to complex biomedical challenges (23). This broad definition covers a diverse range of structures across disciplinary, organizational, stakeholder, and geographic boundaries, from PPPs like the US C-Path, the Foundation for NIH (FNIH), and the EU IMI, to open-source collaborations like the Structural Genomics Consortium and Sage Bionetworks (24), or industry safe havens like TransCelerate (25) (**Table 2**). In the field of ATMPs, the various banking initiatives on stem cells for preclinical, clinical, and pharmacological work are central stage, including the EBiSC and StemBANCC IMI projects, as well as the Human-Induced Pluripotent Stem Cells Initiative (HipSCi) in the UK.

The efficient deployment of partnerships has become a key competency of the healthcare system, leveraging their flexibility

TABLE 2 | Drug development stage classification of biomedical collaborations: examples of consortia addressing different stages of the value chain and further information [adapted from Papadaki and Hirsch (26)].

Innovation level	Collaborative goal	Example	Deliverables
New translational enablers, novel technologies	Increase R&D predictive capacity	Biomarkers Consortium: www.biomarkersconsortium.org/?	Biomarker identification and qualification
	Open-source molecular data gathering and analysis on human disease	Sage Bionetworks: http://sagebase.org/	Technology networking infrastructure; governance policies; disease models
	Increase R&D predictive capacity; safety	International Serious Adverse Event Consortium (iSAEC): www.saeconsortium.org/?	Identify biomarkers that predict the risk of drug-related serious adverse events
	Accelerate development of new drugs	Coalition Against Major Diseases (CAMD): www.c-path.org/camd.cfm	Technologies and tools in drug development for neurodegenerative diseases
Development process optimization	Improve clinical trial efficiency	iSPY 2: http://www.ispytrials.org/home	Advance regulatory standards for novel clinical trials designs and personalized medicine
	Ensure quality of biomanufacturing processes	Biomanufacturing Research Program (BIOman): http://cbi.mit.edu/research-overview/bioman/?	Manufacturing and quality control of biopharmaceuticals
	Improve clinical trial quality and efficiency	Clinical Data Interchange Standards Consortium (CDISC): http://www.cdisc.org	Data Standards and healthcare information
Approval and market access	Advance adaptive development, patient access, post-market learning paradigm	NEWDIGS: http://cbi.mit.edu/research-overview/newdigs/?	Simulation methods/tools; facilitate pilots and knowledge sharing across global jurisdictions
	Advance methods, policies for observational/outcomes research to enable coverage with evidence development	Center for Medical Technology Policy (CMTP): www.cmtpnet.org/?	Clinical research standards, infrastructure, and coverage/reimbursement policy
New business models	Fund late-stage health technologies for the developing world, maximizing returns in mature markets	Global Health Investment Fund	Risk protection for investors; venture funding for late-stage technologies
Disease specific	Cure Parkinson's	Michael J. Fox Foundation	
	Oncology	Cancer Commons: www.cancercommons.org/?	Targeted treatments for patients with cancer
All of the above	Provide ongoing infrastructure and funding for collaborative EU-wide innovation	Innovative Medicines Initiative (IMI) 1 and 2: http://www.imi.europa.eu/	80+ consortia
	Increase drug product development efficiencies by identifying pathways to integrate new scientific advances into the regulatory process	Critical Path Institute: https://c-path.org/programs/	14 consortia

to deconstruct complex challenges into manageable work streams to achieve shared outputs (27). Their significant progress in producing a range of enabling tools, platforms and new processes that advance drug discovery and development, has been extensively documented (28). Moreover, the experience of major consortia on novel governance, IP policies, and other operational models provide valuable lessons for new initiatives (29). Perhaps most importantly, precompetitive consortia have generated safe havens for transparent sharing and alignment, allowing different stakeholders to build intellectual and working proximity and interact in ways not previously possible (30).

With more than 400 consortia estimated to operate globally (31), growth in the number of narrowly scoped collaborations has led to challenges in their coordination, oftentimes seen as duplication, fragmentation, and consortium fatigue (26). In addition, while many have successfully delivered their target outputs, defining their impact on the delivery of better treatments remains elusive, requiring the combination of outputs from different collaborations, each working on some aspect of the development and access pathway. Looking across the diverse range of consortia successes, examples such as standards development and the validation of new tools typify the next level of challenges that go beyond scientific collaboration, having to address additional regulatory processes and barriers.

From Collaboration to Transformation: Redefining Value

The biomarkers and clinical endpoints resulting from collaborations like the Biomarkers Consortium (BC),[1] AD Neuroimaging Initiative,[2] the C-Path Predictive Safety and Toxicology

[1] http://www.biomarkersconsortium.org/.

[2] Alzheimer Disease Neuroimaging Initiative (ADNI): http://www.adni-info.org/.

Consortium,[3] and Coalition Against Major Diseases (CAMD), as well as numerous IMI consortia, are key examples whereby profound regulatory qualification gaps have been limiting their utility (32). In the clinical trial space, however, the BC has laid out a path for the incremental deployment of its biomarker and knowledge outputs, to inform policy changes that subsequently advance new genomic-driven clinical trial designs. Expanding the work of the I-SPY1 consortium on clinical endpoint validation, the follow-on I-SPY2 trial in oncology used "master IND" approach to support multi-asset submission and co-development of diagnostics. With I-SPY2, the BC pushed beyond the adoption of single product-focused biomarkers to inform entirely new adaptive trial practices and regulations that can apply across assets and diseases, revolutionizing current investigational approaches in oncology (33).

In response to the above challenges, several collaborations set out to form strategic connections to drive incremental value

[3]C-Path Predictive Safety Testing Consortium (PSTC): http://c-path.org/programs/pstc/.

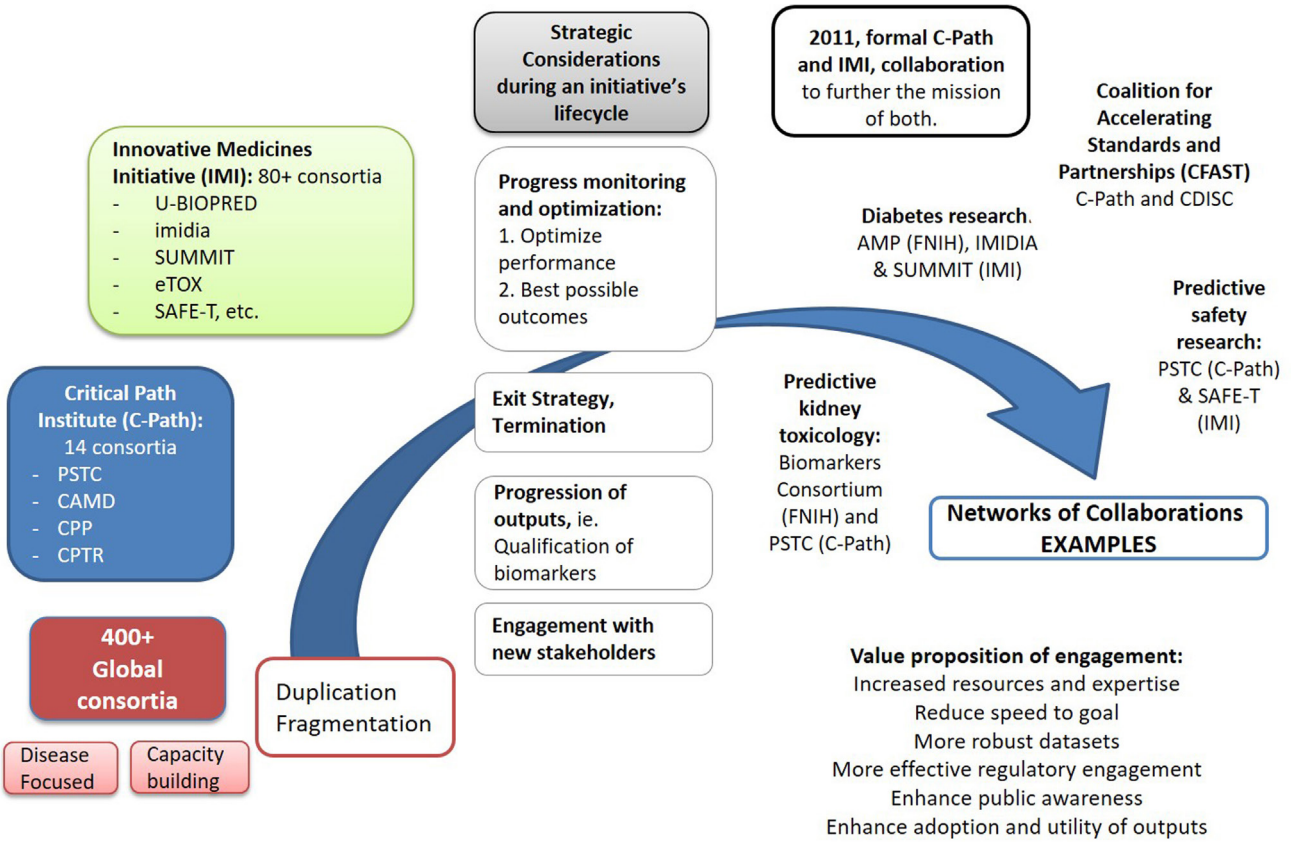

FIGURE 1 | Driving collective impact requires an increasing coordination of activities across global consortia, as well as individual organizations, to reduce duplication of efforts and maximize impact from the use and adoption of their initial separate outputs. A growing number of strategic interactions among the global ~400 partnerships are already emerging. Spearheaded by the formal collaboration between the FDA Critical Path Institute and Innovative Medicines Initiative (IMI), signed in 2011, a number of linkages have been formed among several of their distinct consortia in diseases like Alzheimer's [Pharma-Cog[1] and EMIF[2] working with Coalition Against Major Diseases (CAMD)], tuberculosis (PreDiCT-TB[3] and CPTR[4]), or broader fields like Predictive Safety and Toxicology Consortium (PSTC) (C-Path) and SAFE-T (IMI) in preclinical safety research. A number of global consortia have also joined forces with other initiatives pursuing relevant activities to avoid duplication of their efforts. Notable examples include the partnership of the Accelerating Medicines Partnership (FNIH) with IMIDIA/SUMMIT (IMI) in diabetes, the Biomarkers Consortium (FNIH) with PSTC (C-Path) on the kidney safety project, or in broad fields like data standards, with C-Path and Clinical Data Interchange Standards Consortium (CDISC)[5] forming Coalition For Accelerating Standards and Therapies (CFAST),[6] or CDISC and CAMD working in partnership. As the complexity of biomedical challenges increases, it will be important for initiatives to envision early in their lifecycle the strategic connections that may be needed to explore new combinations of their deliverables and resources and engage additional decision makers, ultimately decreasing uncertainly across the path from basic discovery to patient care.

[1]http://www.imi.europa.eu/content/pharma-cog.
[2]European Medical Information Framework, http://www.imi.europa.eu/content/emif.
[3]http://www.predict-tb.eu/.
[4]Critical Path to TB Drug Regimens: http://c-path.org/programs/cptr/.
[5]Clinical Data Interchange Standards Consortium (CDISC); http://www.cdisc.org.
[6]C-Path Coalition for Accelerating Standards and Therapies; http://c-path.org/programs/cfast/.

from their separate outputs, shown in **Figure 1**. This transition highlights the importance of reaching for more strategic measures of progress for collaborations on the broader context of enhancing the adoption of innovation, through strategic connections between different consortia to explore new combinations of their delivarables and resources and engage additional decision makers.

The Evolution of Engagement Models

For ATMPs, collaboration will undoubtedly be a game changer. The goals of partnerships, however, should exceed beyond good science, to target innovation across the pathway to patients and the interdependent domains of regulation, policy, and human capital development. The stakes are up, calling for increased capacity to use the full spectrum of open innovation and collaboration platforms currently emerging to generate value streams that exceed the traditional, linear model of pharmaceutical development.

Besides the "bricks-and-mortar" collaboration structures typified by the global PPPs and precompetitive consortia, a number of less structured platforms for dialog and interactions also emerged in recent years, integrating and coordinating the activities of different stakeholders and providing additional organizational models to capture, assess, and apply emerging knowledge and outputs in the translational system. Earlier dialog between regulators and payers, as well as developers, has been enabled by the number of Innovation Offices launched recently, from the MHRA Innovation Office and the NICE Office for Market Access in the UK, to the EMA's Innovation Taskforce and the FDA Critical Path Innovation Meeting in the US (**Table 1**). In the regulatory space, by working early with all key global health authorities, the NEWDIGS consortium of MIT was able to generate a series of scenario design exercises on real assets that informed the EMA's eventual pilot launch of the Adaptive Pathways pilots (34).

Similarly, groundwork for more coordinated dialog is already laid out between EMA and EUnetHTA in Europe, and the parallel assessment pilot between FDA and Medicare in the US (35). Moreover, the EU has been deploying a number of initiatives to limit the gap between market authorization and technology assessment, such as AdHopHTA, Advance_HTA, and INTEGRATE HTA that further exemplify the value of safe haven environments in the exploration and development of alignment on key trade-offs for decision-making and follow-on policy.

More Than the Sum of Parts: New Coordination Activities

Taking stock of the progress of global initiatives can illuminate how the follow-on connections between different partnerships or stakeholder groups starting to shape can accelerate both product and process optimization. The complex challenges of ATMPs will require many of these initiatives working on some aspect of the value chain to come together through strategic connections to explore new combinations of their outputs. An important step in this direction will also involve making full use of the flexible discussion environments and taskforces currently emerging globally, which aim to bring together all key players across the value chain, not least regulators, payers, and the patients.

The US is setting an early example in cancer treatments. The National Immunotherapy Coalition brings together large pharma and biotech companies, major academic cancer centers, payers, and financial institutions to turn combination immunotherapies into the next standard of care in cancer (36). The US National Cancer Institute has also joined forces with oncologists and academic medical centers to launch an impressive number of trials to test drug combinations tailored to individuals' immune profiles (37).

Europe's IMI 2, the largest global PPP in the life sciences, has a unique armamentarium of projects targeting different aspects of science and development. The next chapter for ATMPs presents it with an opportunity, and challenge, to identify convergence points between its various initiatives and develop a new model environment for coordination. The EBiSC and STEMBANCC initiatives working on stem cell banks, reference materials, and new standards have significantly increased confidence in the feasibility of cell therapies and could further derisk emerging areas, such as the application of genome editing (38). Planning for the linkage of such consortia could advance the value of their deliverables, allowing for the development of common standards on banking criteria, cell-type definitions, or the harmonization of cultivation protocols toward the comparability of data and cells between different banks or activities outside of IMI2, like HipSCi in the UK (39). A number of the broader IMI consortia have also been focusing on the underpinning infrastructure for emerging paradigm reforms, like the use of real-world data (GetREAL), the development of patient and disease registries (i.e., The CSA for Big data for Better Outcomes), or the Enabling Platform on Medicines Adaptive Pathways to Patients (ADAPT-SMART).

Evidently, the transition from specific outputs to patient-level outcomes is not straightforward (40). One-size-fits-all solutions are unlikely and a range of connections between infrastructures at the global/local and private/public space are wanted to extract add-on value from collaborations, capture knowledge across the differed stages of R&D, and use these to inform the practice and policy updates ultimately decreasing uncertainly across the path from discovery to patient care (**Figure 2**).

Developing Enabling Infrastructure and Test-Beds

Although both the emerging development paradigms and the successful stride of global consortia are important signs of progress toward getting better drugs to patients, challenges for ATMPs are ever more perplexing. The level of mass customization of production, administration specialization, and coordination of development stages that these therapies demand is unmatched. Conceivably, the specialized and bespoke solutions needed likely reside outside traditional company boundaries, further pointing out that strategic partnerships and open innovation could play a significant role in exploring these novel possibilities.

Without prior clinical experience, the shift from traditional predictive approaches to real-time monitoring of development and treatment outcomes is necessary to increase the robustness of benefit/risk knowledge and inform subsequent requirements. The use of single-arm trials will require data from historical or disease-specific control populations (41), whereas HTA evaluations through patient outcomes would also require the inclusion

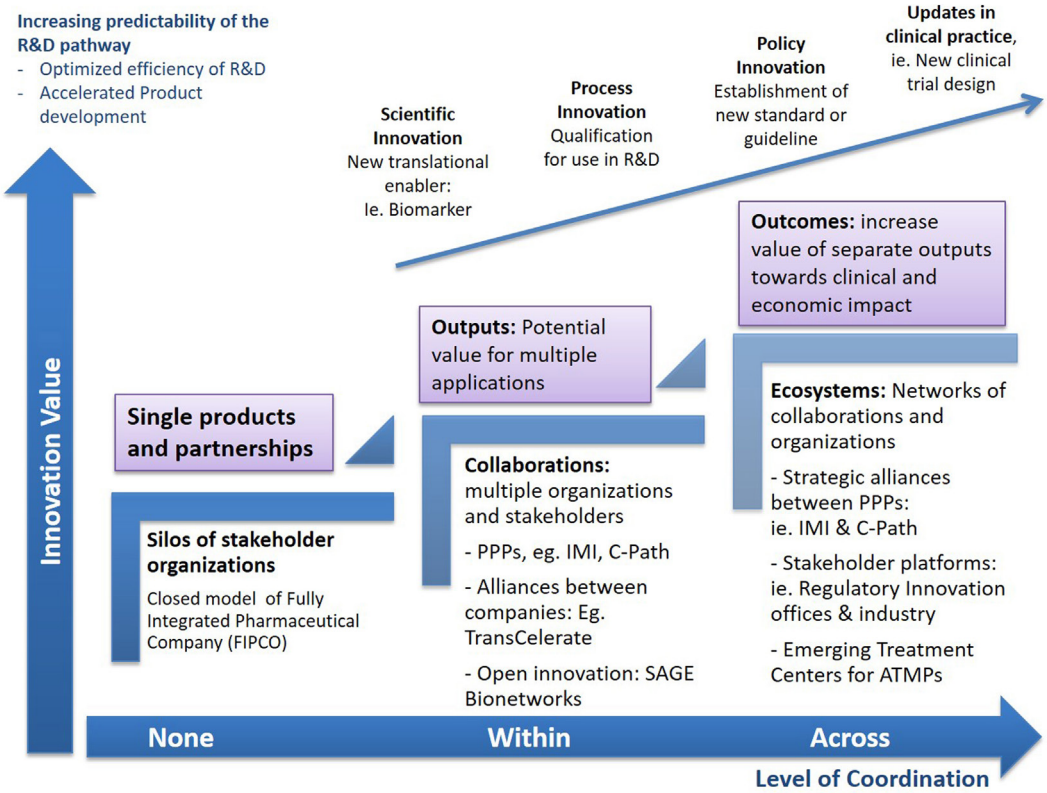

FIGURE 2 | **Increasing impact from collaborations**. The complex challenges of Advanced Therapy Medicinal Products (ATMPs) will require many initiatives working on some aspect of the value chain to come together through strategic connections to explore new combinations of their outputs, converge emerging knowledge, or launch pilots on new challenges within established projects. Through strategic follow-on connections between different consortia, as well as collaborative platforms that allow the convergence of multiple stakeholders, the value of individual deliverables and outputs can be augmented and expand beyond the initial projects, disease areas, or R&D stages, aiming to advance the entire pathway to patients. Multiple routes to synergy may exist for any single consortium, from piloting the use of a new enabling tool, i.e., biomarker, in a research protocol or clinical trial, to customizing data standards for regulatory application or ultimately propelling formal policy and process updates. Accelerating the development and delivery of advanced therapies requires collaborations to move toward higher complexity measures of progress that transcend the scientific space, to devise new organizational and policy frameworks, accelerate product delivery, and maximize process efficiencies.

of cost-effectiveness criteria in ATMP clinical trials (42). Long-term follow-up of patients is paramount in controlling safety and efficacy concerns and similarly, the high degree of batch specificity of single products, also calls for new quality and tracking systems and data infrastructure.

Evidently, technical and historical data and real-world evidence (i.e., from registries, hospital exception, and compassionate use records) become the connective thread between research, development, patient access, and commercialization. For an unobstructed access to ATMPs, data utilization and the design of suitable collection frameworks to monitor safety, effectiveness, and epidemiological endpoints become indispensable in providing stakeholders with sufficient decision-supporting evidence on the use of these therapeutics in real-life conditions. Yet, compensating for the uncertainties of non-conventional ATMP development requires the combination of novel information sources and data-aided technologies that span beyond the capacity of single organizations or stakeholder groups.

A matched effort for innovation from the bench to the patients is indispensable in ATMP manufacturing, implicating all actors across the supply and value chain. Starting from patient material sourcing and control to the strict GMP requirements, the role of specialized facilities from collection to final product administration is obligatory. For gene therapies, manufacturability is a consideration as early as vector design (Quality by Design, QbD), requiring the advent of novel fast, accurate, and robust analytics, whereas ongoing progress in process development and quality assurance presses regulators to step up the quest for new, written, and practice standards.

ATMP Specialized Centers: New Platforms for Data-Enabled Decision and Risk Sharing

However, marrying the high cost of developing and manufacturing these treatments with the growing trends for affordability, further exacerbated by low patient indications, can prove a showstopper for many, requiring that we deliver change in two critical aspects. The first involves the earlier utilization of advanced therapies

in real-world patient settings. The second, the implementation of networked activities between multiple manufacturing and clinical delivery platforms and processes, enabled by greater proximity and collaboration between the different players across the development and supply chain.

On the former, meeting the requirements for earlier patient and market access might be easily achieved through appropriate control of access and prescribing, suggesting that treatment areas needing specialized centers for diagnosis, treatment, and patients' follow-up would be good places to start. This is not far from the current reality for ATMPs, with primary targets still limited to rare or highly genetically defined indications, such as immunodeficiencies, hematologic, and metabolic diseases.

For ATMPs, specialized treatment centers also have to combine administration to patients with capabilities for clinical testing and commercial manufacture in an in-hospital setting, requiring manufacturing units and specialized contractors, academic research and clinical centers, as well as the patient bedside to become development partners with health systems. These networked clinical environments can also spearhead novel business models, where decision-making, cost and risk of establishing efficacy, safety, and quality are being shared and enabled though an infrastructure that links data across stakeholders and stages of development. Systems for continuous patient monitoring can in turn increase our understanding of the molecular underpinnings of disease and treatment response, for example, by enabling the profiling of vector integration patterns across the preclinical and clinical studies of a gene therapy.

Enabled through a shared data infrastructure and aligned decision-making, establishment of such hospital-centered development and access models will kick-start the real-world use of these treatments, allowing an earlier collection of evidence on clinical and cost-effectiveness, and most importantly secure patient delivery. It will also build capacity for clinical manufacturing and formulation of ATMPs at scale and help the development of the accompanying supply chains and logistic support.

So far, ATMP manufacturing has been largely residing within academia and the research space, bearing little GMP congruence and limiting capacity for clinical and commercial transferability. Enabling interactions between the developers of new products with the clinical facilities, as well as manufacturers of novel tools and platforms, can propel the industrialization of technology innovations and their adoption in the clinical setting (**Figure 3**). This can be a significant gain, given that the current costs of ATMP production systems are still affecting their early adoption, which could lead to significant regulatory hurdles and comparability validation work, if they are used later in development. The potential of these clinical centers to accelerate the development of technologies that reduce the cost and increase the efficiency of ATMPs also represents a tremendous opportunity, providing a route for smaller companies and Contract Manufacturing Organizations to engage with the space to develop, prototype, and qualify the equipment currently missing.

The frontman of gene therapy, GSK's Strimvelis, was developed in partnership with Italy's San Raffaele-Telethon Institute for Gene Therapy (TIGET) in Milan, which is also the therapy's only point of access. A joint venture between the San Raffaele Hospital (SR) and the Telethon Foundation, TIGET, comprises an early example for these ATMP specialized centers. Its networked model enables the coordinated design of new therapy approaches, combining Telethon's specialization around gene transfer, genetic modification, and preclinical models of stem cells, with the translational and clinical units, as well as expertise of SR-hospital in regulatory and clinical testing.

From a country's perspective, TIGET's access exclusivity on Strimvelis (43) also shows that these centers could turn into global hubs for ATMP commercialization, further strengthening local health economies, attracting investment and propelling job creation and economic growth. Countries like the UK, with strong-networked foundations already in place, could also capitalize on the current momentum. With a number of excellent GMP facilities across its academic institutions, hospitals, the NHS Blood and Transplant service, as well as commercial players, ongoing national digital initiatives (NHS, Genomics England), and a unique network of Catapult Centers of excellence, the UK could set a global example on industrializing research and development and promoting sector growth for ATMPs.

The UK can give a valuable example of the strategic approach needed in the space, being at a strong position with substantial scientific progress, growing investment appetitive and reforms in its regulatory, reimbursement, and health system currently underway. If it is to deliver its promise to become global leader in the development and delivery of ATMPs, it must acknowledge the challenge of collaboration among all relevant actors, providing funding to support both basic and applied research and developing a sustainable and viable pathway for these products from bench to the bedside. Within its newly launched AAR on accelerated development routes for transformative products, in particular, the early consideration of ATMP challenges could prove instrumental in identifying critical factors for novel systems for assessment, commissioning, and patient access.

PIRATES IN THE NAVY: THE ESSENTIALS OF ATMP BUSINESS INNOVATION

With ATMPs, the bet now is to turn innovations that once where unimagined, into treatments that we will not live without. In a space that combines an unprecedented level of technological progress with the need for systemic reinvention, successful companies will have to turn themselves into innovation powerhouses, radically changing the way they look at structures, teams, and people. As one of the world's biggest innovators, Steve Jobs, once said "it was more fun to be a pirate than to join the navy." ATMPs mark a revolutionary shift from closed biomedical strategies toward collaborative and networked innovation, enabled by the establishment of treatment centers, new supply chain, and business relations. From a company's perspective, understanding how to operate in these new environments will be imperative, requiring an increased ability to deploy collaborations and their networks more efficiently.

As decision-making across the path to the clinic becomes more constant, ATMP developers must also build new "fit-for-purpose" business models that can leverage the adoption reforms underway globally and allow them to plug into the evolving landscape of stakeholder partnerships and networks. An overhaul in organizational practices is in order, if biopharma companies

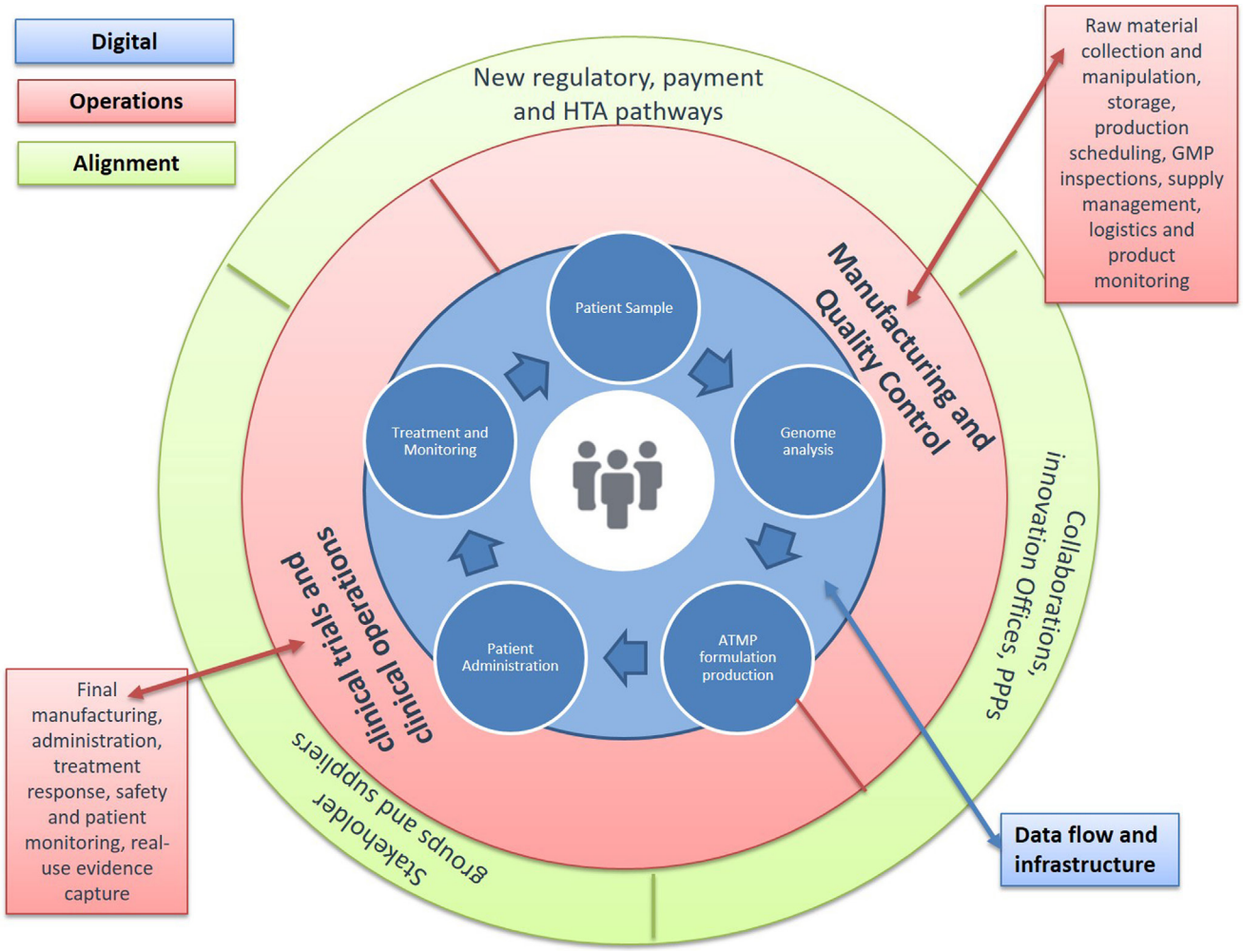

FIGURE 3 | **Advanced Therapy Medicinal Product (ATMP) Treatment Centers**. Developing new environments for decision, cost, and risk sharing. A number of barriers in the space continue to keep production costs high and further challenge licensing and reimbursement success possibilities. Solutions are urgently needed across the continuum from discovery to patient access: (1) new approaches to monitor and improve manufacturing quality, including transfer of production from academia to Good Manufacturing Practice (GMP); (2) availability of standardized tools to aid regulatory decisions around efficacy, safety, and quality; (3) novel clinical trial designs that allow for small patient numbers and outstanding variability; (4) methodologies to understand cost-effectiveness and access; and (5) data structures to improve product use and health outcomes. Achieving these requires changes in two critical aspects: allowing the earlier clinical use of ATMPs and building the necessary environments for the progressive generation of data across the path of new products to the clinic. A key step in this direction would be the establishment of specialized treatment centers for ATMPs that enable networked activities between manufacturing units and specialized contractors, academic research, and clinical centers, as well as the patient bedside. These networked clinical environments would combine administration to patients with capabilities for clinical testing and commercial manufacture in an in-hospital setting. They would also allow for new business models, where decision-making, cost and risk of establishing efficacy, safety, and quality are being shared and enabled though an infrastructure that links data across stakeholders and stages of development. They also provide a key opportunity to address the evidence requirements for licensure and reimbursement, allowing greater stakeholder connectivity around post-authorization commitments.

are to meet this next wave of therapeutics innovation, requiring the establishment of bespoke cross-functional teams from the R&D, clinical and regulatory, HTA/pricing and reimbursement, benefit/risk assessment, as well as business development and legal functions. Even with new organizational blueprints, the most important success factor remains the human capital. The next wave of connected innovation, branded by ATMPs, will require access to a new generation of healthcare leaders with capabilities to design new end-to-end pathways, skills at the interface of cutting-edge technology and commercialization, and ability to work across division and project boundaries.

LAND AHEAD? PLANNING A FUTURE PROOFED STRATEGY FOR ATMPs

So, how are we doing in terms of building and growing this potentially transformative new treatment area? Taken together, the evolution in scientific understanding, new policy frameworks,

and an increasingly collaborative health environment are key signs of progress in our ability to manage uncertainties in ATMP development. However, when it comes to having confidence in the capacity of current health systems to adopt these new treatment paradigms for the benefit of patients, the jury is still out.

Attaining complex measures of progress, such as the delivery of the wave of increasingly elaborate products like ATMPs to patients, involves moving away from the current binary go/no-go model of assessment to a life span approach to monitoring a product's benefit–risk profile. This fundamental shift in the way we develop and test these products, rests on an unparalleled level of openness to early and continuous interactions between unfamiliar bedfellows, from industry and regulators, to payers and patients.

The recent growth in the global landscape of precompetitive collaborations and open innovation consortia introduced a new level of organizational flexibility, allowing the combination of stakeholder resources, knowledge, and objectives. The complex challenges of ATMPs will require many of these initiatives working on some aspect of the development pathway to explore new combinations of their outputs through strategic connections and allow the exploration of disease mechanisms, integrate dispersed knowledge around therapeutic approaches, and address crosscutting technical and clinical issues across development stages and treatment areas.

Taking stock of the progress of global initiatives can illuminate how follow-on connections between different partnerships or stakeholder groups can inform the establishment of a strategy that balances this flexibility with greater coordination within this diverse nexus of players and their networks. The development of new management and organizational infrastructure will be pivotal in driving and coordinating collective efforts within and across collaborations, and ultimately bring closer all stakeholders, not least regulators, payers, and the patients.

With the advent of ATMPs, the era of ecosystem-level innovation is on our doorstep, accenting these rapid changes and requiring that we continue to develop our collective capacity in two critical and synergistic directions. Removing perceived barriers to collaboration through new test-bed environments and connection platforms, and delivering a strategic roadmap that joins up the pathway from basic discovery to the market and the cycle of care.

Against this backdrop, the development of a knowledge base on the organizational frameworks needed to drive the evolution of collaborative innovation will also be important. Complementing our growing understanding of human health and disease with key principles from sociotechnical fields, including open (44) and distributed innovation (45), network theories (46, 47), systems thinking, and complex adaptive systems (48), among others, can provide useful insights on how to build up value from the growing global landscape of collaborations.

Delivering the promise of advanced therapies to tackle, and even cure disease, depends on our collective ability to effect an unprecedented level of change, through initiatives that target scientific challenges, alongside solutions in policy, regulation, business, and funding strategies. Demanding as this may prove, the pressure is on for everyone within our global healthcare systems, and especially those with life threatening or debilitating, unmet needs.

AUTHOR CONTRIBUTIONS

I am the only author of this work, executing all research, manuscript, and figure preparation.

ACKNOWLEDGMENTS

The author is grateful to Dr. Gigi Hirsch, Center of Biomedical Innovation, MIT for numerous constructive discussions on the topic of multi-stakeholder collaborations and its evolution, including instrumental input during the conceptualization of the visual representation in Figure 2.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

ORIGINAL RESEARCH
published: 25 August 2017
doi: 10.3389/fmed.2017.00130

Collaborative Approaches and Policy Opportunities for Accelerated Progress toward Effective Disease Prevention, Care, and Control: Using the Case of Poverty Diseases to Explore Universal Access to Affordable Health Care

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OPEN ACCESS

Edited by:
Bruno Sepodes, Universidade de Lisboa, Portugal

Reviewed by:
Segundo Mariz, European Medicines Agency, United Kingdom
Lise Aagaard, Bech-Bruun Law Firm, Denmark

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *13 June 2017*
Accepted: *24 July 2017*
Published: *25 August 2017*

Citation:
Laokri S (2017) Collaborative Approaches and Policy Opportunities for Accelerated Progress toward Effective Disease Prevention, Care, and Control: Using the Case of Poverty Diseases to Explore Universal Access to Affordable Health Care. Front. Med. 4:130. doi: 10.3389/fmed.2017.00130

Background: There is a massive global momentum to progress toward the sustainable development and universal health coverage goals. However, effective policies to health-care coverage can only emerge through high-quality services delivered to empowered care users by means of strong local health systems and a translational standpoint. Health policies aimed at removing user fees for a defined health-care package may fail at reaching desired results if not applied with system thinking.

Method: Secondary data analysis of two country-based cost-of-illness studies was performed to gain knowledge in informed decision-making toward enhanced access to care in the context of resource-constraint settings. A scoping review was performed to map relevant experiences and evidence underpinning the defined research area, the economic burden of illness.

Findings: Original studies reflected on catastrophic costs to patients because of care services use and related policy gaps. Poverty diseases such as tuberculosis (TB) may constitute prime examples to assess the extent of effective high-priority health-care coverage. Our findings suggest that a share of the economic burden of illness can be attributed to implementation failures of health programs and supply-side features, which may highly impair attainment of the global stated goals. We attempted to define and discuss a knowledge development framework for effective policy-making and foster system levers for integrated care.

Discussion: Bottlenecks to effective policy persist and rely on interrelated patterns of health-care coverage. Health system performance and policy responsiveness have to do with collaborative work among all health stakeholders. Public–private mix strategies may play a role in lowering the economic burden of disease and solving some policy gaps. We reviewed possible added value and pitfalls of collaborative approaches to enhance dynamic local knowledge development and realize integration with the various health-care silos.

Conclusion: Despite a large political commitment and mobilization efforts from funding, the global development goal of financial protection for health—newly adopted in TB control as no TB-affected household experiencing catastrophic expenditure—may remain aspirational. To enhance effective access to care for all, innovative opportunities in patient-centered and collaborative practices must be taken. Further research is greatly needed to optimize the use of locally relevant knowledge, networks, and technologies.

Keywords: universal health coverage, tuberculosis, use of knowledge, research-based guidance, evidence-based integrated care, public–private partnerships, translational research, system thinking

INTRODUCTION

Health for All—A Global Commitment in the Spotlight

Late 2015, the UN General Assembly adopted the sustainable development goals (SDGs) (1). Of those, goal 3 explicitly refers to "ensure healthy lives and promote well-being for all at all ages" and embraces to "achieve universal health coverage" (UHC) (2). During a panel hosted by the Chatham House in London on June 6, 2017, Tedros Adhanom, the freshly elected Director General at World Health Organization, and Amartya Sen, Professor of Economics at Harvard University and former Nobel Prize in Economics, joined their positions to raise awareness on the consequences for countries of not providing UHC with respect to poverty reduction and global development. There is indisputably a massive global momentum to progress toward UHC equitably and cost-effectively. Yet, its assessment represents significant political and technical challenges (3, 4). Among them, the financing strategy on which economists estimated global returns on investment in equity and universal coverage at more than ten times their costs (5). On the one hand, there is still a scarcity of national evidence on effective policies for health coverage. On the other hand, where evidence is available, research findings are too little used. Moreover, evidence that is not disseminated or used can be seen as a source of inefficiency (6). How to translate the powerful concepts of UHC into local actions place a rationale for locally relevant knowledge development and data use for effective decision-making.

Building well-functioning systems to maintain or reach sustainable UHC require constant attention, a long-term development process (7) and difficult trade-offs to make right decisions (8). Today, few countries escape these questions, whether it is for planning, initiation, and development of new programs, expansion and funding of already established programs, or attainment of cross-cutting goals such as equity and efficiency to meet the growing demands of our societies (9). Along with sustainability, a translational perspective toward effective policies is needed (10). Moreover, health policies aimed at removing user fees for a defined health-care package (will continue to) fail at reaching the desired results if not applied with system thinking. System thinking in public health became widely recognized as an approach to reflect on complexity and systems strengthening (11, 12). Much remains to be done to effectively reduce the global burden of disease. Nevertheless, despite considerable progress, many countries experience scarce or wasted resources and do not deliver primary and secondary care services as targeted (13). To date, too many people still face catastrophic health expenditure every year. Approximately 150 million people around the globe with two-thirds forced into poverty as a result of health spending (14).

A Focus on Poverty-Related Diseases

In many ways, poverty diseases would constitute prime cases to better understand the efforts made to, and assess the extent of, effective coverage for high-priority health-care services.

For instance, tuberculosis (TB) could have been a disease of the past since the discovery of the *Mycobacterium tuberculosis* by microbiologist Robert Koch dates from 1882 (15). TB however remains one of the worst health scourges despite an ever growing global commitment to fight and hopefully eradicate the disease burden. Actually, TB even became the world's leading infectious killer, killing more people than HIV/AIDS (16). The case of TB control raised our interest for multiple reasons. To begin with, the End TB strategy recently reached a turning point in adopting a third ambitious goal on financial risk protection, as part of the United Nations SDGs (17). The global strategy aspires to eliminate all sufferings from catastrophic expenditure faced by TB-affected families and set an important milestone to be achieved by 2035. Besides, TB encloses a sub-sector in which innovation with respect to diagnosis, treatment, and prevention is still sought to effectively reach the global targets. Moreover, TB care services involve the first line of health-care providers and fully solicit the provision of quality primary health care (i.e., preventive, promotive, and curative care services), which fairly meets the UHC agenda. Additionally, poverty reduction, economic development, food security, or migration all relate to TB and the SDGs resolution.

In that way, the sound analysis of the patients' care-seeking and care pathway that we propose represents an interesting opportunity to inform policy-making and national and international priorities. Obviously, using a single disease as predictor of health access and adherence barriers to care may not give a complete picture of the whole package of UHC services but can, in return, provide valuable evidence to move forward with evidence-based cost-effective and responsive policies.

Exploring the Case of TB

Tuberculosis national control programs benefited from generous financing, mostly borne by a relatively small number of donors who support a directly observed treatment, short-course (DOTS). The

TB care pathway is known to be particularly long and complex. As a result of these difficulties, we observe persisting inequities in access and catastrophic health expenditure (18, 19),–the latter, despite years of free-of-charge diagnosis and treatment under the global strategy.

As recalled above, financial protection for health remains a matter of concern that need to be tackled to make the global targets toward TB elimination by 2050 real. Freeing the world of the TB threat should involve to alleviate poverty and engage multisectoral actions (20). Further, challenges include to enhance translational research for TB elimination i.e., from "fundamental research to clinical, epidemiological, implementation, health system and social science research" (10) and consequently deliver valuable evidence. Lienhardt et al. stressed the role of both operational and fundamental research to align patients' needs with the requirements of the development of new opportunities, especially for a timely identification of TB suspects as well as better responsive treatment regimens, vaccines, and care provision strategies. Such perspective relates to picture a continuum of prevention, care, and control services supplied in a holistic approach. For instance, new anti-TB drug regimens are expected to (i) ease and shorten the current lengthy first-line treatment of 6-month duration (when successful), which is based on a mixture of multiple drugs, (ii) restrain biomedical and other side effects, and (iii) eliminate the threat of discontinued drug regimens (mainly after the 2-month intensive treatment phase), as well as treatment failures and drug resistance (21). Furthermore, within the new era of global development, which set the WHO's post-2015 End TB strategy in the frame of the SDGs, socio-economic determinants of TB and health systems strengthening stand as key issues (10, 22, 23).

AIM AND METHOD

Secondary data analysis of two country-based cost-of-illness studies was performed to gain knowledge in informed decision-making toward enhanced access to health care in resource-constraint settings.

Original studies were conducted in sub-Saharan Africa, more precisely in Burkina Faso (24) and in Benin (25), using a single research protocol (26). A two-step process relying on state-of-the-art knowledge and peer review was designed to develop a cost-of-illness research protocol (**Figure 1**). First, baseline information was retrieved from an explanatory review of the literature, to determine knowledge gaps, and country situation analyses to determine the particular local needs. Second, a peer review process based on a multidisciplinary expertise was conducted in order to validate our study objectives and conceptual framework. This two-step process allowed us to adapt and refine standard study protocol and operationalization of research.

A cost-of-illness timeline was derived from our preparatory work, which included both a consultation with the key informants and national TB program experts involved in the research project and available literature on delays in TB treatment. According to available evidence, delayed diagnosis and treatment may differ widely between study settings (27). Therefore, beyond the usual "medical" stages related to diagnosis and treatment procedures,

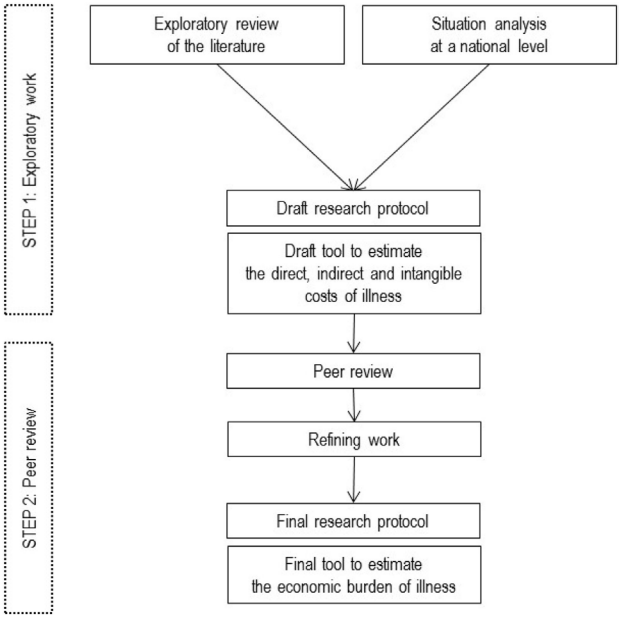

FIGURE 1 | Research protocol development.

a context-oriented approach highlighted the importance of considering what could happen prior to diagnosis and immediately prior the initiation of treatment. We took the specific aspects of the DOTS into account to determine the key steps related to the successive periods of the care-seeking pathway. The first reference was to the onset of TB symptoms (e.g., prolonged cough). Thereafter, the key steps were the time of first contact with a public health-care provider, confirmation of the TB diagnosis, the beginning of intensive treatment, and finally, the beginning of continuation treatment. In total, we covered the entire care-seeking and care pathway from the onset of TB symptoms to the completion of treatment (**Figure 2**).

The data collection process exhaustively recorded all relevant events related to TB that had been already occurred when the study was initiated (retrospective design). Input data were gathered *via* patient survey to produce reliable estimates of the different components of costs and use of care services. This bottom-up study design provided an opportunity for patients to disclose expenses that were often neglected in contemporary investigations thus reducing possible cost underestimation. Similarly, precise estimates of time lost at work due to illness and resource mobilization strategies that were developed to cope with illness could have been collected. Countries specificity and methodology are fully described elsewhere (24, 25).

A secondary analysis of comparative study findings allowed us to highlight a series of policy gaps, producing a knowledge development framework. Subsequently, a research question was identified to explore potential added value of collaborative work approaches with respect to addressing the observed policy gaps. Then, a search strategy using combined keywords was performed through the usual means (electronic databases, reference lists of ancestor searching, and specific websites of organizations).

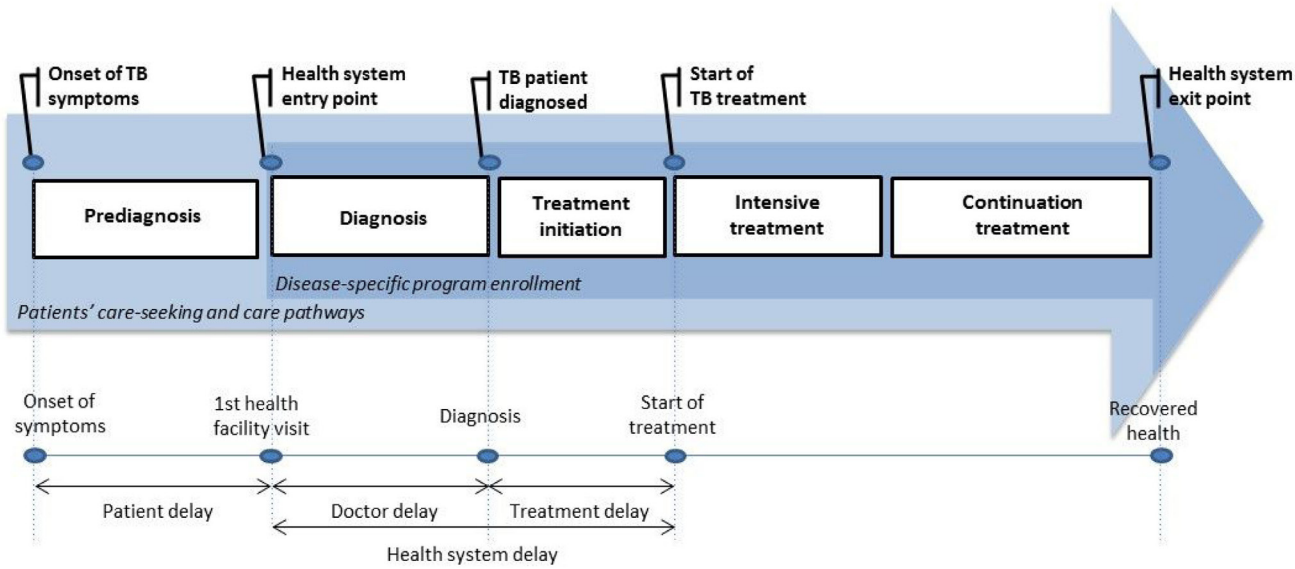

FIGURE 2 | Cost-of-illness timespan: five key steps of the TB patients' care pathway.

Refining the scope, we focused on the specific role of public–private initiatives in reducing the economic burden of disease. A narrative integration of relevant references was performed. The scoping review was therefore implemented to map relevant experiences and evidence underpinning the defined research area.

FINDINGS

Summary of Key Findings

In our two West African studies, three-quarters of the patients treated for TB under the DOTS faced catastrophic health expenditure. Catastrophe refers to health expenditure that placed excessive burdens on TB-affected families and is largely associated with adverse health outcomes and severe financial hardship for their members. Particularly, the incidence of catastrophic expenditure ranged from 38% in the upper income quintile of the study population to 94% in the lower income quintile in Benin, and the intensity of catastrophic expenditure ranged from 5 to 31%, respectively (28). In both studies, removing user fees for medical spending did not prevent the patients from financial distress due to access TB diagnosis and treatment services. While differences occurred with respect to the incidence and intensity rates of catastrophic expenditure across locations or wealth groups, the lack of financial protection remains a common dare for most programs regardless the environment.

It is not only about reaching increased TB control coverage but also about improving patient management, which is required to improve health-care delivery and progress toward UHC. Some authors had shaken the scientific community while saying that solutions to reduce time delays in care should be sought by the care providers (and not the patients); this includes patient delay (27). The findings from Burkina Faso provided new evidence in support of this hypothesis (18). Substantial hidden costs induced by apparent failures in delivery of health care for TB patients were highlighted. These were essentially due to structural and organizational flaws for almost half of the patients. Indeed, with respect to diagnosis only, "*39% of the patients had been charged, between first contact and the end of diagnosis, for sputum examinations, chest X-rays, other examinations or hospitalization (…), which amounted to US$ 8 per patient (…), to be paid within a fairly short period of time*." As stated, the issues behind the reduction in time delays and expenses incurred at each stage of the patient's care pathway remain important.

In sum, our findings indicate that the coverage of TB control programs might be greater than actual program outcomes. Substantial out-of-pocket payments for TB appeared to be generated by expenses falling outside of the free health-care package (e.g., pre-diagnosis, extra-consultations, non-medical spending), which may result in an underestimation of routine estimation of the overall economic burden of TB incurred by households. The series of remaining shortages and hidden failures shown in the health-care delivery system for TB patients highlighted windows of opportunities to facilitate the change in context. These called for data-driven decision-making that is suited to local necessities.

Besides the bleak picture depicted (29), our concern not only pertains to limited access due to excessive direct costs but also to indirect costs that took the form of days and income loss due to TB. In addition to lower resources while facing higher needs, the strategies that patients used to mobilize funds to cope with the substantial direct and indirect costs imposed strains on the families' financial viability, through actions such as exhausting their savings, getting into debt, and even selling livestock and property (18). Damaging asset portfolios of disease-affected households in the long run, the riskier coping strategies result in a public health threat.

Knowledge Development Framework and Informed Decision-Making—The Cornerstones of Strong and Integrated Health Policies

Our study observations were congruent with the literature in the field (19, 30, 31). In various settings, key findings confirmed substantial direct and indirect costs associated with TB. Although the national programs delivered free diagnosis and treatment, the TB control strategy tend to remain unaffordable and inaccessible for TB-affected households living with limited resources (22). This viewpoint features a rather tunnel vision of the previous global strategy with respect to reaching financial protection *via* user fee exemptions for biomedical matters (32). Removal of those fees did allow a major step forward in access to TB control services overseas, but this was no longer sufficient to eliminate TB as a public health problem (21). Therefore, the post-2015 global strategy enlarged his scope to cover adverse economic effects associated with seeking and receiving TB services (16). This establishes the need to assess and monitor catastrophic expenditure due to TB, its drivers, and consequences.

To feed the global agenda, we investigated a series of potential shortcomings to effective policy toward TB elimination and scaling-up areas. We screened bottlenecks on access to care, equity as well as programmatic, implementation, and managerial or behavioral aspects. We attempted an analytical approach to effective TB prevention, care, and control coverage. Based on three closely interrelated patterns, **Figure 3** portrays a complex path where:

- Health-care delivery performance—axis *x* represents the proportion of the population with access to timely and good-quality TB services according to their needs.
- Social rights attainment—axis *y* provides the proportion of the population whose basic individual necessities and capabilities needed are met in order to seek and receive care services effectively.
- Financial risk protection—axis *z* refers to the proportion of the population with access to TB services without being distressed or impoverished as a consequence of using TB services.

There is no single path to effective coverage. Our frame echoes the coverage dimensions of the WHO's UHC cube representing population, services, and direct costs covered (33) and its permutation in the context of TB (32). On each axis, a "double policy gap" intends to highlight both the remaining path to extending TB control strategy and efforts to obtain effective coverage for those already reached by the health program. From our findings, the determination of programmatic flaws and scaling-up coverage needs aim to elude adverse effects incurred by TB-affected households. Those were inherent consequences of erratic patients' pathways, inappropriate use of multiple-care services, supply side weaknesses, and delayed or incomplete recovery of health.

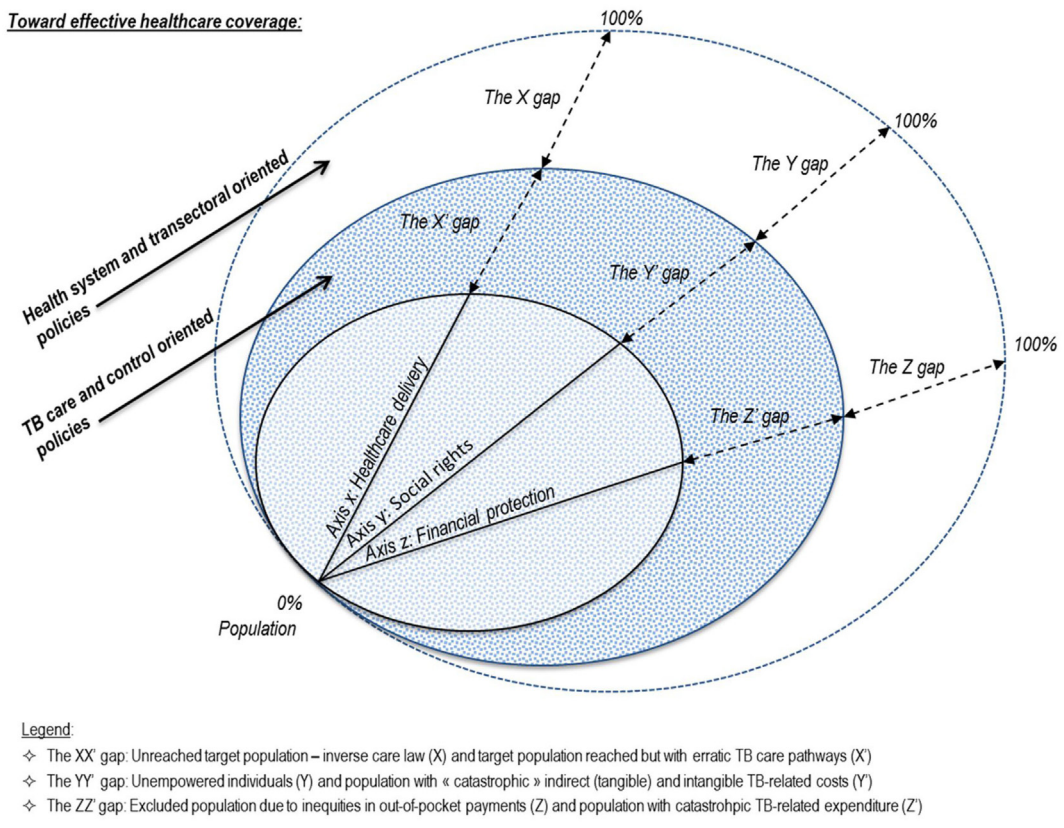

FIGURE 3 | The complex path toward effective TB prevention, care, and control coverage.

Similar to many others, we focused on patients who were already enrolled in the DOTS. We remain able to make the following three observations. First, as there are TB-affected individuals whose illness is undetected and untreated, there is still a target subpopulation that is not reached by the national TB control programs (NTPs). Reasons for the so-called X gap may include limited availability of public health care and TB services, poor case management of comorbidities, inequities in TB knowledge, or a mismatch between supply and demand. Poor health systems organization also relates to the absence of coordination bodies, surveillance studies, and joint actions between various health programs. Indeed, despite a "one-stop TB-HIV" approach recommended by the WHO, TB, and HIV programs often operate independently (34). A similar or even more severe observation can be made for coordination with other programs. Second, there are still sick individuals who suffer from a variety of ailments that make them unable to exercise their rights. Subsequently, there is a non-empowered target subpopulation without access to the needed services, the Y gap. Third, when financial barriers, even to high-priority services such as free diagnosis, persist due to lack of prepayment and pooled schemes, there is a target subpopulation unable to afford TB-related services. The absence of a compulsory financial protection scheme (no prepayment or cross subsidies in the population) results in health system failures, the Z gap. These shortages establish three "primary" policy gaps, which relate to the integration of health programs into health systems and transversal policies.

Analysis of the inner circles highlighted the need for additional policy responses, mostly located at a programmatic level. Drawing on our West African studies findings, we extended this argument further. In addition to the primary policy gaps, there are hidden gaps that plague the fulfillment of various patients' needs. Indeed, we identified several weaknesses within the health-care delivery system for TB patients enrolled in the DOTS. Addressing these weaknesses may be a strategic step toward reducing the primary policy gaps. For each dimension, we established a "side" gap. First, we revealed a quality issue in the management of patients, which may have contributed to erratic care pathways. The X′ gap refers thus to a subpopulation that has been reached by NTP networks but for which suboptimal care coordination and patient management was provided (e.g., provider delays, redundant visits). The findings suggested that the current strategy lacks patient-centered care, a context-oriented approach, and systemic vision. This highlights the need to consider the extent to which the disease-specific programs deliver responsiveness, relevance, effectiveness, and efficiency in their activities and implementation processes. Second, an additional side gap that emerged refers to the adverse effects of indirect and coping costs. To begin, there is the spiral of poverty embodied by labor and income losses and recourse to impoverishing coping strategies such as indebtedness. Furthermore, there is the issue of overburdened individuals and social exclusion effects potentially induced by illness stigma, with a concrete risk of being excluded from services (public health-care services) and participation. This policy gap therefore encompasses costs of a very different nature, which range from tangible costs, such as income loss and charges related to indebtedness, to intangible costs that may have disruptive effects on households and likely affect human rights and health equity. This Y′ gap thus defines a subpopulation unable to elude catastrophic tangible indirect and intangible costs of illness. Third and finally, we recall the importance of considering overall out-of-pocket expenses (medical/non-medical, and pre-/post-diagnosis) incurred by the patients, and their magnitude in relation to households' resources that need to be mobilized. The so-called Z′ gap isolates a subpopulation incurring catastrophic expenditure as a consequence of the use of health care and TB services.

What May Drive the Economic Burden of Illness?—Translating Research Findings into Policy Practice

Addressing the above policy gaps concurrently should remain a major global health issue. Translating evidence into enhanced patients' outcomes rely on efforts from the scientific community to facilitate this complex process. Applying our framework, a simulation on our case study confirmed a potential room for improvements in terms of financial gain for beneficiaries associated with concurrent effective implementation and patient-centered and comprehensive care delivery (35).

Particularly, erratic care-seeking pathways generated inconvenient but potentially remediable health-care expenses for TB. The breakdown analysis of the nature and volume of TB-related direct out-of-pocket costs allowed us to identify a series of areas of progress.

Hidden and potentially provider-induced medical costs (e.g., the systematic prescription of chest X-rays for TB diagnosis in some health facilities) were raised. We investigated whether and to what extent these hidden direct costs may have been reduced *via* improved patient management schemes (i.e., a patient-centered and context-oriented approach). Thus, we simulated the impact of the rationalization of delivery of care by the strict application of the national TB recommendations. Therefore, we made three sets of assumptions. As challenges imply on both the provider (supply) and patient (demand) sides, the following assumptions focused on both sides. First, we assumed that TB suspects were to be correctly informed regarding the symptoms distinguishing TB (e.g., 15 days of coughing) and had direct access to first-line health facilities to allow rapid referral for free TB diagnosis. Thereafter, according to the user fee exemptions for diagnosis, health-care costs incurred by TB patients during the diagnostic stage should remain affordable for them. Second, we assumed that the patients were to begin treatment as soon as their diagnosis was confirmed. One reason for this is that a patient diagnosed with TB is in the most infectious period of the disease at this stage. Indeed, patients with active pulmonary TB increase the risk of primary infection and reactivation of latent TB among their acquaintances. This means that neither treatment delay nor health-care costs had occurred between the diagnosis confirmation and the initiation of the anti-TB treatment. Third, we assumed that the DOTS was truly free of charge, effective, and sufficient to treat TB patients. Therefore, medical costs were required to tend toward 0 during both the intensive and continuation treatment stages. These assumptions may be

considered strong, but the exercise was very informative, as it revealed a median financial gain (IQR) of 50.4% (26.3–67.0%) of overall direct cost by virtue of the removal of care delivery inadequacies and policy gaps.

If TB-related expenses could be halved, one can expect substantial progress in TB outcomes. Educating public health workers in the provision of a patient-centered approach and educating all stakeholders *via* a systemic approach could be relevant in reducing these avoidable hidden patients' costs (**Figure 4**).

Consequently, the economic burden associated with illness ends up multidimensional. It embodies multiple risks and likely fuels the three "double" policy gaps. Moreover, it may start a vicious circle where the burdens of erratic care-seeking and care pathways tend to surge the risk of inappropriate care use and further increase the drug-resistant threat (35).

In view of the above, adopting a syndemic approach would be inspiring to better inform on the multidimensional aspects of effective TB coverage and related challenges with respect to case management of coinfected patients (36). Extrapolating from syndemics would suggest that patients' care pathways are affected by the presence of comorbidities. For instance, multiple burdens such as TB-HIV/AIDS, diabetes, malnutrition (Vitamin D deficiency), or even tobacco smoking may adversely interact with each other and generate increased vulnerability and inequities (37). Both synergisms between TB and other health programs and syndemic interactions (including aspects related to household crowding, socio-economic constraints, and air pollution) are to be further established (38). Quoting the authors, "syndemic interactions play out over a life time and across the generations."

DISCUSSION

Collaborative Work for Affordable Primary Health Care for All—A Tentative Response to Mind the Stated Policy Gaps

Effective implementation of TB control activities depends not only on research-based guidance but also people's performances to convert available inputs into outcomes. On the one hand, people are vehicles of valuable knowledge regarding care provision and consumption. On the other hand, policymakers tend to most value and use local data sources provided through personal contacts (39). Health-care services users and providers, as well as managers, financers, and knowledge agents, turned out to be strategic game changers to promote social justice (40). Beyond a recipe for response to TB and other diseases burden, an evidence base must be sought in resource-poor countries. Particularly, multi-stakeholders and people-centered approaches should be further studied as they appear as an emerging science based on human agency[1] and people carrying system change (40).

Target populations often differ over time and from country to country or region to region. Nevertheless, most populations and certainly in low-income settings tend to seek care from biomedical care providers (public and private sectors) and trusted traditional healers. The private health sector can be defined as all non-state providers, which may cover a wide range of not-for-profit and for-profit actors including faith-based organizations,

[1] "Human choices and ingenuity worn by social, political, and economic constructs."

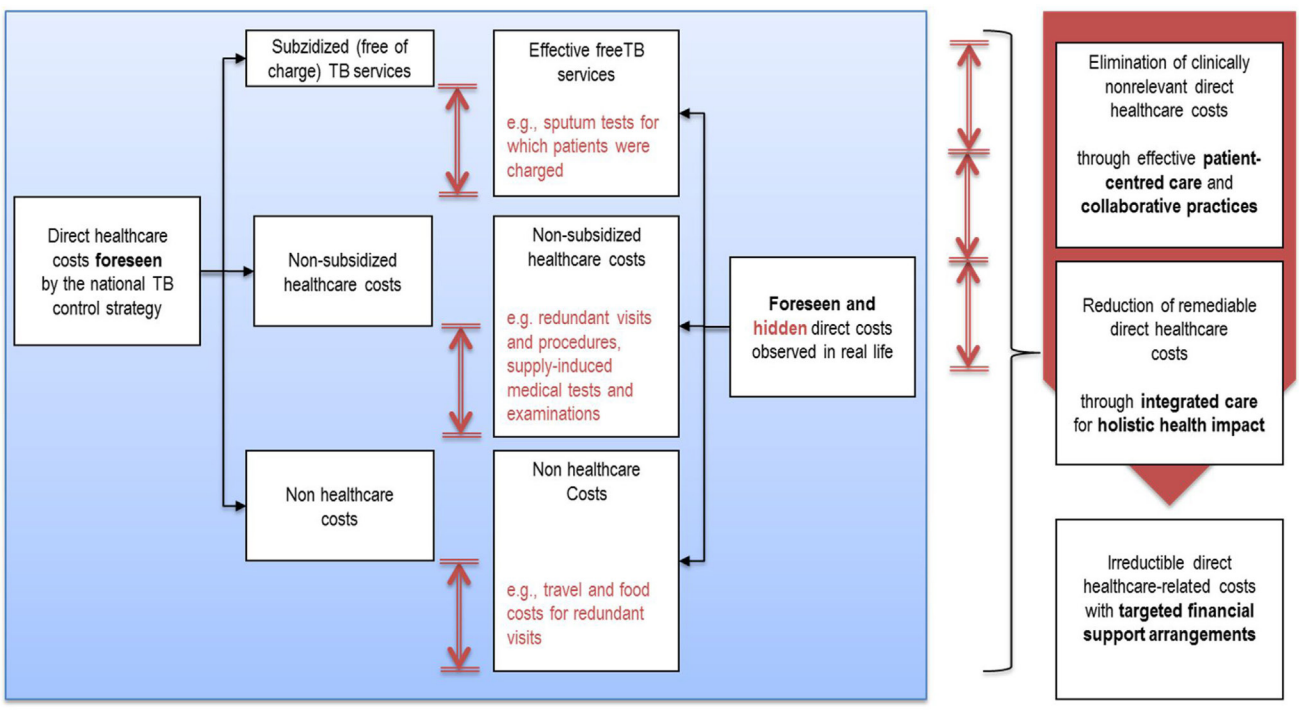

FIGURE 4 | Substantial avoidable health-care costs due to apparent failures in the delivery care system.

private health insurers, pharmacies, practitioners and hospitals, and traditional healers (41). Accordingly, care-seeking behaviors rely on the existence and use of concurrent health-care systems involving a wide range of health facilities and individual practices.

In TB, the DOTS program is traditionally designed for NTP networks of public services. Evidence however suggested that a significant part of TB patients seek and receive care from the private medical sector as a first resort (42). The first point of contact plays a major role in many respects, including early diagnosis and adherence to treatment, which appeared to be two major challenges in TB control. More than a production of care services, health systems should support ill people in realizing their potential health. Therefore, reaching continuity of care is crucial as transition points between services or quality issues mostly occur at the boundaries of services (43). Yet, the success of many health programs is undermined by poor functioning and fragmented primary health-care provision. Recognition of a medical pluralism may then improve equitable access to care and health outcomes. Hence, the first-line health stakeholders tend to be critical pieces of research knowledge translation into action and increased research impact on policy and practice (44).

Private care providers have been substantially involved to improve TB case notification and patient treatment (45, 46). Yet, inappropriate TB management practices of for-profit practitioners were reported in various settings, e.g., use of chest X-rays for diagnosis instead of sputum smear microscopies, irrational drug prescriptions (47). The use of quality care services by the poor was also a core issue in the interrogation of private care delivery (48). In response, public–private initiatives emerged as a mean to address the epidemics of multi-drug and extensively drug resistant (49) and improve health outcomes (50).

Engaging private stakeholders in TB control was endorsed by the WHO as a global approach toward all-patients management according to national guidelines (51). The End TB strategy aims to promote access to quality high-priority care and better respond to national and local critical issues. In sum, engaging all care providers through public–private mix (PPM) initiatives became a core component of the Stop TB Partnership global strategy a decade ago (52). However, the post-2015 era should still bring the answers to the global challenges of effective engagement of PPMs, efficient use of limited resources, and sustainability (53).

Opportunities and Pitfalls of Using Collaborative Approaches to Deliver Holistic Health Impact

To make the TB eradication strategy successful, for-profit practitioners involved in PPMs must not only be well trained to taskwork, which likely refers to the execution of the DOTS (54) but also to teamwork, which refers to interactive behaviors to foster team performance (55). Yet, issues related to role division and collaboration modes were identified as weak components of contracting processes where PPMs were initially implemented (56). Several barriers to effective teamwork may persist, including poor adaptability to changes and seamless dialog between all parties (56). A series of bottlenecks to teamwork were raised in the literature, both within the public and private sectors. They covered inadequate training to collaborative work, absence of operative regulations, perceived little common ground for teamwork, low quality of care, and even reluctance from private providers with respect to "loosing" patients (42); peer influence, care-seeking attitudes, and cultural aspects (46). These aspects mostly refer the XX′ policy gap because of the focus on the supply of care services. To simplify, we opted to emphasize the most direct links with these different aspects and policy gaps. However, provision of care cannot be dissociated with other aspects such as the responsiveness of services offered with respect to beneficiaries' needs (e.g., the need for social support and pre-payments or pooled schemes) (cf. the YY′ and ZZ′ gaps). The systemic reasoning must take precedence over a tunnel vision.

Increased synergy between sub-sectors without burdening public resources remains a crucial issue for many resource-poor countries. Concurrently, positive gains for patients are expected (cf. the ZZ′ gap). So far, most impact measurements of PPMs relied on program-based or medico-focused process and outcome indicators, often neglecting to assess potential gains in financial health protection. Nonetheless, the integrated approach—limited to PPMs in this case—intends to address the economic burden of disease.

Among the first to evaluate PPMs from an economic perspective, an Indian study revealed major drivers of patient costs before TB diagnosis and during treatment, respectively, lost wages and non-medical expenditure on transport (57). For high-burden patients, significant improvement in financial protection and access to quality care were attributed to PPMs. Globally, PPMs were indeed promised as cost-effective approaches to foster equity in TB care access and financial protection for the poorest (51). Recently, such partnerships allowed to lower direct and indirect costs for patients treated in PPM programs versus non-PPM sector, up to five times less for out-of-pocket expenditure and half as much for lost income (58). Particularly, PPM considerably lowered the burden of transportation costs to access TB services (46). Recent evidence on cost savings opportunities for TB patients using PPMs thus confirmed their potential effective contribution to achieve the poverty-related aspirational goal of reducing financial burden of illness (i.e., the newly promoted End TB Goal).

By contrast, other studies highlighted additional consultation fees or spending on diagnostic tests, drugs for complications or herbal medicines in PPMs (cf. the XX′ gap). Recall that these elements were featured as major contributors to the economic burden borne by TB-affected households (the ZZ′ gap). Besides, although pointed as cost-effective at short term in high-burden countries (59, 60), it should be raised that some PPMs require running under substantial investments (notably for orientation and referral procedures sensitization tools and training activities). Moreover, their outcomes varied significantly according to local care delivery settings and contextual factors (58). Then, new evidence is needed to first, better document budget impact of potential extra fees charged for consultation, diagnostic tests, or TB medicines to manage TB and coinfected cases, and second, prioritize services by cost-effectiveness in order to avoid forgoing of potential large gains for patients and health programs. Engaging various actors in PPMs thus impose to deal with

complexity. Future research is expected to actually conclude on cost-effectiveness of PPMs on the long run.

Obviously, there should be numerous innovative ways of achieving the three strategic End TB goals simultaneously. One can be through applying effective collaborative work with the specific aim of improving programmatic performance for TB control together with the patients' perspective (cf. the X′Y′Z′ policy gaps). Showing successful NTP outcomes attributed to a reorganization of the work into a collaborative approach, a "Quality Assurance Project" implemented in rural Bolivia caught our attention (61). The core process was to set up a series of quality improvement teams conducted by collaborative leaders and composed by health workers and NTP regional and national stakeholders. Then, engaged first-line practitioners raised awareness on the benefits of changes in both patients' and providers' behaviors toward improved care use and delivery. Comprehensive measurement guidelines to assess collaborative patterns among all first-line health workers should help reaching evidence-based decision-making. In Bolivia, the focus given on quality performance of collaborative work allowed developing the most appropriate solutions to address the locally identified programmatic gaps and clinical problems. Indeed, the use of monitoring and evaluation indicators was promoted and related to low-performance issues such as the lack of compliance to treatment and early detection, limited DOTS practice in rural areas, weak drug logistics, poor lab quality control, and deficiency of clinical training of health staff—of which most were reported in our case studies. Key concerns in this dynamic would rely in producing the development of relevant knowledge and effective data use for local and programmatic improvements. A sector-wide implementation approach to comprehensive assessment of PPMs would yet serve to better predict catastrophic health expenditure incurred by TB patients as well as local breaches and actors who need to work collaboratively toward improved seek, use, and delivery of care services (37). Getting the right information will definitely help to produce the best value in health.

Heavy reliance on out-of-pocket payments for health, with possibly a large portion of it spent within the private sector calls for utmost caution. Evidence must support the added value of inclusive approaches in terms of positive actions such as improving the quality of patients' care pathways and reducing the associated economic burden of illness. At the same time, it is essential to take account of the risks potentially induced by policies aimed at strengthening or expanding the private sector or its role in public provision of health-care services. A controversial report highlighted several weaknesses of the mainstream optimism in favor of commercial private health-care delivery in poor countries (62). In this respect, the recommendations may include to maintain interest in growth and support in the public sector, to strengthen the evidence that can demonstrate the societal benefits of PPPs, and the importance of capacity building to better regulate health provision.

CONCLUSION

This study brings to the fore that low-income households tend to be hindered from accessing primary care services delivered within pro-poor systems due to a complex pattern of interrelated financial and weak system reasons. It provides critical clues on supply induced catastrophic health expenditure mostly due to a lack of responsiveness to local needs in the implementation of national health programs. Out-of-pocket payments made at the point of services are central in health financial reforms toward increased financial protection and UHC, which are currently operated in many countries over the world. Those countries experience serious challenges for offering and maintaining delivery of quality health care for all.

Comprehensive assessment of the economic burden of illness may inform health planners and decision-makers with the development goals. Used as a lever of change for this purpose, the poverty disease focus sounds promising. The TB control strategy was based on strong scientific evidence. Vertical disease-specific programs such as TB control may have non-negligible positive effects on the accuracy and completion of data collection in monitoring reports. Realizing transversal integration with the silos of health programs such as TB or HIV/AIDS and other medical and social care services can make complex health systems better responsive to the crucial issues of multi-morbidity, erratic care pathways, and economic burden of illness. Congruent and collaborative practices of multiple health entities and practitioners, including private actors and patients themselves, are challenging but needed for holistic health impact and case management optimization.

To conclude, the full spectrum of possible interventions to facilitate cost-effective PPMs would include different approaches i.e., the implementation of locally relevant tools and guidelines for practice, benchmarking practices, taskwork and teamwork training, learning projects to build mutual confidence between parts, early participation of coordinated stakeholders, actors' involvement in planning, process facilitator entities, contracting, and regulation. Joint efforts of the existing health-care sub-sectors, private and public, tend to constitute a way to solve underperforming TB control activities provided in low-income settings. Nevertheless, a common concern of public health workers remains the need to accommodate with the patients' environment and patterns to ensure readiness of and compliance to health programs activities. Funding mechanisms should support collaborative work practices to integrated care delivery and stakeholders' engagement. Additionally, integrated care opportunities should remain flexible to providers co-developed guidelines and other instruments for patient-centered care. These must address local priorities and all health actors' new needs. Rational decisions for efficient and equity-friendly disease-specific control interventions will rely on a transparent evidence base that can be provided through regular assessment and monitoring of policy responsiveness to improved health goals. Various high-level meetings highlighted the importance of measuring the impact of PPMs, both in terms of cost-effectiveness and ability to reduce economic burden of disease (53, 63). Then, comparative patient costs studies and cost-effectiveness evaluations are necessary to build strong and informed health policies. This calls for innovative forms of effective partnerships not only to care but to prevention and control of TB and other illnesses.

AUTHOR CONTRIBUTIONS

SL is the only author of this work, executing all research, manuscript, and figure preparation.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Medicine

PERSPECTIVE
published: 14 May 2019
doi: 10.3389/fmed.2019.00106

From Opioid Pain Management to Opioid Crisis in the USA: How Can Public-Private Partnerships Help?

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The current opioid crisis in the USA arose from (at first) successful opioid pain management in three waves, starting in the'90s. Today, USA patients consume opioid drugs on a massive scale. Considering their potential for tolerance, as well as their potential for lethality in relatively small overdose, the overuse of opioids form an urgent threat to public health in the USA. Since the opioid crisis is a complex phenomenon, several stakeholders are needed to tackle the problem. Both public and private stakeholders should collaborate, e.g., in Public-Private Partnerships. Those collaborations should focus on different aspects related to the opioid crisis such as medical and societal (e.g., pain management process, including addressing opioid use disorders), as well as economical and regulatory issues (e.g., incentivizing the search for alternative non-addictive pain medication and banning aggressive marketing tactics used by the pharmaceutical industry). Additionally, collaborations should cover interdisciplinary education and training of various healthcare actors involved. In conclusion, interdisciplinary collaboration on the various opioid abuse-related aspects is urgently needed to tackle the opioid crisis in the USA.

Keywords: opioid crisis, pain management, public-private partnerships, USA, a perspective

OPEN ACCESS

Edited by:
Laurent Pierre Nicod, University of Lausanne, Switzerland

Reviewed by:
Segundo Mariz, European Medicines Agency, United Kingdom
Domenico Criscuolo, Italian Society of Pharmaceutical Medicine, Italy

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Specialty section:
This article was submitted to Regulatory Science, a section of the journal Frontiers in Medicine

Received: *10 August 2018*
Accepted: *29 April 2019*
Published: *14 May 2019*

Citation:
Bolliger L and Stevens H (2019) From Opioid Pain Management to Opioid Crisis in the USA: How Can Public-Private Partnerships Help? Front. Med. 6:106. doi: 10.3389/fmed.2019.00106

The opioid crisis is a byproduct, and more particularly, an adverse event of medical care (1).

The "opioid drug" class contains four categories according to the Centers for Disease Control and Prevention (CDC): (1) natural opioid analgesics, such as morphine and codeine as well as the semi-synthetic opioid analgesics such as oxymorphone, hydrocodone, oxycodone, and hydromorphone, (2) the synthetic opioid methadone, (3) any other synthetic opioid, such as fentanyl and tramadol, and (4) the illegally-made opioid heroin, synthesized from morphine (2). Legally produced opioids are safe, highly effective analgesics and indispensable in modern pain management, when used for a rightful purpose, during supervised therapy and handled by a competent physician (3).

In 1986, the World Health Organization (WHO) proposed a three-step pain ladder for the treatment of pain (4). The first step comprises non-opioid analgesics, such as paracetamol, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) for managing mild pain. In the second step come weak-opioids like codeine or tramadol for moderate pain. The third step includes strong opioids such as morphine, fentanyl, and oxycodone (5). Opioids should only be prescribed when non-opioid analgesics and adjuvant therapies were unsuccessful. Additionally, opioids should be dosed as low as possible, achieving pain relief with a minimal level of side effects (3).

Dependence is a serious side effect associated with opioid use, which can lead to compulsive use despite negative consequences, a principal characteristic of substance abuse disorders as defined by the Fifth Edition of the Disease and Statistical Manual of Mental Disorders (DSM-5). Opioid use has led to a public health crisis which is characterized by an exponential growth in people suffering from opioid use disorders in several countries, notably the USA. This opioid crisis has been described as the latest self-inflicted threat to public health in the USA where drug overdoses, predominantly caused by opioids, are the leading cause of death for people under the age of 50 (1).

The USA opioid crisis rose from a perfect storm of events with three major waves (**Graph 1**) (6). Since the 1990s, a first wave resulted in increased deaths related to natural and semi-synthetic prescription opioids (7). Since 2010, a second wave was observed with a rapid increase in deaths caused by heroin overdoses. Since 2013, a third wave began with overdose deaths involving synthetic opioids, especially fentanyl (8). Together, this has led to an exponential increase in deaths related to opioid overdose and it has been widely debated what caused those waves.

The opioid crisis has been proposed to initially stem from efforts to address the problem of under-treatment of pain, which motivated practice and policy shifts (9). In the early 1990s, the number of opioid prescriptions increased consequently, not only for the treatment of acute pain (10) but for chronic pain as well (11). Given that up to eleven percent of chronic pain patients using opioids were found to meet criteria for substance abuse disorders (12), these practice and policy shifts may readily explain the steady growth in prescription opioid abuse. This was exacerbated by other factors. Pharmaceutical companies interested in expanding their markets misused the practice and policy shifts with aggressive marketing strategies (13, 14). In 1996, an extended-release oxycodone formulation was introduced to the market that was proposed by the manufacturer to be effective for 12 h while being less addictive (15). At the same time, when patients still experienced pain, they were advised to take higher doses, rather than taking the extended-release oxycodone more frequently (16). This further nurtured so called "pill mills," physicians who prescribe opioids regardless of medical need (17). Moreover, not all prescription opioids are taken by pain patients. Particularly acute pain patients take on average only one third of the prescription opioids (18). Each of those leftover pills can be sold with substantial financial profit, leading to an increased availability of prescription opioids for non-medical use. Due to the disappearance of manufacturing jobs, rising inequality, the economic crisis in 2008 and long-term unemployment, the temptation to sell the drugs for cash or to take them for emotional relief instead of physical pain, increased. Moreover, some of the prescription opioid users discovered that the time-release mechanism of slow-release oxycodone could be defeated by crushing the pills and injecting or snorting the now effectively short-acting and highly addictive opioid. Discussions about how to misuse the prescription opioids and their effects became public and spread quickly, especially through the growing use of the internet (16). In 2010, the government started to crack down on "pill mills" (17). Additionally, an abuse deterrent formula for slow-release oxycodone was announced as an attempt to meaningfully deter abuse by making it more difficult to crush the pills (19). As a result of those actions, some of the people addicted to prescription opioids changed to using heroin, since it is easier to use and cheaper (20). Indeed, as much as eighty percent of heroin users started with taking prescription opioids (21). Compared to heroin, synthetic opioids are relatively easy to produce and traffic in substantial quantities given their very high potency. It is therefore not surprising that from 2014 onwards, the number of fentanyl-related deaths increased by 72% (22).

Pharmaceutical companies provide physicians with free drug samples, including prescription opioids, for promotion purposes. This is a common practice in the USA. While in the European Union (EU), opioids are subject to legal measures since 1992, so far, no initiative to ban the provision of free samples has been introduced in the USA. Even though the difference in drug marketing can be linked to different health care systems between the EU and the USA, banning free drug samples should be urgently considered by policymakers (13, 14). By now, opioids belong to the most widely-prescribed drug classes in the USA. The country faces an extreme situation since it constitutes only five percent of the world's population, but it consumes 56% of the world's opioid drugs (23).

MULTI-STAKEHOLDER COLLABORATIONS NEEDED TO TACKLE THE OPIOID CRISIS

Opioid analgesic abuse is a complex and multifactorial problem. No single stakeholder can solve this crisis independently (24). In 2005, the Food and Drug Administration (FDA) transformed the drug risks and benefits assessment and issued a series of guidance and the so called "risk minimization action plans" (RiskMAPs) including risk minimization tools offered to industry in order to achieve "specific health outcomes related to known safety risks" (25). In 2016, the FDA issued its Opioids Action Plan (26), aiming to reduce opioid prescription behavior through education programs. The corporate social responsibility of the pharmaceutical industry in the USA lacks. In its Opioid Action Plan, the FDA also aims to reexamine the underlying risk-benefit paradigm for opioids (14, 27). The pharmaceutical industry should contribute with its expertise in product abuse risk assessment, product communication and education, and cooperate with federal and state authorities, as well as with law enforcement authorities (24). They should implement product abuse and diversion procedures in their corporate mission statement, comparable as what the European Federation of Pharmaceutical Industries and Associations (EFPIA) have introduced in the healthcare professional code (28).

Already in 2003, collaborative initiatives had been set up to unite diverse investigator groups to cooperate in the field of pain research, such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN). Examples of pain management partnerships include the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) aiming to define an imaging-based signature for pelvic pain, or the Collaborative Health Outcomes Information Registry (CHOIR)

wherein an open-source learning healthcare platform was used as a basis to develop a deep signature of individual patients across several dimensions of social, psychosocial, and physical functioning. This registry generated new insights about what leads to pain persistence and what drives pain in general. However, the setup of those partnerships was not broadly implemented (22) and certainly did not end the trend of the significant increase in non-medical use of prescription opioid analgesics in the USA.

In order to boost collaboration, President Obama dedicated in 2016 more than 1 billion US Dollars to set up evidence-based prevention programs to support monitoring of prescription drugs, take-back events related to prescription drugs, and to facilitate the access to the overdose reversal drug naloxone (29).

Tackling the prescription opioid abuse requires a joint effort of multiple stakeholders involved in the pain management process. Public-private partnership (PPP) models vary depending on the type of participants, the funding, the mission, and objectives (30).

PPPs such as the International Rare Diseases Research Consortium (IRDiRC) (31) could serve as a role model in the fight against opioid addiction. The FDA could benefit from close collaboration with industry to review the system barriers and organizational issues in the regulatory system and work toward official action to end the practice of aggressive marketing strategies. The Orphan Products Grants Program of IRDiRC integrates industry, regulatory agencies and patient advocacy organizations to collaboratively develop recommendations for improved R&D and guidelines, regulation and patient involvement. The FDA jointly works with industry to define incentives including expedited reviews of new drug applications for alternative products, having tamper-resistant properties and support in the development of risk management plans (24). Furthermore, the reimbursement policies could be a subject of the regulatory science-based consortia, aiming to prevent addicted patients to turn to cheaper, but illegal alternatives which are more lethal.

Collaborations should focus on various aspects related to the pain management process, including addressing the industry's lack of interest to invest in developing non-addictive pain medication and addressing opioid use disorders. Since deterring data concerning the development of successful and failed pain medication is one major stumbling block (32), PPPs can be set up that focus on more precompetitive targets, such as the development of data management tools, registries, and shared databases. These data could facilitate the understanding of heterogeneous patient groups and their characteristics when integrated in clinical trials. Also developing biomarkers to stratify patients for trials and demonstrating target engagement, applying new technologies to facilitate pain medication discovery, creating a research trial network, establishing objective pain sensitivity measures, and reengineering preclinical platforms to improve predictive efficacy are topics that can be the focus of early-phase research PPPs. Further, developing subgroups of large cohort studies and repurposing already existing compound, doing molecular profiling to begin validating targets and working on new chemical entities, developing new bioinformatics tools for target discovery purposes and reverse and forward translation, cellular and mechanistic studies are situated in the precompetitive sphere. Another aim of PPPs could be to screen research using preclinical addiction models with focus on reproducibility and reliability of published data. Moreover, PPPs might do research on pharmacogenetics of addiction and focus on working on programs to deliver extended-release formulations of buprenorphine (opioid to treat opioid addiction) in hospital emergency units to prevent opioid overdose, drug-seeking, and drug-taking behavior (32).

Depending on the objectives of the partnership, public and private constituencies affected by this societal crisis need to collaborate, such as healthcare practitioners, patients, professional organizations, researchers, educators, pharmaceutical manufacturers, insurers, public health agencies, the criminal justice system, and various governmental institutions at local, state, and federal level, such as the FDA, the Office of National Drug Control Policy (ONDCP), the Drug Enforcement Administration (DEA), and the Substance Abuse and Mental Health Administration (SAMHSA) (24).

The National Institute on Drug Abuse (NIDA) focuses its research toward new analgesics, alternative delivery systems and formulations, treatment of opioid abuse and addiction, and prevention of overdose deaths. The recommendations formulated stipulate the need for collaboration for prevention, education, and outreach (29, 33). The standard measure for pain assessment currently available may lack adequacy or accuracy. New evidence-based tools and technology platforms could help to deliver information on how to better treat various subpopulations of patients (34). Furthermore, registries should be set up to gather and process data related to various drugs, patient monitoring, expanded electronic medical records (EMR), and therapy. The theoretical framework is present. However, the concrete implementation of the collaboration between various healthcare actors involved in pain management and treatment of addiction in terms of (precompetitive) research, treatment, prevention, and education is not adequate to tackle the growing crisis (29).

More efforts are needed to investigate the development of curricular core competencies in the field of pain management and how to implement new educational approaches. Guidelines and best practices related to risk assessment and management as well as prescription behavior should be developed and implemented in new educational approaches (29). Collaborations should encompass education and training of multiple healthcare disciplines. This new educational models should be taught to the next generation of healthcare providers, including schools of medicine, nursing, physical therapy, and dentistry as well as part of a continuous learning track for all healthcare actors (29).

The search for innovative drugs with reduced abuse, tolerance, and addiction risk is situated in a more competitive environment and will require specific incentives for the pharmaceutical industry to collaborate (30, 32). Abuse-deterrent formulations are used in less than three percent of the cases, most likely due to their high price. Pharmaceutical companies might be reluctant to invest in developing them, when payers are not incentivized to cover such medication. PPPs, driven by the industry as they carry

the burden for this crisis, should develop assisted funding systems for developing alternative drugs.

Investigating how to improve and speed up the regulatory system as well as pricing and reimbursement policies, is hence another key approach to collaborate with each other.

CONCLUSION

The opioid crisis is of complicated and multifaceted nature that calls for urgent collaborative action. An interdisciplinary approach is needed by engaging several disciplines. Various types of PPPs should be set up to focus on research, training, and education. The research PPPs encompass early-phase research developing tools, technologies, and platforms to accelerate the drug development process, as well as the more competitive task of developing new pain medication and also defining the strategies, medication, and behavioral practices to treat opioid use disorders. Training and education partnerships aim to educate the various healthcare actors involved to implement these strategies and best practices in the healthcare system (32). The role of participation of patients, both those addicted due to physical and psychological pain, therein is pivotal.

PPPs are a tool, not an objective *per se*. The key stakeholders involved, each with their accompanying expertise, resources, and experiences are essential to implement the changes needed to tackle this public health crisis. Not one actor is solely responsible for all aspects of this opioid crisis, however, the classical roles of the various actors, such as the pharmaceutical industry, the nonprofit sector, academia, and the government needs to be reviewed with respect to the challenges faced (24). Successful collaborations are built upon trust, clear rules and agreements on the mission, the project objectives, the responsibilities of the different stakeholders, and a good definition of the key performance indicators that will be used to measure the PPP's success (24, 35). All need to work cooperatively to protect the public interest.

Regardless of promising outcomes of PPPs, the National Institute of Health (NIH) must remain critical and take ethical considerations into account when accepting any sort of support from companies of the e.g., pharmaceutical sector, since they have contributed to a large extent to the opioid crisis (14, 36).

It can be concluded that despite novel approaches and alternate formulations being developed to address the opioid addiction, more resources are needed and the urgent situation of the opioid crisis in the USA calls for more attention (32).

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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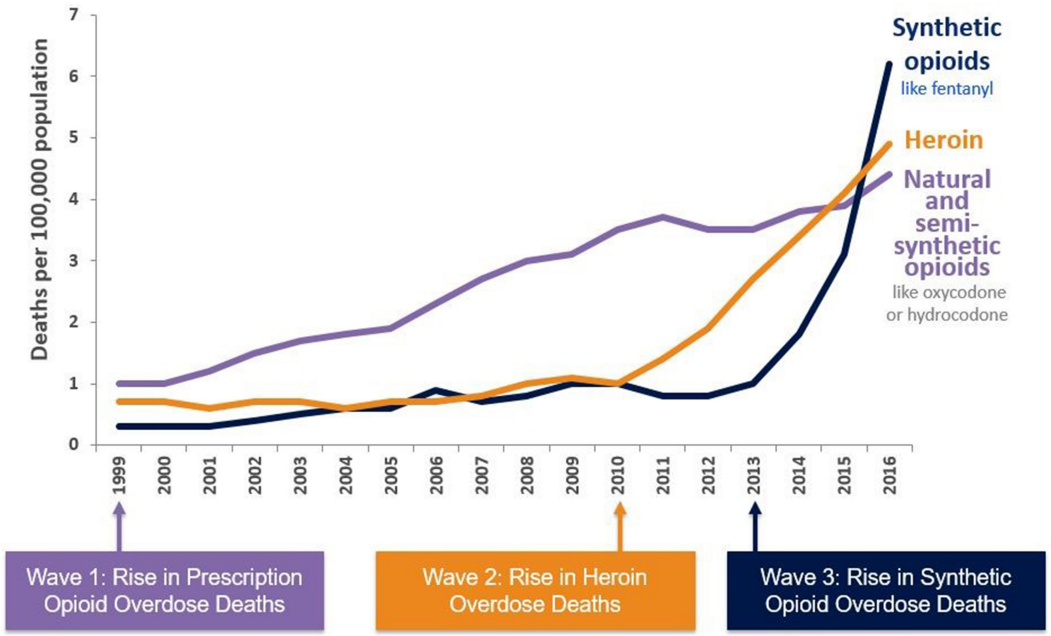
Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX



Graph 1 Three waves of the increasing opioid crisis (6).

frontiers in Medicine

REVIEW
published: 03 December 2019
doi: 10.3389/fmed.2019.00275

The Innovative Medicines Initiative —10 Years of Public-Private Collaboration

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The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Union and the European pharmaceutical industry. Born of the necessity to foster collaboration between different stakeholders in order to address growing challenges in bringing new medicines to market and the rapidly evolving healthcare landscape, IMI has successfully delivered the radical collaboration needed to address these challenges. In this article we reflect on some of the major achievements of the programme by highlighting a few of the key projects funded and the progress they have made, as well as some of the lessons learnt in delivering such an ambitious partnership. Those that drove the foundation of IMI recognized that to address these challenges required not just ambitious scientific approaches, but also an awareness of societal needs. Therefore, actors from beyond the traditional pharmaceutical research communities would be needed. One of the key successes of IMI has been to foster radical collaboration between diverse public and private partners of all types, including large pharmaceutical companies, SMEs, regulators, patient organizations and public research institutions. It has achieved this by being a neutral platform where all partners are bound by the same rights and responsibilities. Since it began there has been an evolution in the understanding of what is considered "pre-competitive," resulting in IMI projects now addressing all of the steps within the pharmaceutical development value chain. With this expansion in the types of projects supported by IMI, different actors from beyond the traditional pharmaceutical research family have been attracted to participate, enriching further the collaboration at the heart of the programme. Finally, such a complex programme brings with it challenges, and we reflect on some of the important learnings that should be applied to future collaborative models to ensure that they are as successful as possible and deliver the expected impact.

Keywords: public-private partnership, healthcare, medicines, innovation, multi-stakeholder, society, European Union, industry

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Translational Medicine, a section of the journal Frontiers in Medicine

Received: *12 August 2019*
Accepted: *11 November 2019*
Published: *03 December 2019*

Citation:
Laverty H and Meulien P (2019) The Innovative Medicines Initiative —10 Years of Public-Private Collaboration. Front. Med. 6:275. doi: 10.3389/fmed.2019.00275

INTRODUCTION—THE NEED FOR A PUBLIC-PRIVATE PARTNERSHIP IN HEALTH

It is clear that the economic sustainability of our health systems in Europe (and elsewhere) is under threat. Whether we are talking about affordable medicines, the lack of sufficient healthcare professional resources, or society's challenge in investing in prevention, all angles of the healthcare ecosystem are currently stretched (1).

Given the scale and complexity of the challenges faced, the only route by which they can be addressed is through multidisciplinary, multi-stakeholder approaches where the risks and benefits of overcoming them are shared. For the past 11 years, the Innovative Medicines Initiative (IMI) has been promoting the radical collaboration necessary to overcome some of these challenges in relation to speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need. There are 4 broad areas in which IMI projects operate; the first is where there are currently market failures i.e., no incentives for private sector investments; the second is in tackling highly complex diseases where pre-competitive consortia are necessary to accelerate knowledge acquisition to a point where product development is envisaged; the third area is providing technology platforms where private and public entities pool resources to improve drug development; and finally, addressing gaps in the drug discovery/development ecosystem where precompetitive collaboration is necessary to overcome the challenge. Information related to the setting up of IMI and progress of the programme has been published previously (2–4). In this article we reflect on how IMI is able to promote collaboration, and what could be delivered by using this collaborative model as the basis for future partnerships. We reflect on some of the challenges faced, and discuss how this collaborative model could be extended to encompass current societal challenges and deliver the changes necessary to help healthcare become more affordable and sustainable for all.

EVOLUTION OF THE IMI PROGRAMME

The Innovative Medicines Initiative Joint Undertaking (JU) is a public-private partnership (PPP) between the European Union (EU), represented by the European Commission (EC), and the European Federation of Pharmaceutical Industries and Associations (EFPIA)[1]. When it was launched in 2008, the overall goal of the first IMI programme (IMI1) was to "significantly improve the efficiency and effectiveness of the drug development process with the long-term aim that the pharmaceutical sector produces more effective and safer innovative medicines."

In order to make progress toward this goal, a budget of EUR 2 billion was mobilized. Half of this budget came from the EU's seventh framework programme for research and innovation (FP7), which ran from 2007 to 2013. The remaining budget came from EFPIA through its member companies and associations, with the majority of support coming as of "in-kind" contributions. In kind contributions are usually in the form of the time of company researchers working on the projects and the reagents and equipment used in the projects. It is important to remember that none of the EFPIA companies receive any EU funding via IMI; the EU funding supports the participation in IMI projects of universities, research centres, small and medium-sized enterprises (SMEs), patient groups, and regulators.

The IMI1 programme focused on addressing challenges in the early pre-competitive space of pharmaceutical research and development. However, it was soon recognized that other areas that had traditionally been viewed by some as "competitive" also required collaborative approaches. Therefore, while the second phase of IMI (IMI2) is still a collaboration between the European pharmaceutical industry and the EU, the partnership has a broader scope in terms of the questions being addressed. It is also more disease specific, more open in terms of project-specific partnerships, and is able to tackle some market or scientific failures important for public health, e.g., antimicrobial resistance and Alzheimer's disease.

IMI2 operates under the EU's current framework programme for research and innovation, Horizon 2020, which runs from 2014 to 2020. IMI2 has a total budget of up to EUR 3.276 billion, half of which comes from Horizon 2020, and half of which comes from EFPIA member companies and IMI Associated Partners. In addition to mobilizing pharmaceutical companies, the legislation creating IMI2 also emphasizes the need to bring partners from other sectors (e.g., diagnostics, animal health, IT, imaging, etc.) into the IMI community. This open nature of the programme is reflected in the creation of "Associated Partner" status that allows organizations that are not EFPIA members to contribute in kind to IMI projects, and have that contribution matched by the EU. This mechanism has acted as a magnet for those partners who see the advantage of the neutral, multi-stakeholder platform that has been created through IMI.

Building Trust With Stakeholders

Now that IMI has passed its 10th year of existence some of the initial skepticism to the programme has been forgotten. When IMI was first discussed two key concerns for public institutions were the ability to publish research papers and the management of intellectual property rights (IPR). The fear was that the involvement of pharmaceutical companies would block the publication of new research findings or they would take any IPR for themselves. In both of these situations these fears have proven to be unfounded. Regarding the ability to publish, IMI undertakes a bibliometric analysis of project outputs each year and publishes the report on its website. The recent report related the period 2010-2018 has identified 4,938 publications in the Clarivate Web of Science database. The majority of these publications (60%) have been published in high impact journals i.e., those journals in the highest quartile ranked by Journal Impact Factor. The impact of IMI project research (as indexed by citation impact) remains high, with the field normalized citation impact of IMI project research of nearly 1.84 nearly twice the world average of 1.00. Given the highly collaborative nature of IMI projects, their multi-disciplinary partners and the diverse datasets involved, the high level of publication and its quality is not surprising. IMI projects are highly collaborative; 62.2% of all IMI project papers were co-authored by researchers working in different sectors, 84.3% involved collaboration between institutions, and 61.3% of all IMI project papers were internationally collaborative. Internationally collaborative IMI research has a citation impact of 2.64, well over

[1]https://www.imi.europa.eu/about-imi/mission-objectives

twice the world average. Some projects such as BTCURE[2] (IMI1 Call2) have been very prolific in publishing with 645 publications as of the end of 2018.

Another area of concern was the management of Intellectual Property (IP) and ownership of results, but again experience has shown that for many companies, tools and methods that improve the efficiency of their processes are more important than the generation of patents. The IMI IP provisions/rules[3] govern the IP regime of all projects supported by IMI and apply equally to all partners (public and private) in the projects. The IP provisions are designed to support innovation while respecting the interests of all project partners along the following principles: the IP rights of the pre-existing assets brought to a project are preserved and are identified before the project begins as "Background," and ownership of results generated during the project follows inventorship. The policy actually empowers the results owners to decide on the best protection modalities. However, to ensure that the project can be implemented by all the partners, basic access rights to results generated within the project are granted on an equal basis and this provides opportunities of further development and/or validation of projects results. When a project asset is mature enough, access rights for exploitation purposes can be negotiated on a case-by-case basis. IMI favors open access dissemination of project results, but this is subject to legitimate interests and therefore results that may generate value can also be protected by project partners.

An important aspect of IMI's IP provisions is their flexibility, which allows them to be adapted to the needs of an individual project and the participants. As a result, different projects can adapt the provisions to suit whether they are developing an open platform for the research community where access to the data is important, or developing late stage assets in challenging areas such as AMR where the value of those assets may need to be protected.

The importance of engaging meaningfully with patients was recognized as a key goal of IMI from its inception. The key actors in drug development such as the pharmaceutical industries and regulatory agencies have historically been perceived as being too far removed from patients and sometimes taking decisions in which patient interests are not fully reflected. Since its creation IMI has been expanding the ways in which it engages with patients. Many IMI projects engage and involve patients to ensure their experiences can be taken into account and as of the end 2018, close to 60% of ongoing IMI projects have patient organizations either as partners in the consortium or represented on advisory boards, ethics advisory boards, or being consulted for topics of relevance. There was also a conscious effort to move beyond paying lip service to patients and recognize them as full partners in the process. Several IMI projects are focused fully on ensuring that patients and their experiences are fully integrated into the drug development process, while ensuring that trust between different stakeholders is enhanced.

EUPATI[4] focused on providing education and training support to increase the capacity and capability of patients to understand and contribute to medicines research and development. It also worked to improve the availability of objective, reliable and patient-friendly information to the public in several different European languages. The integration of patients into medicines development processes needs to be done in a way that is structured, governed by clear rules and modes of operation to be effective and yield the best results for all stakeholders. The EUPATI project has worked closely with all stakeholders to prepare overarching guidances on meaningful and ethical patient engagement for regulatory processes (5); health technology assessment (6); ethical review of clinical trials (7), and pharmaceutical industry–led medicine [R&D; (8)].

The project PARADIGM[5] builds on these initiatives and is attempting to strengthen the understanding of stakeholders' needs and expectations for engagement (including underrepresented and vulnerable populations). In addition, they aim to build further guidance in three key decision–making points in the medicines development process, research and priority setting, clinical trial design, and early dialogues with regulatory and health technology assessment bodies. Another project focused on engaging and involving patients, PREFER[6], will establish recommendations to support the development of guidelines for industry, regulatory authorities and HTA bodies on how and when to include patient perspectives on benefits and risks of medicinal products (9).

The IMI programme office also recognizes its responsibility toward patients and their carers and has explored how to engage better and involve them more in the work of the IMI programme. From having patient representatives on the Scientific Committee (SC, an advisory body to the IMI Governing Board, GB) to patient dedicated workshops, the IMI office has been exploring the best way to involve patients. In 2019 IMI created a patient expert pool who are called upon to provide input on IMI's scientific strategy by taking part in consultations, participating in workshops, panels to review project proposal, reviews of ongoing and closed projects, review content of materials targeted at patients and the wider public as well as participate in IMI events. All patients carry out their activities in a personal capacity and do not represent an organization. In total 157 applicants (118 patients and 39 family members/carers) have been added to the pool, with 57% female and coming from 26 countries. A large majority have knowledge of research and innovation activities. They have direct experience as patients or carers of cancer, infectious disease, inflammatory/immune diseases, metabolic disease, neurodegenerative disease, neuropsychiatric disorders and pain as well as rare and orphan diseases.

Scientific knowledge is one of the keystones of regulatory decision making and many IMI projects generate data that is of direct relevance to regulatory authorities, health technology assessment (HTA) bodies and payers. Experience to date has shown that regulatory authorities are willing to engage with

[2]http://btcure.eu/

[3]https://www.imi.europa.eu/apply-funding/general-overview/intellectual-property

[4]https://www.eupati.eu/

[5]https://imi-paradigm.eu/

[6]https://www.imi-prefer.eu/

IMI projects via a variety of means (10). In some cases, regulatory authorities are members of a consortium, in others they sit on advisory boards and in some cases they even suggest ideas to be considered for launch as a call topic in the IMI programme. The involvement of regulatory authorities covers a range of areas. IMI supports projects addressing challenges in the area of safety sciences in the hope of advancing more reliable tools for the accurate prediction of the safety of medicines. The SAFE-T[7] project addressed the lack of biomarkers for the early detection of different forms of drug-induced toxicity (11). The eTOX[8] project built a unique toxicology information database using legacy report from multiple sources including all pharmaceutical companies involved with the aim of developing better *in silico* tools that can better predict the toxicology of new compounds (12). Another area of interest to regulatory bodies has been the development of new tools and methods for benefit-risk assessment of medicines. PROACTIVE[9] developed Patient Reported Outcome (PRO) tools that improve the capture of physical activity in relation to chronic obstructive pulmonary disease [COPD; (13)]. The PROTECT[10] consortium has produced a set of recommendations for benefit—risk assessment processes and supporting tools (14, 15). Finally, clinical trial design and how to innovate in this area is a key challenge in attempting to speed up the drug development process. In IMI projects the regulatory authorities have been engaging and exploring what is possible in this domain. A good example is the EPAD[11] project, where 10 pharmaceutical companies along with their public partners and other international bodies are collaborating to address the challenges involved in the selection of patient sub-groups, drug candidates, optimal end points, and statistical methodology (16, 17). The consortium members have been engaging and exploring with the regulatory authorities what is acceptable to them in this challenging endeavor.

To date IMI projects have built good interactions with regulatory authorities, however experience has shown that sometimes the projects leave this interaction until too late in the project to experience the full benefits of the interaction. IMI consortia working in the area of Alzheimer's such as EPAD or autism such as EU-AIMS[12] (18, 19) have engaged with regulators at an early stage of the projects and this has resulted in very beneficial interactions in terms of ensuring the projects are on the right track and the buy-in of the regulators for their chosen approaches. In addition to interactions at the project level, the IMI programme office also organizes regular meetings with the EMA and FDA to hold strategic discussions on topics of common interest, underlining the importance of the regulatory environment for the work undertaken and the challenges been addressed by IMI-funded projects.

How IMI Manages Call Evaluations and the Resulting Projects

The features of how the IMI programme works at the evaluation and project monitoring level is available on the IMI website. However, there are several key features that are worth consideration in order to understand how IMI differs from other funding programmes.

At the heart of how IMI works is the topic development process. While IMI is an equal partnership between the EC and EFPIA, with both founding partners contributing equal funding, it is the industry partners who determine the topics that IMI launches in its calls for proposals. Using the IMI2 Strategic Research Agenda (which provides a public health focused framework given it is based upon the WHO Health Priorities Report of 2013[13]), the industry partners come together and agree on where there they have a shared challenge and where working together will overcome the challenge more quickly than individual companies working alone. In addition, while agreeing the scientific focus of the topic, the companies also determine what resources they will commit to the eventual project. It is important to remember that the public funding provided to IMI goes to public beneficiaries identified through a competitive call process and that no public funding goes to industry partners. Based upon the industry resources identified, IMI then matches this with public funding and these two figures determine the overall budget included in the final call topic text. Call topic texts are consulted upon with the EC, SC and States Representative Group (an advisory body to the IMI GB) prior to approval by both founding partners via the GB.

Once a topic has been launched IMI invites applicant consortia composed of public entities to work together and submit a short proposal in response to a given topic text. Any entity may be part of an applicant consortium as long as they have a well-defined and non-redundant role within the consortium. These short proposals are then subject to a review by an independent panel of experts selected by IMI. This review is based on clearly defined, publically available criteria and the original topic text. The panel scores and ranks the proposals and only the top-ranked proposal is invited to the second stage. Only the top-ranked proposal is invited to the second stage, as at the second stage the successful applicant consortium is merged with the original industry consortium that prepared the topic text to form a completely merged full consortium. This full consortium then prepares a full proposal with detailed work plan, milestones and deliverables etc. Once again the full proposal is subjected to independent review by a panel of experts and this panel makes a go/no-go recommendation to the IMI GB. When the GB approves the recommendations the full consortium is invited to the granting stage of the process. During this phase the consortium agree a Consortium Agreement (CA) covering all aspects of project operations, access to data generated, IPR etc. The CA is the sole responsibility of the consortium partners; IMI does not participate in its negotiation, rather, once the CA

[7] http://www.imi-safe-t.eu/
[8] http://www.etoxproject.eu/
[9] https://www.imi.europa.eu/projects-results/project-factsheets/pro-active
[10] http://www.imi-protect.eu/
[11] http://ep-ad.org/
[12] https://www.eu-aims.eu/#
[13] https://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1

is agreed IMI will then sign the Grant Agreement (GA) with the consortium.

Once the GA is signed then the project can start. During the lifetime of the project the IMI office staff monitor the projects very closely to ensure that the project is on track scientifically and that the project is being executed according to IMI's rules. Each project must submit a periodic report in which progress against the original work plan is checked and whether the public funding and industry contributions are being used in line with IMI rules. Although not obligatory under the H2020 rules, all IMI projects are subject to an interim review in which independent experts, usually headed by a member of the IMI SC, review the progress of the project and can make recommendations in case they identify issues. This is complemented at the end of the project with a close out meeting where project representatives come to the IMI office and explain what the project has achieved and what has been learnt.

The Challenge of Forming an Applicant Consortium

Since the launch of IMI1's first call for proposals it has been recognized that the formation of applicant consortia presents a unique challenge for many researchers. Given the scope of many IMI topics applicant consortia need to be composed of multi-stakeholder, multi-disciplinary teams and the identification of these partners in different fields is not always straight forward. Many leading researchers already have established networks of peers in different countries working in different areas of research and these researchers have the advantage of having a pool of talent to draw on when it comes to consortium formation. More junior researchers or organizations, such as patient groups or SMEs, may not have well-established networks outside of their field of interest and therefore struggle to identify all the expertise that may be required to respond to an IMI call. In the interest of transparency and fair treatment, the IMI programme office is unable to assist potential partners to form consortia, adding to the challenge for some of those interested in applying in forming a suitable consortium. While there are different partnering search tools and different fora for researchers to network these are not always effective when trying to form a large consortium of diverse expertise at short notice. Therefore, it is important for anyone interested in collaborative programmes such as IMI that they establish their networks in advance of applying in the future. This challenge will persist in future programmes and may be exacerbated in programmes where the scope is envisaged to be broader than the current programme.

In order to help the formation of the consortia, IMI publishes its scientific priorities and draft topic texts as early as possible, sometimes several months in advance of official publication. However, this cannot fully compensate for having a well-established network of international collaborators.

The fact that industry plays a key role in determining the research priorities of the IMI programme is sometimes criticized as it is seen as giving too much control of the programme to industry partners. However, industry experiences the real challenges of drug development and the regulatory environment first hand, knows where they have failed and understands where the individual companies can collaborate. If we are to make real impacts upon the challenges within drug development processes, then we need to ensure that the challenges being addressed are relevant and will generate the desired impact. It is also important to remember that unlike other governmental or public led collaborations, IMI is not a co-funding model; rather it is a true collaboration. Unlike some other national PPPs with government agencies involved the industry partners are not seeking to buy a service or provide money for the execution of tasks. Within the IMI model, industry partners are fully engaged in the final project as they share the same responsibilities and obligations as the public partners. All industry partners sign the consortium agreement and also the grant agreement. During the project the industry partners have well-defined tasks and it is usual for work packages to have joint leadership with both public and private partners contributing work package leaders.

IMI Progress in Numbers

By the end of 2018, under the two programmes 119 projects had been launched involving over 2,000 participations drawn from a wide range of stakeholders, and the portfolio is constantly growing[14]. The analysis of the data collected up to 31 December 2018[15] shows that almost all the relevant priority areas in the IMI2 Strategic Research Agenda (SRA) have been addressed. For IMI1, as of the end of 2018 EUR 965.7 m of EU funding had been committed matched by EUR 965.1 m of in kind contributions committed by industry partners. For IMI2, EUR 655.6 m of EU funding had been committed matched by EUR 664.9 m of in kind contributions committed by industry partners.

The types of organizations involved in IMI at the end of 2018 include; 597 universities and academic institutions, 61 EFPIA members, 229 SMEs, 33 patient organizations, 29 regulatory authorities and 15 associated partners. The areas that have received the most funding to date include EUR 1.1 billion in the area of infectious disease (includes) AMR and vaccines, over EUR 300 m in the area of brain disorders and neurodegeneration, nearly EUR 250 m in the area of diabetes and metabolic disorders, EUR 214 m in drug discovery, EUR 142 m in cancer and EUR 126 m in the area of data knowledge and management.

IMI has launched projects covering a wide array of disease areas and challenges in the discovery and development of new medicines including infectious control (20), neurodegeneration (21, 22), cancer (23, 24), diabetes (25, 26), immunological disorders (27, 28), drug safety testing (11, 12), clinical trial design (29), and the use of real world evidence in drug development (30) to mention but a few. The outputs from the projects are many and varied and to date, the partners involved in IMI projects have generated 4,983 publications (with a normalized impact factor of 1.84, nearly double the EU average). The examination of the results shows that IMI2 projects have generated 16 assets that completed a significant milestone during the project lifecycle

[14]https://www.imi.europa.eu/projects-results

[15]IMI Annual Activity Report 2018. Available online at: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/AAR2018_final.pdf

(vs. an overall target of 50 for the IMI2 programme), and if we look at both IMI1 and IMI2 programmes together, the analysis shows that 57 assets have completed a significant milestone so far. The definitions of "projects' asset" and "significant milestone" were meticulously defined. Examples of assets are tools, methodologies, processes, services, training materials, etc.; examples of significant milestones are key clinical trial phases, animal models, prototypes, commercialization, patents, publications, etc. A subset of IMI projects has managed to impact the regulatory framework and received acceptance by regulatory authorities: for IMI2 there are 7 completed procedures with 4 regulatory qualified opinions and 3 CE marks granted (vs. an overall target of 15 for the IMI2 programme). If we look at both IMI1 and IMI2 programmes together there are 15 complete procedures. Several new tools and processes generated by IMI2 projects have been implemented by the industry participants (examples of implementations are animal models, standards, biomarkers, SOPs, use of screening platforms, clinical trial networks, etc.). The data shows the take-up and utilization of 19 IMI2 project results (vs. an overall target of 50 for the IMI2 programme) and 122 results taken up by industry partners if both IMI1 and IMI2 programmes are considered together. Many tools and new methodologies have been published and information on tools available to researchers are available on the IMI website[16]. It is worth considering that many IMI2 projects have not yet reached their midpoint and there are many more projects to be launched. The data so far suggests that the programme is on track to meet its objectives and the projects are well on track to meet the expected targets for the key performance measurements of the initiative.

In such a short article it is impossible to do justice to all of the projects that have been launched under IMI2. This article will therefore focus on three areas: drug discovery, infectious diseases, and addressing unmet societal needs. It describes a couple of projects from each, demonstrating what can be achieved when different stakeholders collaborate at a scale which is in proportion to the challenge.

COLLABORATING TO SPEED UP THE DISCOVERY OF NEW MEDICINES

Antimicrobial resistance (AMR) is a major global public health threat with bacteria becoming increasingly resistant to existing antibiotics. The rising mortality rates and extended hospitalisations for patients associated to this resistance is also translating into increasing treatment costs for health services. In 2018, the European Centre for Disease Prevention and Control (ECDC) released figures showing that 33,000 people die every year in Europe from infections that prove resistant to treatment, a number that is rapidly increasing. So there is an urgent need to discover and develop new anti-infectives, especially new antibiotics. However, not only is this scientifically challenging, but antibiotics have a low return on investment compared to other medicines, making them an unattractive area for drug developers. Indeed, as the use of new mechanism of action antibiotics will be limited by governments and health authorities in order to slow resistance acquisition, this area represents a true market failure and incentives for industry participation are thus warranted.

Through its New Drugs for Bad Bugs (ND4BB)[17] programme, IMI has invested heavily in a portfolio of projects that address most of the challenges along the entire value chain of AMR R&D, facilitating collaboration and de-risking novel approaches (31). The first projects were launched in 2013 in response to the EU's action plan on AMR. The COMBACTE[4] projects have now set up a network of hundreds of hospitals and laboratories to facilitate the conduct of pan-European clinical trials and studies (32, 33). The network is already being used extensively for a broad range of studies, including trials of potential new antimicrobials.

A very important element of the ND4BB programme is the discovery of new candidate antibiotics through the ENABLE project. ENABLE[18] focuses on the discovery and pre-clinical stages of drug development, attempting to identify and accelerate the development of new compounds coming from both the public and private sectors. A key objective of ENABLE is to share the risk of developing new antibiotics between different partners, encouraging researchers to progress more compounds in this area (see ENABLE Call for Action—European Gram-negative Antibacterial Engine[19]). Compounds are sought from all researchers (from academia, SMEs, research organizations etc…) through an open call meaning anyone with an interesting molecule can apply. Spanning 13 countries, ENABLE has brought together 32 partners including 11 SMEs to help researchers overcome these thresholds. To date 70 programmes from SMEs and research organizations have been received and over 15 programmes have been integrated within its portfolio, of which 5 are currently running.

Recently, it reached the important of milestone of selecting as a potential antibiotic, apramycin, as a clinical candidate. Identified by researchers from the University of Zurich and further progressed in a university spin-out company Juvabis, the data package supporting apramycin's development was submitted to ENABLE and it was selected as a clinical candidate[20].

In another example of how ENABLE is enhancing and speeding up drug discovery, compounds targeting Gram-negative infections were identified by Chris Schofield at the University of Oxford via the novel drug screening programme of another IMI project, the European Lead Factory's (ELF)[21]. After further refinement within the ELF, the compounds were submitted to ENABLE. When the compounds were reviewed by the ENABLE partners, they were found to have exciting

[16]https://www.imi.europa.eu/projects-results/catalogue-project-tools

[17]https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb

[18]http://nd4bb-enable.eu/enable-portfolio

[19]ENABLE Call for Action - European Gram-negative Antibacterial Engine https://www.youtube.com/watch?v=yUS607nwgIQ&feature=youtu.be (accessed July 23, 2019)

[20]ENABLE Juvabis Press Release, 2018: Tackling Antimicrobial Resistance: ENABLE Selects First Clinical Candidate available from http://nd4bb-enable.eu/press-release (accessed July 23, 2019).

[21]http://www.europeanleadfactory.eu/

potential and were included in the ENABLE programme with the hope of further development toward the clinic[22]. This access to drug discovery platforms and the rate of development is unprecedented and reveals the potential of IMI projects to help researchers rapidly go from a novel idea to potentially taking compounds into the clinic in the matter of a few years while addressing important areas of unmet need.

The European Lead Factory is not only limited to identifying new antimicrobials molecules, but is open to drug target programmes related to all human disease and all types of small molecules. It provides researchers unprecedented access to pharmaceutical company compound collections and high throughput screening (HTS) technology, allowing researchers to test their drug target ideas. The output from the project is a list of identified compounds for each target screened that can then be developed further by the researchers.

The project is composed of two arms. The first is the European Screening Centre housing the equipment and expertise to run the HTS services for the selected public projects. The second is a unique compound collection, the Joint European Compound Collection, coming from seven industry partners and complemented by compounds that have been sourced from European researchers. This compound collection is unique, being composed of compounds coming from the libraries of seven industrial partners and complemented by compounds coming from public partners. The over 500,000 compounds in the collection are not commercially available and cannot be found anywhere else in the world.

Through this unique platform, 88 new targets public programmes have been validated and screened, while nearly 6,000 qualified hits have been granted to public and private target owners, meaning that many researchers now have a valuable first step toward setting up their own new drug discovery programmes (34). Some of the results are already well-advanced. Dr Margit Mahlapuu from the University of Gothenburg had identified a target which could be used to reverse metabolic complications in type two diabetes (35). She submitted this target to ELF and the resulting screen identified a set of selective and potent small molecules which interfere with the target. Based on her research and armed with these new compounds, she created a spin-out company, ScandiCure, with the aim to develop the compounds further so that they could become a first in class anti-diabetic drug. The compounds have such promising potential that ScandiCure has now entered into an agreement with Servier for the further development of the compounds for the treatments for type 2 diabetes and the liver disease non-alcoholic steatohepatitis[23].

In another example, Richard Mead of the University of Sheffield had grown frustrated with a lack of results after many attempts screening publicly available libraries and commercially sourced compound collections. He approached ELF with his target, a protein involved in oxidative stress that had been found to play an important role in motor neuron disease, Parkinson's disease and other neurodegenerative disorders. The results of the screens proved so interesting that Parkinson's UK decided to set up a "virtual biotech" company, Keapstone Therapeutics, based upon further developing the identified compounds[24]. Although there is still a long way to go, the compounds identified are very good starting points for developing potential Parkinson's treatments[25].

Taken together it is clear that in the area of early drug discovery, there is much to be gained by collaborating, pooling resources, and expertise. Through the ELF and ENABLE projects, IMI is making resources available to the research community that are not available elsewhere, the results of which are kick starting new drug development programmes. These programmes offer patients and society the hope that new treatments may one day be found for currently difficult to treat conditions, or diseases where no treatment is available.

COLLABORATING TO TACKLE EBOLA

IMI launched two calls for proposals focused on Ebola in response to the outbreak that occurred in western Africa in 2014–2016. This outbreak was unprecedented in scale, with around 29,000 people infected and over 11,000 of them dying in the west African nations of Guinea, Liberia and Sierra Leone. As a result of these two calls, IMI now supports 12 projects addressing various aspects of Ebola. These include testing new vaccines, the implementation of clinical testing in outbreak areas, speeding up manufacturing routes, speeding up deployment of vaccines, as well as community engagement to educate and help with the uptake of the vaccines in the affected communities.

With no licensed vaccines available in 2014 there was an immediate need to bring forward safe and effective vaccines. IMI projects supporting vaccine development include EBOVAC1[26], EBOVAC2[13] and EBOVAC3[13] as well as VSV-EBOVAC[27], VSV-EBOPLUS[28] and PEVIA[29] among others. EBOVAC1, 2 and 3 focus on assessing the safety and tolerance of the prime boost Ad26.ZEBOV and MVA-BN-Filo vaccines. EBOVAC 1 supports Phase I trials testing the safety and tolerability of the vaccines in healthy volunteers in both Europe and west Africa. Further phase II and phase III trials aimed at speeding up the clinical development are being supported by both EBOVAC 1 and 2 projects, again, focused on west African communities. EBOVAC3

[22]ELF Press release, November 2016: Promising antibiotic programme gets European boost https://us12.campaign-archive.com/?u=d2300afdcb71d3d71dfe70fbd&id=57013abee0; http://www.europeanleadfactory.eu/node/52 (accessed July 23, 2019).

[23]Servier press release, April. 2018. "Servier and Scandicure Enter into Agreement to Conduct Research in the Field of Metabolic Diseases." https://servier.com/wp-content/uploads/2018/04/PR-Servier-Scandicure_2018.04.03.pdf

[24]https://www.europeanleadfactory.eu/news-events/virtual-biotech-company-launched-battle-parkinson%E2%80%99s

[25]Parkinson's UK press release March 2017. Keapstone Therapeutics launched in world-first partnership to develop new drugs for Parkinson's. https://www.parkinsonsvirtualbiotech.co.uk/single-post/2017/03/08/Keapstone-Therapeutics-launched-in-world-first-partnership-to-develop-new-drugs-for-Parkinson%E2%80%99s (accessed August 08, 2019).

[26]https://www.ebovac.org/

[27]http://www.vsv-ebovac.eu/en/home.html

[28]https://vsv-eboplus.eu/

[29]http://www.pevia-ebola.eu/

builds on this work and aims to run clinical trials in the very vulnerable children populations of Sierra Leone, Guinea and the Democratic Republic of Congo.

The data so far from the EBOVAC1 clinical trials demonstrate that the vaccines are safe and well-tolerated. Phase 1 findings so far reported indicate that Ad26.ZEBOV prime immunization readily induces an immune response which is enhanced further by MVA-BN-Filo, and that the Ad26.ZEBOV/MVA-BN-Filo heterologous prime-boost regimen induces durable immunity to the Zaire strain of Ebola, and that both the prime and boost are well-tolerated with a good safety profile (36).

The projects VSV-EBOVAC and VSV-EBOPLUS attempt to advance the development of the VSV-ZEBOV vaccine candidate. The recombinant vesicular stomatitis virus (rVSV) vaccine expressing the Zaire Ebola virus (ZEBOV) glycoprotein has been found to be efficacious following single-dose injection, with antibody responses sustained across dose ranges and settings (37). Finally, PEVIA aims to develop second generation vaccines that will be better suited to large scale vaccination programmes in sub-saharan Africa, specifically vaccines that will not require storage at low temperatures.

The challenges faced in trying to vaccinate populations in affected areas and ensure compliance with vaccination regimens are being addressed by the EBODAC[13] project (38). The EBODAC project has developed communication strategies and tools to promote the acceptance and uptake of new Ebola vaccines. These include the development of many creative strategies including radio shows, drama performances and community meetings. Thanks to the efforts of EBODAC's team over 450 adults and children received both doses of the vaccine regimen in the Sierra Leone study and what has been learnt can be applied to current and future outbreaks (39).

To complement the projects focusing on vaccine development and running clinical trials in the field, IMI supports projects designing new or improving existing rapid diagnostic tests. A key feature of these tests is their ability to be used in the field where laboratory facilities may be minimal or non-existent (40). Rapid diagnostic test projects include Mofina[30], FILODIAG[31], EbolaMoDRAD[32] and VHFMoDRAD[33]. The MOFINA project team built on the existing automated device "Alere q" to develop a portable assay system that can give an accurate diagnosis within 75 min. EbolaMoDRAD has developed technologies that allow Ebola samples to be handled safely outside of high containment laboratories. Finally, Filodiag has delivered a highly sensitive system that can deliver results in just 30 min. All these systems have been tested in the field and found to deliver reliable results much more quickly than previously used systems.

With new infectious diseases emerging all the time, these challenges can only be addressed through collaboration of all stakeholders, whether on the development of new treatments and vaccinations, their deployment in the field, or new diagnostic methods. In order to be prepared and able to cope with future outbreaks, all of society's stakeholders need to engage and work together.

COLLABORATING TO ADDRESS UNMET SOCIETAL NEEDS

While the IMI programme supports many projects directly addressing specific challenges in pharmaceutical R&D, it is also an appropriate vehicle to foster the necessary collaboration to overcome some wider societal challenges in areas such as pediatric medicines or the use of medicines in pregnancy. Based on previous assessments, only 30% of marketed drugs in Europe and worldwide include a pediatric authorization, and <50% of authorized medicines commonly used in children have been properly tested in this population (41, 42). This rate drops to 10% in the vulnerable patient population in neonatal intensive care units (43). In order to address this deficit, the "Pediatric Regulation" came into force in the EU on 26 January 2007 with the objective of improving the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years[34]. A review of the landscape in 2017[35] found that there had been an increase in medicines for children in many therapeutic areas in the last 10 years, most notably in rheumatology and infectious diseases. However, it also found little progress had been made in diseases that only affect children, or where the disease shows biological differences between adults and children, particularly rare diseases.

One of the reasons for the slow progress is that running clinical trials in children is very difficult and this has inspired IMI to launch the conect4children[36] (c4c) project to create a sustainable, integrated, pan-European collaborative pediatric network. The c4c consortium aims to create a network that will deliver high quality "regulatory grade" clinical trials (phase I to IV) from different sponsors, in different therapeutic areas, and across all age groups. The viability of the network will be tested in pilot studies from industry and non-industry partners. The first four pan-European pediatric studies will be conducted by academic institutions and will generate data on high priority medicines commonly used in babies, children and young people in Europe[37]. In addition to facilitating the testing of new medicines, the new network will also provide expert advice and ensure that the voices of young patients and their families are heard to guarantee the conduct of feasible, innovative and scientifically sound pediatric clinical trials. It should be noted that c4c is already attracting attention internationally and plans are already in the making for creating a productive interface with a similar initiative in the US called the Institute for Advanced Clinical Trials for Children (I-ACT)[38].

[30]https://www.imi.europa.eu/projects-results/project-factsheets/mofina
[31]http://www.filodiag.eu/
[32]http://www.ebolamodrad.eu/
[33]https://vhfmodrad.eu/

[34]Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use.
[35]State of Pediatric Medicines in the EU 10 years of the EU Pediatric Regulation COM (2017) 626.
[36]https://conect4children.org/
[37]https://conect4children.org/news/press-release-launch-of-the-non-industries-study/
[38]https://www.iactc.org/

Another area of current unmet need is in the information available to guide decision making for the safe and effective use of medications during pregnancy and breastfeeding (44, 45). Pregnant and breastfeeding women with chronic diseases may need to continue their medicines to treat their conditions in order to prevent irreversible damage to their health and the health of their unborn child that may be caused in some situations by the disease itself when the treatment is stopped. However, prescribing information leaflets generally lack clear information to inform decision-making, meaning that practitioners and patients alike are unable to make informed decision on treatment approaches.

Pregnant and breastfeeding women have been purposively excluded from clinical trials and currently a common source of post-authorization safety data on medicines in pregnancy comes from product-specific pregnancy registries. According to a Food and Drug Administration (FDA) review based on 59 pregnancy registries, only a minority (12%) generated data that was used to inform the label to adequately advise patients and healthcare providers (HCPs). Where data was not used to inform the label, this was usually due to the inadequate recruitment of subjects and a lack of internal comparator groups (46). Hence, many compound-specific pregnancy registries close several years after initiation. In addition, there is no consistent standard of data quality (data collection and analytical methods) recognized as warranting inclusion in product labels. The situation is even worse concerning breastfeeding.

IMI launched the ConcePTION[39] project to address the major public health concern for a robust, evidence-driven approach to define the standards for generating data on medicines used during pregnancy and breastfeeding. This is a unique endeavor gathering lead experts in the field from both public and private sectors that will build an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding. To change current practices, the project sets out to define more timely and efficient data collection and analytical approaches compared to current pregnancy registries. It is hoped that this improved information will enable HCPs and pregnant patients to make informed decisions regarding medication use, and enhance their care. The project also aims to support more basic research approaches such as the development of better animal lactation models that more closely reflect human lactation physiology. The intention is also to build a Europe-wide breast milk biobank and support an analytical centre for the analysis of drug concentration in milk so that samples are more readily available and analytical methods can be improved.

In the two examples described there is a key healthcare challenge for society and the scientific questions underpinning these can only be addressed by different actors analyzing the problem, sharing their results, and agreeing the way forward. IMI plays an important role by bringing these different stakeholders together to collaborate with the aim that the results will benefit children and their mothers. The ability to mobilize many different stakeholders and bring together data at a scale not achieved before should ensure that the results of the collaborations are transformative for the respective fields. The fact that these collaborations occur as part of a public-private partnership ensures that there is a fast feedback mechanism for results to flow back to the pharmaceutical companies. It also provides a neutral interface with which the regulators can interact so that the results can help inform regulatory science.

MOBILIZATION OF OTHER STAKEHOLDERS

Over the past 10 years we have witnessed an evolution in the challenges been addressed by the IMI programme. It has also become apparent that other stakeholders beyond the pharmaceutical industries are needed if these challenges are to be effectively addressed. During the IMI1 programme several non-EFPIA industries participated however the rules of IMI1 did not allow IMI to match the in-kind contributions provided. Under IMI2, the in-kind contributions of non-EFPIA organizations can be matched by public funding as long as the entities agree to become Associated Partners of the IMI2 programme and be bound by the same rules and obligations of all other partners participating in projects. In this way additional non-EFPIA contributions can be brought onboard and be leveraged by public funding. This change makes the programme much more attractive for other funders and companies to participate. Indeed, IMI has become a magnet, attracting new partners who understand the value of becoming involved in these collaborative projects if advances in many challenging areas of public health are to be achieved. As of June 2019, 31 entities had become Associated Partners to IMI2, participating in 44 projects (launched or in preparation) and are contributing nearly EUR 180 million to the programme. IMI2 Associated Partners are listed in **Table 1**. On top of this, many more organizations, primarily from other industries, are aligning with EFPIA so that they can contribute to specific IMI projects as EFPIA "Partners in Research"[40]. While the participation of APs may help boost the funding available for the programme it is important that APs are fully aligned with the objectives of the IMI2 programme and share the collaborative vision of combining knowledge and expertise so that challenges can be overcome much more effectively.

SOME LESSONS LEARNED

From experience to date, it is clear that IMI works as a collaborative platform allowing different stakeholders to work together to resolve problems and address issues that single entities are unable to address alone no matter their size or wealth. However, it is also clear that when mobilizing many different actors to tackle a diverse range of different problems, whether in scientific research or healthcare, this raises its own challenges. The first obvious challenge is how to get different organizations to work together. When IMI was set up many doubted whether pharmaceutical companies would engage with such a platform

[39]https://www.imi.europa.eu/projects-results/project-factsheets/conception

[40]https://www.efpia.eu/about-us/membership/#tab3

TABLE 1 | IMI2 JU Associated Partners as of June 2019.

Associated partner	Project/topic
Accelerate Diagnostics	VALUE-Dx
Autism Speaks	AIMS-2-TRIALS
Autistica	AIMS-2-TRIALS
BD Switzerland Sarl	VALUE-Dx
Bill and Melinda Gates Foundation (BMGF)	PERISCOPE Call 15, Topic 08—AMR (Pillar B)
Bio-rad Laboratories	VALUE-Dx
Cepheid Europe	VHFMoDRAD
CHDI Foundation	Call 15, Topic 06—Digital Endpoints
Children's Tumor Foundation (CTF)	Call 15, Topic 01—Integrated Research Platform
Datapharm	Call 18, Topic 03—Improving Patient Access: Integrated digital health
Diamond Light Source	Call 17, Topic 02—Open Access Chemogenomics Library
European Hematology Association	Call 18, Topic 06—Supporting the development of engineered T-Cells
International Diabetes Foundation	HYPO-RESOLVE
Invicro	Call 15, Topic 05—Platforms supporting Synaptopathy Drug Discovery
JDRF	INNODIA BEAT-DKD HYPO-RESOLVE Call 15, Topic 04—Emerging Translational Safety Technologies Call 17, Topic 01—Optimizing Future Obesity Treatment Call 18, Topic 02—Health Outcomes Observatories
KTH Royal Institute of Technology	Call 17, Topic 02—Open Access Chemogenomics Library
Leona M. And Harry B. Helmsley Charitable Trust	INNODIA HYPO-RESOLVE
McGill University	Call 17, Topic 02—Open Access Chemogenomics Library
Medicines for Europe	Call 18, Topic 03—Improving Patient Access: Integrated Digital Health
Medicines for Malaria Venture (MMV)	ESCulab
Obesity Action Coalition	Call 17, Topic 01—Optimizing Future Obesity Treatment
Ontario Institute of Cancer Research	Call 17, Topic 02—Optimizing Future Obesity Treatment
Parkinson's UK	NEURONET PD-MitoQUANT PD-Mind Call 15, Topic 06—Digital Endpoints
Simon Foundation Autism Research Initiative (SFARI)	AIMS-2-TRIALS
Software AG	RADAR-AD
Springworks Therapeutics	Call 15, Topic 01—Integrated Research Platform
T1D Exchange (formerly Unitio)	HYPO-RESOLVE Call 17, Topic 01—Optimizing Future Obesity Treatment
TB Alliance	Call 15, Topic 01—Integrated Research Platform Call 15, Topic 08—AMR (Pillar B)
Trial Nation	Topic 02—Health Outcomes Observatories
University of Dundee	Call 15, Topic 08—AMR (Pillar B)
Wellcome Trust	VALUE-Dx

and collaborate with each other. Experience has shown that not only have pharmaceutical companies engaged with the programme, but they recognize that for certain challenges, this is the only way to advance scientific knowledge. When the programme began there was a reluctance from some parties to engage as it was not clear what would be the benefit for public entities collaborating so closely with industry consortia. Experience has shown that the collaborations are very fruitful and that public partners can generate the good quality publications they need as well as accessing data and resources simply not available elsewhere in the public domain. In fact many of the networks established in IMI projects are sustained beyond the IMI funding period leading to long lasting collaborations between different sectors.

Today many other stakeholders, whether they be patients, researchers or regulatory agencies, are eager to engage with IMI and participate in its projects. They recognize the value of the platform for the sharing of different experiences, knowledge and approaches. It is the role of IMI as a neutral platform to encourage this engagement and to allow stakeholders to build the trust in each other that will then facilitate collaboration. The neutrality of the IMI Programme Office is a key foundation upon which successful projects are built.

The monitoring of these projects both from a scientific and an administrative point of view can also be very challenging. Therefore, it is important that projects are well-managed and in particular have leadership that enables the project partners to stay on track. Large projects can also be scientifically unwieldy resulting in difficulties for the consortia to change the course of the research once the objectives have been set. Although there is flexibility in the IMI programme to allow changes when scientifically justified, it is sometimes difficult for IMI projects to respond to rapid advances in knowledge as quickly as they would perhaps like.

The projects cited in this review operate under the same sets of legal rules as other FP7 or Horizon 2020 projects. Whether it is researchers clinically testing an Ebola vaccine in the field, or a HTS project identifying new compounds as the starting points for medicines, or researchers building biobanks to help understand the exposure to medicines in breast milk, the same legal framework applies to all. This ensures consistency across all projects and in the majority of cases the frameworks are well-constructed and appropriate so the projects operate very well. However, sometimes the IMI platform could achieve even more if it were able to mobilize additional resources not in the public domain or apply the rules in a more flexible way than is currently allowed. Hence this lack of flexibility, where "one size fits all" can sometimes hinder the adoption of radically innovative approaches.

One of the questions often asked is what is the impact of the IMI platform on the health of European citizens; after all, a large amount of public funding is being invested through the programme. The IMI Programme Office invests a lot of energy in defining appropriate measures of impact and progress. Some measures are relatively straight forward to collect, such as bibliometrics, patents, tools developed etc. However, tracking impacts outside the project becomes increasingly difficult,

especially after a project has finished, and the further we move from the domain of pre-competitive research into the healthcare space. Many of IMI's projects tackle challenges in the early pre-competitive space. Given that the time to develop new medicines can be 10–15 years, this is a long time to wait for an impact to appear eventually in the healthcare system. Also, healthcare is a very complex system where medicine, society and politics come together, meaning that attribution of a given project result to a given impact is incredibly difficult.

A great example of this is the impact coming from IMI's PROactive project. This project had as its main objective to obtain a regulatory accepted patient reported outcome (based on physical activity) in the context of new treatments for COPD (chronic obstructive pulmonary disease). Although this goal was indeed achieved, the qualification opinion from the EMA was given 2 years after the official end of the project[41]. Many other projects will see the impact of their work materialize many years after the funding cycle.

WHAT NEXT FOR COLLABORATION IN THE HEALTHCARE SPACE?

As the population ages, the burden of disease is increasing with the result that healthcare costs continue to rise with no sign of slowing. Beyond an aging population, infectious diseases are becoming increasingly resistant to treatment with new infectious diseases emerging. These are just two examples of the challenges we will continue to face. We are unable to avoid the conclusion that current and future challenges in healthcare can only be addressed by all stakeholders working together. Therefore, we need to find the mechanisms to harness the talents of the different stakeholders and bring them together to work toward achieving a single goal. Healthcare is an area where collaboration is inescapable, and platforms that allow the problems and issues to be addressed in a neutral space will be essential. An essential first step for these future collaborations will be the building of trust between industries and organizations that may not currently be used to working together. This is particularly relevant when industries with different cultures, different business models and different objectives are being asked to work together for the first time. This is equally true for the different governmental agencies and regulators that will be required to work together as healthcare challenges are tackled.

An ongoing debate is whether public investment in research and in PPPs, such as IMI, in particular demands a quid pro quo with regards to pricing and the affordability of new treatments derived from IMI-funded research. IMI was originally set up to address key challenges in the pre-competitive space of drug development. Recently several IMI projects have been launched supporting the late stage development of assets in areas of high societal need such as AMR and Ebola. In these cases, the approach of the IMI programme has been one of sharing the risk in these difficult areas to ensure that society benefits from having new anti-infective agents and vaccines that might otherwise not be developed. If the programme is successful in making R&D processes more efficient it follows that these efficiencies should be reflected somehow in the affordability of medicines. The questions related to public investment in research and the eventual pricing of medicines is a legitimate one, but one which IMI was not designed to address. This key question will need careful consideration in the planning and design of future collaborative approaches.

Ultimately, researchers and clinicians working in the drug discovery and medicines space are motivated by the desire to understand and tackle disease. We need patients as partners in this cause to ensure that the work that is undertaken is relevant to their needs and we can deliver the treatments that they are waiting for. Under IMI2, we have already taken steps to better involve patients in our programme through the launching of the 'IMI pool of patients experts' where patients can help us by providing input into our strategy, our documents, our reviews, etc.[42]. And we can help them understand better and become more involved in scientific research as equal partners. Patients are an essential partner in all future collaborations.

As mentioned above, solutions to healthcare challenges involve disciplines and industries beyond the pharmaceutical industry and in some cases traditional healthcare providers. New approaches are needed to engage with ICT providers, artificial intelligence industries and those platforms generating personal data so that a more holistic approach is adopted for treating individuals. The issue of ensuring data quality should not be underestimated in these new approaches. A large amount of resources will be needed to ensure the quality, interoperability and standardization of the different types of healthcare-related data that are available and will be generated in the future. In IMI2 we already have a programme called Big Data for Better Outcomes[43] focused on bringing real world data into the programme and using it to help provide solutions. Future programmes will have to redouble efforts in these areas as we will soon be unable to afford the continuously growing burden of chronic diseases. It will be necessary to use new technologies and approaches to improve prevention, and to speed up the early detection of chronic diseases.

We also need to recognize and accept that to deliver change in the healthcare space is very challenging. Healthcare systems have evolved over a long time and the actors involved are under intense political and societal scrutiny, so delivering change is not an easy task and should not be underestimated. If it is expected that future collaborations will be judged on their ability to drive this change, then we need to invest in ways in which to measure the expected changes in what is a highly dynamic and complex system. Therefore, the measures by which future collaborations are judged will have to be carefully chosen otherwise it may not be possible to assess whether the collaboration had any impact at all, never mind the desired impact.

In addition, in complex systems such as healthcare the goals of future collaborations need to be focused. Sometimes in the desire

[41] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-proactive-chronic-obstructive-pulmonary-disease-copd_en.pdf

[42] https://www.imi.europa.eu/get-involved/patients/imi-pool-patient-experts

[43] https://www.imi.europa.eu/projects-results/project-factsheets/bd4bo

to keep all stakeholders and sections of society engaged, there is a tendency to promise that a programme or a project will be able to do everything. If those behind a future collaborative platform follow this approach, then it is highly likely that the programme will fail simply because the impact it might have had will be so diluted to the point that it may be impossible to demonstrate any impact at all. Therefore, it is essential that future collaborations are focused with clear, achievable objectives.

Since its inception, IMI has been a highly successful experiment in collaboration across a range of different and challenging areas. Not everything has gone smoothly; some approaches have been very successful, while others are less well-adapted to the current framework. It is important that these learnings are incorporated into any future programmes. At the dawn of this digital age in which data and artificial intelligence are becoming ever more important, the boundaries between traditional disciplines are blurring and falling away. Future collaborations will involve entities and disciplines currently not involved in healthcare. Against this dynamic backdrop the challenge for us all is to ensure that future collaborations in healthcare are fit to address these new challenges and deliver the more effective, safer medicines that patients deserve.

AUTHOR CONTRIBUTIONS

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

FUNDING

The IMI programme office is funded by contributions from the European Union and the European Federation of Pharmaceutical Industries and Associations. The IMI1 programme received its funding from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in kind contribution. The IMI2 programme currently receives support from the European Union's Horizon 2020 research and innovation programme (H2020/2014–2020), as well as, EFPIA's and IMI Associated Partners' in kind contributions.

ACKNOWLEDGMENTS

The authors would like to thank Elisabetta Vaudano, Nathalie Seigneuret, and Catherine Brett with their help in reviewing and proof reading the manuscript.

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Conflict of Interest: HL and PM are employees of IMI, the IMI programme office has no role in the day to day management of the projects or the scientific research undertaken by the projects.

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