NETWORKS IN MOVEMENT DISORDERS

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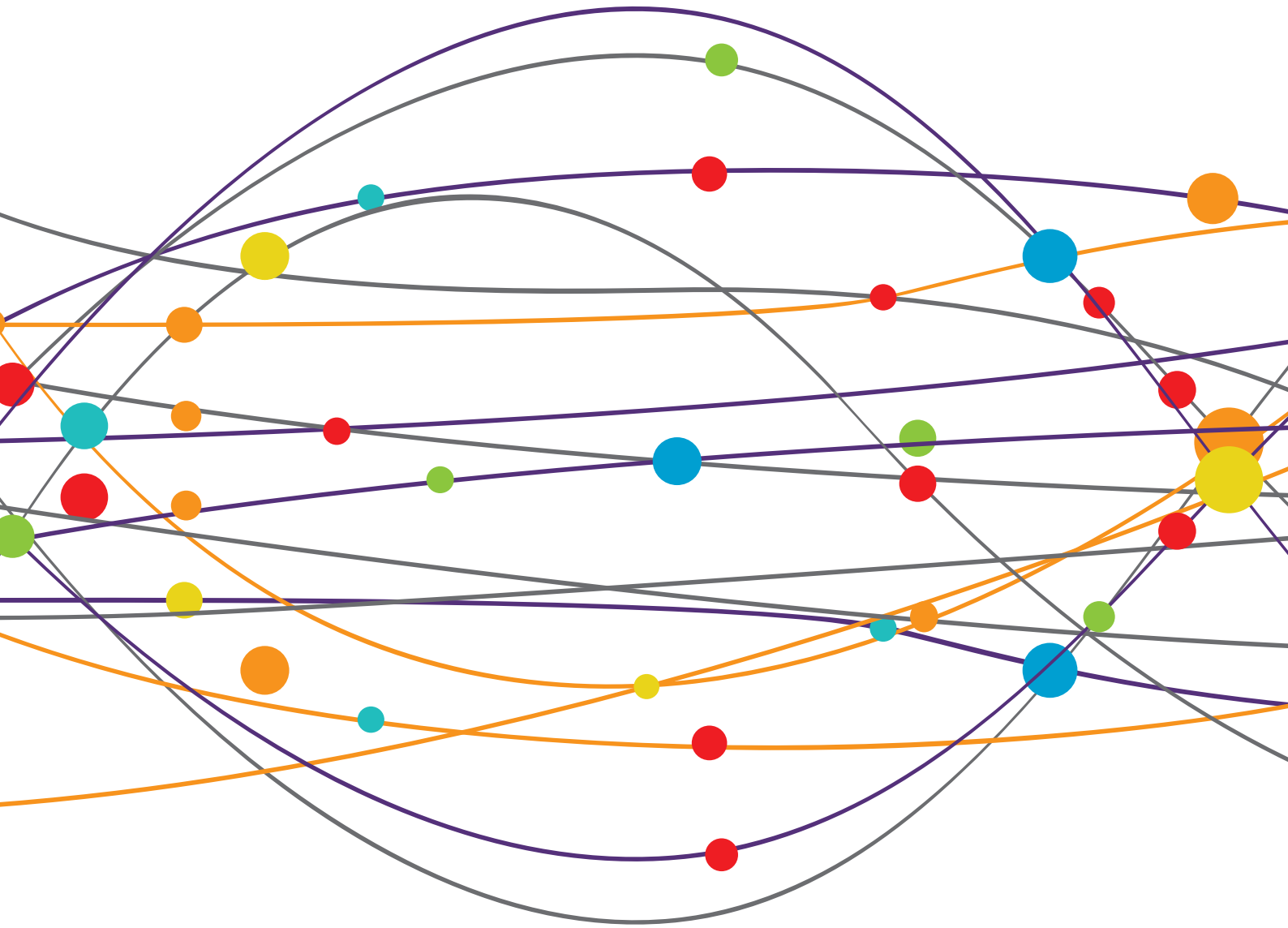

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NETWORKS IN MOVEMENT DISORDERS

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EDITORIAL
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Editorial: Networks in Movement Disorders. To Move or Not to Move

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Keywords: networks, movement disorders, rare movement disorders, care, research

Editorial on the Research Topic

Networks in Movement Disorders. To Move or Not to Move

Movement disorders are a growing field in clinical neuroscience with a strong translational value. Expert assessment is required for managing patients with movement disorders, which is more and more often being provided by multidisciplinary teams at expert centers due to the complexity of the diseases with regards to clinical features, diagnostics, and sophisticated tools to assess the course of disease and measure disease progression. There is need for scientific interaction among a variety of specialized domains and for patient-centered management of this quickly evolving area of knowledge.

Research-driven knowledge is constantly providing new information that directly influences clinical practice in the field of movement disorders. An increasing number of movement disorders will soon be treated by candidate therapeutics or devices ready for testing in clinical trials; thus, trial readiness for well-defined cohorts has become a highly important challenge. Lumping together patients with specific movement disorders subtypes may be necessary to reach sufficient power in trials and to implement best clinical practice.

Thus, collaborative networks have been formed to enable sharing of knowledge and data, further the development of clinical standards and of best practice, and enable pursuing research projects, particularly to develop innovative therapeutic approaches. It is a logical consequence that these networks focus on specific diseases or disease groups that allow the efficient and effective bringing together of key stakeholders (**Table 1**). A third logical consequence is that these collaborative networks are most frequent and successful in rare movement disorders for which the complexity and fragmentation inherent in health care and research is largest. Nine of the eleven manuscripts of this special issue actually focus on rare movement disorders. Networks in rare movement disorders, motivated by the need to put together patients and experts, very often have an international breadth.

Although collaborative networks are a very efficient method to address the issues mentioned above, the established networks do not implement a unique or similar conceptual and constitutional models. The experience and expertise, as well as exemplary concepts and solutions provided by the existing disease networks in movement disorders, promote mutual learning and broker expert knowledge for additional novel networks.

Despite differences in the networks and manuscripts, a few cross-cutting generic topics can be identified that are characteristic of collaborative networks in movement disorders and, moreover, determine the focal point of some of the manuscripts. Firstly, the issue of care organization, improvement, and operation is being discussed from different perspectives and for different disease groups in Van de Warrenburg et al., Reinhard et al., Smit et al., and Albanese et al..

Secondly, a multi-stakeholder oriented establishment of network and infrastructure to enable

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TABLE 1 | Overview of disease group focus of the *Networks in Movement Disorders* manuscripts.

Manuscript	Disease group	Title of manuscript
Reinhard et al.	Rare neurological diseases	The European Reference Network for Rare Neurological Diseases
Van de Warrenburg et al.	Rare movement disorders	The Architecture of Contemporary Care Networks for Rare Movement Disorders: Leveraging the ParkinsonNet Experience
Albanese et al.	Parkinson's disease	Design and Operation of the Lombardy Parkinson's Disease Network
Smit et al.	Dystonias	Dystonia Management: What to Expect From the Future? The Perspectives of Patients and Clinicians Within DystoniaNet Europe
Kilic-Berkmen et al.	Dystonias	The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies
Lin et al.	Spinocerebellar Ataxias (SCA)	Collaborative Efforts for Spinocerebellar Ataxia Research in the United States: CRC- SCA and READISCA
Traschütz et al.	Autosomal Recessive Cerebellar Ataxias (ARCA)	The ARCA Registry: A Collaborative Global Platform for Advancing Trial Readiness in Autosomal Recessive Cerebellar Ataxias
Kleimaker et al.	Tourette Syndrome	Networks in the Field of Tourette Syndrome
Karin et al.	Neurodegeneration with Brain Iron Accumulation (NBIA)	Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON)—An International Network on Care and Research for Patients With Neurodegeneration With Brain Iron Accumulation (NBIA)
Sathe et al.	Huntington's disease (HD)	Enroll-HD: an integrated clinical research platform and worldwide observational study for Huntington's disease
Respondek and Höglinger	Progressive supranuclear palsy (PSP)	DescribePSP and ProPSP: German Multicenter Networks for Standardized Prospective Collection of Clinical Data, Imaging Data, and Biomaterials of Patients With Progressive Supranuclear Palsy

care improvement and research in a specific disease field is featured in Kleimaker et al. and Karin et al. Thirdly, the value of clinical research platforms for structuring research as well as achieving trial readiness is described in Sathe et al. and Traschütz et al. Finally, Lin et al., Respondek and Höglinger, and Kilic-Berkmen et al. focus on clinical and translational research that is done in collaborative networks.

Research networks represent a fundamental shift in the geography of science, as they not only facilitate integration of research in the era of globalization, but also provide a powerful tool for stimulating societal changes (1). The latter goal requires significant interactions between academic science and policy makers. Networks do not succeed naturally. Key enabling factors for the development of collaborative networks in health have been identified, including knowledge sharing, a positive social climate, and strong co-worker ties. In particular, knowledge sharing is important (2). Knowledge sharing strategies may include the distribution of knowledge, knowledge brokerage to encourage and support participation, and engagement of stakeholders in the network as well as knowledge governance to support the establishment of formal partnerships and policies (3).

Much of what is described in the manuscripts of this issue can be seen as the establishment, implementation, and exploitation of knowledge and data sharing. The featured collaborative networks in movement disorders can be seen as successful knowledge processing networks and should be conceptualized as such. In this sense, building of specialist networks is key in movement disorders or—the other way round—without disease networks, movement disorders will not move forward to develop new therapies and promote significant societal changes in support of the patients.

AUTHOR CONTRIBUTIONS

HG, AA, and LS are co-editors of the Networks in Movement Disorders topic and wrote the publication together. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Design and Operation of the Lombardy Parkinson's Disease Network

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Background: Parkinson's disease (PD) is one of the most common chronic neurological conditions leading to disability and social burden. According to the 2016 Italian National Plan on Chronic Diseases, regional health authorities are implementing dedicated networks to manage neurological diseases, including PD.

Methods: A panel of experts representing health-care providers in Lombardy reached consensus on the organization of a patient-centered regional PD healthcare network.

Results: The panel proposed a structure and organization implementing a hub-and-spoke PD network model. Three levels of neurological services were identified: General Neurologist, PD Clinic, PD Center. This model was applied to health service providers currently accredited in Lombardy, yielding 12 candidate PD Centers, each serving an area of ~1,000–2,000 km^2, and not less than 27 PD Clinics. The panel agreed on uniform diagnostic and staging criteria for PD, and on a minimum common clinical data set, on PD patient management by the network at initial and follow-up assessments, on the cadence of follow-up visits, on patient referrals, and on outcome measures for the assessment of network activities.

Conclusions: The implementation of disease-centered networks for chronic neurological diseases provides an innovative opportunity to improve patient management, facilitate research and education.

Keywords: Parkinson disease, health maintenance organizations, disease management, managed care programs, consensus

INTRODUCTION

Aiming to improve multidisciplinary management and reduce inhomogeneity of interventions, the 2016 Italian National Plan on Chronic Diseases stated that each regional health system must establish health networks dedicated to the management of chronic diseases (1). The implementation of this plan started last year and was recently delayed by the outbreak of Covid-19 epidemic. Parkinson's disease (PD) is one of the most common neurological conditions and constitutes a model of treatable chronic neurological disease. It is characterized by a variety of neurological and non-neurological features and progresses variably towards a stage of social burden and disability (2). Management of PD requires specific medical expertise and dedicated resources.

In Italy regional health authorities are the payers for the National Health System (NHS); they finance health-care providers (HCPs) through yearly budget plans. A disease-centered regional PD network is expected to reduce inequalities in treatment and to harmonize the use of regional resources. A panel of neurologists with expertise on PD reviewed the available evidence and developed a consensus on the set-up and the general organization of a regional PD network. The primary objective was to improve PD patient care while optimizing resources, a secondary objective was to facilitate patients' participation in research programs through the network.

MATERIALS AND METHODS

As a preparatory work, the Directorate General for Health collected data related to medical certificates, prescriptions, and hospital admissions from 2012 through 2017. The following data were retrieved from the electronic dataset: prevalence and incidence of PD cases, acute admission of PD patients to Lombard hospitals, consumption of antiparkinsonian medications, and outpatient consultations for PD patients.

A panel of neurologists representing Lombard HCPs with expertise on PD was convened. The represented HCPs encompassed three private and seven public institutions, four universities, five research hospital, and three general hospitals. The panel was composed by neurologists responsible for PD care in each of the participating HCPs, who were asked to design a general model of the regional PD network. The methodology for nominal group consensus process was implemented, involving the following principles: all members contribute to the discussion, can state each issue in their own words, have the opportunity and time to express their opinion about each issue, and agree to take responsibility for the implementation of a decision.

The panel reviewed the established PD networks in Italy and Europe and took into account the Lombard guidelines on healthcare networks (3) that apply to all chronic diseases. The list of accredited Lombard HCPs was downloaded from the Lombardy HCP repository. Hospitals and ambulatory care clinics were included, whereas rehabilitation centers and assisted living residences were excluded. For each HCP with neurological facilities expertise on PD was assessed and ranked. The network structure was outlined and the PD patient's journey through the network was assessed before drafting a final consensus.

A first draft of the manuscript was prepared based on the results of data analysis, discussion, and comments from panel members. To reach the final consensus, the last draft and the preliminary conclusions were critically discussed with representatives from PD patient associations.

Abbreviations: ADL, Activity of daily living; HCP, Health-care provider; NHS, National health system; PD, Parkinson's disease.

RESULTS

The Lombardy regional health service is managed through eight territorial branches, spanning from the northern mountainous regions, through urbanized areas in the middle region, to plains in the south. In 2016 there were 36,217 PD patients and 10,036,258 residents, yielding an annual prevalence of 277 cases per 100,000, in the high range of epidemiological findings in Europe (4). The regional dataset showed an 11% increase in PD prevalence from 2012 to 2017. The number of patients with lower burden of concomitant chronic diseases increased by 55.5% and those with a higher burden by 16%. Acute admissions to hospitals did not vary over years. In general, about a half of outpatient consultations were neurological, half with other specialists (**Table 1**).

This analysis supported the need to design a patient-centered regional network to serve as a basis for building a multidisciplinary PD management in the Lombardy region.

Neurological Facilities for PD

The management of PD patients in the early and advanced stages involves a variety of health settings, according to disease progression and to changes in patients' needs. The panel recognized that three main neurological settings are involved in the management of PD patients: General Neurologists, Parkinson Clinics and Parkinson Centers.

General Neurologists see a variety of neurological patients, whom they occasionally refer to specialized neurological services, particularly if there is need to manage complications or medical emergencies. General Neurologists see also PD patients, usually until the advanced disease stage. In addition, outpatient services with dedicated expertise on PD, called **PD Clinics**, look after PD outpatients and deploy specific skills for the management of the advanced stages. Finally, more articulated settings, called **PD Center**s, implement complex diagnostic and treatment protocols on PD patients. Non-neurological consultations involve the patient's general practitioners and specialists outside neurology: unless strictly connected with neurological centers, they may lack expertise on the specific needs of PD patients and on the possible interactions of antiparkinsonian medications.

The panel provided a definition for **PD Clinics**. They are outpatient neurology services of a hospital or an ambulatory neurology care clinic devoid of inpatient facilities, whose dedication to PD is recognized at administrative level (by the regional or the HCP administration). PD Clinics include at least one neurologist with post-residency training in movement

TABLE 1 | Data on PD patients in Lombardy (years 2012–2017).

Variable measured	2012	2013	2014	2015	2016	2017
Prevalence of PD patients	33,109	33,844	34,458	34,934	36,217	36,637
Prevalence of PD patients stratified by regional burden scale (3)						
• High burden	10,251	10,593	10,895	11,116	11,426	11,882
• Intermediate burden	7,991	7,909	7,973	7,917	8,073	7,951
• Low burden	690	775	851	904	1,036	1,073
Incidence of PD cases (per 100,000 inhabitants)	12.7887	12.6222	13.4328	13.3789	13.1253	11.3656
Acute admissions to hospitals (number per 1,000 resident population)	0.21	0.20	0.20	0.21	0.18	0.19
Consumption of antiparkinsonian medications (defined daily dose)	1,256.9531	1,244.8152	1,299.4366	1,311.0817	1,337.9097	1,101.3466
Outpatient consultations related to PD (number per 1000 resident population)	44.07	45.49	45.16	44.99	43.43	42.44
Outpatient consultations related to PD (total number)						
• Neurology	37,564	37,570	38,250	37,482	37,874	37,596
• Ophthalmology	7,888	7,804	7,714	7,510	7,544	7,462
• Orthopedics	7,010	7,016	7,350	7,318	7,030	7,328
• Physical medicine	4,140	4,558	4,616	4,796	4,998	5,222
• Endocrinology	4,250	4,732	4,790	4,730	4,690	4,786
• Cardiology	3,898	3,988	3,908	3,752	3,612	3,751
• Otolaryngology	3,043	3,228	3,120	3,210	3,269	3,213
• Urology	2,930	2,793	2,935	3,008	3,057	3,248

PD, Parkinson's disease.

disorders. Here PD patients receive assessment and personalized prescription of specific PD treatments. PD Clinics provide care across the full spectrum of patients' needs, including motor, non-motor and cognitive assessment.

The panel implemented the profile of a higher level network centers outlined by Lombard regional guidelines (3) and took into consideration also the definition of PD excellence centers provided by non-governmental organizations. **PD Centers** are defined as hospital HCPs which: (1) have a neurological ward; (2) deliver care according to a coordinated team model and include two or more neurologists with post-residency training in PD and movement disorders; (3) have taken in charge at least 700 unique patients with parkinsonism in the last 12 months; (4) regularly perform interventional treatments for advanced PD; (5) implement national and international research programs related to PD; (6) provide educational programs related to PD; (7) implement multi-disciplinary and multi-professional PD care; (8) receive referrals of patients with complex or rare PD variants.

The panel agreed that a regional PD network is composed by two levels of specific expertise: PD Centers and PD Clinics that interact with General Neurologists, General Practitioners and other health professionals to deliver high standards of care to PD patients (**Figures 1**, **2**).

Review of HCPs accredited by the NHS in the Lombardy region reported 322 ambulatory care clinics (142 public, 180 private), which deliver neurological consultations, but have no inpatient facilities. There are 232 hospitals (106 public, 126 private): 183 are general hospitals (including 12 university hospitals), 19 are research hospitals endorsed by the Ministry of Health (5 public, 14 private). Neurological services are present in 94 general/university hospitals and in 10 research hospitals (2 public and 8 private; **Table 2**). Interventional treatments for advanced PD are currently offered by 11 general/university hospitals and by six research hospitals; deep brain stimulation (DBS) is offered by 11 hospitals, enteral levodopa infusion by 14 hospitals.

It was reckoned that ∼12 centers in the Lombardy region meet all criteria for a PD Center, whereas approximately eight additional centers meet all but one criterion (**Figure 3**). The latter group includes HCPs that only implement one type of advanced treatment (usually enteral levodopa infusion) or do not perform clinical trials. Considering that the Lombardy region covers a surface of 23,844 km^2, each PD Center would serve a geographic area of 1,000–2,000 km^2 and would interconnect with up to 27 network PD Clinics.

Disease Progression

Progression of PD is marked by an increase in severity of motor symptoms, the emergence of levodopa-induced motor complications and the occurrence of dopaminergic resistant non-motor phenomena. This motor progression is nonlinear, with a variable speed of decline in motor and non-motor functions (5). The Hoehn and Yahr staging system, which combines functional disability with objective impairment, is commonly used to measure disease progression (6). When a patient reaches stage 3, risk of dementia increases, survival expectation decreases, and the total Unified PD rating scale (UPDRS) scores increase despite drug adjustment (6). Late stage PD is defined as stages 4 and 5 on the Hoehn and Yahr scale, which correspond to a stage with a progressive loss of physical independence that is irreversible in most patients (7).

The Lombardy regional guidelines ranked the burden of chronic diseases according to three levels, depending to the

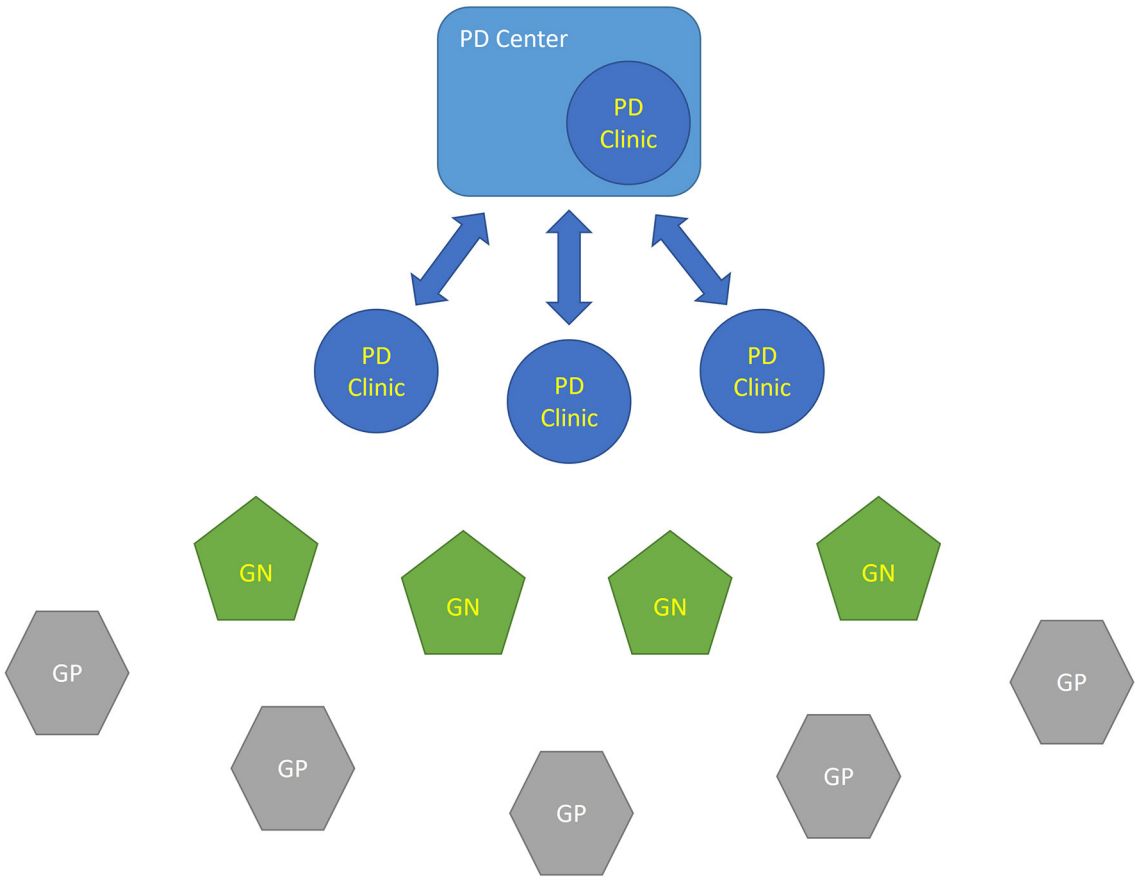

FIGURE 1 | Schematic relationship between different HCP centers within the PD network. The patient's journey is indicated by lines. A PD Center is a high level excellence center for PD with multidisciplinary inpatient facilities and an outpatient PD Clinic. PD Clinics, General Neurologists (GNs) and General Practitioners (GPs) interface with a PD Center in order to address patients' needs or contribute to research programs. GN, General Neurologist; GP, General Practitioner; PD, Parkinson's disease.

TABLE 2 | Accredited HCPs listed in the official repository of the Lombardy region (see methods).

	HCPs with neurology service		**Location**	
	Public	**Private**	**Milan metropolitan area**	**Outside Milan**
Outpatient clinic	142	180	122	200
General hospital/university hospital	42 (6)	52 (1)	24 (3)	70 (4)
Research hospital (IRCCS)*	2 (2)	8 (3)	8 (4)	2 (1)

**The number of potential PD Centers is reported in brackets. Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS).*

number of concomitant chronic diseases, their severity and the patient's dependence (3). The panel agreed that there is no reliable tally between the classification of burden proposed by the Lombardy region and PD staging used in neurological practice. For the purpose of clinical management, it was agreed to identify three PD stages [early, advanced and late (8)]. The early stage is characterized by mild symptoms and minimal or no functional impairment; the advanced stage denotes patients with motor complications. The late PD stage, instead, defines patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor or non-motor symptoms. Late-stage PD patients have a higher burden of chronic disease, are less manageable by the PD network, and often reside at residential and home care facilities.

A simplified approach suggests that early PD patients are prevalently seen by General Neurologists or at PD Clinics, advanced PD patients may need some consultation at PD Centers, and patients in the late stage will prevalently be seen by General Practitioners and referred to General Neurologists. PD Clinics and PD Centers may provide specific consultations to late stage PD patients when deemed relevant. A dynamic interaction between PD Clinics and PD Centers is considered a strength of

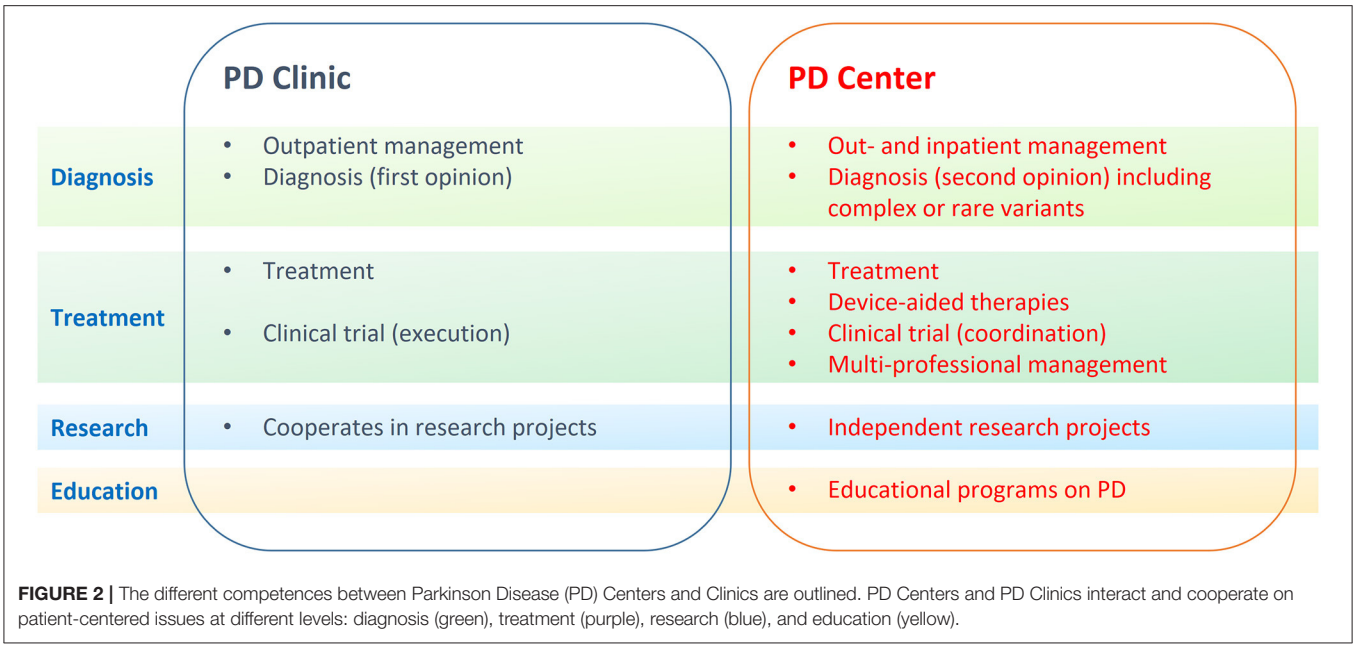

FIGURE 2 | The different competences between Parkinson Disease (PD) Centers and Clinics are outlined. PD Centers and PD Clinics interact and cooperate on patient-centered issues at different levels: diagnosis (green), treatment (purple), research (blue), and education (yellow).

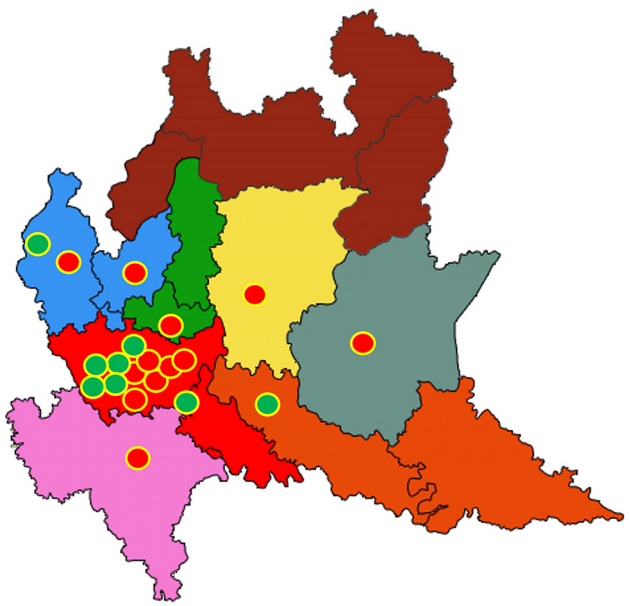

FIGURE 3 | Geographic distribution of potential Parkinson Disease (PD) Centers in the Lombardy region. Twelve health care providers (HCPs) fulfilling strict criteria for PD Centers are represented by red circles; eight additional HCPs fulfilling more lenient criteria are shown by green circles. The eight territorial branches of the Lombardy region Health Directorate are shown by different colors. Provincial districts are shown by lines. See text for further details.

the regional network at all disease stages. It is reckoned that early PD patients, if seen by a General Practitioner or by a General Neurologist, will be referred at least once to a PD Clinic to facilitate their enrollment in dedicated clinical trials. PD Clinics and PD Centers are competent to prescribe genetic and other specialized testing, when appropriate, to diagnose atypical cases.

PD Network

The network is a patient-centered model of care, connecting high specialty centers (PD Centers) to less specialized centers scattered throughout the network territory. A first aim is to treat PD patients consistently throughout the regional territory, to offer homogeneity of treatment and access to more specialized care whenever needed. A second aim is to avoid unnecessary fragmentation, repetition or delays in diagnosis and treatment of PD patients. A third aim of the network is to facilitate scientific programs by developing active interconnection among centers dedicated to PD. The network structure depicts a patient's journey guided by clinical decisions that combine scientific and methodological rigor, quality of care, fairness of performance, diagnostic, and therapeutic appropriateness.

Network Operations

The network takes charge of patients with PD symptoms based on referral from a General Practitioner, a General Neurologist or the patient himself.

Entry Visit

The main purpose of the first visit at a PD Clinic is to define diagnosis. The PD network implements current diagnostic criteria for PD set by the International Parkinson Disease and Movement Disorders Society (9) to establish a patient's diagnosis upon entry. According to these criteria, patients may receive one of the following clinical diagnoses: Clinically established PD, Clinically probable PD, Parkinsonism (likely not PD), Non-parkinsonism.

A personalized set of diagnostic tests is performed based on the patient's clinical presentation. Diagnostic tests include

TABLE 3 | Diagnosis and staging of PD patients as assessed by network centers.

Assessment	Clinically established PD	Clinically probable PD	Parkinsonism (likely not PD)	Non parkinsonian
MDS-UPDRS	✓	✓		
NMSS	✓	✓		
Hoehn-Yahr staging	✓	✓	✓	
Early/advanced/late staging	✓	✓	✓	
Other disease-specific rating scales			✓	
Treatment information	✓	✓	✓	
Genetic panel	✓		✓	
Imaging	✓	✓	✓	✓

MDS-UPDRS, Movement Disorders Society Unified Parkinson's disease rating scale; NMSS, Non-motor symptoms scale.

morphologic neuroimaging (brain MRI or CT), functional neuroimaging (DAT scan, FDG-PET, etc.), genetic assessment (NGS panel or individual gene testing), neuropsychological assessment, autonomic assessment, vascular, or systemic workup. The neurologist in charge of the entry visit identifies the appropriate diagnostic tests. In case of uncertainty, the patient is referred to a PD Center within the network.

Patients who receive a diagnosis of clinically established or probable PD are assessed using the following tools: MDS-UPDRS scale (10), the non-motor symptoms scale (11), and the modified Hoehn and Yahr scale (6). The patients are classified as having early-, advanced-, or late-stage PD (8).

Patients who receive a diagnosis of Parkinsonism (likely not PD) are further assessed for alternative diagnoses fitting current diagnostic criteria for parkinsonian syndromes other than PD, such as multiple system atrophy (12), progressive supranuclear palsy (13), corticobasal degeneration (14), etc. Patients who do not fit with any diagnosis alternative to PD are subject to a full diagnostic reassessment upon follow-up.

Patients who are denied a diagnosis of parkinsonism are evaluated again for diagnosis upon request by their general practitioner. **Table 3** summarizes the assessments performed at each network visit depending on the clinical diagnosis.

Follow-up Visits

Patients with a diagnosis of clinically established PD are followed-up every 6 to 12 months, depending on clinical stage and comorbidity. Patients with a diagnosis of clinically possible PD are followed-up every 6 months and reassessed for diagnostic refinement. Patients with a diagnosis of non-PD parkinsonism, who do not have an alternative diagnosis, are reassessed every 3 to 6 months, depending on the clinical stage and comorbidities. Patients with uncertain response to chronic dopaminergic treatment may receive an acute levodopa challenge test (15).

At each follow-up visit, all patients are subject to a quick diagnostic reassessment that is expected to be confirmatory in most instances; but may occasionally lead to reconsider the diagnosis. Additional diagnostic testing may be prescribed at this stage, particularly to patients with a diagnosis of clinically probable PD, in order to refine the diagnosis or reconsider the prescribed treatment.

TABLE 4 | Main non-motor symptoms leading to referrals of PD patients to specialized practices outside the PD network.

Non-neurological specialist practice	Main non-motor symptoms
Ophthalmologist	Blurred vision, diplopia
Orthopedist	Shoulder pain, back pain
Physical therapy specialists	Freezing of gait, loss of postural control, falls
Endocrinologist	Diabetes, thyroid dysfunction
Cardiologist	Cardiac dysrhythmias, postural hypotension, blood pressure variability
Otolaryngologist	Dysphagia
Urologist, gynecologist, andrologist	Urgency, incontinence, sexual dysfunction
Neuropsychologist	Cognitive dysfunction, dementia
Psychiatrist	Anxiety, depression
Gastroenterologist	Constipation, digestive problems
Nutritionist	Overweight or underweight

*Non-neurological consultations are listed in decreased order of frequency based on data published by the Lombardy region (see **Table 1**).*

Patient Referrals

A valuable network facilitates referrals between participating centers and with outside practices. Referrals within the network may have different motivations, such as: (1) seeking expert advice on a diagnostic or treatment issue; (2) requesting device-aided treatments unavailable at the referring center; (3) enrolling patients in clinical trials. Referrals from a PD Clinic are expected to be addressed to a neighboring PD Center, although there should be freedom to contact any network center.

All network centers should meet at least once a year, in order to align standards of care and share information on experimental trials and new procedures. Each PD Center should organize at least another yearly meeting with the neighboring PD Clinics to review referrals and patient outcomes. Significant changes in medical staff may require realignment of practices or update of operational standards during dedicated network meetings.

Outside referrals are mainly related to comorbid conditions that are best treated by a non-neurological specialist practice

TABLE 5 | Main indications and contraindications to device-aided therapies.

Favor device-aided therapy	Disfavor device-aided therapy
• Excellent and sustained levodopa response	• Dysphagia
• Levodopa resistant tremor	• Freezing of gait (OFF-related)
• Troublesome dyskinesia	• Dysarthria
• Pain	• Psychosis
• Intact cognitive function	• Dementia
• Night-time sleep disturbances	• Apathy
• Impulse control disorder	• Hallucinations
• Depression	• Postural impairment and gait disturbance
• Anxiety	• Older age (>70)
• Limitation with ADLs	• Insufficient compliance
• Younger age (<70)	• Lack of caregivers
	• Living in a nursing home

(**Table 4**). Patients with a high comorbidity burden are likely to be seen by multiple centers, including those within the PD network. Most commonly, PD Clinics and PD Centers refer patients outside the network to obtain a multidisciplinary consultation for non-motor or systemic symptoms. Assessment of non-motor symptoms with the non-motor symptoms scale (11) is a prerequisite to referring PD patients to non-neurological centers. The PD network maintains a database of non-neurological specialist centers that have expertise on PD.

Device-Aided Therapies

Device-aided (also called interventional or advanced) therapies allow to manage PD patients with a treatment potential, whose motor symptoms cannot be controlled adequately by oral medications. The main reason for addressing a patient to device-aided therapies is the occurrence of PD-related fluctuations and dyskinesias that change the patient's conditions during the day, often abruptly or unpredictably.

Having reached the advanced stage of PD does not necessarily mean that a patient is fit for device-aided therapies. Suitable patients are rather a sub-group of patients with advanced PD. A set of clinical criteria for addressing patients to device-aided treatments has been recently defined (16). The panel reached consensus on a simplified list of clinical features favoring or disfavoring device-aided therapies for PD (**Table 5**). These treatments currently encompass DBS and enteral levodopa. New device-aided treatments are under development, including subcutaneous levodopa delivery, intrathecal infusion of anti-sense oligonucleotides, cell-based approaches, and viral gene delivery (17).

General Neurologists or PD Clinics select patients for device-aided treatments and refer them to a PD Center, where the indication is reviewed and the most appropriate treatment is implemented according to current guidelines. At the end of the procedure, the patient is readdressed to the referring center for follow-up visits. As a rule, changes in stimulation settings are performed by PD Clinics and PD Centers; General Neurologists can test PD patients with stimulation on or off and adjust the infusion rate of enteral or subcutaneous antiparkinsonian medications. Based on specific protocols, particularly for research purposes, some follow-up visits may be performed at the treating PD Center.

Late PD Stage

PD patients in the late stage are highly dependent on caregivers for daily living activities, owing to treatment-resistant motor symptoms or non-motor symptoms; these patients usually have a score on the Schwab and England Scale of <50% during periods of adequate symptomatic treatment (8). When a PD patient fits into the category of late-stage PD, the responsible neurologist informs the patient's General Practitioner.

Data Collection and Retention

After obtaining informed consent, the patient's clinical data are collected at each scheduled visit and entered in the network database. Collection, storage and use of identifiable data and biological material beyond standard medical practice is performed in compliance with national and international guidelines. Data security should be part of the network's data management policy that includes retention, storage and disposal of health information. It should also include management of electronic and physical aspects, with appropriate steps taken to protect against intentional and inadvertent loss or breach. Access to health records should be protected by robust password control and regular password changes.

The network steering committee proposes and the general assembly approves the minimal clinical dataset to be shared by all network centers. This encompasses a set of rating scales, information on treatment and on relevant laboratory tests (see **Table 3**). In order to harmonize collection of clinical data, training for specific rating scales is provided by the network during dedicated training sessions. The network centers share a platform containing electronic case report forms to be filled when assessing patients. Collection of additional clinical data (including biobanking, imaging, etc.) may be performed by network centers who cooperate on specific research protocols.

An annual quality control of the data-entry process should be performed.

Funding and Sustainability

Funding for the network functioning should be provided by the regional health government. While clinical activities are currently supported by the national health system, the network organization and functioning needs dedicated organizational and infrastructural resources. The business plan has to consider organizational, financial, and community sustainability, with periodic review and updates. Additional expenses for funding network activities are expected to be counterbalanced by the savings generated.

Quality Assessment and Governance

Network performance is reviewed periodically with measures related to network efficacy and efficiency and to patient satisfaction. The shared platform containing electronic case report forms should contain a dashboard with updated performance information that is automatically displayed as clinical data are entered.

The panel reached consensus on the following measures that can be used to assess network performance: (1) Yearly consultations to emergency departments for PD patients followed by the network; (2) Yearly emergency admissions to neurological wards for PD patients followed by the network; (3) Efficacy of device-aided therapies (motor improvement 1 year after device-aided treatment compared to pre-treatment condition); (4) Waiting time at PD Centers and PD Clinics (waiting days before consultation by a PD network center); (5) Patient satisfaction questionnaires (marks given by PD patients and caregivers).

Governance can be provided by a network Steering Committee and a network General Assembly. The Steering Committee, composed by all PD Centers, elects a President and a Secretary with a two-year term. The President represents the network toward the regional Health government. The General Assembly, composed by all PD Clinics, meets yearly to review measures of outcome and to approve changes in the organization or functioning of the network.

DISCUSSION

The development of a regional PD network is expected to improve the standards of care and to optimize resources at the regional level. This is of high relevance, considering that the financial burden of PD on the society is quite high (18), with specific costs expected to increase more than the average health costs (19). Italian regions have a direct responsibility for governance and allocation of resources, regulate and organize health services and define financing criteria for regional HCPs. We provide a consensus agreement on the general organization based on clinical operational criteria, applicable to all HCPs accredited by the NHS. This model can serve as a basis to define the operational algorithm of health professions other than neurologists involved in PD care. This model has been implemented based on a political legislative decision and requires field-testing particularly to test its efficiency and advantages over standard practice.

A recent review showed that clinical networks can improve the delivery of healthcare (20). Coordinated and responsive care, tailored to the individual, with regular and timely medication reviews and information provision, is expected to improve the quality of life of PD patient. This is supported by the observation that patients who seek skilled care are at a lower risk of complications and have better quality of life (21), and that clinical networks can improve the delivery of healthcare (20). The hub-and-spoke organization of a PD network may increase the number of patients who receive early diagnosis and appropriate care. Predefined outcome measures contribute to the overall network quality.

A review of HCP facilities in Lombardy showed that PD Centers are mainly concentrated in and around Milan, with the northern and southeastern districts notably devoid of PD Centers. The first is a mountainous Alpine district; the latter is flat area bordering the neighboring Emilia region. More lenient criteria for PD Centers would only mildly mitigate such clustering around main towns (**Figure 3**). In the case of PD, where time-sensitive emergencies are uncommon, an uneven geographical representation of network centers may still be acceptable. In addition, telemedicine consultations may be performed by distant network centers and integrated within the PD network (22).

Few Italian regions have recently approved the design of regional PD networks. Apulia defined a regional networks that have some features in common with this consensus (23). The Piedmont region, instead, appointed two regional centers with expertise on DBS as network hubs, without delineating a detailed network structure (24). In both cases no dedicated resources were allocated for network activity, and quality measures of network performance were not defined. Other Italian regions have not yet deliberated on the structure of regional networks; some regions have consulted expert panels, and all are expected to proceed soon in accordance with a national measure on chronic diseases (1). Disease-centered networks provide an innovative opportunity to improve patient management, facilitate research and education on chronic neurological disease. We report a scientific consensus on the organization and implementation of a PD network in Lombardy that may serve as a first comprehensive organizational model. We provide a consensus definition of tertiary and secondary PD services and detail their interaction with the primary neurologist and the General Practitioner. The network structure depicted here may also apply to other chronic neurological conditions, such as dementias and amyotrophic lateral sclerosis. Regional disease networks may further cooperate at a national level, as foreseen by the national plan on chronic diseases (1). Agreement on a common structure may facilitate such cooperation.

A possible fallout of this consensus is the support of a sustainable healthcare systems. A structured network may reduce costs, improve timely access to treatment, facilitate earlier diagnosis, enhance patient outcomes, decrease hospital stays, and increase quality and duration of life. The network structure proposed here differs from other networks primarily aimed at sharing clinical experiences among professionals, such as the UK Parkinson's Excellence Network. This patient-funded initiative is mainly devoted to standardizing practices and sharing information. The Dutch ParkinsonNet was originally designed to train physical therapists who treat PD (25). Other research networks have different structures: the NS-Park lists 24 expert French centers designated by the Ministry of Health, the Kompetenznetz Parkinson is a German network of 40 movement disorder expert centers who conduct clinical trials on PD.

The availability of adequate resources is essential for network functioning. A solid infrastructure for data sharing must be created. The Lombardy region has an innovation technology company that can support the development of IT structure needed for the PD network. Support is also required for administration, training, and meetings. The initial investment is expected to be repaid by later savings on health resources, particularly after few years of operation.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. The list of Lombard HCPs can be found here: http://www.regione.lombardia.it/wps/portal/istituzionale/HCP/DettaglioServizio/servizi-e-informazioni/Cittadini/salute-e-prevenzione/strutture-sanitarie-e-sociosanitarie/ser-strutture-sanitarie-accreditate-sal/strutture-sanitarie-accreditate. Official statistical data on PD in Lombardy can be found here: https://www.dati.lombardia.it/stories/s/etgr-wnvm.

AUTHOR CONTRIBUTIONS

AA: conception, design, first draft, review. AD, VF, AF, MG, GM, CP, AP, GR, and MV: review of manuscript. DC: data search, data analysis, and review of manuscript. All authors contributed to the article and approved the submitted version.

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Collaborative Efforts for Spinocerebellar Ataxia Research in the United States: CRC-SCA and READISCA

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Spinocerebellar ataxias are progressive neurodegenerative disorders primarily affecting the cerebellum. Although the first disease-causing gene was identified nearly 30 years ago, there is no known cure to date, and only a few options exist for symptomatic treatment, with modest effects. The recently developed tools in molecular biology, such as CRISPR/Cas9 and antisense oligonucleotides, can directly act on the disease mechanisms at the genomic or RNA level in disease models. In a nutshell, we are finally just one step away from clinical trials with therapies targeting the underlying genetic cause. However, we still face the challenges for rare neurodegenerative diseases: difficulty in obtaining a large cohort size for sufficient statistical power and the need for biomarkers and clinical outcome assessments (COA) with adequate sensitivity to reflect progression or treatment responses. To overcome these obstacles, ataxia experts form research networks for clinical trial readiness. In this review, we retrace our steps of the collaborative efforts among ataxia researchers in the United States over the years to study and treat these relentless disorders and the future directions of such research networks.

Keywords: ataxia, cerebellum, network, consortium, spinocerebellar ataxia

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INTRODUCTION

Spinocerebellar ataxias (SCAs) are a group of neurodegenerative disorders involving the cerebellum with an autosomal-dominant pattern of inheritance. SCAs are monogenetic disorders with a high disease penetrance and defined clinical presentations with the core feature of cerebellar ataxia; therefore, SCAs can serve as disease models for novel disease-specific therapeutic approaches, such as gene therapies or antisense oligonucleotides (ASOs).

The pooled prevalence of hereditary ataxia is ∼2.7–38.35 per 100,000 (1–3); therefore, SCAs are considered orphan diseases. The major research challenges for orphan diseases are patient recruitment, development of reliable and responsive disease-specific clinical outcome assessment (COA) measures, collection of biosamples for biomarker discovery, uniform acquisition of brain imaging data, and the understanding of natural history. Addressing these challenges through collaborative research by a network of investigators specializing in such diseases is a powerful approach to establish clinical trial readiness.

The goal of this article was to review the history, the current state, and the future perspectives of an ataxia research network in the United States. Through the collaboration between the ataxia

research networks and industries, several clinical trials for SCAs have been launched. These milestones for SCA research bring hope to SCA patients and their family members.

HISTORY OF SCA RESEARCH IN THE UNITED STATES

The history of collaborative ataxia research could be dated back before the genetic discovery to define each SCA subtype. In 1957, the National Ataxia Foundation (NAF) was established, marking the prelude of organized collaboration for clinical studies of ataxia (**Figure 1**). In 1975, the first joint meeting for ataxia research took place in Minneapolis, chaired by Dr. Lawrence Schut, to achieve the goal of promoting research collaboration between clinical, genetic, and basic science research of ataxia. Subsequently, the first International Symposium on Inherited Ataxias was held in 1977 in Los Angeles, which drew almost 100 researchers representing five countries. These meetings, which were the first of their kind focusing solely on ataxia, led to collaborative efforts between investigators.

In 1993, a group of investigators led by Huda Zoghbi and Harry Orr identified a heterozygous expansion of CAG repeat that encodes a polyglutamine (polyQ) tract in a novel gene, *ATXN1*, in a family with an autosomal-dominant cerebellar ataxia, now known as spinocerebellar ataxia type 1 (SCA1) (4). This pivotal work triggered a "gold rush" in the discoveries of new SCAs, particularly those caused by polyQ expansions in the coding region, including dentatorubral pallidoluysian atrophy (DRPLA), SCA2, SCA3, SCA6, SCA7, and SCA17. In addition, SCAs caused by repeat expansions in the non-coding regions (e.g., SCA8, SCA10, SCA12, SCA31, SCA36, and SCA37) and other traditional mutations have been identified, which are still growing in number today (up to SCA48) (5, 6). There has been no more coding-region polyQ expansion SCAs identified after 1999, but polyQ SCAs are collectively the most common among all SCAs.

Although the discovery of polyQ expansion mutation has given rise to a strong hope for the development of rational therapeutic interventions, successful clinical trials have not been forthcoming for efficacious treatments. However, understanding of the pathogenic molecular pathways triggered by the polyQ expansion has been advancing at an accelerating pace for the past 10 years, and several promising drug development programs have emerged. Among them, RNA silencing is attracting strong attention by academic investigators, the pharmaceutical industry, and patient support groups. While preclinical studies of ASOs, microRNAs (miRNAs), and other RNA silencing technologies are progressing nicely, clinical trial readiness remains suboptimal.

However, the first effort for clinical trial readiness was not successfully put together until 1997, when the Ataxia Neuropharmacology Committee of the World Federation of Neurology introduced the International Cooperative Ataxia Rating Scale (ICARS) (7). Although clinical ataxia researchers started using ICARS extensively, ICARS was soon found to be cumbersome, with redundancy in the subscale structure and concerns about its usefulness for future interventional trials. Meanwhile, a NAF-sponsored group of US clinical investigators formed the first clinical ataxia consortium, the Cooperative Ataxia Group (CAG). The CAG had constructed and validated the Friedreich's Ataxia Rating Scale (FARS) (8) and was intensely revising ICARS to address this problem when European investigators published the Scale and Assessment for Rating of Ataxia (SARA) in 2006 (9). Because SARA closely resembled what the CAG was drafting as a new ataxia scale, the Unified Ataxia Disease Rating Scale (UADRS), the CAG made a decision to abandon their own efforts. This was a critical decision that later enabled unifying the clinical researchers of ataxia across the Atlantic. While the Europeans launched the European Integrated Project on Spinocerebellar Ataxias (EUROSCA) and Prospective Study of Individuals at Risk for Spinocerebellar Ataxia (RISCA) (10, 11), the CAG started conducting the first multicenter natural history study of SCAs in the United States (12). The CAG was registered as one of the National Institutes of Health (NIH) Rare Diseases Clinical Research Consortia and acquired a new designation, "Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA)." Upon conclusion of the 2-years natural history study of SCA1, SCA2, SCA3, and SCA6, the CRC-SCA changed the acronym for SCA to "Studies of Cerebellar Ataxia" under NAF sponsorship. In 2017, the CRC-SCA initiated an NIH-funded 5-years project, "Clinical Trial Readiness for SCA1 and SCA3 (READISCA)." READISCA (NCT03487367) is the first US–European collaborative SCA project and focuses on premanifest and early-stage subjects of SCA1 and SCA3 mutation carriers. This 5-years longitudinal study uses SARA as the primary COA measure with corresponding magnetic resonance spectroscopic (MRS) and MR imaging (MRI) biomarkers, collects biofluid samples, and assesses trial designs by simulations using the clinical and biomarker data.

CRC-SCA

The natural history study of CRC-SCA (NCT03487367) originally focused on the various COAs and genetic modifiers for SCA1, SCA2, SCA3, and SCA6 and later expanded to other repeat expansion SCAs, including SCA7, SCA8, and SCA10. This ongoing natural history study currently has 14 patient enrollment sites (**Figure 2A**) to investigate the clinical characteristics and progression of genetically confirmed, symptomatic SCA patients (**Figure 2B**). The natural history records the longitudinal progression data of ataxia severity (measured by SARA), depressive symptoms associated with ataxia (measured by Patient Health Questionnaire-9, PHQ-9), and functional capacity (measured by the Unified Huntington's Disease Rating Scale Part IV, UHDRS-IV). Various extracerebellar features, such as dystonia or tremor, are captured by the Inventory of Non-Ataxia Signs (INAS) (13). After the development of the Cerebellar Cognitive Affective Syndrome Scale (CCAS) in 2018 (14), this scale is also included to comprehensively assess SCA patients' cognitive function.

As the result of the CRC-SCA natural history study, we found that the rates of disease progression of SCA1, SCA2, SCA3, and SCA6 (annual increase in SARA by 1.61, 0.71, 0.65,

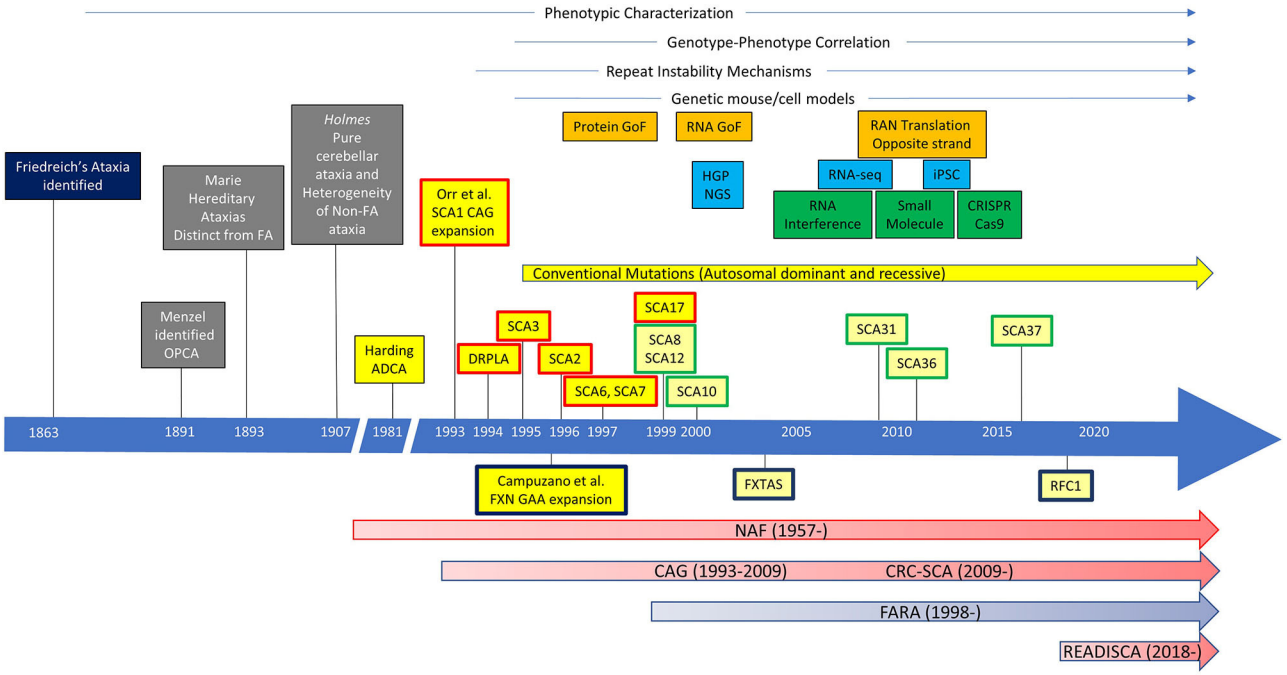

FIGURE 1 | The history of ataxia research. Ataxias caused by repeat expansions were labeled, with autosomal-dominant ataxias above and autosomal-recessive ataxias below the timeline. Spinocerebellar ataxias (SCAs) with repeat expansion in the coding region are in boxes with a red outline. SCAs with repeat expansion in the non-coding region are in boxes with a green outline. GoF, gain of function; HGP, Human Genome Project; NGS, next-generation sequencing; RNA-seq, RNA sequencing; iPSC, induced pluripotent stem cells; OPCA, olivopontocerebellar atrophy; FA, Friedreich's ataxia; ADCA autosomal-dominant cerebellar ataxia; DRPLA, dentatorubral pallidoluysian atrophy; FXN, frataxin; FXTAS, Fragile X-associated tremor/ataxia syndrome; RFC1, replication factor C subunit 1; NAF, National Ataxia Foundation; CAG, Cooperative Ataxia Group; CRC-SCA, Clinical Research Consortium for Spinocerebellar Ataxias/Clinical Research Consortium for Studies of Cerebellar Ataxias; FARA, Friedreich's Ataxia Research Alliance.

and 0.87 points, respectively) (12) are consistent with those in EUROSCA (15). In addition, we found that the severity of depressive symptoms also tracks along with ataxia progression (16), while dystonia and tremor could be prominent features of SCA patients in a subtype-specific manner (17–19). Another important piece of information from this cohort is that we found that the occurrence of cardiovascular risk factors is quite low (20), which will have implications in assessing the vulnerability to side effects for novel therapies.

In addition to the clinical data, blood samples for DNA extraction were sent to the University of Utah to determine the repeat expansions in various genes to further investigate the consequences of repeat interactions in SCAs (21). Specifically, clinical presentations of tremor and dystonia could be influenced by the repeat expansions outside of the pathological SCA allele (17, 18). We also recently identified that the pathological repeat expansions of *C9orf72* occur in a small subset of SCA patients, and the intermediate repeat expansions of *C9orf72* can be a genetic modifier for depressive symptoms (22), further underscoring the importance of repeat interactions. Another discovery related to genetic modifiers is that ethnicity can play a role in SCA disease progression (23).

A critical aspect of the ongoing CRC-SCA is the recent expansion to collect blood and cerebrospinal fluid (CSF) for biomarker discovery for symptomatic patients. These fluid samples will be collected longitudinally; therefore, we will have the capacity to discover markers that track disease progression.

READISCA

READISCA, an extensive NIH-funded multinational clinical trial readiness study, was initiated in 2017 and currently has 20 US and two European sites for clinical assessment and biofluid collection, and among these, four sites are performing neuroimaging studies (**Figure 2A**). A component of READISCA overlaps with CRC-SCA to study early symptomatic SCA1 and SCA3 patients with SARA $\leq$ 9.5. However, different from CRC-SCA, which enrolls patients from all stages of diseases, READISCA studies the early stage of diseases to plan for future clinical trials studying disease-modifying therapies. READISCA thus includes pre-symptomatic SCA1 and SCA3 patients and also 50% at-risk patients who do not exhibit ataxia symptoms and who do not know their genetic status. Patients in READISCA are anticipated to enter clinical trials in the next 5 years. The reasons for choosing SCA1 and SCA3 are that SCA1 is the fastest progressing polyQ SCA (12) while SCA3 represents the most common SCA in most regions of the world (24).

In READISCA, there is an emphasis on MR as an imaging biomarker for SCA1 and SCA3. While conventional structural

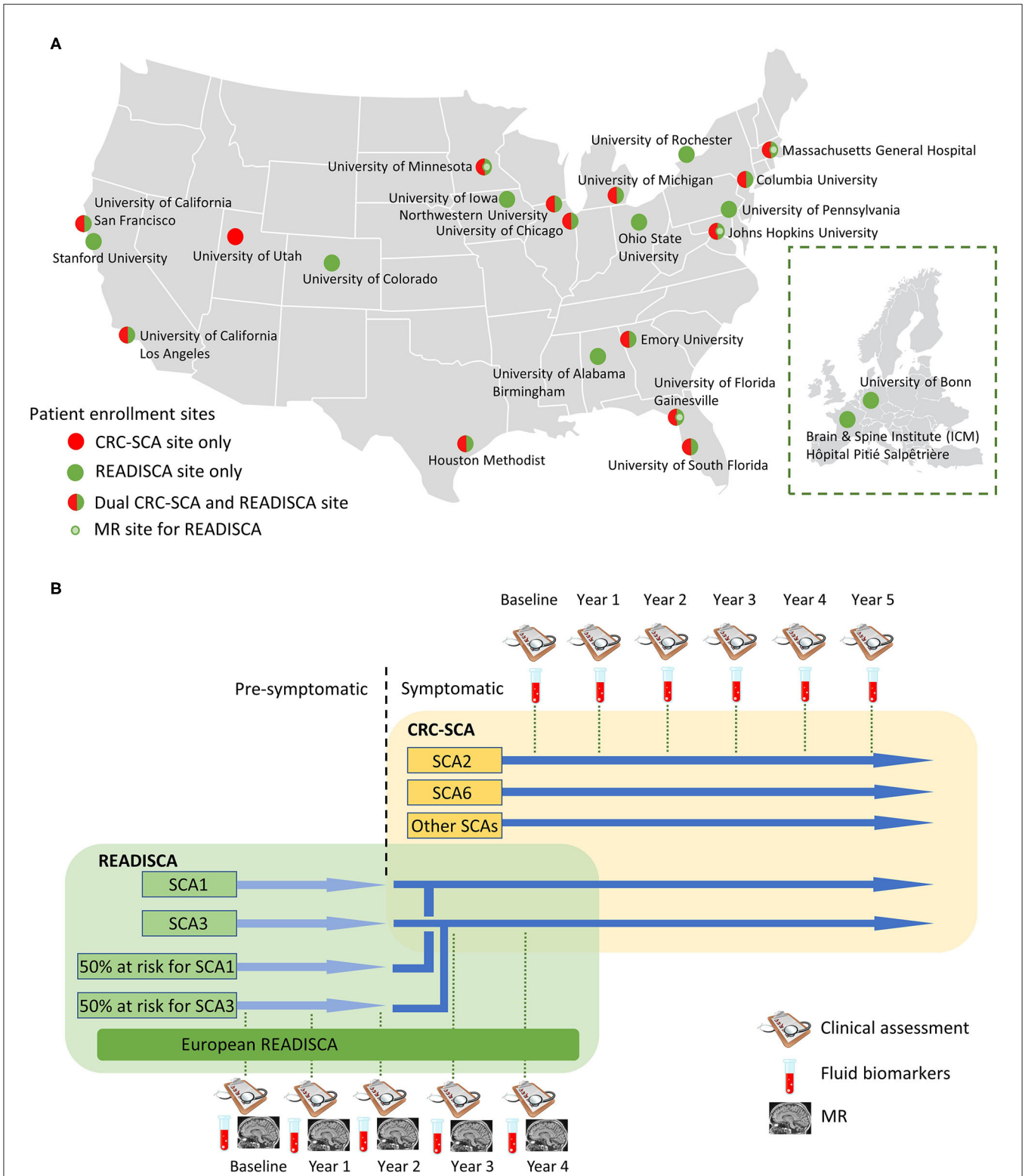

FIGURE 2 | Site and study overview of the Clinical Research Consortium for Spinocerebellar Ataxias (CRC-SCA) and Clinical Trial Readiness for SCA1 and SCA3 (READISCA). **(A)** Patient enrollment sites for CRCSCA and READISCA. Inset: participating sites of READISCA in Europe. **(B)** Study design of CRCSCA and READISCA.

MRI has been the standard of care to monitor the characteristic cerebellar and brainstem atrophy in patients with SCA1 and SCA3, this technique is limited by the lack of sensitivity in the premanifest stages (25, 26). On the other hand, the use of multimodal MRI with a combination of volumetry, voxel-based morphometry, and diffusion tensor imaging, along with MRS and resting-state functional MRI, can serve as sensitive imaging biomarkers for presymptomatic and early stages of SCAs. Specifically, MRS has been demonstrated to measure neurochemical abnormalities in the presymptomatic stages (27) and the treatment effects of transgenic SCA1 mouse models with high sensitivity and specificity (28). For SCA1 and SCA3, volumetric analysis showed that the rate of cerebellum volume decrement correlated with the rate of SARA increase (29, 30). Similarly, diffusion tensor imaging revealed that metrics, such as fraction anisotropy and mean diffusivity in the brainstem and cerebellum can reflect the change in SARA (31, 32) and ICARS (33). The validation of the use of MR techniques in this patient population is highly relevant and will have implications for disease-modifying therapies in the early stages. Similar to CRC-SCA, READISCA also prospectively collects patient blood and CSF samples for biomarker discovery.

Another unique component of READISCA is that it includes two sites in Europe, one in Paris, France, and the other in Bonn, Germany (**Figure 2B**). The data will eventually be compiled and analyzed together with sites in the United States, which can serve as the basis for trans-Atlantic collaboration.

CENTRALIZED DATA AND BIOSPECIMEN STORAGE

Since CRC-SCA and READISCA have many shared components in terms of investigators, patients and their family members, COAs, and biospecimens, these two ataxia networks also share a centralized data storage to facilitate the integration and analysis of the data throughout the disease courses. The storage of data and biospecimens is monitored by the leadership of the respective ataxia networks. Clinical data are stored at the University of South Florida Health Informatics Institute, whereas imaging data are stored at the University of Minnesota. Biospecimens, including blood and CSF, are sent to BioSEND, which is the National Institute of Neurological Disorders and Stroke (NINDS) biomarker repository at Indiana University. These biospecimens are made available to academic and industry researchers through committee review and approval by the Biospecimen Resource Access Committee. Finally, the blood DNA samples are stored and analyzed at the University of Utah. All these facilities have extensive experience in performing clinical studies and serve as key foundations for CRC-SCA and READISCA.

CHALLENGES FOR CRC-SCA AND READISCA

READISCA is designed to recruit early-stage patients, pre-symptomatic patients, and subjects with unknown genetic status but with affected first-degree relative(s). The goal of this non-treatment study may not meet the expectations of early-stage and pre-symptomatic patients who are seeking for a cure or a disease-modifying treatment. Similar challenges also occur in CRC-SCA. The other "challenge" is the development of new clinical trials studying therapeutic agents. Many patients might choose to participate in these clinical trials instead of continuing in the natural history study of CRC-SCA and READISCA. This particular challenge is in fact the original goal of CRC-SCA and READISCA, to eventually transition SCA patients into clinical trials.

CRC-SCA and READISCA were also challenged by difficulties in patient recruitment, meeting the expectations of different funding agencies, and the recent changes in the laws regulating personal information sharing. These challenges may also be encountered by clinical trials studying other rare diseases. The lessons learned below may benefit future clinical trials.

An intrinsic challenge for both CRC-SCA and READISCA is recruiting a sufficient number of patients. This was partly overcome by the active participation of patients and their families, who are highly motivated to participate in the natural history study with the hope of finding therapies for SCAs.

The funding sources for CRC-SCA and READISCA are from NAF and NINDS, respectively. Sustained funding from the industry is needed in the future. While many pharmaceutical companies are interested in supporting these ataxia networks, each industry partner might want to support different components of the study. For example, CSF biospecimen will have profound implication to test for target engagement of ASOs for disease-modifying therapies, and physiological measures may be relevant for monitoring the effects of ion channel modulators aimed at symptomatic treatments for ataxia. Organizing the diverse interests among individual pharmaceutical companies to support the ataxia research networks will be one important challenge. Along this line, the other consideration is the data sharing policy in different companies.

In May 2018, the General Data Protection Regulation (GDPR), a data protection law, was enforced across all European Union countries to set the boundaries and regulations for acquiring, processing, and storing personal information (34). GDPR is also applicable outside of Europe, as long as the personal information being processed belongs to someone who is physically located in the European Union. As READISCA proposed to merge the databases of SCA patients from the United States and Europe, it needs to be GDPR-compliant. While the Health Insurance Portability and Accountability Act and the Genetic Information Non-discrimination Act are less stringent equivalents to GDPR in the United States, several states have followed the steps of the European Union to legislate their own versions, such as the California Consumer Privacy Act (35). The strict GDPR laws clash with the NIH policy of widely sharing data and resources obtained with the NIH grants. This discordance resulted in countless sessions with attorneys on both sides of the Atlantic, with a substantial delay in the READISCA enrollment. READISCA and CRC-SCA will need to continue to adapt as additional regulations from different states emerge to eventually merge the data with the European counterpart.

FUTURE PERSPECTIVES

ASOs have been successfully applied for the treatment of spinal muscular atrophy (36) and demonstrated promising results in Huntington's disease (37). These results have shown promise for ASOs to treat monogenetic neurological disorders. Therefore, ASOs and other RNA silencing molecules have been developed in SCA preclinical models and have been shown to mitigate motor symptoms in mouse models of SCA1 (38, 39), SCA2 (40), and SCA3 (41) as well as prevent blindness in a mouse model of SCA7 (42). While ASOs, virus-mediated gene therapies, and other molecular interventions targeting pathways specific for each SCA (43) have been developed in an unprecedented speed at the preclinical stages, READISCA and CRC-SCA are pivotal SCA networks to prepare for the clinical trials by (1) recruiting SCA patients, (2) developing and validating COAs, and (3) discovering imaging and fluid biomarkers. In addition, gene-editing technologies, such as zinc finger nuclease and CRISPR/Cas9, with their ability to precisely edit the genome, have brought hope to SCA patients to manipulate the disease at the genomic level. In particular, CRISPR/Cas9 has been successfully applied to delete the expanded CAG repeats in induced pluripotent stem cells (44). Another innovative therapy on the horizon is mesenchymal stem cell infusion (45). These new therapies can be developed on the established platforms of CRC-SCA and READISCA.

READISCA can be viewed as the first step in preparing for foreseeable clinical trials for disease-modifying therapies. While READISCA combines the forces of the United States and Europe, future efforts are needed to strengthen global collaboration. SCAs are a group of rare diseases, and only international cooperation can achieve sufficient sample sizes to reach enough power. Furthermore, certain types of SCAs may have high incidences regionally, for example, SCA1 in Poland, Russia, South Africa, Serbia, Italy, and India; SCA2 in Cuba, Mexico, Korea, India, Italy, and Spain; SCA3 in Portugal, Brazil, China, Netherlands, Germany, Japan, and Taiwan; and SCA8 in Finland (6, 46–49). An international task force with shared data will also be important to investigate how the ethnic, genetic, and/or environmental factors influence monogenetic disorders, such as SCAs. Finally, it is critical to standardize the COAs so the results obtained from one study can be compared with the other. Although SARA is the most extensively used and well-validated COA today, further modifications to improve SARA's responsiveness are ongoing. To further strengthen the international collaborations for these important goals, several international networks for ataxia research have recently been established. The Pan-American Hereditary Ataxia Network aims to facilitate the communications between Latin American countries and the United States. At the same time, the SCA Global initiative was established to enhance collaboration between researchers from the United States, Asia, and Europe. The SCA Global initiative will include not only the data from CRC-SCA but also those from EUROSCA, RISCA, and the Spastic Paraplegia and Ataxia Network. These strong networks for clinical SCA research will be the hope in bringing the new therapies for SCAs to reality.

AUTHOR CONTRIBUTIONS

C-CL, S-HK, and TA together wrote and contributed substantially to the manuscript as well as providing critical comments to the content. All authors contributed to the article and approved the submitted version.

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The European Reference Network for Rare Neurological Diseases

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While rare diseases (RDs) are by definition of low prevalence, the total number of patients suffering from an RD is high, and the majority of them have neurologic manifestations, involving central, peripheral nerve, and muscle. In 2017, 24 European

Reference Networks (ERNs), each focusing on a specific group of rare or low-prevalence complex diseases, were formed to improve the care for patients with an RD. One major aim is to have "the knowledge travel instead of the patient," which has been put into practice by the implementation of the Clinical Patient Management System (CPMS) that enables clinicians to perform pan-European virtual consultations. The European Reference Network for Rare Neurological Diseases (ERN-RND) provides an infrastructure for knowledge sharing and care coordination for patients affected by a rare neurological disease (RND) involving the most common central nervous system pathological conditions. It covers the following disease groups: (i) Cerebellar Ataxias and Hereditary Spastic Paraplegias; (ii) Huntington's disease and Other Choreas; (iii) Frontotemporal dementia; (iv) Dystonia, (non-epileptic) paroxysmal disorders, and Neurodegeneration with Brain Iron Accumulation; (v) Leukoencephalopathies; and (vi) Atypical Parkinsonian Syndromes. At the moment, it unites 32 expert centers and 10 affiliated partners in 21 European countries, as well as patient representatives, but will soon cover nearly all countries of the European Union as a result of the ongoing expansion process. Disease expert groups developed and consented on diagnostic flowcharts and disease scales to assess the different aspects of RNDs. ERN-RND has started to discuss diagnostically unclear patients in the CPMS, is one of four ERNs that serve as foundation of Solve-RD, and has established an RND training and education program. The network will facilitate trial readiness through the establishment of an ERN-RND registry with a minimal data of all patients seen at the ERN-RND centers, thus providing a unique overview of existing genotype-based cohorts. The overall aim of the ERNs is to improve access for patients with RDs to quality diagnosis, care, and treatment. Based on this objective, ERNs are monitored by the European Commission on a regular basis to provide transparency and reassurance to the RD community and the general public.

Keywords: rare neurological diseases, standards of care, training and education, virtual healthcare, European reference network

INTRODUCTION

Rare Diseases in Europe—The Current Situation and Challenges

In Europe, a disease is considered as "rare" if it affects <1 person in 2000 (1). Although rare diseases (RDs) have–per definition–a low prevalence, the total number of patients with an RD is high, concerning about 3.5–5.9% of the population that equates to 263–446 million persons affected globally at any point in time (2). The majority of RD have neurological manifestations, involving central, peripheral nerve and muscle (3). Most RDs are associated with high unmet needs due to the lack of available and effective diagnosis and treatment measures as well as the relative lack of research to develop such measures, at least partly due to the low number of medical experts available for each condition and limited financial resources. A current analysis of Orphanet has shown that of the 5,304 diseases defined by point prevalence, 84.5% of those analyzed have a point prevalence of <1/1,000,000 (2) and can thus be characterized as ultra-rare diseases. This means that no single European Union (EU) member state can provide access to the best possible healthcare to its citizens in all areas of highly specialized healthcare for RD patients on its own.

European Reference Networks for Rare Diseases

As response to this challenge, European Reference Networks (ERNs) were launched in 2017 by the European Union Board of Member States as a pan-European initiative to facilitate access to highly specialized healthcare for patients with rare or low-prevalence complex diseases. It also aims to reinforce the cooperation of Healthcare Providers in the field of RDs at the European level.

ERNs are legally based on the European Directive 2011/24/EU on patients' rights in cross-border healthcare.

This worldwide-unique initiative resulted in 24 ERNs being formed, involving more than 900 specialized healthcare units from over 300 hospitals in 26 Member States (4). There are three ERNs with a neurological focus: ERN EpiCARE[1] on rare epilepsies, Euro-NMD[2] on rare neuromuscular diseases, and European Reference Network for Rare Neurological Diseases (ERN-RND) that will be described in more detail below.

[1]https://epi-care.eu/
[2]https://ern-euro-nmd.eu/

Each ERN had to fulfill a number of criteria for implementation, evaluation, and knowledge sharing, while the respective national authorities endorsed the individual healthcare providers to become an ERN member. For a detailed description of the conceptual framework, see Heon-Klin (5).

The central political aim of the ERNs is that medical expertise "travels," and that only in a few cases (e.g., for highly specialized interventions and for diagnostic and therapeutic measures that are not available in the country the respective person lives in) the patient has to travel. This marks a significant step toward improving healthcare quality, harmonizing medical (diagnosis) procedures, reducing access inequalities, and increasing overall medical experience and knowledge in the whole of Europe.

In addition, the ERNs open the possibility to get sizable cohorts of patients in the perspective of therapeutic trials and the development of research collaborations.

Travel of Knowledge Put Into Practice—The Clinical Patient Management System

To improve the diagnosis and treatment of RDs in practical terms, the European Commission has set up the Clinical Patient Management System (CPMS[3]), a web-based clinical software application, enabling secure remote multi-national and multidisciplinary case discussions.

The CPMS can be used by healthcare professionals of all ERNs, who can upload patient data in a structured manner following an informed consent procedure. Clinicians from outside the ERNs can request CPMS-based advice from ERNs on specific patients through referring them to the nearest national ERN healthcare provider. So far, over 40 CPMS case discussions have been performed by ERN-RND members.

The European Reference Network for Rare Neurological Diseases

The ERN-RND is a network of the European RND expertise centers. At present, it has 32 full members and 10 affiliated partners from 21 countries (a list of the actual ERN-RND full members and affiliated partners, their countries, and their respective areas of expertise are provided as **Supplementary Material**); however, through a currently ongoing expansion process, the ERN-RND will be including the vast majority of EU countries by mid-2021. Thus, ERN-RND will be the first truly pan-European rare neurological disease (RND) network that brings together all respective European expertise centers. Governance and activities of ERN-RND are patient centered that is reflected by the active involvement of European Patient Advocacy Groups (ePAGs) representatives.

The formation of ERN-RND is timely since RNDs present a topic of continuously growing importance in neurology. Rapid advances in clinical knowledge in recent years have been facilitated by the emergence of genetic and other diagnostic technologies, helping us to develop a deeper understanding of RDs and their causes. The defined genetic etiology of the majority of RNDs has, moreover, been facilitating the development of targeted molecular therapies for RND, such as viral vector-based gene therapy and antisense oligonucleotides.

The huge heterogeneity of RND and healthcare systems in Europe, as well as the still limited clinical expert workforce base for RND at a time of rapid clinical innovation, means that there is a very real risk that significant parts of estimated more than 500,000 RND patients across Europe might not benefit from improved diagnosis, care, and treatment opportunities.

Consequently, the objectives of the ERN-RND are as follows:

i. To significantly increase the overall percentage of RND patients with a confirmed (molecular) diagnosis
ii. To improve and harmonize care including neurorehabilitation and transition of RND patients across the EU
iii. To develop, share, and implement care pathways and guidelines for all RND groups represented in ERN-RND
iv. To create, develop, and enhance the capacity to design, implement, and supervise RND training, education, and capacity building activities at the level of member states and of the network
v. To develop comprehensive and data-based European RND cohorts to be able to deploy digital solutions, including artificial intelligence-based tools, for diagnosis and patient-centered integrated care, in order to better understand these conditions and thus improve their management and help developing and testing treatments
vi. To define the minimum quality and interoperability criteria for RND registries allowing the exchange of data between existing registries and the ERN-RND registry.

Building on existing mature RND European disease networks, such as the European Huntington's Disease Network[4], the Ataxia Study Group[5], and DystoniaNet[6], which have already strong clinical collaborations, ERN-RND focuses on the following disease groups at the moment:

1) Cerebellar Ataxias and Hereditary Spastic Paraplegias (Coordinators: Enrico Bertini, Alfons Macaya, Caterina Mariotti, Rebecca Schuele)
2) Huntington's disease and Other Choreas (Coordinators: Anne-Catherine Bachoud-Lévi, Bernhard Landwehrmeyer, Juan Dario Ortigoza Escobar)
3) Frontotemporal dementia (Coordinators: Isabelle Leber, Markus Otto, Rik Vandenberghe)
4) Dystonia, (non-epileptic) paroxysmal disorders, and Neurodegeneration with Brain Iron Accumulation (Coordinators: Tobias Bäumer, Belen Pérez Dueñas, Giovanna Zorzi)
5) Leukoencephalopathies (Coordinators: Odile Boespflug-Tanguy, Ingeborg Krägeloh-Mann, Samuel Groeschel, Nicole I. Wolf).

[3]https://cpms.ern-net.eu/login/

[4]http://www.ehdn.org

[5]http://www.ataxia-study-group.net

[6]https://dystonia.net/

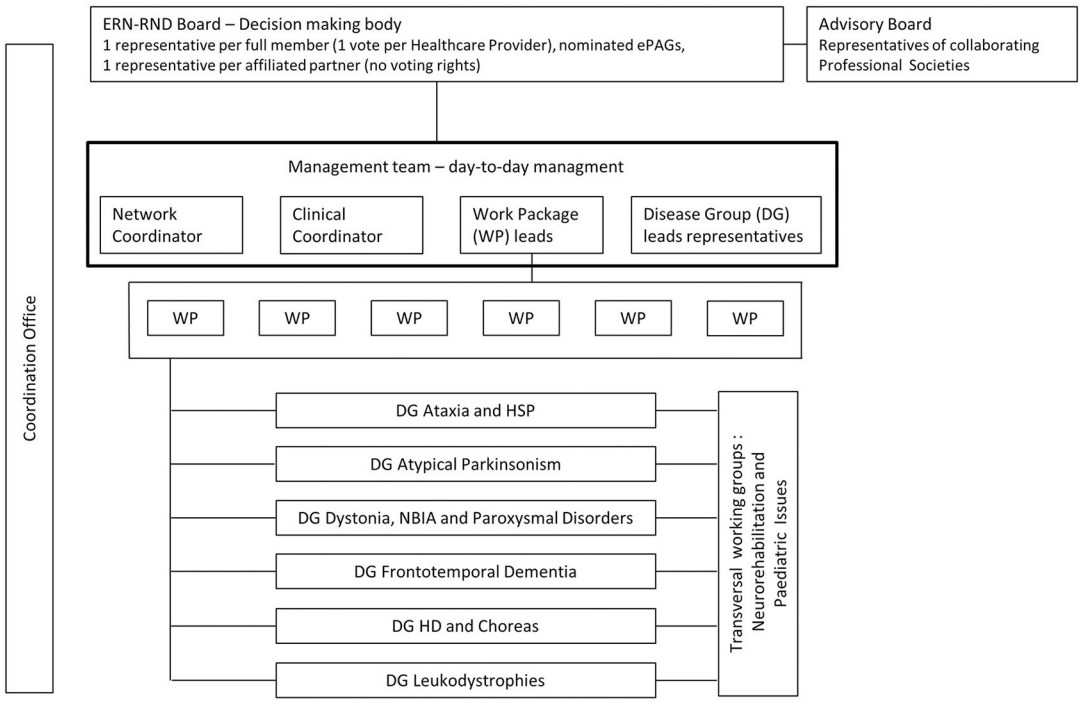

FIGURE 1 | Network and governance structure of ERN-RND.

6) Atypical Parkinsonian Syndromes (Coordinators: Thomas Gasser, Wassilios Meissner).

ERN-RND is coordinated at the University Hospital Tübingen, Germany, with Holm Graessner being the coordinator and Ludger Schöls the clinical lead. An overview about the network and governance structure of ERN-RND is given in **Figure 1**.

Activities of ERN-RND are coordinated based on the covered disease groups as well as the following cross-cutting lines of work that address the objectives:

1) RND diagnostic pathways (Coordinator: Alexandra Durr)
2) Expert RND Care Coordination (Coordinator: Marina de Koning-Tijssen)
3) Training, education, and capacity building (Coordinator: Maria Judit Molnar)
4) Information sharing and disease resources (Coordinator: Holm Graessner)
5) Guidelines, pathways, and best practice (Coordinator: Antonio Federico)
6) Registries and Research (Coordinator: Thomas Klockgether)
7) Pediatric issues (Coordinators: Juan Dario Ortigoza Escobar, Caroline Sevin, Nicole I. Wolf)
8) Neurorehabilitation (Coordinators: Annemieke I. Buizer, Antonio Federico, Maria Judit Molnar, Jorik Nonnekes, Lori Renna Linton).

RND DIAGNOSTIC PATHWAYS

To improve the diagnosis of RND patients, ERN-RND has been implementing four activities. Firstly, the visibility of the ERN-RND expertise centers has been improved through collaboration with Orphanet, by providing contact information on a newly created website[7] and by rolling out a comprehensive multi-channel information campaign. Secondly, disease knowledge documents have been created and are being provided to the different stakeholder groups. In particular, disease expert groups developed and consented on RND diagnostic flowcharts, as well as on disease scales to assess the different aspects of RND. ERN-RND recommends the use of these flowcharts and disease scales and actively disseminates them to clinicians, national and European professional societies, and patient organizations[8]. Thirdly, ERN-RND has started to discuss patients without a definitive diagnosis in the CPMS. Fourthly, ERN-RND has been collaborating with the EU rare disease diagnostic research flagship project Solve-RD (Solving the unsolved Rare Diseases[9]); ERN-RND is one of four ERNs that serve as foundation of Solve-RD.

EXPERT RND CARE COORDINATION

RND care needs and situations differ between disease groups as well as between countries. In order to capture and assess care needs ERN-RND can address, a care need survey has been performed for all disease groups covered by ERN-RND across all EU countries (6). The survey is based on a respective publication for dystonia (7). Main measures to improve the management

[7] www.ern-rnd.eu
[8] http://www.ern-rnd.eu/disease-knowledge-hub/.
[9] www.solve-rd.eu.

of RND patients that have been identified include the (i) development of multidisciplinary teams, (ii) implementation of educational activities to enhance recognition of RND among healthcare professionals and in the general population, (iii) improvement of the accessibility to standard and advanced genetic testing and to clinical geneticists, and (iv) development of more dedicated tertiary centers meaning more expertise in the field.

In addition, treatment algorithms and the composition of the multidisciplinary care team for all covered RND will be developed and consented on. By this process and the activities regarding diagnostic flowchart and assessment scales, ERN-RND will help to develop a comprehensive knowledge body of RND care standards within ERN-RND.

TRAINING, EDUCATION, AND CAPACITY BUILDING

ERN-RND has implemented an RND training and education program[10] based on the following pillars:

1) Educational webinar series in collaboration with the European Academy of Neurology (EAN) and the European Reference Network for Neuromuscular Disorders (Euro-NMD).
2) Hands-on training winter and summer schools for young neurologists past topics ranging from "Diagnostic of rare movement disorders" to "Hereditary white matter diseases—clinics, genetics, therapy".
3) Short-term mobility fellowships for RND healthcare professionals.

In particular, the webinar series has attracted a high number of attendees both across Europe and globally and has been expanded from topics based on disease knowledge to neurorehabilitation.

INFORMATION SHARING AND DISEASE RESOURCES

ERN-RND aims to become the information hub for all available information for the diseases covered by the network. Therefore, ERN-RND collects and edits available information as well as produces new information and knowledge. Disease knowledge, to be included in ERN-RND disease knowledge pages, needs to undergo an affirmation process that includes patients' representatives as well as expert clinicians from the network. ERN-RND reached out to 27 European national neurological societies with regard to setting up an RND webpage on their respective society website to increase the visibility of RNDs across the European community of neurologists. Although this has not yet been implemented, it is an important part of our awareness strategy. In addition to this, the ERN-RND monthly newsletter is sent to a varied audience including patients, patient advocates, clinicians, and researchers in Europe to inform them about the latest developments within the network and in the RND field in general. All disease information is compiled on the ERN-RND website[11]. Efforts are provided to multiply document access to patients from different languages.

GUIDELINES, PATHWAYS, AND BEST PRACTICE

Clinical practice guidelines for RD are scarce and difficult to find (8). Therefore, ERN-RND will use the expertise of its partners to adopt and develop clinical practice guidelines for the diseases covered by the network. GRADE methodology[12] will be used, following the recommendations by the EAN (9, 10). The work on European guidelines for diagnosis and treatment of Metachromatic Leukodystrophies has recently started.

Furthermore, ERN-RND endorses or affirms the value of existing guidelines, depending on whether an EAN equivalent methodology was used or not. Examples are: Management of the ataxias toward best clinical practice (11) and the International Guidelines for the Treatment of Huntington's Disease (12).

As a matter of fact, guideline development in RND often struggles with the lack of systematic reviews and strong evidence. ERN-RND actively contributes to the project of the EAN on guidance for developing and reporting guidelines in the field of RNDs, as well as the critical appraisal of all existing RND guidelines.

Furthermore, in the context of the Value of Treatment project[13], ERN-RND has set up a collaboration with the European Brain Council to assess the benefits of expertise centers for rare neurological disorders in consideration of the quality of care being provided and cost-effectiveness.

REGISTRIES AND RESEARCH

With the foundation of ERN-RND, a large network of potential trial sites for RND has been formed. As the ERN-RND expertise centers are very likely those centers that are performing and will perform RND treatment trials in Europe, the network will facilitate trial readiness through three activities. Firstly, it is about to establish an ERN-RND registry that is going to comprise minimal data of all patients seen at the ERN-RND centers. This registry will thus provide a unique overview of existing genotype-based cohorts. The minimal data set being used is based on the "Set of common data elements for Rare Diseases Registration" as recommended by the European Platform on Rare Disease Registration[14]. Secondly, ERN-RND has organized and will be organizing multi-stakeholder workshops focusing on the different aspects of trial readiness. Thirdly, ERN-RND will strive to support trial readiness platforms, such as ARCA and SCA Global[15], in order to help in addressing major knowledge gaps that preclude further progress toward the development of effective therapies in RNDs.

[10] http://www.ern-rnd.eu/education-training/

[11] www.ern-rnd.eu

[12] http://www.gradeworkinggroup.org/

[13] https://www.braincouncil.eu/activities/projects/the-value-of-treatment

[14] https://eu-rd-platform.jrc.ec.europa.eu/_en.

[15] http://ataxia-global-initiatives.net/.

PEDIATRIC ISSUES

The working group on pediatric issues has been formed recently to specifically address the different needs of pediatric RND. The cross-cutting pediatric issues should be addressed (i) within ERN-RND, (ii) in collaboration with other ERNs, and (iii) linked with the European Pediatric Neurological Society (EPNS).

As a first step, a mapping exercise is being performed on the specific neuropediatric expertise of the ERN-RND centers as well as on existing pediatric scales that are used across the disease groups to identify potential gaps. Patient information leaflets with a focus on pediatric issues as well as information about clinical trials should be collected and made available on the ERN-RND website. In addition, collaboration with the EPNS, e.g., focusing on joint training activities, has been implemented.

NEUROREHABILITATION

As causal treatments are only scarcely available for RND, neurorehabilitation is an important aspect in the management of these diseases. To address this need, a specific working group has been formed with the following goals: (i) organization of teaching courses on neurorehabilitation of the different RNDs. As a first step, online training webinars focusing on neurorehabilitation of RND have been organized. (ii) Organization of national/regional networks for RND neurorehabilitation. (iii) Guidelines production in collaboration with EAN panels and the European Federation for Neurorehabilitation.

As a first step, a mapping of the locally used neurorehabilitation protocols including the evidence on which they are based and the possibility of transfer to other centers is underway.

MONITORING AND EVALUATION OF ERN-RND

The overall aim of the ERNs is to improve access for patients with RDs to quality diagnosis, care, and treatment. Based on this objective, ERNs are monitored on a regular basis by the European Commission to guarantee transparency and provide reassurance of both the RD community and the general public. Additional reasons for monitoring include quality improvement, accountability, and identification of needs for strategy adjustments and promotion of patient empowerment.

DISCUSSION AND CONCLUSIONS

ERN-RND provides an expertise-based infrastructure for sharing knowledge and coordinating care for patients affected by RNDs. The evolving network presents a new unique organization able to create, take up, and implement emerging diagnostic, care, and treatment innovations.

Built as a virtual network, ERN-RND provides–besides the flagship CPMS–also e-solutions for all other areas of cooperation of the different project bodies and stakeholders, including webinars, cloud-based document-repositories, and web conferences.

Future challenges include equity of quality of care being provided across the EU as well as the systematic integration of ERN into the national healthcare systems.

AUTHOR CONTRIBUTIONS

HG and CR are the coordinator and project manager, respectively, of the European Reference Network for Rare Neurological Diseases and wrote the publication. LS is the clinical lead of ERN-RND. SH and AB are members of the coordination office. RS, CM, EB, AM, RV, IL, SG, IK-M, NW, A-CB-L, BL, JO, TG, WM, BP, and TB are disease group coordinators. AF, MT, MM, TK, JO, AIB, JN, LR, and AV are working group coordinators. All authors are responsible for the work described in their respective project roles and critically reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.616569/full#supplementary-material

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REVIEW
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Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON)—An International Network on Care and Research for Patients With Neurodegeneration With Brain Iron Accumulation (NBIA)

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In order to improve clinical care, coordinate research activities and raise awareness for the ultra-orphan Neurodegeneration with Brain Iron Accumulation (NBIA) disorders, a group of NBIA clinicians and researchers, industry partners and patient advocacies from six European countries, Canada and the US joined forces in 2010 to set-up the collaborative initiative TIRCON (Treat Iron-Related Childhood-Onset Neurodegeneration). As a research project, TIRCON received funding in the 7th Framework Programme (FP7) of the European Union (EU) from 2011 to 2015. After successful and timely completion of the initial FP7 project, funding and donations from industry and patient organizations have sustained the further development of TIRCON's dedicated clinical research infrastructure and its governance architecture, as well as the ongoing efforts undertaken in the NBIA community to establish a network of care. From the beginning, the University Hospital of the Ludwig-Maximilians-University in Munich, Germany has been coordinating the TIRCON initiative. It consists of 8 work packages, of which the first double-blind, placebo-controlled, randomized, multi-site clinical trial in NBIA (deferiprone in PKAN, completed) and a global patient registry and biobank, currently comprising baseline and follow-up data of > 400 NBIA patients have gained particular importance. Here we describe TIRCON's history with all the challenges and achievements in diagnosing and treating NBIA. Today, TIRCON lays the ground for future clinical care and research. In these times, it may also serve as a good example of well-directed governmental funding and fruitful international scientific collaboration.

Keywords: NBIA, TIRCON, patient registry, clinical network, orphan disease, movement disorder

INTRODUCTION

Over the last decade, interest in rare diseases has steadily grown both politically and scientifically. To raise awareness, EURORDIS, a European non-governmental organization for rare diseases funded mainly by patient organizations (www.eurordis.org), the European Commission (EC) and private corporations, initiated the first Rare Disease Day® in February 2008. Ever since, rare diseases have gained increased coverage within popular media.

Per definition, a condition is considered a rare (or orphan) disease if its prevalence is <5:10,000. Compared to widespread diseases such as cerebral stroke or ischemic heart disease, this number may sound negligible: however, all 5,000–8,000 rare diseases together affect no <27 million patients alone in the European Union (EU) (1). Even among orphan diseases, Neurodegeneration with Brain Iron Accumulation (NBIA) disorders are still exceedingly rare and are thus referred to as ultra-orphan diseases. For instance, the estimated incidence of one of the more frequent NBIA forms (Pantothenate Kinase-Associated Neurodegeneration, PKAN), is around 2 in 1,000,000 live births among the non-African world population (2). The causative gene, *PANK2*, was the first NBIA gene discovered, published in 2001 by the Hayflick group (3). To date, mutations in 10 genes have been linked to NBIA (4). NBIA disorders show a broad phenotypic spectrum ranging from movement disorders manifesting as dystonia, spasticity, and parkinsonism to other predominantly neurological symptoms such as optic atrophy, neuropsychiatric symptoms, and cognitive decline. NBIA disorders can be distinguished from other diseases by the eponymous MRI patterns of increased brain iron levels (5).

The TIRCON project received EU funding from the 7th Framework Programme (FP7) with 5.2 million € from Nov 1st, 2011 to Oct 31st, 2015. It consists of 8 different work packages, with the international NBIA patient registry and biobank (work package 1) being the nucleus for further clinical and basic research (see **Figure 1**) (6). TIRCON is coordinated by the Friedrich-Baur-Institute at the Department of Neurology of the University Hospital of Munich supported by the Bavarian Research Alliance (BayFOR).

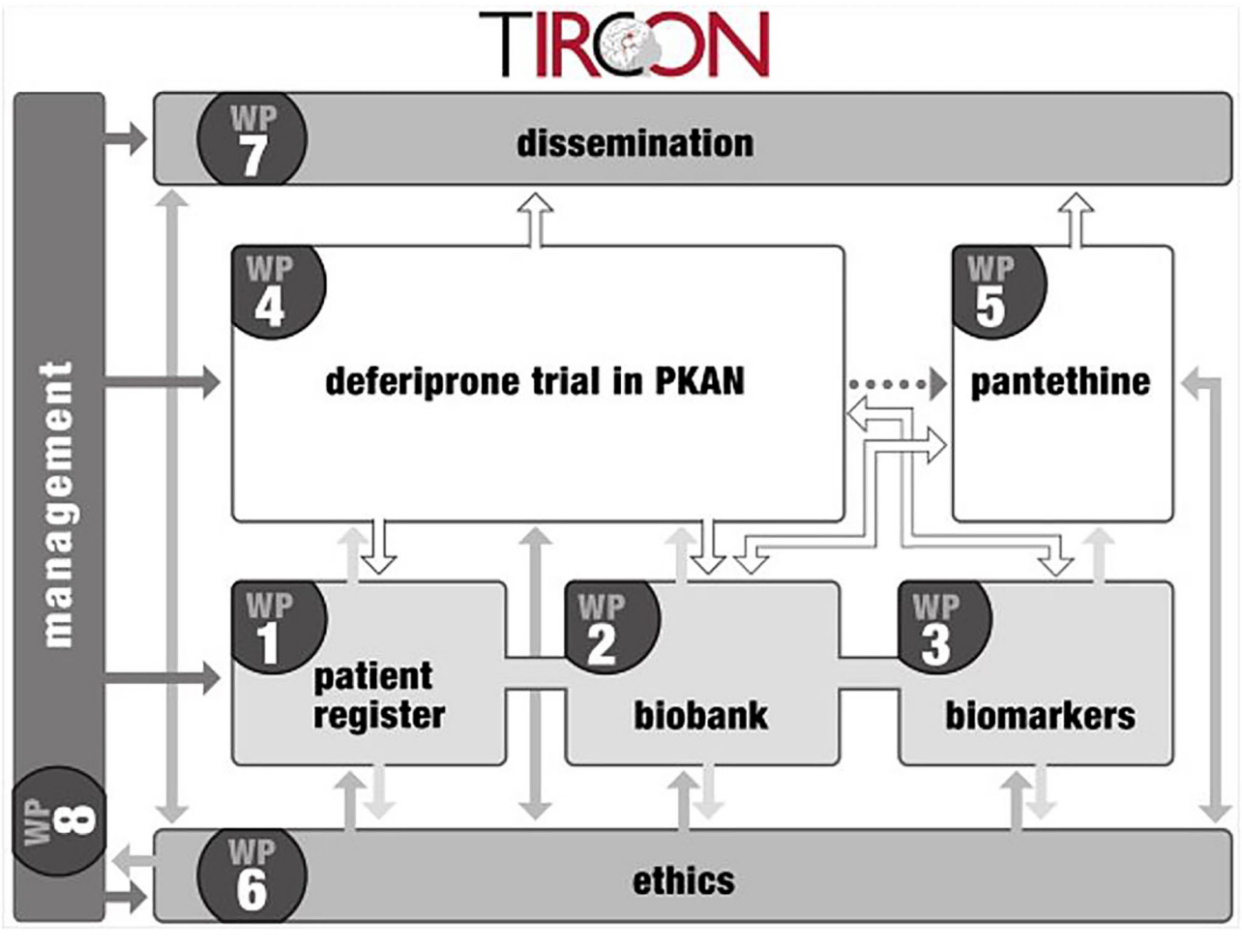

FIGURE 1 | Overview of TIRCON work packages.

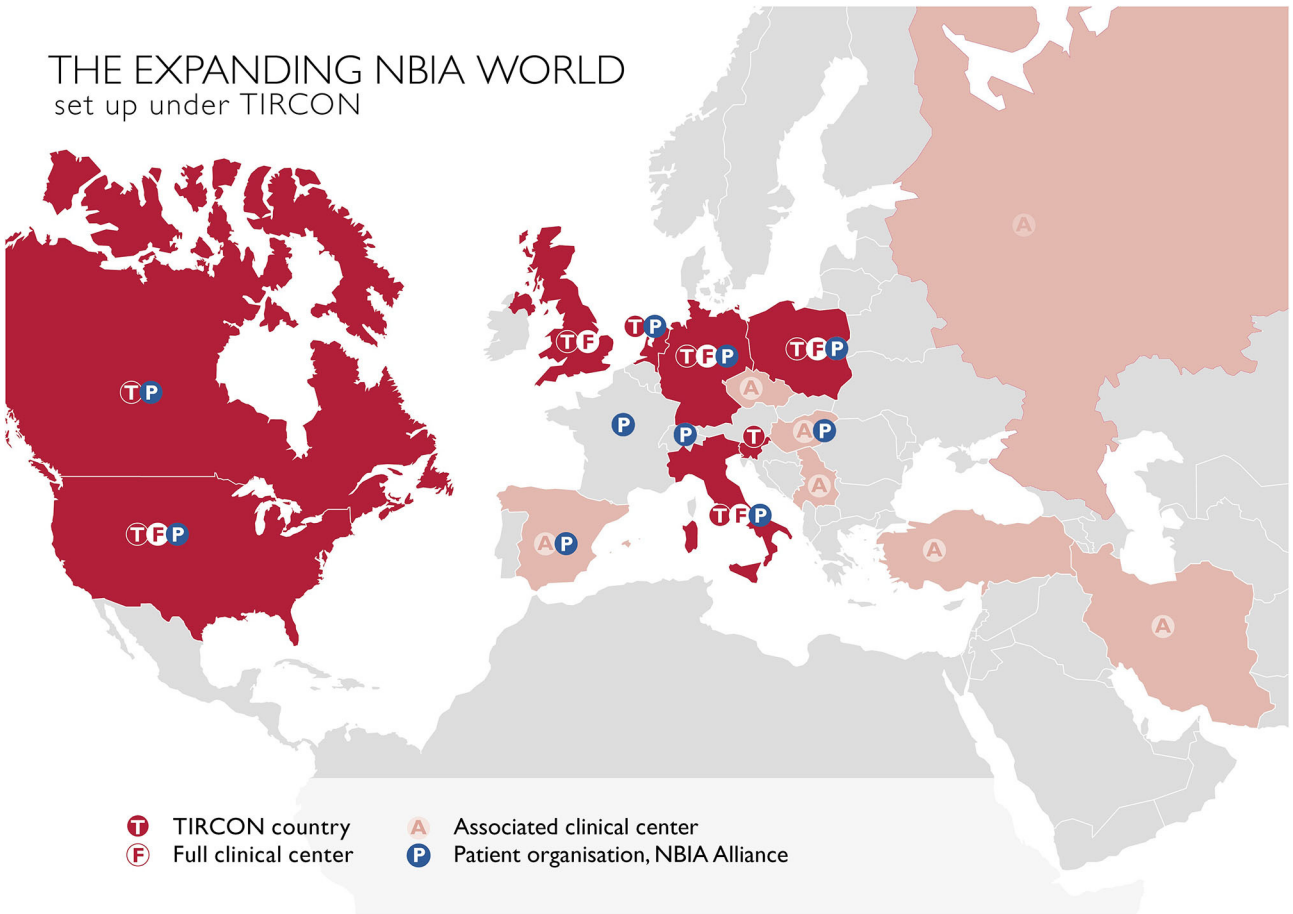

FIGURE 2 | TIRCON centers: T / F, initially involved TIRCON partners, full clinical centers and their respective countries; A, centers/countries, joined the network after the project start; P, patient organizations.

IMPACT ON CLINICAL RESEARCH: THE PATIENT REGISTRY AND ITS STRUCTURE

The main goal of TIRCON's work package 1 has been to create the first international NBIA patient registry. The NBIA patient registry has been fully operational since 2013. Since the end of the FP7 funding, TIRCON has received further monetary support from the international NBIA patient organizations gathered under the umbrella of the NBIA Alliance and from pharmaceutical companies including ApoPharma Inc. (Toronto, Canada), CoA Therapeutics (San Francisco, CA; USA) and Retrophin Inc. (San Diego, CA; USA) To date, clinical centers in several European countries, the United States and Asia are contributing to the registry, including the TIRCON core partners who laid the foundation for the establishment of the registry as well as clinical centers which have been associated over time (see **Figure 2**). All clinical centers have been approved by their respective local ethics committee to include patients into the patient registry.

The registry is open for all patients with a genetically established diagnosis of NBIA or clinically suspected NBIA. It is designed as a multicenter, prospective, cross-sectional, and longitudinal study with yearly follow-up visits. The first patient was enrolled in February 2013. Since then, > 420 patients with different NBIA subtypes have been recruited (see **Figure 3**). Including follow-up visits, the registry contains > 1,200 entries (see **Figure 4**).

Before inclusion, patients or their caregivers sign an appropriate informed consent in their respective local language. All patients undergo a complete body examination and a detailed neurological examination by a neurologist trained in movement disorders, and have their medical history taken at each visit. In order to standardize symptom reporting, each investigator is asked to provide clinical data in accordance with the Human Phenotype Ontology (HPO) (7). Recorded demographic data include year of birth, gender, ethnic background and country of residence of the patient, as well as ethnic background, country of residence and potential consanguinity of the parents. The date of onset of first symptoms is recorded as well as the date of clinical diagnosis. Whenever possible, genetic results are obtained. If a patient presents without genetic testing, next generation sequencing (NGS) or whole exome sequencing (WES)

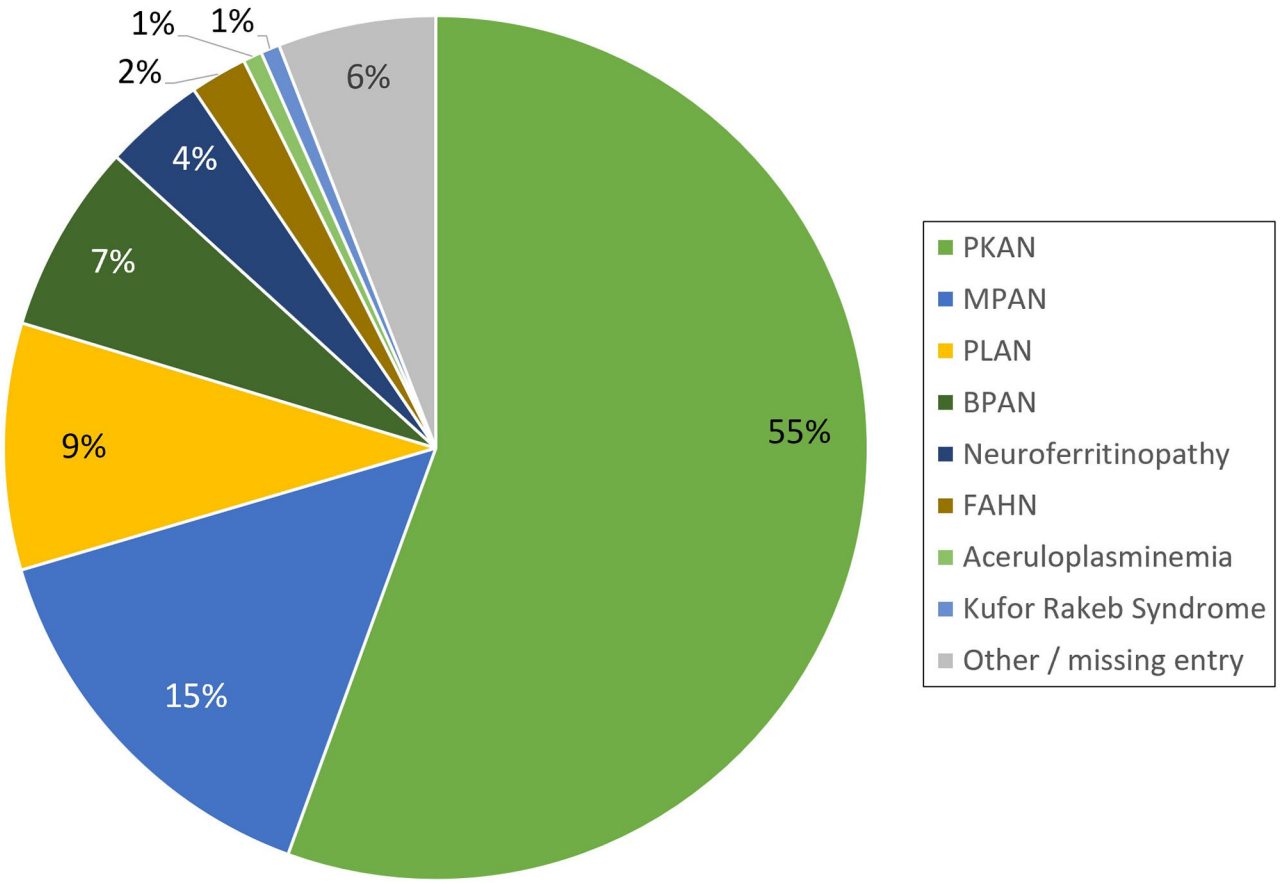

FIGURE 3 | Distribution of NBIA subtypes in the TIRCON patient registry (PKAN, Pantothenate Kinase-Associated Neurodegeneration; MPAN, Mitochondrial-membrane Protein-Associated Neurodegeneration; PLAN, *PLA2G6*-Associated Neurodegeneration; BPAN, Beta-propeller Protein-Associated Neurodegeneration; FAHN, Fatty Acid Hydroxylase-Associated Neurodegeneration).

can be initiated at most full clinical centers. All pharmacological and non-pharmacological therapies such as physical therapy or special dietary regimes are recorded, including start date, end date (if applicable) and dosage. The patients are asked to bring all relevant medical records with them including neuroimaging and discharge letters. If consented, a family tree can be generated linking diseased family members to each other. Results from routinely performed blood assessments (i.e., blood count, liver enzymes, creatinine, iron, ferritin, creatine kinase, ceruloplasmin, lactate, TSH) can be collected, too. To assess progression of motor symptoms, two well-established scales have been implemented. The Barry-Albright Dystonia (BAD) Scale measures the severity of dystonia in eight body regions (eyes, mouth, neck, trunk, and each upper and lower extremity) and ranges from 0 (no dystonia) to 32 (severe dystonia) (8). To rate the severity and progression of motor symptoms not limited to dystonia, parts I, II, III, and VI of the Unified Parkinson's Disease Rating Scale (UPDRS) are obtained (9). Although validated for patients with Parkinson's disease, the UPDRS seems to reflect impairment of motor functions even in patients without pronounced Parkinsonian features sufficiently (clinical experience from treating physicians). Quality of sleep is recorded through the Pittsburgh Sleep Quality Index (PSQI) (10). To assess quality of life, each patient is requested to fill out the Pediatric Quality of Life (PedsQL™) Inventory version 4.0; in addition, for patients up to the age of 25 years a separate scale for the caregiver is provided (11).

The data is entered into a secured online platform. Its security and privacy concept builds upon the security architecture of the German mitoNET registry and is conformant with the German Data Protection Act (12). Every entry is monitored by staff from the Friedrich-Baur-Institute. Monitored entries are then reimbursed at predefined rates depending on the integrity of the data. Clinical data may be shared upon request in accordance with all ethical and data protection requirements.

While collecting more and more data throughout the years, we hope to gain better insight into natural disease progression. Growing patient numbers enrolled into the registry will help to increase trial readiness by enabling the formation of large cohorts.

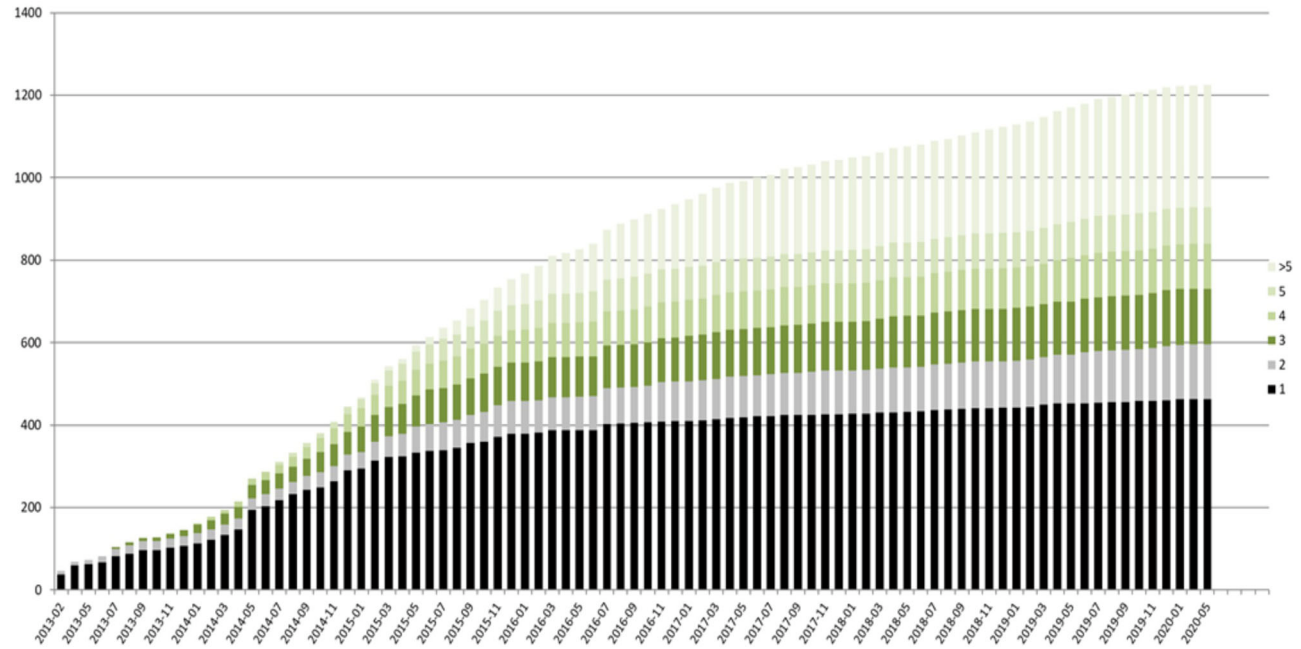

FIGURE 4 | TIRCON registry—baseline (black) and follow-up visits (different colors used, depending on the total number of follow-up visits) over time.

IMPACT ON CLINICAL RESEARCH: CLINICAL TRIALS

Thanks to intense efforts by medical professionals and especially patient organizations in recruiting patients for the patient registry, the first two phase III trials in NBIA could be conducted. The randomized, double-blind, controlled trial of deferiprone for PKAN enrolled 88 patients for phase III and its open-label extension study (13). Initially designed as an investigator-initiated trial, ApoPharma Inc. (Toronto, Canada; now part of Chiesi Group) soon took over as the primary sponsor. Deferiprone has shown to be a well-tolerated and safe drug in PKAN. As proof of concept, it decreased brain iron levels in the basal ganglia significantly and seemed to slow disease progression but did not reach overall significance. After completion of the deferiprone trial, a second phase III trial was conducted to evaluate the safety and effectiveness of fosmetpantotenate for the treatment of PKAN (14). The study was sponsored by Retrophin Inc. (San Diego, CA; USA). The study failed to reach its primary and secondary endpoints and the open-label extension trial was discontinued (15).

Before TIRCON, no randomized trials evaluating disease-modifying treatment options were available but only case reports or small open-label studies (16, 17).

IMPACT ON PATIENT CARE: CLINICAL EXPERTISE

With TIRCON, several NBIA clinical centers have been founded that now serve as centers of excellence where neurologists and neuropediatricians can refer patients to in order to confirm an NBIA diagnosis or to get a second opinion on standard of care. For patients with this ultra-rare disease with which even most specialists are unfamiliar, it is crucial to know that they have a center where they can turn to in order to receive a consultation. As a result of their targeted networking and collaboration, NBIA specialists published the first consensus guidelines for the treatment of an NBIA disorder (18), a work that was supported by TIRCON.

IMPACT ON BASIC RESEARCH: NBIA BIOBANK

In close association with the NBIA patient registry, TIRCON's work package 2 has focused on establishing an international NBIA biobank. At each patient visit, either for the registry and/or for the deferiprone trial, patients and their caregivers are asked to provide biosamples for the biobank. Each individual patient (or his/her caregiver) consents by signing a separate informed consent form. Each sample kit contains two EDTA tubes for plasma and DNA analysis, one PAXgene^{TM} tube for RNA analysis and one tube for a urine sample. All samples are initially stored at −20 or −80°C at the local center before being sent along with basic anonymized demographic and medical history data to the Technical University of Munich (TUM) for central storage. The biosample collection is used in TIRCON's work package 3 for genomic, proteomic, transcriptomic and metabolomic analyses to identify biomarkers reflecting disease course and treatment effects. The biobank is permitted to share its biosamples with external collaborators. Recently, a paper on residual PANK2

activity in patients' erythrocytes has been published by a group of non-TIRCON researchers who received biosamples from the biobank (19).

Members of the TIRCON consortium have contributed significantly to the discovery of several new NBIA genes such as *c19orf12*, *WDR45*, and *COASY* (20–22).

IMPACT ON BASIC RESEARCH: DISCOVERING NEW COMPOUNDS

It was shown that in Drosophila models the enzymatic defect in PKAN can be bypassed by downstream compounds such as pantethine (23). In TIRCON's work package 5, two TIRCON partners, Acies Bio (Ljubljana, Slovenia) and the University Medical Center Groningen (UMCG, Netherlands), worked together to conduct basic research on the efficacy and safety of pantethine and pantethine derivatives in cell and mouse models. The fruitful collaboration resulted in a successfully filed patent to the European Medicines Agency (EMA) (24). A clinical trial with a very similar approach using 4'-phosphopantetheine is currently recruiting patients in North America (25).

PIVOTAL WORK IN THE BACKGROUND: ETHICS, DISSEMINATION, AND MANAGEMENT

The activities in work packages 6–8 were mostly related to non-scientific aspects of conducting a large-scale research project as TIRCON.

Work package 6 focused on ethical, regulatory and legal aspects concerning access to and use of patient data and biomaterials, as well as the involvement of animals in preclinical research. The preparation, translation and adaptation to local or national requirements of informed consent forms for the international registry, biobank and the multi-site deferiprone trial were also part of this work package. Child-friendly ICFs were made available. Preparing for the clinical trial in Munich and the different sites abroad included missionary work with local academic and public health institutions. The safety during the clinical trial was monitored by an appointed Data and Safety Monitoring Board (DSMB). Clear intellectual property rules were needed and implemented to guarantee transparent and scalable cooperation among the two industry partners as well as between the academic and the industry partners.

Work package 7 raised awareness for NBIA by running the official TIRCON web page, handling press relations and releasing educational material for both the public and the scientific community and put emphasis on educational training (See also below). In both work packages, the architecture designed to support the registry, the biobank and the clinical research has kept its value and validity.

The activities in work package 8 included overall administrative and financial coordination. A specific challenge was to facilitate and manage the full participation of Canadian and US-partners receiving funding from the EU. This work package monitored in addition good practice in communication. Here again, the governance mechanisms put in place for TIRCON in the Consortium Agreement are still valid today.

TIRCON FROM THE PERSPECTIVE OF PATIENT ORGANIZATIONS

The NBIA Disorders Association (NBIADA, USA) and Hoffnungsbaum e.V. (HoBa, Germany) have been involved in TIRCON from the very beginning of the FP7 application process. Finally, both became full partners in TIRCON, including budget granted by the EU for their responsibilities in work package 7. HoBa, due to being located in an EU member state, took over the work package lead and thus became member of the Scientific Steering Committee with its monthly meetings, represented in absence by the NBIA Disorders Association. This way, patient organizations have been actively integrated in all aspects and decisions of this consortium throughout the project. This framework enables a trust-based cooperation between the patient representatives and the other partners within TIRCON. HoBa and NBIADA have developed dissemination instruments, including brochures, presentations, newsletter-articles and web-based information that are tailored to patient families and target groups like clinicians, scientists or further advocacies. Moreover, scientific NBIA symposia, TIRCON meetings, and NBIA family conferences have been held in TIRCON partner countries to create networking occasions for a mutual exchange among all interested stakeholders in the field of NBIA on research projects in TIRCON and best practices in clinical care for NBIA (see **Figure 5**).

Regarding Europe, TIRCON has significantly contributed to the setup or empowerment, respectively, of the clinical NBIA expert centers in Munich, Milan, Warsaw and Newcastle, establishing them as first-rate contact points for patients and clinicians from all over the world requiring consultation with NBIA experts. As a consequence, TIRCON has eased the work of patient organizations remarkably. They now can connect the patient families directly with clinical NBIA experts. It was far more difficult before TIRCON for Patient Advocacy Organizations (PAOs) and patients to identify and reach out to clinical NBIA experts. While in the USA at least one NBIA center in Portland, Oregon had already been established since the 1990's, there was not a comparable infrastructure for NBIA patients in Europe before TIRCON.

A first step to strengthen the patient community was the launch of the "NBIA Alliance" as part of TIRCON dissemination tasks at the TIRCON kick-off meeting in Munich in 2012. The NBIA Alliance, which is not a legal entity but a federation of independent patient associations, was founded by HoBa, NBIADA, the Italian patient advocacy Aisnaf and the French association AIDNAI (www.nbiaalliance.org). In the following years, TIRCON has supported the emergence of new NBIA patient organizations according to the subsidiarity principle. Subsequently, new NBIA associations were founded in Spain (ENACH Asociación), the Netherlands (Stichting Ijzersterk), Switzerland (NBIA Suisse), Canada (NBIA Canada), Poland (NBIA Polska), and Hungary (NBIA Hungary). Interestingly, in

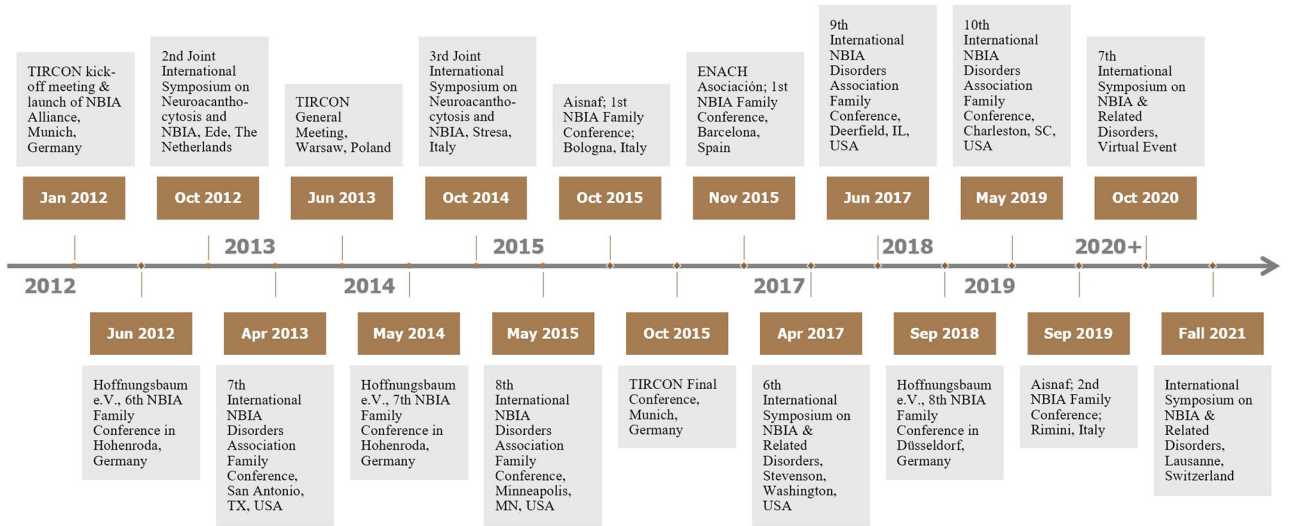

FIGURE 5 | Major NBIA events since 2012—TIRCON meetings, scientific symposia, family conferences.

countries where active new NBIA patient organizations could be established, clinical NBIA expert centers emerged or were empowered by the respective NBIA advocacy. NBIA research activities are strongly supported or even initiated by the new patient advocacies, often preferably in their home countries. This again demonstrates how the deliberate empowerment of the patient organizations in TIRCON up to becoming co-responsible partners has been instrumental to success.

The PAOs were partners in work package 1 (Patient registry), 4 (Deferiprone trial for PKAN patients), and 6 (Ethics), where they contributed patients' needs and points of view and have continuously supported patient recruitment for registry to date. Challenges the small associations had to face as TIRCON partners included the bureaucratic demands within such an EU-funded project and the high proportion of work that had to be done on a volunteer basis. However, the PAOs consider that the impact TIRCON has had since then on the NBIA patient community and the development of their advocacies made all efforts worthwhile.

DISCUSSION

TIRCON has set up a solid foundation for future NBIA research by bringing together this formerly scattered NBIA community of basic scientists and clinicians, while including patient organizations from the very beginning. Even several years after completion of the FP7 project, the NBIA community has not dispersed but remains highly collaborative: the patient registry and biobank are fully operational and have secured financial support for the years to come, sustainable collaborations in basic and clinical science have developed and academic experts, industry partners and patient representatives meet on a regular basis to network. Recently the NBIA Disorders Association, the patient advocacy in the US, hosted the 7th International Symposium on NBIA & Related Disorders. The event took place for the first time as a virtual conference due to the Covid-19 pandemic from September 30th to October 3th 2020. TIRCON has contributed to publish > 30 peer-reviewed papers including some key publications in discovering new NBIA genes (21, 22). What defines and differentiates TIRCON is the close integration and the invaluable commitment of the patient organizations. The number of patient organizations has grown ever since, with new members in North America and Europe (see above).

Still, several challenges remain in the future. For severely affected patients, a face-to-face consultation may not be a feasible option due to their critical condition. Besides telephone or e-mail, other means of communication are necessary in such cases. The concept of 'flying-doctors' with the physician coming to the patient and not the other way round seems promising, but financial reimbursement and time consumption constitute limiting factors. The Covid-19 pandemic has shown that online consultations *via* video chats may offer an alternative. Fortunately, legal hurdles for online consultations have been reduced over the last few years. When conducting clinical trials in ultra-rare diseases, not only is recruiting a sufficient number of patients challenging but also defining reasonable endpoints. Further basic research is urgently needed to discover relevant biomarkers of disease progression. The lack of disease-specific scales is another limiting shortcoming. Thus, to assess all relevant symptoms of the disease, more than one rating scale must be applied, with each one of these scales, besides not being validated for NBIA, only reflecting some aspects of the disease. In PKAN however, first steps have been taken in creating disease-specific scales rating motor function and activities of daily living (26, 27). The TIRCON clinical center in Poland is currently validating a disease-specific rating scale for MPAN (private communication).

In conclusion, TIRCON can serve as a model for an international public and private funded research project creating

more than the required deliverables: truly enduring bonds and new ways of working together in science, industry and patient care. Beyond the novelty of the TIRCON's research architecture, it remains true that such initiative can only prosper on the ground of personal dedication from professionals, patients and their families.

AUTHOR CONTRIBUTIONS

IK wrote the first draft of the manuscript. BB, FG, AK, and TK contributed substantially to the manuscript as well as providing critical comments to the content. All authors approved the submitted version.

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The Architecture of Contemporary Care Networks for Rare Movement Disorders: Leveraging the ParkinsonNet Experience

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In this paper, we present a universal model for implementing network care for persons living with chronic diseases, specifically those with rare movement disorders. Building on our longstanding experience with ParkinsonNet, an integrated care network for persons living with Parkinson's disease or a form of atypical parkinsonism, we provide a series of generic, supportive building blocks to (re)design comparable care networks. We discuss the specific challenges related to rare movement disorders and how these challenges can inform a tailored implementation strategy, using the basic building blocks to offer practical guidance. Lastly, we identify three main priorities to facilitate network development for these rare diseases. These include the clustering of different types of rare movement disorders at the network level, the implementation of supportive technology, and the development of interdisciplinary guidelines.

Keywords: network, Parkinson's disease, rare disorders, integrated care, telemedicine, movement disorder

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INTRODUCTION

Over the past decade, we have witnessed the emergence of care networks for a wide variety of diseases. Driving forces have been partially externally driven (e.g., governmental or insurance bodies), but were more often internally motivated, fueled by the conviction among healthcare professionals that collaboration is key to increase the quality of care. Networks strive to facilitate access to specialized healthcare workers and supportive services, increase the expertise for specific conditions, reduce unwanted variations in care practice, and smoothen care coordination. Optimal collaboration within integrated networks should also boost the experience of care delivery among healthcare professionals. Building such care networks is in line with the World Health Organization (WHO) global strategy on people-centered and integrated health services and their call for "integrated health services that are managed and delivered in a way that ensures people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services, at the different levels and sites of care within the health system, and according to their needs throughout their life course." (1).

A challenge is that the various existing care networks vary greatly with regard to scale (from local to for example European), focus (single disorder vs. a group of related disorders), extent of care delivery (some are monodisciplinary, others multidisciplinary, but with a great variety of disciplines involved), scope, sustainability, level of professionalism, governance structure, etc. Such variability is explained by many factors. These include financial and infrastructural resources, density of available experts, frequency of the disease(s) covered, density of the overall population, specific characteristics of regional or national healthcare systems, and cultural aspects.

It appears that new initiatives for care networks, well-intended as they may be, are often either re-inventions of the wheel, neglecting the opportunity to learn from previous and current care networks, or duplications of other networks, insufficiently addressing the question of compatibility with specific aims and requirements. We here share our view on several *generic* principles and ingredients for care networks, which can and need to be tuned toward the specific network that is being designed and built. Our view is based on our rich experience with the Dutch ParkinsonNet approach, which we will introduce first. We will then discuss a framework of generic aims and strategies of care networks, as well as the specific challenges related to networks that target rare (movement) disorders.

PARKINSONNET—HISTORY, MERITS, AND LESSONS LEARNED

The Dutch ParkinsonNet is a multidisciplinary professional network that aims to improve the quality of care delivery for patients with Parkinson's disease (PD) or a form of atypical parkinsonism (2, 3). The network consists of a limited number of specifically trained healthcare professionals (every participant has received an intensive 3-day baseline training course according to the latest guidelines), who attract a high caseload and thereby continuously improve their Parkinson-specific expertise. The network started in 2004 in the Netherlands, motivated by two concurrent developments. The first motivations came directly from clinical practice, where there was a widely felt need for an easily accessible community-based network of allied health professionals with dedicated expertise in treating patients with PD (4). This disorder is characterized by a wide range of motor and non-motor symptoms, many of which respond insufficiently to symptomatic pharmacotherapy (5). Allied health interventions such as physiotherapy, occupational therapy or speech-language therapy can potentially treat many of these otherwise treatment-resistant symptoms, in particular in light of the underlying pathophysiology: basal ganglia dysfunction in PD leads to loss of automated movements, but this can be bypassed using a range of compensatory strategies, such as cueing strategies to improve gait, or specific strategies to improve the intelligibly of speech (6). However, optimal delivery of such interventions requires a good understanding of both the complex clinical presentation and underlying pathophysiology of PD, as well as knowledge of specific treatment strategies. At the time, it was impossible to initiate a dedicated referral to a motivated allied health professional who sufficiently understood PD and who had considerable experience in treating PD patients. Some professionals have built up rich expertise in their daily practice, but they are not readily retrievable in the "yellow pages" of PD. And even when such professionals can be found, it was very difficult to initiate an integrated and multidisciplinary treatment for patients, because most professionals knew very little about what other professional disciplines had to offer (7), and easy communication channels were lacking. A network approach was felt to be an appropriate solution for these challenges.

The second motivation was the need to build a better evidence-base for the various allied health interventions in the field of PD. Although allied health interventions were widely considered to be potentially useful therapies for PD, robust scientific evidence to support the merits of these approaches was lacking. Performing clinical trials was deemed to be a risky enterprise, because at the time, allied health professionals had received very little Parkinson-specific training as part of their routine educational programs, and also treated very few patients in their daily practice annually. Having such poorly experienced providers as the deliverers of care in an intervention trial carried an enormous risk of creating a false-negative result. This further motivated the installation of a network of initially only specifically trained physiotherapists, who were trained according to a newly developed practice-based guideline. This created the necessary infrastructure for subsequent clinical trials.

The first ParkinsonNet network was launched in the eastern part of the Netherlands, and consisted of a small and selected group of healthcare professionals from three different professional disciplines (physiotherapy, occupational therapy, speech-language therapy) (8). All participants were trained according to practice-based evidence guidelines, and were also educated about the offerings of the other professional disciplines. Using simple brochures, referring physicians were informed about the presence of these specifically trained professionals, allowing a dedicated referral and a subsequent increase in caseload. Following positive experiences with this initial small regional network (8), eight further networks were launched in different regions of the Netherlands, consisting initially of only specifically trained physiotherapists, with the aim of using this infrastructure for a subsequent cluster-controlled trial (9). Eight other comparable regions initially served as controls, but following the positive outcome of the trial, these regions also received a professional physiotherapy network. In subsequent years, the network was extended both geographically (reaching a full nationwide coverage by the year 2010), and also in terms of numbers of attached professional disciplines. The network currently exists of over 3,400 specifically trained healthcare professionals, from now 19 different professional disciplines (not only allied health, but also dieticians, Parkinson nurses, social workers, etc.). The active "ingredients" of the ParkinsonNet approach are summarized in **Table 1**.

The merits of this network approach have subsequently been evaluated in a series of clinical studies, including both carefully controlled trials (9–12) and large-scale uncontrolled analyses of a national medical claims database (13). Taken together, these studies provided consistent and converging evidence that supports the cost-effectiveness of a network approach, which appears to be mediated by an improved care delivery (3): the knowledge and use of professional guidelines has enhanced; the caseload of the network participants has increased significantly, not only initially, but the concentration of care continues to improve over the years (14); professionals are much better aware of what other disciplines in the network potentially have to offer; interdisciplinary collaboration has improved; health outcomes are better for patients treated within the network,

TABLE 1 | Overview of the supportive building blocks of care networks, including a detailed description and examples of how these have been implemented in ParkinsonNet.

Building blocks	Description	The way ParkinsonNet implemented this
Selection and certification	A selection process combined with a baseline training leads to selective inclusion of motivated and specifically trained healthcare providers. Periodic re-certification based on quality criteria is important to guarantee a high-quality expert network.	• Each year, ParkinsonNet includes new healthcare professionals in the network. In each region we strive to reach an appropriate number of allied health professionals. The required number depends on the discipline and the geographic area. • ParkinsonNet requires members to treat a minimum number of PD patients each year. • Members commit to work according to evidence-based guidelines. • Every 2 years a mandatory re-certification is required based on quality-of-care criteria.
Support centre	An overarching support centre that supports regional networks of providers to work together to improve regional healthcare delivery.	• A national ParkinsonNet coordination centre that provides active guidance to 71 ParkinsonNet regional networks and >3,400 ParkinsonNet healthcare professionals. ○ Supporting regional networks with personal advice ○ Financial support to organize regional meetings ○ Sharing best practices among regional networks ○ Sharing successful formats for organizing interesting regional meetings
Guideline development and implementation	Guideline development is a solid base for healthcare improvement, both to improve quality of care in daily practice and as important basic training material. Guideline development alone is not enough. It is crucial to support healthcare professionals to work in accordance with guidelines. Accessible guidelines -possibly with some decision support – are a prerequisite for achieving this.	Together with several associations for healthcare professionals, and with the Parkinson Patient Association, ParkinsonNet has developed guidelines: • Monodisciplinary guidelines for physiotherapy, speech-language therapy, occupational therapy, dietary issues, Parkinson's disease nurses and palliative care. • A multidisciplinary guideline, including a consensus-based model for regional and transmural organization of multidisciplinary care
Continuous mono- and interdisciplinary learning	To become an 'expert', healthcare professionals should participate in continuous learning cycles, including interaction and information exchange between providers.	• Eligible members must follow a baseline PD-specific training according to evidence-based guidelines (3 days). • After completing this training it is crucial to start learning on the job; expertise can only be increased by treating many patients and by discussing the treatment of complex patients with other health care professionals • Multiple specific trainings, for example about cognition and palliative care • Multiple short animated videos about topics as 10 tips for carers and psychosocial care • Annual conferences • Regional interdisciplinary meetings (twice a year) • Participation in web-based national and regional online communities
Online and offline meetings	Regularly meeting other professionals is important to learn from each other, to inspire each other and to facilitate contact between professionals when this is needed to discuss the treatment strategy for individual patients within a multidisciplinary team.	• Network participants must meet each other in their own region at least twice a year • National annual conference (to learn and meet other professionals) • Online interaction between professionals via an online community tool (ParkinsonConnect)
Visibility and accessibility of experts	Patients should be able to readily find and access specialized experts.	• Providing a web-based search engine (www.ParkinsonZorgzoeker.nl) • Providing experts with a dedicated promotion package to enhance their visibility
Patient education and engagement	Key to patient empowerment is education of patients and the behavior of providers within the individual patient-provider relationship.	• National level: ○ Strategic partnership with Dutch Parkinson Patient Association ○ Advisory patient panel for novel technologies or other innovations ○ Patient representation at regional and national conferences ○ Educational web-based television program (www.parkinsonTV.nl) ○ PD management guideline in lay language for patients ○ Website with reliable information about ParkinsonNet (www.ParkinsonNet.nl) • Regional level: ○ Collaboration with local branches of Parkinson Patient Association • Individual patient-provider relationship: ○ Training participating providers to engage patients as partners in healthcare ○ Promoting shared decision making

(Continued)

TABLE 1 | Continued

Building blocks	Description	The way ParkinsonNet implemented this
Continuous evaluation and improvement of the network	Continuous evaluation and improvement of the network is key. Transparency about performance indicators is also important to inform stakeholders about the merits of the network.	Insight into: • Quality (e.g. adherence to guidelines) • Outcomes (e.g. complications) • Costs • Average caseloads of network participants • Utilization of the network by patients • Experiences of healthcare professionals • Experiences of patients Health care insurance data and surveys among network participants are used to collect this information. Results are published on the ParkinsonNet website.
Supportive technology	Technology can support interdisciplinary collaboration within the network of each individual patient, and also within regional or national networks of health care professionals.	• ParkinsonConnect, a web-based community tool that enables easy communication between healthcare professionals. • ParkinsonTV • ParkinsonNEXT • ParkinsonNet.nl

including a marked reduction in hip fractures and hospital admissions for orthopedic injuries or aspiration pneumonia; and healthcare costs have reduced significantly, as a result of both prevented disease complications and a greater efficiency of care (ParkinsonNet professionals require significantly fewer treatment sessions to achieve their treatment goals). One study even showed a tendency toward a lower mortality rate for patients receiving network care, presumably because of the prevented disease complications (13).

The scientific publications that documented these positive outcomes stirred a fast rising international interest in building similar networks for Parkinson patients in other countries. We have meanwhile introduced comparable networks in, among others, United States (a partnership with Kaiser Permanente in California, and a network in Rochester), Norway and Luxembourg, while additional trainings are currently taking place or are being planned in Germany, Italy and China. An important lesson learned from this international experience is that the networks in other countries each time have to be adjusted to the local needs, as well as to the existing infrastructure and available services. Supporting other countries in building similar networks was all but a "copy paste" enterprise, but instead was always preceded by a careful inventory of what existing services were already operating well, which challenges existed regionally, and which of the solutions offered by ParkinsonNet could help to address these existing challenges. A further important lesson was that each international network is to be governed by regional leadership, and that it is essential to locally train "super experts" for each associated professional discipline, so these can subsequently oversee the quality of the regional network in the other country. Capitalizing on these lessons, the initial experience with the international network in California has been very positive, showing a significant change in referral patterns toward the specifically trained ParkinsonNet participants (15).

We previously already alluded to the opportunity to consider ParkinsonNet as a scalable model for other chronic conditions, including other movement disorders (3). The management of these disorders is equally challenged by very comparable issues such as lack of specific expertise, care fragmentation, and insufficient collaboration between disciplines. These challenges are presumably even more prominent for rare disorders, for which dedicated expertise and optimal collaboration with fellow peers in the expert network is presumably extra important. Most of the key components of ParkinsonNet can be considered as generic ingredients ("building blocks") for care networks, although the specific requirements for each professional network will undoubtedly have to be adjusted to the unique needs of each condition as well as the specific regional circumstances. Next, we will discuss these generic ingredients, which we refer to as supportive building blocks, according to the why, how and what principles.

SUPPORTIVE BUILDING BLOCKS OF CARE NETWORKS

Why?

The ultimate objective of the integrated network care model is to reach the quadruple aim of healthcare, with (1) better health outcomes, (2) lower cost of care, (3) improved patient experience, and (4) improved staff experience (**Figure 1**). To reach this quadruple aim, the model focuses on four concrete goals: (1) patients should always receive personalized treatments, (2) care is delivered by professionals with adequate specific expertise for the disease at hand (specialized experts), (3) experts from different disciplines and organizations should work together with other professionals within interdisciplinary teams (interdisciplinary care), and (4) patients should be seen as real partners in the healthcare process, and be supported to make an active contribution to their own health (patient engagement). These driving forces are in line with the values of integrated care identified by Zonneveld et al. (16) in their systematic review that aimed to identify factors that drive behavior, decision-making, collaboration and governance processes within integrated care networks.

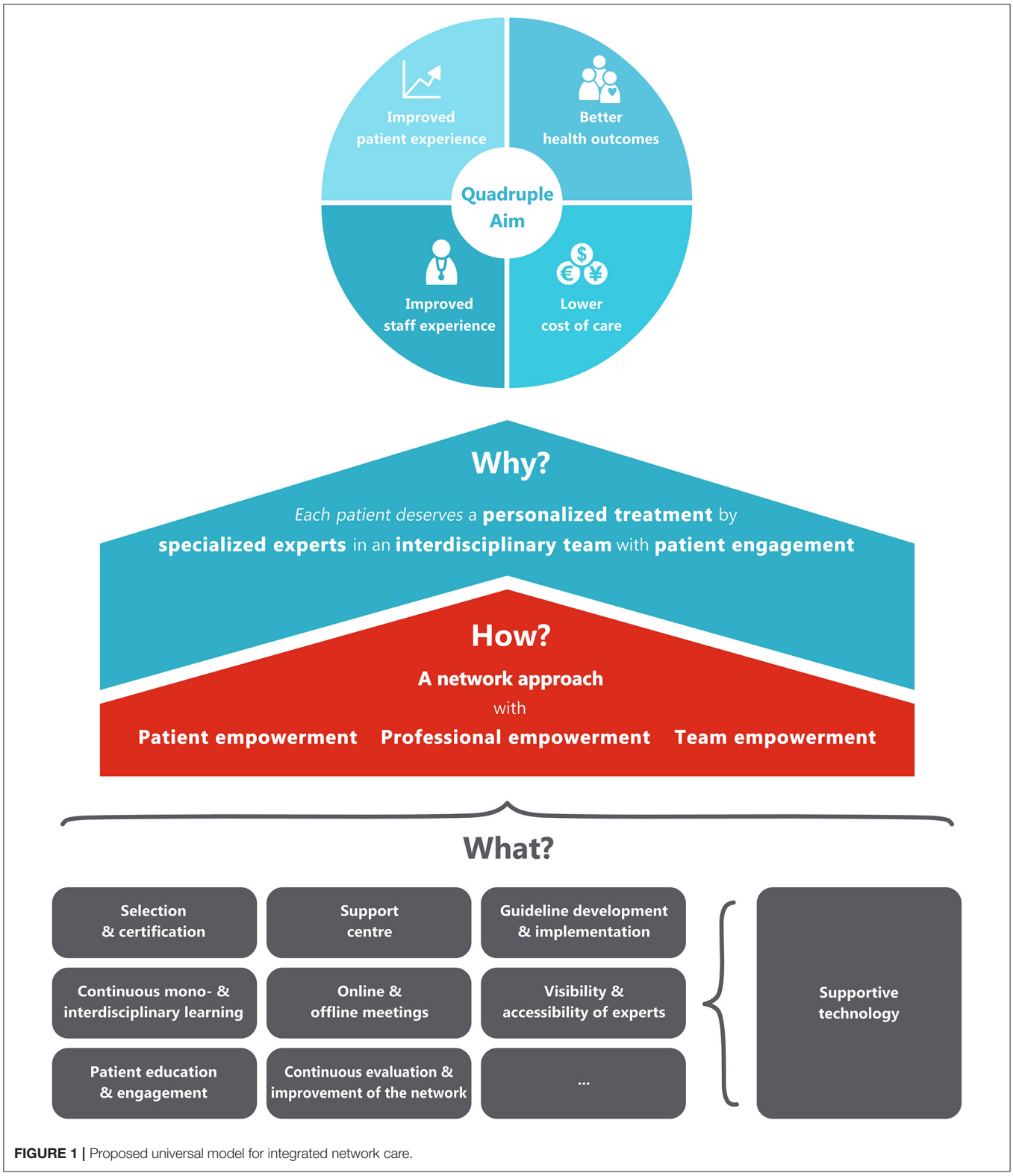

FIGURE 1 | Proposed universal model for integrated network care.

How?

Central to the model that we present here is a managed multi-level network. In this network approach, patients and professionals from different disciplines and organizations work closely together in different networks and at different levels, in order to improve the quality of care for all patients with

the same disease in a certain geographical area. In this regard, it is good to realize that the word "network" is often used to denote various forms of collaboration at very different scales. The smallest scale of a network is formed by the healthcare team that is involved in the management of any given individual patient. To provide a concrete example, the neurologist, nurse, physiotherapist, dietician and general practitioner together from the personal care network of Mr. Johnson. But networks also exist at a larger scale. Specifically, at a higher level, larger numbers of healthcare professionals, all with dedicated expertise in the same disease, can meet each other in local, regional or national networks, not so much to provide care to an individual patient, but rather aiming to learn from each other and to agree about regional healthcare management issues (for example, do we have a sufficient number of specifically trained physiotherapists to optimally manage the population within this specific geographical area?). The geography of these networks depends on the incidence of a disease. For diseases with a high prevalence, regional or even local networks of professionals can be formed. For diseases with a much lower incidence, these networks can be organized at a state or national level. The members of the regional networks should ideally be supported by a national support center, which provides among others generic support and advice to the various regions. Patients, professionals and teams are empowered by this support center with a range of activities to reach the three goals. The most important activities are described as the building blocks in the "what-section." In the building process of the care network, four development phases of integrated care can be followed: "initiative and design phase," "experimental and execution phase," "expansion and monitoring phase," and "consolidation phase." These phases have been described and validated by Minkman et al. (17, 18).

What?

The generic building blocks to organize the network and to empower patients, professionals and teams are presented in **Table 1**. This overview of building blocks is not inclusive, and the building blocks can differ between diseases, and will also depend on the specific regional circumstances, including the characteristics of the healthcare system. For example, in the aforementioned collaboration between the Dutch ParkinsonNet and Kaiser Permanente in California, a decision was reached to use only a restricted number of building blocks (e.g., guideline development, professional training, patient empowerment), whereas others were deemed to be unnecessary (e.g., use of some of the supporting digital technologies, since these were already available as part of the Kaiser Permanente offerings) (15).

SPECIFIC INGREDIENTS AND CHALLENGES FOR RARE MOVEMENT DISORDERS

The main challenges for networks that focus on rare disorders are obviously related to the rarity of each of the individual conditions. There are estimated to be 600–800 different rare diseases, each with individually low prevalence rates. We should therefore not strive to have specifically dedicated networks for each of the rare movement disorders separately, also because there are often mixed types of movement disorders in these conditions (for example, many patients with a hereditary ataxia may present with additional movement abnormalities, such as dystonia or chorea).

As expertise results not only from having received a baseline training but also to a large extent from accumulating experience in daily clinical practice, a sufficient exposure to large numbers of patients with a certain condition is required. This clearly necessitates efforts to centralize the care for specific conditions among a restricted number of specifically trained professionals. The concentration of care was a successful cornerstone of the ParkinsonNet approach, but this will presumably be at least as important for networks focusing on rare movement disorders. In this regard, it is a promising development to see the presence of an increasing number of expert centers for rare disorders (sometimes self-proclaimed, but increasingly also formally recognized according to established objective criteria) in many countries. In accordance with our ideas about the supportive building blocks (**Table 1**), such experts centers would be ideally positioned to take on the role of support centers when new networks are being formed.

To be designated as an expert center by national authorities requires that various predefined criteria have to be met, which serve a quality control purpose. These criteria should address relevant issues such as minimal patient numbers, optimal team size and composition, research performance, and other tangible metrics. A next step would be to evaluate these centers based on actual patient-relevant performance measures, but such quality-of-care criteria remain to be established for rare movement disorders.

In the Netherlands, we have seen a steep rise in the number of expert centers, sometimes even for a single rare disease. As a response, future applications should target clusters of rare diseases in order to obtain a formal recognition by the Ministry of Health. Such clustering can be reached at various levels, such as a comparable etiology, overlapping functional deficits, or similarities in treatment. This clustering also serves to achieve a certain caseload, which is needed to develop, maintain and ultimately expand the required level of expertise. Clustering could lead to a dilution of expertise for single disease entities, but the advantages and necessity hereof outweigh this potential disadvantage. Moreover, one could argue that recognizing the overlap between and co-existence of multiple movement disorders—which is more likely secured in centers that host clusters—actually aids the disease-specific expertise.

One example of how clusters for rare movement disorders could look like, are those that have been proposed within the European Reference Network for Rare Neurological Diseases (ERN-RND; see contribution by (19); doi: 10.3389/fneur.2020.616569). This network has a strong focus on rare movement disorders, and has used (1) cerebellar ataxias and hereditary spastic paraplegias, (2) Huntington's disease and other choreas, (3) dystonia, paroxysmal disorders, and neurodegeneration with brain iron accumulation, (4) atypical parkinsonian syndromes as the four main clusters.

Ideally, all patients with rare movement disorders should be seen, at least once, in expert centers, in particular to establish a definitive diagnosis whenever possible, and to outline the contours of a therapeutic management program for the following years. However, this will not always be possible, for example because of long travel distance and costs or patient immobility, or simply because of insufficient capacity. Additionally, lack of awareness of the presence of centers of expertise further hampers a dedicated referral to these centers. Realizing that physical consultations are not always feasible, we feel that an important task of such an expert center within the network structure is to transfer knowledge and skills to local healthcare professionals working close to the patients' home. Many patients prefer to be (also) followed up by their local neurologist, and from studies in the PD field we now know that neurologists who work in community hospitals deliver better quality care for patients if they are supported remotely by an expert via telemedicine (so-called peer-to-peer consultations) (20).

One of the main challenges in the allied health domain is to identify professionals who are indeed motivated to be equipped with greater knowledge and better skills for a specific rare disease, of which the total number of patients in their practices will remain extremely low. This is in clear contrast with the original ParkinsonNet model, where trained participants in the network have witnessed a very tangible increase in the number of patients with PD in their daily practice. This notion raises the question where for example allied healthcare interventions should be delivered best. This could still a local trained therapist, but may also very well be a rehabilitation facility as close as possible to the patient. Regardless of the scenario, well-designed and preferably evidence-based guidelines are needed. For rare movement disorders, such guidelines are often lacking, particularly for non-pharmacological interventions. The absence of such guidelines—a crucial building block in the model we present here—makes it very difficult to have local professionals execute an intervention proposed by an expert center. Having guidelines is also essential as baseline training materials for professionals who wish to join a professional network, and to help reduce unwanted variations in care delivery. For some of these guidelines, particularly those that involve rehabilitation, one will need to consider clustering at the level of shared or overlapping movement disorders, as eluded to earlier. This has also been done in ParkinsonNet, where professionals now deliver care to both PD and atypical parkinsonism patients. A treatment guideline for ataxia will benefit patients with MSA-c and Freidreich's ataxia alike, while separate guidelines will prevent professionals to become acquainted with the commonalities in symptoms, functional deficits, and treatment principles. Some recent studies on rehabilitation in for example ataxia and cervical dystonia will be useful starting points for the development of such guidelines, which should have priority for rare movement disorders (21, 22).

The quality of care provided by expert (and support) centers will be improved further if there is between-center collaboration and knowledge exchange. To achieve this, cross-state and international networks of expert centers have been established, e.g., the European Reference Networks (ERN). By demanding clustering, the European Union wisely prevented the emergence of too many networks that deal with a single or limited set of diseases. One of the ERN's specifically addresses the cluster "rare neurological disorders" (ERN-RND; see contribution by Reinard et al. in this series), including movement disorders. This development offers opportunities to widely harmonize disease management, to deliver cross-border care, to provide access to facilities to low-resource countries, and to draft joint research programs. While advantages are omnipresent, such international networks do, however, also add layers of complexity, such as reimbursement issues for cross-border care, complex network governance, and asymmetry in knowledge and resources that prevent guideline harmonization. An elegant solution to provide cross-border care, or at least get access to an international panel of experts, is provided by an IT-platform that the European Union has installed for ERN's, in harmony with "supportive technology" identified by us as one of the building blocks.

CONCLUDING REMARKS

Based on our experience with ParkinsonNet, a network for integrated care in PD, we have here shared our view on a universal model for care networks. We have presented supportive building blocks of such a network, which are generic ingredients that ultimately allow the network to reach the quadruple aim of healthcare. The rarity of various movement disorders imposes certain unique challenges and barriers that prevent a full and immediate adoption of the model as laid down here. However, our view on the generic ingredients can serve as the starting point for shaping a new care network. Also, existing networks and centers that are part of these networks can identify which building block(s) they wish to adopt or improve, which can be jointly and transparently prioritized. Ideally, innovations such as care networks should be tested against current standards of care and demonstrate added benefit and/or cost-effectiveness. We appreciate that this will be a challenge on its own for cross-border networks for rare disorders.

For rare movement disorders, it seems that three aspects have priority. First, clustering of rare movement disorders at the network level is needed, not only to identify the expert professionals and centers, but also to ensure a certain caseload and to exploit the fact that specific care interventions may overlap across different conditions. Second, supportive technology is a true necessity in order to facilitate exchange of and access to knowledge and expertise. Technological solutions are particularly important, because the density of experts and expert centers for rare movement disorders is low in most regions and countries, so physical in-person meetings are difficult to organize. In fact, the many challenges imposed by the unfolding COVID-19 crisis have only further helped to accelerate the introduction of telemedicine solutions to ascertain a good quality of care delivery for people living with chronic neurological conditions (23). Lastly, interdisciplinary guidelines need to be developed,

as these are quite central to the model, facilitating training of professionals, harmonizing care, and evaluating performance of professionals, centers and the network.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

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

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REVIEW
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The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies

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Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal postures, repetitive movements, or both. Research in dystonia has been challenged by several factors. First, dystonia is uncommon. Dystonia is not a single disorder but a family of heterogenous disorders with varied clinical manifestations and different causes. The different subtypes may be seen by providers in different clinical specialties including neurology, ophthalmology, otolaryngology, and others. These issues have made it difficult for any single center to recruit large numbers of subjects with specific types of dystonia for research studies in a timely manner. The Dystonia Coalition is a consortium of investigators that was established to address these challenges. Since 2009, the Dystonia Coalition has encouraged collaboration by engaging 56 sites across North America, Europe, Asia, and Australia. Its emphasis on collaboration has facilitated establishment of international consensus for the definition and classification of all dystonias, diagnostic criteria for specific subtypes of dystonia, standardized evaluation strategies, development of clinimetrically sound measurement tools, and large multicenter studies that document the phenotypic heterogeneity and evolution of specific types of dystonia.

Keywords: dystonia, blepharospasm, cervical dystonia, laryngeal dystonia, rare diseases, spasmodic dysphonia, torticollis, writer's cramp

INTRODUCTION TO DYSTONIA

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal postures, repetitive movements, or both (1). Dystonic movements are typically patterned, twisting, or may resemble tremor. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Dystonia is not a single disorder but a family

of heterogenous disorders with varied clinical manifestations and many different causes (2, 3).

The many different clinical manifestations of dystonia are grouped according to age at onset, body region affected, temporal aspects, and associated clinical features (1). The term "isolated dystonia" (previously known as "primary dystonia") is used when dystonia is the only movement disorder identified, with or without tremor. In contrast, the term "combined dystonia" (previously known as "secondary dystonia" or "dystonia-plus") is used when dystonia is combined with other neurological problems, such as parkinsonism, myoclonus, or ataxia). The most common subtypes of isolated dystonia emerge in adults over a period of weeks or months in one region of the body, with spread to other regions over many years. Any region of the body can be affected, but the most common regions include the neck (cervical dystonia, also known as torticollis), the face (blepharospasm and related craniofacial dystonias, sometimes called Meige syndrome), the larynx (laryngeal dystonia, also known as spasmodic dysphonia), or a limb (e.g., writer's cramp or musician's dystonia). Children are less commonly affected than adults, although more likely to advance to more severe generalized forms.

There are many known etiologies for dystonia. They include lesions of the nervous system, exposure to drugs or medications, infections and autoimmune processes, and other causes (2–4). However, for the vast majority of cases of isolated dystonia, a cause cannot be identified, even after extensive laboratory testing. Approximately 10–15% of cases have an affected family member. This observation points to inherited mechanisms. More than 100 genes capable of causing dystonia are known, most of which cause early-onset or combined forms of dystonia (2, 4, 5). Recent whole-exome sequencing studies have suggested that an etiology can be identified in ∼20% of cases, depending on the associated clinical features (6, 7). A genetic etiology is disclosed more often in young-onset cases, those where dystonia is combined with other problems, or those with a family history of dystonia. A genetic etiology is found in only ∼4% of the most common adult-onset cases.

Dystonia causes substantial disability (8, 9). For example, cervical dystonia is associated with neck muscle spasms that make it difficult for patients to control head movements for basic activities of daily living such as looking straight ahead to drive a car, read, see a computer or television screen, or even walk. Blepharospasm is associated with periocular spasms leading to frequent sustained eye closures. These spasms make it difficult to do many of same activities of daily living and may render subjects functionally blind. Laryngeal dystonia is associated with spasms of laryngeal muscles making it difficult to speak and communicate with others. Patients with limb dystonia may have trouble writing, typing, or walking. When this affects professionals such as musicians, dystonia can end a career. Patients with broader distributions of dystonia such as segmental or generalized patterns have even greater disability.

In addition to the abnormal movements that interfere with activities of daily living, dystonia is often associated with pain. Approximately two thirds of all patients with cervical dystonia have significant pain in the neck or shoulders (10). Approximately half of all patients with dystonia of the upper limb have arm or hand pain (11, 12). Many patients with generalized dystonia have pain relating to the most prominent areas of spasm. In addition to muscle pain, orthopedic complications that result from abnormal postures are a source of chronic pain for many patients with dystonia.

These abnormalities and limitations of mobility and pain degrade quality of life. In fact, standardized tests for quality of life in dystonia fall in the same range as patients with Parkinson's disease, multiple sclerosis, and stroke (8, 9).

THE NEED FOR NEW TREATMENTS

Existing Treatments

Current treatments include physical therapy to address spasms or pain. Oral treatments are available to target the causal mechanisms for a few rare dystonia subtypes (13), but most are treated symptomatically with benzodiazepines, anticholinergics, or muscle relaxers (14, 15). The botulinum toxins are considered first-line treatments for many patients (16). Surgical interventions are offered for severe, medically refractory dystonias (17, 18). Deep brain stimulation (DBS) is most popular, but ablative procedures involving the basal ganglia or thalamus can also be helpful (19).

Despite these many treatment options, all have significant limitations. Physical therapy is popular; but benefits are variable and often short lived. There are many small open trials describing their value, but the largest and most rigorous studies fail to show any consistent benefits (20, 21). The most popular oral agents produce only partial benefits and doses are limited by side effects (3, 15).

The botulinum toxins suffer limitations too. Since they must be injected into affected muscles, they are most useful in the focal and segmental dystonias where a small number of muscles can be targeted. Because their benefits last only 2–4 months, injections must be repeated 3–4 times yearly. Despite dramatic efficacy on standardized tests of motor function in clinical trials, the botulinum toxins produce low levels of patient satisfaction, especially toward the end of a treatment cycle (22–24). Longitudinal studies have indicated that ∼30% of patients discontinue using botulinum toxins (25), and cross-sectional studies indicate ∼40% of patients are not using botulinum toxins (14). The reasons for low patient enthusiasm are only partly understood but appear to include lack of efficacy, side effects, difficulty in finding experienced injectors, hassle associated with repeated injections, and cost (24, 25).

For DBS, outcomes depend on etiology (e.g., genetic subtype or acquired) and certain clinical characteristics (e.g., age, duration, and combination with other problems) (17, 18, 26, 27). Therefore, DBS is not a suitable solution for many patients. Immediate complications are uncommon, but include 1–2% risk of stroke or infection. In addition, proper programming requires an experienced team, and it may take many months to optimize. Long-term complications are not uncommon, such as lead migration, equipment failure, or infection. In summary, all existing therapies provide at least partial relief

of symptoms for many individuals with dystonia, but all have significant limitations.

Experimental Therapeutics

When considering the development of novel therapeutics, clinical and etiological heterogeneity among the dystonias creates challenges. On the one hand, the different clinical manifestations seem to require different management strategies. In addition, the varied biological substrates may require targeting different mechanisms. On the other hand, several observations imply that certain forms of dystonia are mechanistically related (28, 29). In fact, there already are some treatments that have broad efficacy across many clinically and etiologically distinct subtypes, such as anticholinergics, botulinum toxins, and DBS.

These observations have encouraged attempts to identify the mechanisms that are shared across multiple types of dystonia. These mechanisms then become attractive targets for therapeutic interventions that may be useful across certain subgroups (30–32). At the genetic level, the identification of a large number of genes that may cause dystonia has facilitated the identification of several molecular mechanisms that are shared by at least certain subgroups of dystonia (5). For example, numerous studies in both animals and humans have linked dystonia with altered dopamine transmission. Although there are numerous reports describing good responses of certain cases to dopamine-related drugs, they are not generally effective treatments for most types of dystonia. It has been suggested that the failure of prior studies to demonstrate more consistent benefits might result from etiological heterogeneity, and clinical trials in more selected populations may be needed (33).

Pharmacological studies have also pointed to striatal cholinergic pathways as a common theme spanning several different types of dystonia in both animal models (34) and human studies (35). Although anticholinergic drugs can be at least partly effective across many different types of dystonia in humans, they are often poorly tolerated due to side effects including cognitive impairments, memory loss, dry mouth, blurred vision, constipation, and urinary retention. Current clinically available anticholinergics such as trihexyphenidyl non-specifically block muscarinic receptors. Numerous studies have focused on identifying novel compounds that may address these limitations (36). For example, by developing anticholinergics with more selective effects on the relevant muscarinic receptors in the striatum, it may be possible to avoid the many side effects that arise from non-specific blockade of receptors in the cortex or autonomic system.

Another common theme has involved abnormalities of neuronal excitability or neural plasticity among individuals with different types of dystonia (37). Glutamate receptors play a key role in neuronal excitability. Antagonists targeting several different subtypes of glutamate receptors (AMPA, NMDA, and mGluR5) have been shown to reduce dystonic movements or normalize abnormal striatal physiology in several animal models of dystonia (38). In humans with cervical dystonia, an open label study described small improvements with the non-selective glutamate antagonist riluzole (39), and there are anecdotal reports describing improvement with amantadine, a weak NMDA antagonist. These findings have led to interest into more methodical studies of repurposing glutamate-related drugs as potential therapeutics for dystonia. For example, the AMPA antagonist perampanel is FDA approved for epilepsy, and a trial for subjects with cervical dystonia has recently concluded recruitment (Clinicaltrials.org, NCT02131467).

Numerous other mechanisms are actively being studied as therapeutic targets for dystonia. At the end of year 2020, clinicaltrials.gov listed a total of 291 clinical studies for dystonia. Of this total, 156 have been completed and 49 are actively recruiting. Many of these are clinical trials of novel therapeutics (**Table 1**). However, many are small or unblinded pilot trials, and larger more rigorous trials are needed. Clinical trial readiness is therefore an immediate need. This readiness involves multiple ingredients including easy identification of research subjects for efficient recruitment, thorough understanding of phenotypic heterogeneity and diagnostic criteria for relevant subtypes of subjects, baseline information on how the disorder evolves over time, easy identification of experts who can participate in trials, clinimetrically sound measurement outcome tools for clinical trials (objective measurement tools and patient-reported outcomes), and fully objective or biomarker measures.

THE DYSTONIA COALITION (DC)

Mission

The DC was established to address some of the challenges associated with research in rare disorders by facilitating large-scale collaborations. Its main focus has been on studies that address clinical trial readiness. The DC has focused its major projects on key unmet needs for translating scientific discoveries into potential new therapies. These unmet needs are identified via focused workshops, which are conducted in collaboration with Patient Advocacy Groups (PAGs). The main needs have included developing a better understanding of the phenotypic heterogeneity and evolution of various types of dystonia, more precise and widely accepted diagnostic criteria, appropriate measurement tools to monitor patients in clinical trials, and identification of useful biomarkers.

Sponsorship and Endorsement

The DC is sponsored in large part by the National Institute of Neurological Disorders and Stroke (NINDS) and Office of Rare Diseases Research (ORDR) in the National Center for Advancing Translational Sciences (NCATS) at the National Institute of Health (NIH) through grants NS065701, TR001456, and NS116025. The DC is part of the NIH Rare Diseases Clinical Research Network (RDCRN), an initiative of the NIH to encourage collaborative research for all types of rare disorders (www.rarediseasesnetwork.org). The DC also receives critical support and sponsorship from PAGs, industry, professional societies, and relevant study groups.

PAGs have been integrally involved in all major activities of the DC. So far, the DC has engaged 17 PAGs across four countries in its different projects. Many of these regularly contribute to the DC mission (**Table 2**). PAGs have been integrally involved in identifying research topics and designing

TABLE 1 | Selected clinical trials on dystonias (https://clinicaltrials.gov).

Drug/Intervention	Targeted mechanism	Type of dystonia	Study design	Date
Ampicillin	Immune system	DYT1 dystonia	Phase I double-blind	2011–2017
DBS	Basal ganglia or thalamic nuclei	Dystonia and other disorders	Open label-single group assignment	2011–Present
Levetiracetam	Synaptic neurotransmission	Oromandibular and cranial dystonia	Phase II double-blind	2014–2017
Botulinum toxin plus physical therapy	Neuromuscular junction and musculoskeletal activity	Cervical dystonia	Phase 4 randomized	2014–2017
DBS	Pallidal and thalamic nuclei	Secondary hemi-dystonia	Phase I randomized	2015–Present
Hand physiotherapy	Individual finger movement training	Writer's cramp	Randomized-double blind	2016–Present
Perampanel	Glutamate receptor, AMPA	Cervical dystonia	Phase I/IIa open-label	2017–2020
Zolpidem	GABAa receptor chloride channel modulator/agonist	Writer's cramp or musician dystonia	Phase I crossover	2017–Present
Sodium oxybate	GABAb receptors	Laryngeal dystonia	Phase II/III double-blind	2017–Present
Daxibotulinumtoxin A	Neuromuscular junction	Cervical dystonia	Phase III double-blind	2018–2020
Daxibotulinumtoxin A	Neuromuscular junction	Cervical dystonia	Phase III open-label	2018–Present
Botulinum toxin and treadmill	Neuromuscular junction	Cervical dystonia and blepharospasm	Pilot monocentric, non-randomized, controlled	2019–Present
Deutetrabenazine	VMAT2 inhibitor	Dystonia	Phase I/II open-label	2020–Present
Tele-yoga	Mind-body awareness	Cervical dystonia	Single group intervention	2020–Present

DBS, deep brain stimulation; GABA, gamma-amino butyric acid; VMAT2, vesicular monoamine transporter type 2.

TABLE 2 | Patient advocacy groups currently affiliated with the Dystonia Coalition.

Patient Advocacy Group	Country
Benign Essential Blepharospasm Foundation	USA
Cure Dystonia Now	USA
Dystonia Europe	Belgium
Dystonia Ireland	Ireland
Dystonia Medical Research Foundation	USA
Dystonia Medical Research Foundation, Canada	Canada
National Spasmodic Dysphonia Association	USA
National Spasmodic Torticollis Association	USA
The Dystonia Society	USA
Tyler's Hope	USA

DC projects, developing a focus and plan for DC annual meetings, supporting studies of particular interest, supporting junior investigators, and facilitating patient recruitment. The Dystonia Medical Research Foundation (DMRF), in particular, plays an essential logistical role for the DC infrastructure, at no additional cost. In addition to aiding the organization of DC meetings and reviewing projects submitted for DC funding, DMRF staff provide support for managing subcontracts for paying all recruiting sites for the various DC projects. This unique model provides enormous savings for both research costs and time, enabling DC investigators to focus on clinical and scientific needs.

Coordination of Sites

The DC has had an open-door policy in which new investigators and institutions may join the effort at any time. The DC began in 2009 with eight sites but has since engaged 56 sites in the North America, Europe, Asia, and Australia (**Figure 1, Supplementary Table 1**). Many patients come to these centers for expert clinical care, as well as research opportunities. The DC sites are grouped in three tiers. As capabilities and interests change over time, centers may change tiers. *Affiliate Centers* are sites that may not have the ability to recruit subjects or direct projects but wish to remain informed about the DC activities and opportunities. *Recruiting Centers* are sites with sufficient expertise and clinical volumes to recruit subjects for clinical research projects. *Project Centers* are sites that take responsibility for directing multicenter clinical research projects. Individual investigators at these sites are given responsibility for developing and implementing projects using the DC infrastructure.

All DC activities are centrally coordinated. The coordinating center supervises the conduct and progress of its main clinical research projects, its smaller pilot projects, and its career awards. It also supervises the annual meeting and other activities. For multicenter projects, data are entered via the internet into a central database (**Figure 2**). Training webinars are held for recruiting sites. These webinars address protocol details such as recruitment goals, participant eligibility, inclusion/exclusion criteria, forms/questionnaires, data entry, and reimbursements. To ensure others outside the DC are aware of its activities, there are also annual meetings that describe all DC projects, accomplishments, how to get involved, or how to access data or materials. The annual meeting is not restricted to members of the

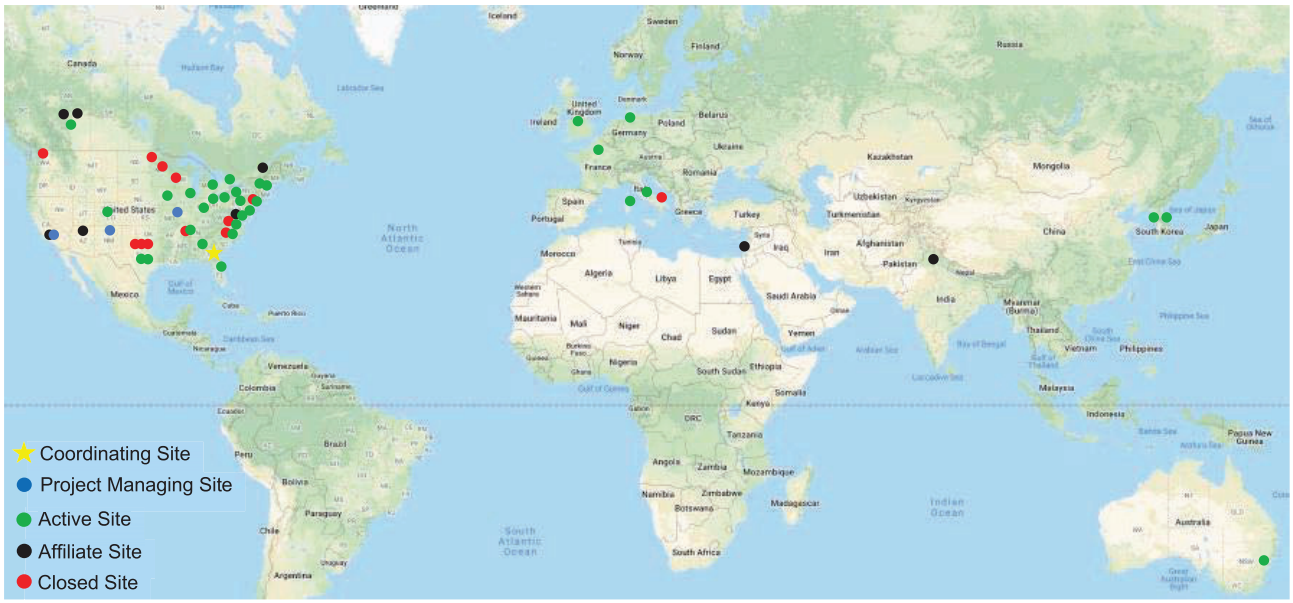

FIGURE 1 | Dystonia Coalition sites. The main coordinating center is at Emory University (star). Sites responsible for directing large multicenter projects are shown in blue. Green shows sites that recruit patients for various studies or are recipients of Pilot Project grants or Career Awards. Affiliate sites are shown in black, and closed sites are shown in red.

DC; it is open to all academic investigators and their staff, PAG members, and representatives from NIH, and industry.

The central coordinating center also manages the financial aspects of paying other centers for specific activities. It uses a direct subcontract to reimburse sites for the effort it takes to manage large clinical research projects (**Figure 3**). All other activities are financially managed through a subcontract with the DMRF. For example, *Recruiting Sites* are paid on a fee-for-service basis for each subject they recruit. The cost per subject depends on the study they were recruited for, and how much effort it takes the site to collect all data and samples for the study. Pilot projects and Career awards are also paid through the DMRF.

Sharing Policies

The DC's open-door policy and broad collaborations have led to the collection of unprecedented amounts of detailed clinical data, video recorded examinations, and DNA samples from large numbers of dystonia subjects from different projects. Data and materials from DC projects are shared broadly with investigators both inside and outside the DC (**Figure 2**). All requests for data or material are granted, provided that the project has local IRB approval and does not directly conflict with ongoing DC studies. Access to DC data and materials is available via three different processes.

Data or materials may be requested directly from the DC through the *Data and Materials Request Form* (www.dystoniacoalition.org). Access to any original unpublished data or materials collected and stored by the DC is supervised by its Executive Committee. Data shared directly by the DC are provided in a de-identified manner, with a code number only. Video recordings of the face are classified as Protected Health Information (PHI) according to Health Insurance Portability and Accountability Act (HIPAA), and therefore are considered identifiable data. These recordings are shared only with extra security provisions. Data and materials collected by the DC also are compliant with the European General Data Protection Regulation (EU GDPR). DC policy requires all investigators requesting data or samples to sign a standard Bylaws agreement, which explicitly outlines the rights and responsibilities for sharing, as well as how investigators who contributed the material are most appropriately acknowledged.

Some of the de-identified key data elements collected by the DC are also sent to the NINDS Human Genetics Resource at Coriell, along with a blood sample for DNA extraction (www.coriell.org). Since the NINDS biorepository is a public resource, data and materials are collected by Coriell from non-DC members too. All materials are distributed by the NINDS Biorepository directly to qualified investigators by direct request.

De-identified data and materials are also stored by the NCATS-designated Data Management & Coordinating Center (DMCC). Sharing of these materials is governed by the policies and procedures of the RDCRN (www.rarediseasesnetwork.org/). Historically, materials stored by the DMCC have been subject to an embargo period during the period of active collection, analysis, and reporting by DC members.

Since 2009, the DC has received 47 requests for data or materials for studies that were beyond the scope of its existing projects. Except for projects that competed

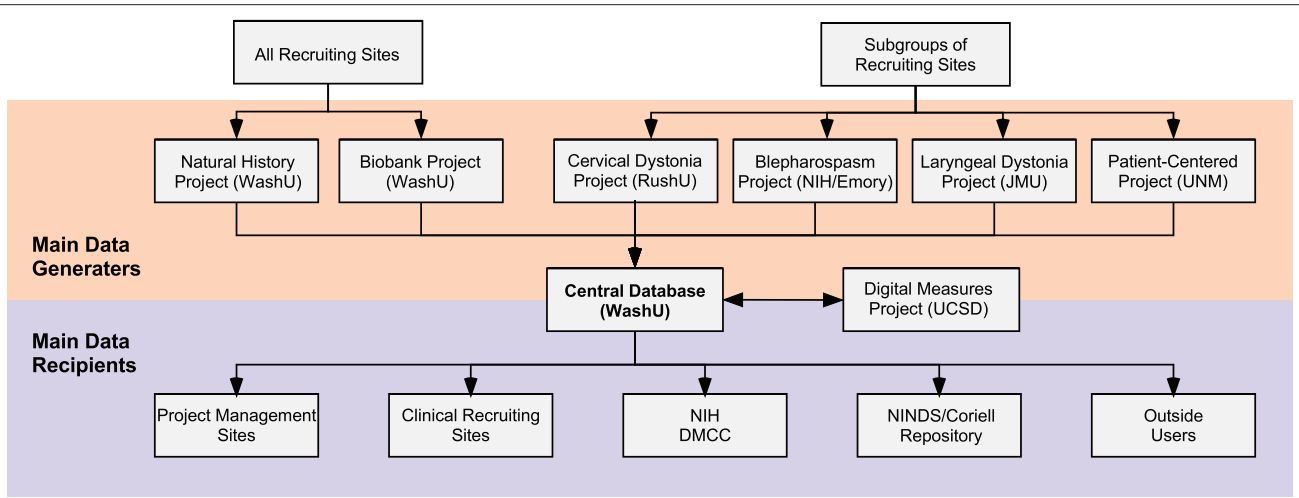

FIGURE 2 | Data collection and sharing. Data for large multicenter projects are organized by individual sites (orange) and collected into a central database for checking, storage, and distribution. All Recruiting Sites (top left) may recruit subjects for the Natural History Project and the Biobank Project. Subgroups of Recruiting Sites are selected to participate in the other large multicenter projects including the Cervical Dystonia Rating Scale Project, The Blepharospasm Diagnosis and Rating Scale Project, the Laryngeal Dystonia Diagnosis and Rating Scale Project, and the Patient-Centered Outcomes Project. The Digital Measures Project analyzes video data collected by all projects. Data submitted to the central database are verified and organized and returned to the sites who manage the large multicenter projects, and are also shared with multiple additional users. For example, Recruiting Sites may request a summary of data they entered. Data are also shared with the National Institutes of Health (NIH) and the Data Management and Coordinating Center (DMCC) of the Rare Diseases Clinical Research Network. Subsets of data are also shared with the National Institute of Neurological Disorders and Stroke (NINDS) Repository at Coriell and with other users by request. DMRF, Dystonia Medial Research Foundation; JMU, James Madison University, RushU, Rush University; UCSD, University of California in San Diego; UNM, University of New Mexico; WashU; Washington University in St. Louis.

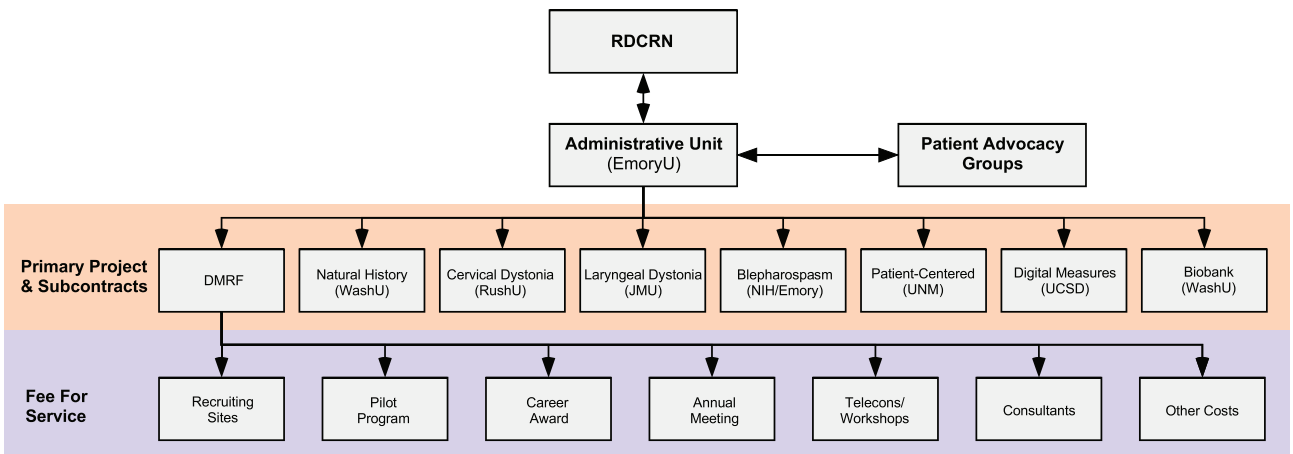

FIGURE 3 | Financial structure. The majority of funding comes from the NIH Rare Diseases Clinical Research Network (RDCRN), although some funding and other resources also come from Patient Advocacy Groups. The Administrative Unit at Emory University provides payments by direct subcontracts to sites that organize large international multicenter projects. The Administrative Unit also has a subcontract with the Dystonia Medical Research Foundation (DMRF), which is responsible for disbursing funds on a fee-for-service basis to Recruiting Sites (depending on numbers of subjects recruited), smaller projects (such as Pilot Grant Projects or Career Awards), meetings, consultants, and others. JMU, James Madison University; NIH, National Institutes of Health USA; NINDS, National Institute of Neurological Disorders and Stroke; RushU, Rush University; UCSD, University of California in San Diego; UNM, University of New Mexico; WashU, Washington University in St. Louis.

directly with ongoing projects, all requests were granted. Many of these projects have since been completed and published, or served as pilot data for grant proposals. Results from some of these projects are summarized in **Tables 3–5**.

Co-authorship Policies

In a large collaborate effort, it is important to appropriately acknowledge the varied effort of the many different individuals involved. Guidelines for these acknowledgments are shared with all DC members in a written document that all

TABLE 3 | Dystonia Coalition career development award program recipients.

Recipient	Institution	Year	Project title
M. Carbon-Corell, Ph.D.	Feinstein Inst, Manhasset, NY, USA	2009	Sensorimotor network activity as a functional imaging marker for dystonia
M. Zurowski, MD	Univ Toronto, Canada	2010	Development of a psychiatric screening tool for cervical dystonia
A. Espay, MD	Univ Cincinnati, Cincinnati, OH, USA	2010	Sensory and emotional processing in psychogenic dystonia: a functional magnetic resonance imaging study
M. Karimi, MD	Washington Univ, St. Louis, MO, USA	2011	Basal ganglia induced plasticity in primary cervical dystonia
T. Kimberley, PT, Ph.D.	Univ Minnesota, Minneapolis, MN, USA	2011	Determining the efficacy of synergistic intervention in focal hand dystonia with repetitive transcranial magnetic stimulation and sensorimotor retraining
B. Berman MD	Univ Colorado, Denver, CO, USA	2012	Functional connectivity of the basal ganglia in primary focal dystonia: a pilot study
A. Wagle-Shukla, MD	Univ FL, Gainesville, FL, USA	2012	Subthalamic nucleus DBS in primary cervical dystonia: a pathophysiological insight
M. Bologna, MD	Univ Rome, Italy	2013	Effects of cerebellar theta-burst stimulation on arm and neck movement kinematics in patients with primary dystonia
S. Pirio-Richardson, MD	Univ New Mexico, Albuquerque, NM, USA	2013	Identification of optimal stimulation site for cervical dystonia symptoms: an exploratory study
D. Peterson, Ph.D.	Univ California, San Diego, CA, USA	2013	The contribution of blinks and spasms to blepharospasm severity
D. Arkadir, MD	Hadassah Univ, Israel	2014	Reinforcement learning in DYT1 dystonia
A. Shaikh, MD	Case Western, Cleveland, VA, USA	2016	Physiology of head tremor in cervical dystonia
K. Udupa, MD	Univ Toronto, Canada	2016	Phase-amplitude coupling of local field potentials in internal globus pallidus in dystonia
M. Hammer, MD	Univ Wisc, Madison, WI, USA	2017	Laryngeal somatosensory evoked cortical potentials in spasmodic dysphonia-an initial study to elucidate abnormal sensory mechanisms in laryngeal dystonia
N. Bukhari-Parlakturk, MD, Ph.D.	Duke Univ, Durham, NC, USA	2020	Non-invasive neuromodulation to study long-term plasticity mechanisms in task-specific dystonia
L. Rocchi, MD	Univ Rome, Italy	2020	Repetitive somatosensory stimulation in focal hand dystonia: a study on inhibitory circuitry plasticity of the somatosensory system and primary motor cortex

investigators sign. In brief, the effort for recruiting patients and conducting study procedures is acknowledged in part by including recruiting investigators on relevant publications. The investigators conducting the study may offer authorship to any relevant study team members. In addition, other investigators who recruited patients essential to the study may also be offered co-authorship. Typical criteria for authorship for recruiting investigators include at least 20 subjects for the study under consideration, and evidence for ongoing and active participation as judged by the recruitment of at least one subject per month. This policy discourages investigators from assuming they will be co-authors for recruiting only a few cases, or from recruiting 20 cases and expecting co-authorship for all future studies. The study organizers notify the site PI of any publication taking advantage of cases they recruited, and the site PI is asked to nominate the most appropriate co-author at the site. If more than 40 cases were recruited, the site PI can nominate two co-authors, and an additional co-author for every additional 20 cases recruited. Authorship must also meet the usual criteria outlined by Council of Science Editors. All other active investigators are listed in acknowledgments.

INTERNATIONAL MULTICENTER DYSTONIA COALITION PROJECTS

Natural History Project

Historically, there has been a relatively limited appreciation of the full phenotypic spectrum and evolution of all types of dystonias. Most evidence came from relatively small studies, often focusing on a single subtype of dystonia. Most studies came from single centers, leading to differences of expert opinion.

A thorough understanding of clinical features and especially their evolution with time is an essential prerequisite for testing any disease-modifying therapies that could halt or slow progression. The aim of *Natural History Project* has been to better characterize the heterogeneity of clinical manifestations in dystonia and how these manifestations evolve over time. Centers in multiple countries collect a standardized dataset that they enter into a central database, and record a standardized

TABLE 4 | Pilot projects funded by the Dystonia Coalition.

Recipient	Institution	Year	Project title	Selected outcomes
M. Ledoux, MD Ph.D.	Univ Tennessee, Memphis, TN, USA	2009	*THAP1* sequence variants in dystonia	(40, 41)
G. DeFazio, MD Ph.D.	Univ Bari, Italy	2010	Diagnostic guidelines and rating tools for blepharospasm	(42–44)
E. Roze, MD	University Hospitals Pitié Salpêtrière, Paris, France	2010	Cerebellar cortical plasticity in focal dystonia	(45)
K. Bhatia, MD FRCP	Univ Coll London, UK	2010	DYT6: A window to mechanisms in primary dystonia?	(46)
D. Peterson Ph.D.	Univ California, San Diego, CA, USA	2010	Increasing CERTainty in blepharospasm	(47)
C. Klein, MD	Univ Lubeck, Germany	2011	Endophenotypes in focal dystonias	In progress
H. Houlden, MRCP, Ph.D.	Univ College London, UK	2011	Neuropathology of DYT1 and DYT6 dystonia	(46)
S. Frucht, MD	Mt. Sinai School of Med, NY, USA	2013	Rating scales for musician's dystonias	(48)
S. Eichenseer, MD	Rush Univ, Chicago, IL, USA	2013	A novel method for rating scale assessment in cervical dystonia	Completed
M. LeDoux, MD Ph.D.	Univ Tennessee, Memphis, TN, USA	2013	Targeted sequencing in primary dystonias	(49)
H. Jinnah, MD Ph.D.	Emory Univ, Atlanta, GA, USA	2013	Resource for induced pluripotent stem cells	In progress
S. Norris, MD	Washington Univ, St. Louis, MO, USA	2013	Functional magnetic resonance imaging in laryngeal dystonia and muscle tension dysphonia	(50)
K. Lohmann, Ph.D.	Univ Luebeck, Germany	2013	Whole genome sequencing in focal dystonias	In progress
M. Zurowski, MD	Univ Toronto, Canada	2014	Development of a psychiatric screening tool for cervical dystonia	(51–53)
J. Mink, MD	Univ Rochester, NY, USA	2015	A rating scale for children with dystonia	Completed
M. Hammer, MA, Ph.D.	Univ Wisconsin, Whitewater, WI	2020	Non-invasive mechanosensory perturbation technique to test voice-related motor and somatosensory cortical responses in spasmodic dystonia	In progress

video shown in **Supplementary Table 2** (69). All data and videos are checked for accuracy and completeness. Since 2009, more than 3,200 cases have been recruited, many of whom continue to be followed. This study has led to several comprehensive articles that have raised awareness of the phenotypic spectrum of dystonia (49, 56–58, 62, 63, 70). This study has also led to several multicenter articles demonstrating progression of adult-onset dystonias over time (12, 61, 68). These studies provide critical baseline information for testing any future disease-modifying treatments, by revealing how many patients would have to be studied, and for how long (68). This project also led to several articles summarizing evidence that available treatments are not as satisfactory as commonly believed (25, 71, 72).

Another outcome from this project relates to the very definition of dystonia. Prior to starting of DC, the definition of dystonia varied in different parts of the world. Furthermore, many subtypes were recognized, but they were organized in different ways. This heterogeneity led to confusion in the interpretation of many studies because of diagnostic uncertainties of the patient cohorts studied. The DC sponsored a series of meetings with PAGs in America and Europe to develop an internationally accepted consensus on its definition (1, 73). The same group also presented a new classification for the many subtypes. The results of the consensus group were published in 2013, they were accepted internationally almost immediately, and the article has been cited more than 1,287 times already. Now, when articles on dystonia are published, most investigators understand exactly what subgroups are being studied.

Clinical Rating Tools for Cervical Dystonia

All clinical trials need good outcome measures. The main goal of this project was to revise and re-evaluate the most popular clinical rating scale for cervical dystonia, the TWSTRS. This scale had known deficiencies in its clinimetric properties including inconsistent scoring among items, double weighting of duration factors, and variable approach to different aspects of the disorder (74, 75). Additionally, the scale neglected non-motor features such as depression and anxiety, which are known to have a strong impact on quality of life (9, 51, 76–82). This project was designed to address these shortcomings by producing and clinimetrically validating the Comprehensive Cervical Dystonia Rating Scale, which has three modules addressing motor features, non-motor features, and quality of life. This project completed recruitment in 2014, with 209 subjects recruited from 10 sites (52, 53). Thus, a tangible deliverable from this project is a fully validated and comprehensive rating scale for both motor and non-motor features of cervical dystonia that can be used in modular format or in whole.

Although the primary goal of this project has been completed, the rich database collected inspired a number of secondary studies (49, 54, 61, 83, 84). Ongoing work involves testing the new scale by experts in other countries for international validation, and development of a teaching tape for its use. Most importantly,

TABLE 5 | Pilot projects supported with Dystonia Coalition data or materials.

Recipient	Institution	Year of request	Topic	Status
Neepa Patel, MD; J. Jankovic, MD	Baylor College of Medicine, Houston, TX, USA	2012	Sensory tricks in cervical dystonia	(54, 55)
M. Zaribaf; G. Kilic-Berkmen, Ph.D.	Emory Univ, Atlanta, GA, USA	2012, 2019	Family structures in dystonia	In progress
A. Shaikh, MD	Emory Univ, Atlanta, GA, USA	2013, 2016	Tremor in dystonia	(56–60)
T. Douglas, Ph.D.; G. Kilic-Berkmen, Ph.D.	Emory Univ, Atlanta, GA, USA	2013, 2019	Patterns of segmental and cervical dystonia	In progress
H. Sarva, MD; S. Bressman, MD	Mt Sinai, New York City, NY, USA	2014	Long term clinical outcomes in DYT1 dystonia	In progress
S. Norris, MD	Washington Univ, St. Louis, MO, USA	2014, 2016	Clinical characteristics of cervical dystonia	(61)
J. Junker, MD	Univ Lubeck, Germany	2015	Non-motor features of dystonia	(62)
J. Junker, MD; N. Bruggeman, MD	Univ Lubeck, Germany	2015-2017	Alcohol-responsiveness in Dystonia	(63)
J. Junker, MD	Univ Lubeck, Germany	2015, 2017	Quality of life in dystonia and its predictors	(9)
A. Shaikh, MD	Case Western Reserve Univ, Cleveland, OH, USA	2015	Quantitative analysis of dysphonia and voice tremor	In progress
S. Pirio-Richardson, MD	Univ New Mexico, Albuquerque, NM, USA	2015, 2017	Patterns of medication use	(14, 31)
L. Scorr, MD	Emory Univ, Atlanta, GA, USA	2016, 2020	Descriptive study of oromandibular dystonia	Manuscript submitted
Y. Sun, Ph.D.	Emory Univ, Atlanta, GA, USA	2016	Genome-wide association study for cervical dystonia	Manuscript in revision
Y. Sun, Ph.D.	Emory Univ, Atlanta, GA, USA	2016	Metabolomics in cervical dystonia	(64)
N. Patel, MD	Henry Ford Health System, Detroit, MI	2016	Substance abuse in dystonia	(65)
A. Espay, MD	Univ Cincinnati, Cincinnati, OH, USA	2016	Tremor in cervical dystonia	(57)
L. Froescheke, Ph.D.	Elmhurst College, Elmhurst, IL, USA	2016	Phonatory breaks in spasmodic dysphonia	(66)
A. Morris, MD	Washington Univ, St. Louis, MO, USA	2016–2018	Acoustic quantification of laryngeal dystonia	(67)
B. Berman, MD	Univ Colorado, Denver, CO, USA	2016, 2017	Psychiatric symptoms in dystonia	Merged with related project
C. Klein, MD Ph.D.	Univ Lubeck, Germany	2017	Penetrance and risk modifying variants in dystonia	In progress
D. Peterson, Ph.D.	UCSD and Salk, LA Jolla, CA, USA	2017	Objective phenotyping in cervical dystonia	In progress
H. Sarva, MD	Cornell, New York City, NY, USA	2017	Gait in blepharospasm	In progress
V. Fung, MD; F. Chang, MD	Westmead Hospital, Australia	2017	Torticollis in hemidystonia	In progress
S. Cho, MD; M. Hallett, MD	NINDS, Bethesda, MD, USA	2017	Sensory tricks in blepharospasm	Merged with related project
B. Berman, MD	Univ Colorado, Denver, CO, USA	2017	Patterns of spread in dystonia	(68)
S. Norris, MD	Washington Univ, St. Louis, MO, USA	2018, 2020	Spread of limb dystonia	(12)
D. Martino, MD	Univ Calgary, Canada	2018	Demographic and clinical predictors of spread in adult-onset idiopathic dystonia	In progress
M. Powell, Ph.D.	Vanderbilt Univ, Nashville, TN, USA	2019	Artificial intelligence for diagnosing, and monitoring laryngeal dystonias	In progress
C. Klein, MD Ph.D.	Univ Lubeck, Germany	2019	Genome-wide association study for dystonia	In progress
N. Harrison, MD; S. Norris, MD	Washington Univ, St. Louis, MO, USA	2019	Shoulder dystonia in upper extremity vs. cervical dystonia	In progress
A. Cotton; H. A. Jinnah, MD Ph.D.	Emory Univ, Atlanta, GA, USA	2019	Patient-reported outcomes vs. clinical rating scales	In progress
E. Reid, Ph.D.	Loma Linda Univ, Loma Linda, CA	2019	Phonetic analysis of spasmodic dysphonia	In progress
K. Lohmann, MD	Univ Lubeck, Germany	2020	Large-scale sequencing of dystonia	In progress
K. Peall, MD	Cardiff Univ, United Kingdom	2020	Predictive models for phenotypic subgroups across the dystonias	Manuscript submitted
L. Scorr, MD	Emory Univ, Atlanta, GA, USA	2020	A descriptive study of blepharospasm	In progress
M. Sousa, MD; S. Fox, MD	Univ Toronto, Canada	2020	Anxiety in cervical dystonia	In progress
M. Tosin, Ph.D. student	Rush Univ, Chicago, IL, USA	2020	Head tremor in cervical dystonia	In progress
N. Koirala, Ph.D.	Haskins Lab, New Haven, CT, USA	2020	Machine learning algorithms for detection of dystonia	In Progress

this project has served as a model for other subtypes of dystonia, where clinical rating scales were less well-developed or absent.

Diagnostic Tools for Laryngeal Dystonia (Spasmodic Dysphonia)

Workshops aimed at delineating research priorities for laryngeal dystonia sponsored by the National Spasmodic Dysphonia Association (NSDA) have repeatedly identified the lack of widely accepted diagnostic criteria and rating tools as major obstacles for clinical and basic research for laryngeal dystonias (85, 86). The goals of this project were parallel to those of the cervical dystonia project described above. However, in the case of laryngeal dystonia, widely accepted rating tools were not available. This project completed recruitment goals in 2015 with 197 subjects that had a detailed evaluation by a multidisciplinary team that included a laryngologist, neurologist, and speech language pathologist. The evaluation included audio and video recordings of voice characteristics during standard voice tasks, audiovisual recordings of laryngoscopy to evaluate the vocal folds with standard tasks, audiovisual recordings of a standard neurological exam, and a blood sample for the DNA biorepository. Initial analyses revealed strikingly poor diagnostic agreement, even among the most experienced experts. As a result, rating tools could not be developed. Instead, a Delphi panel was established to develop more universally acceptable diagnostic criteria (70). Thus, a tangible deliverable of this project is novel diagnostic criteria that may now be used to distinguish subtypes of laryngeal dystonia and to discriminate them from related voice disorders.

This project also led to numerous unexpected directions. For example, several investigators have accessed audiovisual recordings for different types of perceptual or acoustic analyses, including machine learning approaches, which are ongoing.

Diagnostic and Rating Tools for Blepharospasm

Historically, there have been no widely accepted diagnostic criteria for blepharospasm and related craniofacial dystonias. Clinical rating tools were available, but suffered numerous limitations (75). Thus, the goal of this project was to address these needs. Diagnostic criteria and a novel clinical rating scale were first established in pilot studies (42, 43), and then tested in a larger international multicenter design. Eleven centers in four countries recruited 200 individuals with blepharospasm along with individuals with other disorders often mistaken for blepharospasm, such as tics or ptosis. Analyses of these data are nearly complete, and tangible deliverables from this project will be internationally validated diagnostic criteria and clinical rating scale that can support clinical trials.

Patient-Centered Outcomes Project

The projects described above focus mostly on clinician-determined assessments. Sometimes, clinician assessments do not match patient views. For example, the botulinum toxins produce highly significant effects using clinician-rated scales for many types of dystonia, yet patients often report low levels of satisfaction (22, 23, 25, 71, 72, 87), with at least 30% discontinuing use (25). There are many reasons for frequent discontinuation of botulinum toxins, one of which has been dubbed the yo-yo effect (31). Typically, injections are required about every 3 months. Therapeutic benefits emerge within the 1st week and then wear off after 8–16 weeks, creating a cyclical response known as the "yo-yo" effect. Although this cyclical effect is widely known, there are few data describing its frequency, magnitude, and temporal aspects. In order to design clinical trials for any potential add-on therapy, it is essential to have clear understanding of the cyclical responses to botulinum toxins.

The aim of the *Patient-Centered Outcomes Project* is to delineate both between-subject and within-subject variations over time in response to the standard of care treatment with botulinum toxin, from the perspective of the patient. Existing tools to measure efficacy rely on clinical rating scales which are subjective, cumbersome for repeated frequent use, and require extensive expertise to apply. This project aims instead to develop a patient-facing tool on a hand-held electronic device, such as a smartphone. It will focus on the most common dystonias, cervical dystonia, blepharospasm, and laryngeal dystonia. This tool will have 10–15 disorder-specific questions that can be answered on a more frequent basis than existing scales (e.g., weekly), to provide a more direct and more precise temporal appreciation of responses over time. This tool will be ideal for any novel clinical trial that proposes an "add-on" therapy, as well as for comparing durations of responses among different botulinum toxins.

Objective Measures Project

Current tools for diagnosis and assessment of severity depend almost entirely on subjective clinician-rated or patient-rated tools, but advances in modern technology have opened the door to more objective strategies. The *Objective Measures Project* aims to exploit technological advances in digital tools to measure the severity of dystonia. Specifically, this project will exploit advances in computer vision and machine learning to semi-automatically analyze common abnormalities evident in video recordings of blepharospasm, cervical dystonia, and laryngeal dystonia. This new technology could ultimately replace subjective clinical rating scales as outcome measures and enable remote assessment for telemedicine.

In pilot studies, this strategy was used to quantify blinks and spasms among subjects with blepharospasm (47). The results demonstrated good correlations with clinical rating scales. Additional studies will address other manifestations of blepharospasm, such as apraxia of eyelid opening. They will also exploit similar technology for assessment of abnormal head movements in cervical dystonia and abnormal vocal fold movements in laryngeal dystonia. Thus, an important deliverable from this project is a truly objective measure of abnormal movements in dystonia, which may be applied to videos for remote assessments.

Biobank Project

Biomarkers can also provide valuable tools for clinical trials. Genes can provide useful diagnostic tools. However, existing genes account for only a small fraction of all

subjects with dystonia and do not predict penetrance, severity, onset, or rate of progression. There are no practical biomarkers for addressing severity of the dystonias. Neuroimaging abnormalities provide a potential "endo-phenotype" (88, 89), but most are not practical as clinical biomarkers. Several studies also have identified subclinical defects in sensory function (90–92), but their significance and whether they can serve as biomarkers remains unclear.

The aim of the *Biobank Project* is to develop a resource that permits sharing of DNA samples with carefully annotated clinical data. This resource was started with DNA collection in 2009 and currently has more than 3,000 samples. This is the largest and most carefully clinically annotated biobank in the world. DNA samples have been accessed numerous times, for example, for validation studies (49). They have also been accessed for genome-wide association studies (GWAS) and whole exome sequencing (WES) studies, which are ongoing. In 2020, the Biobank added collection of RNA and plasma that will allow for additional studies including transcriptomics, proteomics or lipidomics, epigenomics, and others. A pilot study of metabolomics has provided hints that this approach may be successful (64). The goal is to create a resource for biomarker discovery and validation.

OTHER DYSTONIA COALITION ACTIVITIES

In addition to the large multicenter studies described above, the DC also encourages the development of new investigators and new studies relevant to dystonia. Like the large multicenter projects, these other activities focus on clinical or translational research. A collaborative approach is encouraged. Scientific advisory board members from dystonia PAGs are integrally involved in the review of potential new projects, results of the review process are shared with PAG leaders, and PAGs are involved in final project selection and often funding too.

Career Development Award

The goal of the Career Development Award is to promote career development for investigators interested in research in dystonia and related rare disorders. The DC is particularly interested in applications aiming to exploit data and/or resources already collected by the DC or projects that encourage collaborations by involving different centers of the DC. All applicants may apply regardless whether they are part of the DC or not. US citizenship and affiliation with a US institution are not required. Most awards are directed toward junior faculty interested in developing careers in clinical and translational research in dystonia, but more senior investigators may apply if they are redirecting their efforts from another area of research to dystonia. Advanced postdoctoral fellows who are transitioning to their first faculty appointment may also be considered. Applications are reviewed by the DC, and successful applicants are asked to provide written progress reports. Since 2009, the DC received a total of 40 applications for this award and provided funding for 16 candidates in 4 different countries. A summary of recipients and their projects is provided in **Table 3**. Further information regarding this opportunity can be found at www.dystoniacoalition.org.

Pilot Projects Program

The goal of the Pilot Projects Program is to foster promising pilot studies to a point where they can be published or compete for independent funding. The DC is particularly interested in applications focusing on clinical or translational projects with direct relevance to dystonia, projects aiming to exploit data and/or resources already collected by the DC, and/or projects that encourage collaborations by involving different centers of the DC. Applicants may come from DC centers, although membership in the DC is not required. US citizenship and affiliation with a US institution are not required. Applications are reviewed by the DC, and successful applicants are asked to provide written progress reports. Since 2009, the DC received 80 applications and provided funding for 16 applications in five different countries (**Table 4**). Most projects have received $10,000–50,000 in financial support. Further information regarding this opportunity can be found at www.dystoniacoalition.org.

The DC also supports Pilot Projects by providing DC data and materials, rather than direct financial support. For example, the DC has received more than 47 formal requests for data or materials. All requests were approved except for two, which were requests that overlapped with existing projects (**Table 5**). Further information regarding how to make a request for data or materials is described above in *Sharing Policies*, and at www.dystoniacoalition.org.

SUMMARY AND FUTURE DIRECTIONS

The dystonias are a rare and very heterogeneous group of disorders. They have a profound impact on quality of life, and existing treatments all have significant limitations. New or improved treatments are sorely needed. There are multiple ongoing efforts to improve existing therapies or develop entirely novel approaches. Any novel approach to therapy will require rigorous clinical trials. As a result, the majority of studies by the DC have focused on clinical trial readiness. The DC has addressed the need to identify experts who can participate in trials. It has also conducted multiple studies of clinical heterogeneity among different dystonias, the progressive nature of some dystonias, diagnostic criteria, clinical rating tools, patient-reported outcomes, digital measurement tools, and biomarkers for diagnosis or severity. Along the way, the DC has supported more than 150 articles, numerous grant proposals, and 13 meetings or workshops.

The dystonia community looks forward to a day when all affected individuals can get a rapid and expert diagnosis, and ready access to effective treatments that control the debilitating consequences of the disorder. The dystonia community also looks forward to reaching a better understanding of the etiology and pathogenesis of dystonia, so that truly disease-modifying therapies can be designed to halt progress or even reverse it. For a rare disorder like dystonia, The Dystonia Coalition has demonstrated that broad collaborations and cooperation are essential to these goals.

AUTHOR CONTRIBUTIONS

GK-B and HAJ drafted the initial manuscript. JSP, CCo, MH, SPR, DAP, CCr, LJW, CL, and JT: reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.660909/full#supplementary-material

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REVIEW
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Networks in the Field of Tourette Syndrome

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Gilles de la Tourette syndrome (TS) is a neuropsychiatric neurodevelopmental disorder with the cardinal clinical features of motor and phonic tics. Clinical phenomenology can be complex since, besides tics, there are other features including premonitory urges preceding tics, pali-, echo-, and coprophenomena, hypersensitivity to external stimuli, and symptom dependency on stress, attention, and other less well-defined factors. Also, the rate of comorbidities, particularly attention deficit hyperactivity disorder and obsessive-compulsive disorder, is high. Mirroring the complexities of the clinical course and phenomenology, pathophysiological findings are very diverse, and etiology is disputed. It has become clear, though, that abnormalities in the basal ganglia and their connections with cortical areas are key for the understanding of the pathophysiology and as regards etiology, genetic factors are crucial. Against this background, both adequate clinical management of TS and TS-related research require multidisciplinary preferably international cooperation in larger groups or networks to address the multiple facets of this disorder and yield valid and useful data. In particular, large numbers of patients are needed for brain imaging and genetic studies. To meet these requirements, a number of networks and groups in the field of TS have developed over the years creating an efficient, lively, and supportive international research community. In this review, we will provide an overview of these groups and networks.

Keywords: Gilles de la Tourette syndrome, European Multicenter Tics in Children Studies, European Society for The Study of Tourette Syndrome, the Tourette Association of America, research networks

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TS AS A PROTOTYPE NEUROPSYCHIATRIC NEURODEVELOPMENTAL SPECTRUM DISORDER

Gilles de la Tourette syndrome (TS) is a multifaceted neuropsychiatric disease defined by multiple motor and at least one phonic tic starting before the age of 18 and lasting for at least 1 year (1). Disease onset is usually in early childhood (2). Clinical phenomenology varies widely with tic repertoire reaching from simple motor and phonic tics including, for instance, eye blinking, mouth pouting, throat clearing, or sniffing to complex movements or vocalizations like body turning or squatting, or the utterance of single words or phrases (3). Although public perception is strongly dominated by coprophenomena, i.e., the utterance of swear words (coprolalia) or the execution of obscene gestures (copropraxia), coprophenomena are present in only about 20% of patients (4, 5).

While first motor tics usually occur around the age of 6, phonic tics tend to emerge several years later (6). However, there is also a group of children who first develop phonic tics, which may or

may not be followed by the occurrence of motor tics. Both tic repertoire and intensity fluctuate over time, i.e., they "wax and wane" (6). In the majority of cases, tics are preceded by various

perceptual phenomena referred to as premonitory urges (7). They typically decrease after tic execution (6, 8–10). Moreover, tic severity is influenced by cognitive processes. For instance, while there is an ongoing discussion on what kind of stress might result in an increase or decrease of tic severity (11), it is undisputed that distraction can lead to an amelioration of symptoms (12, 13). Many TS patients suffer from psychiatric comorbidities. About 90% of TS patients have comorbidities including attention deficit, hyperactivity disorder, and obsessive-compulsive disorder (40%) (14).

In most cases, the disease course is benign. Following a peak in pre-puberty, or puberty, symptoms usually considerably improve until the age of 18 (6). Thus, more often than not, therapy concepts based on counseling are sufficient. However, TS can impair psychosocial development, can lead to significant secondary morbidity and impair quality of life (15, 16). In about 20% of cases symptoms persist into adulthood and then often affect personal life markedly (15, 17, 18). However, it has to be pointed out that data on the clinical course, particularly evolution of symptoms, severity fluctuations and percentage of remissions are limited, particularly because longitudinal studies are scarce.

The gold standard clinical intervention is comprehensive behavioral intervention for tics including habit reversal therapy with the core components awareness training and the acquisition of a competing response that is incompatible with the tic (19). Exposure and response prevention is an alternative behavioral intervention (20). The mainstay of pharmacological treatment are antipsychotic drugs including tiapride or aripiprazole (21, 22). When tics affect few muscles or muscle groups, botulinum toxin injections might be used (23, 24). Deep brain stimulation is a treatment option in severely affected TS patients refractory to conventional therapy. Most frequently used targets are the centro-median-parafascicular complex of the intralaminar thalamus (25) and the globus pallidus internus (26–28).

Regarding the underlying pathophysiology, there is still no uniform concept and several explanatory approaches coexist. Research work dates back to the late nineteenth century. While in the early part of the twentieth century until the 1970s, TS was primarily considered a psychiatric disorder (29), neurophysiological findings (30), as well as successful medical treatment with antipsychotic drugs (22) and accumulating genetic data (31), have changed this view (32). TS is now conceptualized as a neurodevelopmental neuropsychiatric spectrum disorder predominantly of genetic origin (33). The role of environmental factors and their interaction with genetic predisposition, though, is unclear.

Given its nature as a multifaceted, often complex disorder affecting both children and adults, it comes with no surprise that abnormalities in patients with TS have been delineated in different research fields. For instance, at a neuroanatomical level, alterations have been described in cortical regions including reduced gray matter volume in prefrontal and sensorimotor areas (34), or the basal ganglia (e.g., reduced caudate nucleus volume) (34, 35).

Neurophysiologically, sensorimotor abnormalities, including altered sensory processing such as deficient prepulse inhibition (36) serving as a measure for sensorimotor gating (37), and altered short afferent inhibition as a measure for sensorimotor integration (38, 39), are a common theme in TS research.

In the field of cognitive psychology, a higher tendency for habit formation (40), abnormalities concerning interoceptive awareness (41), and altered inhibitory control (42) have emerged as relevant findings in TS. Also, abnormally increased binding between actions and perceptions has been shown in these patients (43). Furthermore, many family studies have been conducted suggesting that TS is largely a genetic disorder (44).

Against the background of the natural course of TS and numerous findings derived from various research fields, it has become clear that different specialties, particularly neurology, child and adolescent and adult psychiatry, pediatric neurology, (neuro-) genetics, and research teams covering different fields of neuroscience, e.g., neuroanatomy, neuroimaging, neurophysiology, neurogenetics, (cognitive) psychology, need to join forces to better understand the neurobiological background of TS over the lifespan and to develop more individualized management strategies. Mutual exchange of information between specialties and research fields has become a prerequisite for innovative and efficient research.

NEED FOR INTERDISCIPLINARY AND GLOBALLY CONNECTED NETWORKS

For a long time, scientific findings and breakthroughs have been associated with exceptional scientifically outstanding individuals. Gilles de la Tourette, who first delineated TS as a neuropsychiatric syndrome, is one of many examples (45). However, as scientific knowledge and therapeutic options are constantly accumulating globally rather than locally, there is a strong need for structures and organizations connecting the different researchers to facilitate international collaboration and exchange.

This is corroborated by the fact that the number of multiauthored publications has increased (46). Before the Second World War, most cited papers were written by single authors. Since the 1950s, the number of collaborative papers has risen steadily (47). Of note, research dealing with scientific and economic networks and collaborations has also evolved with focuses not only on the number of people engaged within networks but also their composition and inner structure (48).

Two opposing views have emerged (48). On the one hand, high diversity of network participants is considered

Abbreviations: COST, Cooperation in Science and Technology; EMTICS, European Multicenter Tics in Children Studies; ESSTS, European Society for The Study of Tourette Syndrome; GGRI, Gilles de la Tourette Syndrome GWAs Replication Initiative; GWA, genome-wide association study; TAA, The Tourette Association of America; TIC Genetics, Tourette International Collaborative Genetics; TS, Tourette syndrome; TSAICG, Tourette Syndrome Association International Consortium for Genetics; TS-Eurotrain, Structuring EUROpean TRAINing capacities for neurodevelopmental disorders; TSGeneSEE, Tourette Syndrome Genetics-The Southern and Eastern Europe Initiative.

advantageous, potentially increasing the spectrum of skills and perspectives and thus fostering the capacity for problem solving (49). Also, it is argued that high diversity within a team results in cross-fertilization processes due to a combination of different perspectives and expertise (50–52). On the other hand, it has been put forward that communication between team members in more heterogeneous groups might be more complicated and efficiency reduced due to a lack of shared identity compared to homogeneous groups (48).

In addition to these more general and theoretical considerations, optimal group, i.e., network composition, is obviously also determined by the area of research and the overarching aims of respective networks. Given the multifaceted nature of TS with respect to clinical manifestation including a large age range and etiological/pathophysiological background, TS research networks should ideally be composed of international, multiprofessional groups.

NETWORKS IN THE FIELD OF TOURETTE SYNDROME

Patient Organizations

First and foremost, a number of national patient organization promote and support patient-related matters and also international research. For a comprehensive overview of various activities in many different countries, please see https://www.essts.org/directory.

Examples are the Tourette Association of America (USA), the Caribbean Tourette Association, Asociación Argentina para el Síndrome de Tourette, the Israel Tourette Association, the Tic Disorders and Tourette Syndrome Association of China, the Tourette Association Japan, the Tourette Syndrome Association of Australia, Tourette Action (UK), the Association francaise du Syndrome de Gilles de la Tourette, and the German Tourette Association.

For instance, founded in 1972, The Tourette Association of America (TAA) is the largest TS patient organization worldwide (https://philanthropynewsdigest.org/npo-spotlight/tourette-association-of-america). It serves the purpose of financing research, educating both patients and professionals, and creating awareness of TS. Up to now, more than $22 million have been awarded to over 450 research projects in 16 countries (https://tourette.org/about-us/mission-and-history/). In addition, public relations activities are a major component of its work. In this context, the Tourette Association of America Youth Ambassador Program was created. In this program, children suffering from TS are being trained in proliferating up-to-date information on their disease in their social surroundings (https://tourette.org/about-tourette/overview/living-tourette-syndrome/teens-13-17/youth-ambassador-program/).

In the UK, in 1980, the Tourettes Action was brought into being by a group of parents of affected infants, first known as Tourette Syndrome Association (UK). The primary objective of this organization was to provide mutual assistance for coping with everyday life and to promote social acceptance of TS patients. In 2006, the association moved its headquarters to London, and in 2008, the name was changed in Tourettes Action. Besides supporting patients and relatives, the aim has also become to promote research. Tourette Action is also active in organizing workshops, conferences, and activities for young people and offers subsided CBITS training for clinicians and professionals across the UK (Tourettes-action.org.uk).

The German Tourette Association (Tourette-gesellschaft.de) was founded in 1993. Its declared aim is to provide current and valid information on TS and to communicate treatment options. The association has, for instance, developed a geographical map providing an overview of specialists and clinicians, simplifying the search for medical support. In addition, it provides help in finding support groups and organizes activities for young people with TS.

Outreach Activities

An example of TS-related outreach activities by professional artists is Manhattan's La MaMa Experimental Theater Club that presented the play *The Elephant in Every Room I Enter*, a play about the challenges of working as an actor with Tourette Syndrome. The Agency of Surplus, a neuroscience/theater/performance/film group based in Hamburg, Germany, can serve as an example of a multiprofessional network comprising professionals from the field of neurology, neuroscience, philosophy, theater sciences/performance studies, stage design, and film aiming at promoting and proliferating outreach activities related to TS. The Agency of Surplus has produced theater plays where patients with TS participated as performers. For instance, the theater play "Theater of disgraceful people" (*Das Theater der infamen Menschen*) (https://www.ballhausost.de/produktionen/theater-of-disgraceful-people/) was part of the official program of the International Parkinson and Movement Disorder Society Congress in Berlin in 2016. In 2020, the Agency of Surplus produced an international documentary film ("TICS"), a road movie, where three patients with TS first visited the Salpêtrière Hospital in Paris, where Tourette syndrome was first described and which is still a major center for Tourette research worldwide, then traveled to the Universities of Cologne, Hannover, and Lübeck (Germany) and ultimately to Lapland, where the reception of tics in a different social context was explored. The documentary also provides information on behavioral treatment in TS including new approaches, for instance, attention training techniques (53).

Research Organizations

There are several international scientific organizations dedicated to the coordination of research related to TS. An overview is given in **Table 1**.

The European Society for The Study of Tourette Syndrome (ESSTS) is a pan-European society initially founded in Copenhagen, Denmark, in 2000 by Professor Mary Robertson. Its main aims include promoting research, educating professionals, patients, and their relatives, and creating awareness of TS. This is achieved, for example, by providing funds, organizing targeted events like training schools transferring knowledge to young doctors or researchers, or developing best-practice

TABLE 1 | Examples of research initiatives in the field of Tourette syndrome.

	Name *(Abbreviation)*	Countries involved	Year of Foundation	Objectives/aims	Notes
Scientific organizations					
1	Tourette Syndrome Association International Consortium for Genetics *(TSAICG)*	Canada, Germany, Netherlands, UK, USA	1986	Research on the genetic underpinnings of TS	
2	The European Society for the Study of Tourette Syndrome *(ESSTS)*	Pan-European	2000	Promoting research, educating professionals, patients & relatives, create public awareness	
3	The European Network for the Study of Gilles de la Tourette Syndrome	Pan-European	2010	Share knowledge, improve pan-European coordination of research, create public awareness	Inactive
4	TEC4Tic Research Unit	Germany, Hungary	2019	Investigation of the role of perception-action integration in TS	
5	Gilles de la Tourette Syndrome GWAs Replication Initiative *(GGRI)*	Austria, Canada, France, Germany, Greece, Hungary, Italy, Poland, USA		Collaboration and data sharing for genome-wide association studies	
6	Tic Disorders and Tourette Syndrome Study Group	Canada, France, Germany, Netherlands, Spain, UK, USA	2019	Increasing international collaborative research on TS, research on epidemiology and pathophysiology of TS	
7	Tourette Syndrome Genetics - The Southern and Eastern Europe Initiative *(TSGeneSEE)*	Albania, Greece, Hungary, Italy, Poland, Russia, Ukraine		Research on TS genomics, building a central repository of biomedical data	Inactive
Multi-center studies					
8	European Multicenter Tics in Children Studies *(EMTICS)*	Pan-European	2013	Examine the role of environmental factors on TS onset and course	
9	TS-Eurotrain	Pan-European	2012	Investigating the etiology and pathophysiology of TS	Inactive
10	Tourette International Collaborative Genetics Study *(TIC Genetics)*	Europe, South Korea, USA	2011	Sharing clinical data and biomaterials from patients and relatives, research on genetic architecture of tic disorders, building a central repository of biomedical data	

guidelines for the diagnosis and treatment of TS (21, 54–56). Meetings are held annually, and officers are elected periodically. Another important area of activity is developing alliances with patient support groups. The success of these efforts is evidenced by the fact that in 2012 "The First International Meeting of Tourette Syndrome Support Groups" took place. Particularly noteworthy was the cooperation between ESSTS and the European Cooperation in Science and Technology (COST), which in turn is a funding organization providing funds for scientists all over Europe. The European Network for the Study of Gilles de la Tourette syndrome, established in 2010 and active until 2014, can be regarded as one of the outcomes of this cooperation, aiming to share knowledge, to improve coordination of research at a European level, and to create public awareness of this disease (57).

In 2011, ESSTS was awarded a European grant amounting to €6 million with the objective to promote the investigations of immunological, infectious, and genetic processes in children and adolescents suffering from TS (https://cordis.europa.eu/article/id/92780-linking-tic-disorders-with-infection/de). In this context, in January 2013, a longitudinal observational multicenter study, the European Multicenter Tics in Children Studies (EMTICS) involving 17 clinical centers, were initiated (58). EMTICS was designed to examine the new appearance of tics within a group of children and adolescents with first-degree relatives suffering from tics, as well as the course of tics in previously diagnosed cases. Therefore, this study is composed of two different arms called "ONSET" and "COURSE" (58). The ONSET cohort encloses 260 children aged between 3 and 10 years, the COURSE cohort includes 715 children and adolescents between the ages of 3 and 16 years (58). The main focus of this study is the role of environmental factors including new infections caused by group A *Streptococcus*, related autoimmune processes, or group A *Streptococcus* carriage status on tic onset or course (58). Furthermore, the impact of other recent infections, psychosocial stress and pre- and perinatal adversities are being looked at (58). EMTICS is the largest observational study investigating new-onset tics within an at-risk population and the course of TS in already affected patients (58). The study was terminated in June 2018. The as-yet most relevant finding is that there is no evidence to indicate a relationship between new group A *Streptococcus* infections and the onset or course of tics (https://cordis.europa.eu/project/id/278367/reporting) (59). In addition to these important insights, through close cooperation of many different clinical centers all over Europe, new infrastructure and cooperation have developed (58).

With support from the European Commission, a research group of the ESSTS, the Marie Curie Training Network called TS-Eurotrain (Structuring EUROpean TRAINing capacities for neurodevelopmental disorders) was founded in 2012 with the

objective to set up a database on genetic and environmental factors underlying TS (60).

Against the background of accumulating evidence suggesting that TS is predominantly a genetically determined disorder (61, 62), several national and international initiative consortia have been founded with the aim to unravel the genetic basis of TS.

As early as 1986, the Tourette Syndrome Association International Consortium for Genetics (TSAICG) was founded bringing together genetic researchers from the Netherlands and the USA to exchange knowledge and data (63). Initial projects focused on chromosomal aberrations or mutations in single genes (64, 65). After realizing that TS is not a monogenetic disease, the consortium was enlarged to include additional sites in the USA, Canada, Germany, the UK, and the Netherlands (63). Joint endeavors have led to the discovery of a number of rare variants of pathogenic relevance in individual families or small cohorts (66–68).

In this context, genome-wide association studies (GWAs), are of prime importance. Using this method, the whole genome is analyzed looking for intragroup variations in genomic DNA in the form of an altered single nucleotide. They are referred to as single nucleotide polymorphisms and are stored in databanks in single centers. It rapidly became apparent that sample sizes of single centers were far too small to obtain reliable results. Therefore, the different centers started to join forces combining their data in meta-analyses (69).

This progress has further fostered the development of large cooperative networks and open-access repositories (70). This resulted in the foundation of the Gilles de la Tourette Syndrome GWAs Replication Initiative (GGRI).

Likewise, the Tourette International Collaborative Genetics (TIC Genetics) Study funded by the American National Institute of Mental Health was launched in 2011. This ongoing project comprises more than 20 sites from the USA, Europe, and South Korea (70). By sharing biomedical data for GWAs, TIC Genetics and TSAICG closely cooperate (63). TIC Genetics follows two main approaches. First, genetic alterations shared by affected individuals within affected families are analyzed focusing on familial genetic variants. Second, trios, consisting of TS patients and their unaffected parents are investigated to identify *de novo* mutations using exome sequencing. Data collected in this way also allow to draw conclusions on the interaction between perinatal environmental factors and genetic alterations (70). Medical and biomedical data collected from ∼2,000 people is stored in a shared repository domiciled within the National Institute of Mental Health Center for Collaborative Genomics Research on Mental Disorders, USA, and is accessible to a broader scientific community. This approach has been very fruitful, leading, for instance, to the discovery that *de novo* likely gene disrupting variants and copy number variations contribute to the genetic risk in TS (68, 71).

Another network focusing on genetic investigations in TS was established in Southern and Eastern Europe encompassing researchers from seven different countries (Greece, Hungary, Italy, Albania, Poland, Russia, and Ukraine), called Tourette Syndrome Genetics-The Southern and Eastern Europe Initiative (TSGeneSEE). Similar to TIC genetics, its objective was to build a central repository of biomedical data, predominantly based on trio whole exome sequencing in *de novo* TS patients and their parents enabling scientists to further investigate genetic variants associated with TS. It is not active anymore. Data are stored in a preexisting databank in Hungary (http://tsgenesee.mbg.duth.gr/index.html).

The Tic Disorders and Tourette Syndrome Study Group of the International Parkinson and Movement Disorder Society (https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Study-Groups/Tic-Disorders-and-Tourette-Syndrome-Study-Group.htm) aims at joining efforts to increase international collaborative research with regard to epidemiology and pathophysiology of tic disorders, enhancing the identification of biomarkers, investigating the efficacy and safety of novel treatment approaches, and accelerating the route toward personalized treatment plans by improving patient selection and increasing access to established treatments. More specifically, the group is currently working toward a consensus definition of tics and addresses perception and knowledge on tic disorders across the international plenum of movement disorders professionals with a particular view to clinical presentation, pathophysiology, assessment methods and tools, and treatment methods, including access to different types of treatment. Also, it aims at developing recommendations of instruments to capture comorbid conditions for clinical and research purposes and operationalizing clinically and scientifically relevant definitions, including, for instance, refractoriness to treatment. The study group includes adult and pediatric neurologists, child/adolescent and adult psychiatrists, neuropsychologists, neurosurgeons, as well as scientists involved in TS research, e.g., computational neuroscientists, behavioral scientists, and pharmacologists. The group aims also to include representatives of health professionals, in particular behavioral therapists, social workers, psychologists, and occupational therapists.

The TEC4Tic Research Unit (Cognitive Theory for Tourette syndrome—a novel perspective) (https://www.tec4tic.uni-luebeck.de) founded in 2019 and funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, FOR 2698) comprised researchers from different fields, i.e., neurology, child/adolescent and adult psychiatry, (neuro-)pediatrics, cognitive and experimental psychology, neurophysiology, mathematics, and computational neuroscience based at the Universities of Lübeck, Dresden (Germany) and Budapest (Hungary). The Unit has been set up in the framework of the theory of event coding representing a cognitive theory for perception-action integration paying particular attention to their interdependency (72). The core hypothesis is that binding, or coupling, between perceptions and actions is particularly strong in TS (3, 43, 73, 74), because, clinically, there is a strong link between motor phenomena (tics) and perceptual abnormalities (premonitory urges preceding tics) (6). In addition to EEG, the Research Unit also applies functional and structural imaging, neuronavigated transcranial magnetic stimulation, electrical stimulation, and functional near-infrared spectroscopy addressing perception-action processing in different domains (visual and somatosensory), studying the neuropharmacology and developmental trajectories of perception-action processing,

investigating effects of the social context on binding and also delineating the neural basis of coprophenomena.

SUMMARY

Given its complex phenomenology, etiology, and pathophysiology requiring expertise from different clinical disciplines including neurology, psychiatry, child and adolescent psychiatry, and adult psychiatry, as well as different research area, for instance, neuroanatomy, neurophysiology, neurogenetics, and cognitive psychology, both clinical care and research activities in TS need to be organized and structured in multidisciplinary, multiprofessional, and globally interconnected networks. A number of overarching umbrella organizations like the TSAICG and ESSTS coordinating international research and ensuring an exchange of information between groups already achieve these goals.

For many future research projects, particularly those requiring large amounts of data, e.g., genetic or brain imaging studies, successful realization, i.e., generation of valid and meaningful data, will crucially depend on international cooperation within structured and mutually beneficial networks. Against the background of the developments and achievements outlined in this review, this has now become a very realistic scenario, not least because of an overall friendly and supportive atmosphere and attitude in the field of TS research.

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AK, MK, and AM: gathering information, writing of the first draft, and review and critique. AB: gathering information, AW, TB, CB, and VR: review and critique. All authors: contributed to the article and approved the submitted version.

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*Describe*PSP and *ProPSP*: German Multicenter Networks for Standardized Prospective Collection of Clinical Data, Imaging Data, and Biomaterials of Patients With Progressive Supranuclear Palsy

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Background: The German research networks *DescribePSP* and *ProPSP* prospectively collect comprehensive clinical data, imaging data and biomaterials of patients with a clinical diagnosis of progressive supranuclear palsy. Progressive supranuclear palsy is a rare, adult-onset, neurodegenerative disease with striking clinical heterogeneity. Since now, prospective natural history data are largely lacking. Clinical research into treatment strategies has been limited due to delay in clinical diagnosis and lack of natural history data on distinct clinical phenotypes.

Methods: The *DescribePSP* network is organized by the German Center for Neurodegenerative Diseases. *DescribePSP* is embedded in a larger network with parallel cohorts of other neurodegenerative diseases and healthy controls. The *DescribePSP* network is directly linked to other *Describe* cohorts with other primary diagnoses of the neurodegenerative and vascular disease spectrums and also to an autopsy program for clinico-pathological correlation. The *ProPSP* network is organized by the German Parkinson and Movement Disorders Society. Both networks follow the same core protocol for patient recruitment and collection of data, imaging and biomaterials. Both networks host a web-based data registry and a central biorepository. Inclusion/exclusion criteria follow the 2017 Movement Disorder Society criteria for the clinical diagnosis of progressive supranuclear palsy.

Results: Both networks started recruitment of patients by the end of 2015. As of November 2020, $N = 354$ and 269 patients were recruited into the *DescribePSP* and the *ProPSP* studies, respectively, and $N = 131$ and 87 patients received at least one follow-up visit.

Conclusions: The *DescribePSP* and *ProPSP* networks are ideal resources for comprehensive natural history data of PSP, including imaging data and biological samples. In contrast to previous natural history studies, *DescribePSP* and *ProPSP* include not only patients with Richardson's syndrome, but also variant PSP phenotypes

as well as patients at very early disease stages, before a diagnosis of possible or probable PSP can be made. This will allow for identification and evaluation of early biomarkers for diagnosis, prognosis, and progression.

Keywords: disease networks, progressive supranuclear palsy, corticobasal syndrome, rare neurological disease, natural history, biobank

INTRODUCTION

In 2015, *two* German multicenter research networks, *DescribePSP* and *ProPSP*, were set up by the authors with the ultimate goal to improve early clinical diagnosis, monitoring, and prediction of disease progression in patients with progressive supranuclear palsy (PSP).

DescribePSP and *ProPSP* are acronyms. DEsCRIbE stands for "DZNE Clinical Register Study of Neurodegenerative Disorders." DescribePSP is the register study for PSP patients. ProPSP stands for "Prospective observational study to investigate demography, clinical course and biomarkers of PSP."

PSP is a rare neurodegenerative disease, defined by the unique neuropathology, which is characterized by intracellular aggregation of the microtubule-associated protein tau (1). Onset of first symptoms occurs usually between the 5th and the 7th decade and mean disease duration is approximately 8 years (2, 3). Clinico-pathological studies suggest that PSP has previously been underdiagnosed during lifetime and that the correct ante-mortem diagnosis of PSP has been delayed for several years, due to a lack of specific symptoms at early disease stages and due to heterogeneous clinical presentations (2, 4). Variant clinical phenotypes of PSP (vPSP) have been described in multiple clinico-pathological studies, which differ from the classical Richardson's syndrome not only with regard to the initial clinical manifestation, but also with regard to progression rate and survival (5). Former clinical diagnostic criteria for PSP, the National Institute of Neurological Disorders and Stroke and the Society for PSP criteria [NINDS-SPSP criteria (6)] preferentially recognized patients with Richardson's syndrome, and therefore lacked sensitivity for the broader spectrum of PSP manifestations (7). Although treatment strategies are presently restricted to symptomatic therapies, several tau targeting therapies are being developed for PSP (1). These developments further increase the need for correct and early clinical diagnosis of PSP and reliable prediction of disease progression, to set the stage for early disease-modifying interventions.

To reduce diagnostic delay and to improve diagnostic sensitivity, the new Movement Disorder Society clinical diagnostic criteria for PSP, short MDS-PSP criteria, introduced the diagnostic category "suggestive of PSP" (s.o. PSP) alongside with "possible PSP" and "probable PSP" (8). S.o. PSP represents the lowest level of diagnostic certainty and significantly increases diagnostic sensitivity and reduces time to diagnosis for PSP according to retrospective studies with autopsy cases (9–11). However, the sensitivity, specificity, positive and negative predictive value of the diagnosis of s.o. PSP has not been studied prospectively so far.

TABLE 1 | Methodological differences between *DescribePSP* and *ProPSP*.

	DescribePSP	***ProPSP***
Organization	German Center for Neurodegenerative Diseases (DZNE)	German Parkinson's Association (DPG)
Recruitment centers	Affiliated with the DZNE (**Figure 1**)	Affiliated with the DPG (**Figure 1**)
Web-based database	WebSpirit	MACRO, Elsevier®
Central imaging platform	XNAT	Not provided
Follow-up schedule	12-months follow-ups	6-months follow-ups
Parallel cohorts	Other neurodegenerative diseases and healthy controls	Not provided
Brain banking	Central brain banking program	Individual neuropathological institutes

The main goals of the *DescribePSP* and the *ProPSP* networks are to collect prospective natural history data of patients with PSP, to prospectively validate the new MDS-PSP criteria, and ultimately to improve early clinical diagnosis, monitoring, and prediction of disease progression in patients with PSP. These two networks collaborate synergistically and were set up separately mainly for organizational reasons.

In this paper, we outline the *DescribePSP* and the *ProPSP* network structures as well as study designs and achievements of both networks up to now.

METHODS

DescribePSP and *ProPSP* share many similarities with regard to methodology, including criteria for patient inclusion and collection of clinical data, imaging data and biomaterials. However, there are some organizational and methodological differences between both cohort studies. For a better overview, differences between *DescribePSP* and *ProPSP* are also summarized in **Table 1**.

Network Structures

DescribePSP is organized by German Center for Neurodegenerative Diseases (DZNE), which is a member of the Helmholtz Association and is funded by the German Federal Ministry of Education and Research (BMBF) and the German federal states (Bundesländer) in which DZNE sites are located. The steering committee of the *DescribePSP* network consists of the principal investigator (G. Höglinger, Deputy G. Respondek)

and a representative of the database management, as well as a principle investigator representative per recruitment center.

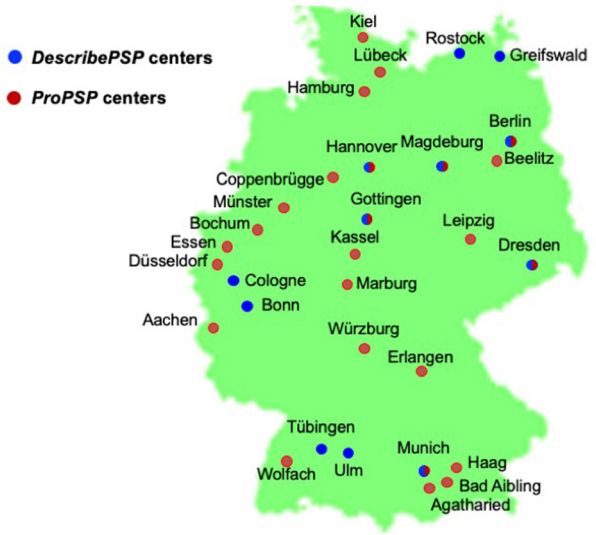

FIGURE 1 | Geographic distribution of *DescribePSP* and *ProPSP* centers throughout Germany.

DescribePSP recruitment centers currently comprise of 11 tertiary care centers with expertise in movement disorders and other neurodegenerative diseases, which are located in Berlin, Bonn, Dresden, Gottingen, Greifswald, Hanover, Cologne, Magdeburg, Munich, Rostock, and Tubingen (**Figure 1**). The central data management and the central biorepository of *DescribePSP* are located at the DZNE headquarters in Bonn. The *DescribePSP* study is embedded in a larger network with parallel *Describe* cohorts that recruit other neurodegenerative diseases, including Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD), motoneuron disease (MND), ataxias, and vascular diseases, including stroke, cerebral amyloid angiopathy, as well as healthy controls (**Figure 2**).

ProPSP is organized within the German Parkinson and Movement Disorders Society (https://www.parkinson-gesellschaft.de), which is a non-profit organization based in Berlin. The *ProPSP* network is also supported by the German PSP Association (https://www.psp-gesellschaft.de), which is a patient support group and a non-profit organization.

The steering committee of the *ProPSP* network consists of the principal investigator (G. Höglinger, Deputy G. Respondek), a representative of the database management, and a representative of the recruitment centers elected by a simple majority.

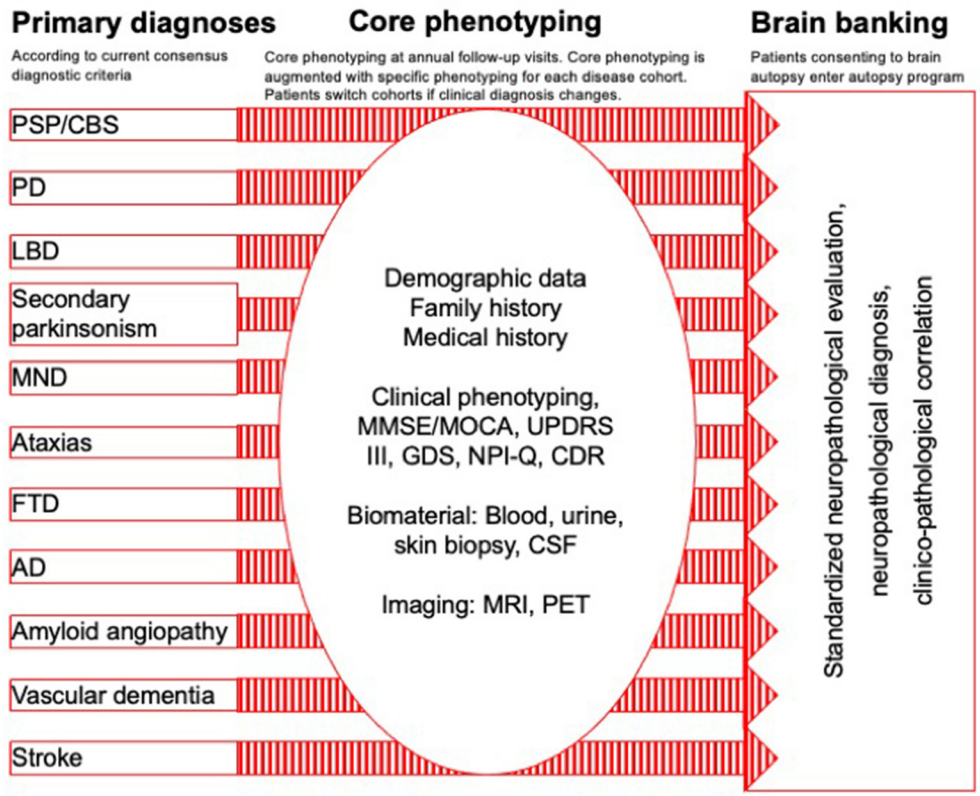

FIGURE 2 | Describe parallel cohort design: primary diagnoses, core phenotyping, and brain banking.

The *ProPSP* study currently comprises of 25 centers with expertise in movement disorders and other neurodegenerative diseases, which are located in Aachen, Agatharied, Bad Aibling, Beelitz, Berlin, Bochum, Coppenbrugge, Dresden, Dusseldorf, Erlangen, Essen, Haag, Hamburg, Hanover, Kassel, Leipzig, Lubeck, Magdeburg, Marburg, Munich, Munster, Rostock, Ulm, Wolfach, and Wurzburg (**Figure 1**).

The study sites Berlin, Dresden, Gottingen, Hanover, Magdeburg, and Munich have access to both networks (**Figure 1**) and recruit patients randomly either into the *DescribePSP* or into the *ProPSP* study.

Study Design

DescribePSP and *ProPSP* are both multicenter longitudinal observational studies for PSP in Germany. Both networks prospectively follow up patients with a clinical diagnosis of PSP and collect comprehensive longitudinal natural history data, imaging and biomaterials according to the same core protocol.

Each network runs a central web-based data registry and a central biorepository.

Inclusion Criteria

Since 2017, inclusion criteria for both studies are the MDS-PSP diagnostic criteria (8). As defined by the MDS-PSP diagnostic criteria, patients with corticobasal syndrome (CBS) receive a diagnosis of s.o. or possible PSP with predominant CBS (PSP-CBS) (8) and are therefore also recruited into both cohorts.

At the time of the initiation of both studies in 2015 and until 2017, inclusion criteria for both studies were the NINDS-SPSP criteria (6). Patients that meet the NINDS-SPSP criteria also meet the MDS-PSP diagnostic criteria.

Recruitment of Participants

Participants are consecutively recruited into both studies through referrals from the associated outpatient or inpatient clinic of the recruitment centers. Patients who meet the inclusion criteria and give written informed consent are enrolled.

Follow-up Schedule

The follow-up intervals are set to 6 months in the *ProPSP* study and to 12 months in the *DescribePSP* study. If the patient or the recruitment center cannot comply with this schedule, smaller or larger follow-up intervals are permitted without specific restrictions.

Termination Criteria

The observation period of the individual participant ends in both studies with the withdrawal of the participant's consent, with the death of the patients, or with the termination of study. Patients can withdraw their consent at any time and without stating reasons. They can request anonymization or deletion of their stored data. This only applies if the data has not already been released to other researchers or anonymized. A medical decision can also be made to terminate the study if the continuation of the study would result in an unjustifiable burden for the patient or if the patient does not fulfill inclusion criteria anymore.

TABLE 2 | *DescribePSP* and *ProPSP* core protocol.

Inclusion criteria	MDS-PSP diagnostic criteria for probable, possible, and suggestive of PSP (8)
Clinical phenotyping	PSP-specific clinical scales: • PSP Rating Scale (PSPRS) (12) • PSP Staging System (PSP-SS) (13) • PSP-Quality of Life Scale (PSP-QoL) (14) • PSP-Clinical Deficits Scale (PSP-CDS) (15) Parkinsonism-specific clinical scales: • Schwab and England Disability Scale (SEADL) (16) • MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (17) • Starkstein Apathy Scale (SAS) (18) Generic clinical scales: • Clinical Global Impression—Severity Scale (CGI-s) (19) • Geriatric Depression Scale: a 30 item a self-report assessment used to assess current mood in elderly patientes (20) • Montreal Cognitive Assessment (MoCA) (21)
Biobanking	Blood, RNA/DNA, CSF, urine, skin biopsy
Imaging	MRI: MPRAGE, DTI, SWI, T2, FLAIR
Brain banking	Histopathological evaluation

Acquisition of Clinical Data, Biomaterial, and Imaging Data

Both, the *DescribePSP* and the *ProPSP* networks follow the same core protocol with regard to acquisition of clinical data, biomaterial, and imaging as shown in **Table 2**. At baseline visit, demographic data, medical history, medication, family history, and education and job history are collected and are updated at every follow-up visit. The diagnostic certainty level as well as the PSP predominance type according to the MDS-PSP diagnostic criteria (8) are documented at every visit.

Storage of Clinical Data and Imaging Data

Each recruitment center enters the collected data into an electronic case report form (CRF) on a central, web-based data platform. For *DescribePSP*, the central data platform is managed by the DZNE headquarter in Bonn. The *DescribePSP* data platform uses the clinical data-management system WebSpirit. The *DescribePSP* network uses XNAT for a separate imaging platform.

For *ProPSP*, the central data platform is provided by the "Münchner Studienzentrum" (https://www.mri.tum.de/studienzentrum) at the Klinikum rechts der Isar, Technical University of Munich in Munich. The *ProPSP* data platform uses the software MACRO Electronic Data Capture by Elsevier®. The *ProPSP* does not run a separate imaging platform to upload MR images, but collects information in the central data platform on date and place of the MRI, MR sequences and atrophy patterns.

Storage of Biomaterial

The biomaterials collected within the *DescribePSP* network are centrally stored in the biorepository of the DZNE in Bonn. For *ProPSP*, central storage is currently reorganized and will be transferred from the Technical University of Munich to

TABLE 3 | Baseline characteristics of patients.

	DescribePSP	ProPSP
Number of recruited patients (as of November 2020)	354	269
Age in years (mean ± SD [range])	71.6 ± 7.7 [46–87]	69.8 ± 6.9 [51–85]
Disease duration in months (mean ± SD [range])	60 ± 36 [14–222]	51 ± 34 [1–189]
Gender (male in %)	60.3	54.8
PSPRS total score (mean ± SD [range])	34 ± 12.8 [10–75]	35 ± 14.4 [3–76]
PSP-SS (mean ± SD [range])	3 ± 1.1 [1–5]	3 ± 1.1 [1–5]
PSP-CDS total score (mean ± SD [range])	6 ± 2.4 [1–13]	8 ± 3.1 [2–18]

PSPRS, PSP Rating Scale (12); PSP-SS, PSP Staging System (13); PSP-CDS, PSP-Clinical Deficits Scale (15).

the Hannover Unified Biobank at Hanover Medical School in Hanover.

Brain Banking

During the participation in *DescribePSP* and *ProPSP*, the patients and their caregivers are informed about the option of post mortem brain autopsy for verification of the clinical diagnosis and brain banking for research purposes. Written informed consent is obtained by the clinician involved in the patient's care.

DescribePSP and all other *Describe* cohorts have a central brain banking program run by the DZNE (https://www.dzne.de/en/research/brain-bank/) with the neuropathological institute located in Tubingen, Germany. It allows for central clinico-pathological correlation and verification of the clinical diagnosis, if the patient consented to autopsy. For *ProPSP*, brain banking is performed in individual neuropathological institutes that are collaborating with the *ProPSP* recruitment centers and is therefore not centralized. If patients within the *ProPSP* study consent in post-mortem brain autopsy, they are also asked to consent in the correlation of their collected clinical data and the histopathological data generated by the respective neuropathological institute.

RESULTS

Since initiation of both networks, extensive natural history data, imaging data and biomaterials of patients with a clinical diagnosis of s.o. PSP, possible PSP, and probable PSP according to the MDS-PSP criteria have been collected within both, the *DescribePSP* and the *ProPSP* networks.

The following preliminary results are available for *DescribePSP* and *ProPSP* as of November 2020.

A total of 354 patients with a clinical diagnosis of PSP have been enrolled into *DescribePSP*, and 131 patients have completed at least one follow-up visit. A total of 269 patients with a clinical diagnosis of PSP have been enrolled into *ProPSP* (**Table 3**), and 87 patients have completed at least one follow-up visit. Preliminary patient characteristics of *DescribePSP* and *ProPSP* at baseline are shown in **Table 3**.

Biological samples from 298 *DescribePSP* participants, including blood, RNA, DNA, CSF, urine, and skin biopsies have been collected, and standardized MR imaging from 85 *DescribePSP* participants has been performed and uploaded to the *DescribePSP* imaging platform. As of November 2020, five patients from the *DescribePSP* study entered the brain bank program.

Approximately 25% of participants in both, the *DescribePSP* and the *ProPSP* studies did not complete follow-up according to schedule. Reasons for termination included (1) deceased, (2) patient's or caregiver's wish, (3) lost to follow-up, (4) immobility, (5) participation in interventional trial, and (6) moved away.

Clinical data, imaging and biomaterials from both networks have been shared with national and international collaborators for projects that serve the primary goal of *DescribePSP* and *ProPSP*. The Progressive Supranuclear Palsy Clinical Deficits Scale (PSP-CDS), a clinical scale to monitor clinical deficits in patients with PSP across its broad phenotypes, has been developed with baseline and follow-up clinical datasets of *DescribePSP* (exploratory) and *ProPSP* (confirmatory) (15).

For the creation of a modified version of the Progressive Supranuclear Ratings Scale [PSPRS (12)], longitudinal datasets from *DescribePSP*, *ProPSP*, and from the TAUROS trial (22) have been analyzed (23).

DescribePSP and *ProPSP* have served as platforms to recruit patients for a video tutorial that demonstrates diagnostic symptoms of different PSP phenotypes (24). Novel tau PET tracers for PSP were established at two *DescribePSP* centers (Cologne, Munich) (25, 26). Patients of the *DescribePSP* and *ProPSP* cohorts received 18F-GE-180 PET imaging which detected microglial activation in the brain of patients with PSP and CBS (27). A subset of patients from the *DescribePSP* and *ProPSP* cohorts has entered into a genetic study that demonstrated genetic determinants of survival in PSP (28).

DescribePSP and *ProPSP* have served as trial ready cohorts to recruit patients with PSP into interventional trials (29, 30).

DISCUSSION

DescribePSP and *ProPSP* are unique and synergistic research networks in Germany to prospectively study the natural history of patients with PSP.

Both networks comprise of centers with specialization in movement disorders and other degenerative diseases. Although the organizational structure of both networks differs, they follow the same core protocol with regard to inclusion criteria and collection of clinical data, imaging data and biomaterials, which allows for high quality comparisons between both cohorts.

There are some organizational differences between both networks. *DescribePSP* has a parallel cohort design, which allows for good comparison of collected data and biomaterials between different primary diagnoses. *DescribePSP* has central

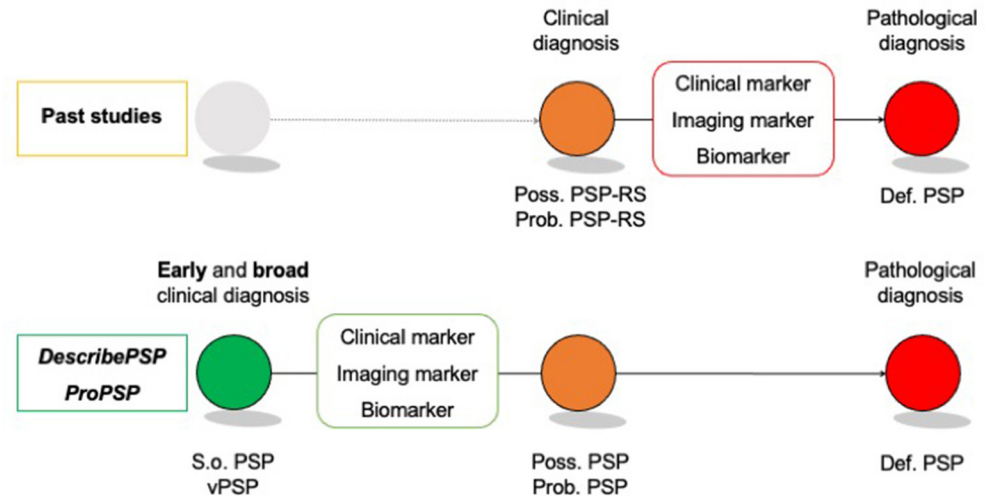

FIGURE 3 | Identification of early disease markers in "suggestive" of and "variant PSP". Def. PSP, Definite PSP; Poss. PSP, Possible PSP; Prob. PSP, Probable PSP; S.o. PSP, Suggestive of PSP; vPSP, Variant PSP.

brain banking, while brain banking in *ProPSP* is decentralized at the moment. *ProPSP* has a higher number of recruitment centers, which results from the fact that centers that are not affiliated to the DZNE can also participate. *ProPSP* uses follow-up intervals of 6 months instead of 12 months, which might increase the probability of collecting follow-up data in patients that would not return after 12 months due to severe immobility. However, the utility of this shorter follow-up interval still needs to be evaluated.

In contrast to previous natural history studies in PSP [for review: (4)], which included only patients with clinical presentation of Richardson's syndrome, *DescribePSP* and *ProPSP* networks recruit patients with diagnoses of s.o. PSP and vPSP according to the MDS-PSP criteria (8). S.o. PSP was designed to serve for early identification of individuals who may develop "possible PSP" or "probable PSP" as the disease evolves, "thereby justifying close clinical follow-up examinations, especially in longitudinal observational studies to further characterize the natural history of PSP with the overall goal of improving diagnosis of patients in early-stage disease"(8).

The *DescribePSP* and the *ProPSP* cohorts will serve as invaluable resources to study the specificity of s.o. PSP and vPSP for underlying PSP pathology and to allow for identification and evaluation of early biomarkers for diagnosis, prognosis, and progression (**Figure 3**).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethic committees of all centers involved in the presented studies. The patients/participants provided their written informed consent to participate in this study.

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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APPENDICES

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REVIEW
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Dystonia Management: What to Expect From the Future? The Perspectives of Patients and Clinicians Within DystoniaNet Europe

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Improved care for people with dystonia presents a number of challenges. Major gaps in knowledge exist with regard to how to optimize the diagnostic process, how to leverage discoveries in pathophysiology into biomarkers, and how to develop an evidence base for current and novel treatments. These challenges are made greater by the realization of the wide spectrum of symptoms and difficulties faced by people with dystonia, which go well-beyond motor symptoms. A network of clinicians, scientists, and patients could provide resources to facilitate information exchange at different levels, share mutual experiences, and support each other's innovative projects. In the past, collaborative initiatives have been launched, including the *American Dystonia Coalition*, the *European Cooperation in Science and Technology (COST*—which however only existed for a limited time), and the Dutch *DystonieNet* project. The European Reference Network on Rare Neurological Diseases includes dystonia among other rare conditions affecting the central nervous system in a dedicated stream. Currently, we aim to broaden the scope of these initiatives to a comprehensive European level by further expanding the DystoniaNet network, in close collaboration with the ERN-RND. In line with the ERN-RND, the mission of DystoniaNet Europe is to improve care and quality of life for people with dystonia by, among other endeavors, facilitating access to specialized care, overcoming the disparity in education of medical professionals, and serving as a solid platform to foster international clinical and research collaborations. In this review, both professionals within

the dystonia field and patients and caregivers representing Dystonia Europe highlight important unsolved issues and promising new strategies and the role that a European network can play in activating them.

Keywords: dystonia, DystoniaNet, collaboration, unmet needs, European network

INTRODUCTION

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both (1). Besides motor symptoms, dystonia syndromes also include several non-motor symptoms, with an independent significant impact on health-related quality of life (2–8).

Dystonia has remained a rather enigmatic disorder despite it being the third most common movement disorder after parkinsonism and tremor and despite its major impact on health. One key problem, which remains today, is the multiplicity of causes of dystonia. This has meant that the traditional approach of looking for a unified pathophysiological model for a disorder, from which one can develop diagnostic biomarkers and treatments, has been difficult to apply. The possibility that pathophysiological and treatment efficacy studies are contaminated by inclusion of people with dystonia of differing etiologies is a real one and is perhaps an important reason why progress in treatment development has been slow.

Over the past 1–2 decades, gradual progress has been made in understanding the genetic underpinnings of some forms of dystonia, allowing the prospect of studying genetically defined cohorts of patients. In addition, pathophysiological studies have become more sensitive to the possibility of combining multiple etiologies of dystonia, alongside advances in identifying important subgroups of people with dystonia with specific etiologies, for example, functional dystonia. The wide spectrum of symptoms in dystonia has also been recognized, including its impact on mental health and cognitive and sensory processing. Treatment advances have been made, particularly in the successful use of deep brain stimulation (DBS) for certain types of dystonia, with intracranial recordings performed during these surgeries providing a novel source of pathophysiological data.

However, many gaps in knowledge remain, and efforts have been made in recent years to build networks that foster international research collaboration. One recent EU-focused infrastructural initiative is the European Reference Network (ERN) for Rare Neurological Diseases (RND), born with the aim to improve quality of life for RND patients and to facilitate the exchange of knowledge between healthcare professionals across borders (9). A patient can be virtually presented to a specialist in another country, with the aim to provide the best medical care without the need to travel. Moreover, it facilitates the collection of patient data, which is important for research purposes. The ERN-RND will interconnect tightly with DystoniaNet Europe as regards goals, PIs, and activities.

Specifically for dystonia, a research network was formed in 2011 by the European Dystonia Cooperation in Science and Technology (COST) Action. This action was aimed at promoting genetic studies, stimulating the development of experimental animal models, standardizing and harmonizing patient care, strengthening the scientific or medical expertise of young researchers and doctors through international exchanges between European research laboratories and expert centers, and educating the public and professionals about the disorder. The original workgroup included applicants from 18 European countries but later increased to encompass 24 European countries. There was also collaboration with the American Dystonia Coalition. Moreover, an important partner was Dystonia Europe, which is an umbrella organization for 22 national dystonia patient associations in 18 European countries, aiming at improving quality of life for people living with dystonia by focusing on the following: raise awareness, spread information, promote education and research, support lobbying and advocacy, and add value to the work of member associations.

Another collaborative multidisciplinary network was initiated in The Netherlands. In 2010, the Movement Disorders workgroup of the Dutch Neurological Society brought together several movement disorders specialists and physiotherapists to initiate *DystonieNet*. The main goal of this national network was to optimize cervical dystonia (CD) treatment by facilitating collaboration between experts, educating more healthcare providers, and promoting research. Another aim was to facilitate the patients' access to dystonia experts to quicken and improve diagnosis and treatment. In this context, a Dutch website (dystonia.net) was developed that serves as a platform for healthcare professionals. This website gives information on regional, national, and international meetings, focused skills workshops, and ongoing research studies on dystonia. A special feature on the website is the "Care Searcher" tool that lists all botulinum toxin units, movement disorder neurologists, or physical therapists specialized in dystonia, who can then be located by patients and clinicians by typing their zip code area. In addition, a newsletter is issued several times a year to spread the most recent news in the field of dystonia, and a special mobile phone application has been developed that provides information about the national guidelines for botulinum toxin treatment, as a handy tool in the outpatient clinic.

From the experience of the COST Network and the Dutch *DystonieNet*, the network was expanded to become *DystoniaNet Europe*. The aim of this European project is to expand the scope of the Dutch *DystonieNet* project to a European level. In the initial phase, Ireland and Slovakia joined the website project, and currently, more countries are in the process of joining. All the authors of this paper (see Authors/collaborative working group) represent countries, invited to be part of *DystoniaNet Europe*. Authors were selected based on their previous participation in European initiatives about Dystonia,

but the participation in the Network is surely not exclusive. The topics of the paper were assigned to different members of the writing committee. A draft of the paper was shared with all the authors in the Authors/collaborative working group, who contributed important intellectual content.

The above-mentioned projects are major steps to provide answers to important knowledge gaps. In this paper, we will identify some of the unmet needs, not only both from the perspective of health professionals and researchers but also of the patients and caregivers across Europe. Patients' quotes, collected by DystoniaEurope, highlight the unmet needs shared by professionals and patients. We will also try to define the role that a European network such as *DystoniaNet* can have in facilitating the solution to these problems, as summarized in **Table 1**.

DIAGNOSTIC PROCESS

Improving Dystonia Awareness Among Patients and Clinicians

Currently, the diagnosis of dystonia is merely based on physical examination and recognition of patterns by an experienced clinician. This can be a diagnostic challenge due to a wide range of dystonia phenotypes and etiologies as well as dystonia mimics (such as functional dystonia). Dystonia can have different characteristics and can be the only symptom but also present as part of a mixed neurological and even systemic disorder (10). The etiological and clinical classification can be particularly difficult in childhood onset dystonias (11).

Due to the rarity of the disorder and the complexity of the presentation, there is often a significant delay in diagnosis. In CD, which is the most prevalent form of dystonia with well-defined clinical symptoms, the mean time from symptom onset to diagnosis varied in several studies from 3.7 (12) to 6.8 years (range, 0–53 years) (13) (for a patient's experience, see **Box 1**). Similar diagnostic delays were observed for other adult-onset focal and segmental dystonias, where in almost half of the cases, it took more than a year to reach the diagnosis (14).

Improvement of dystonia awareness and knowledge can be expected to enable patients to be referred more quickly to an experienced clinician and to obtain a correct diagnosis and addressing their symptoms more rapidly (for a patient's experience, see **Box 2**). The introduction of a nationwide Care Searcher tool could then help gain access to a more advanced diagnosis by a movement disorder specialist (including syndrome characterization and genetic profile) and to adequate treatment, including identifying patients who are candidates for more advanced treatments such as surgical therapies, including DBS. Besides that, in some countries (e.g., France), government actions have labeled Centers of Excellence for Rare Diseases, whose mission is to identify places of diagnosis and therapeutic expertise, as close as possible to patients and to ensure regional and national networks.

Education of medical professionals is one of the most important steps to achieve these goals. Here, a European network can play a role by the organization of training for general practitioners, general neurologists, and physical therapists. There is a need for a more structural practical education around dystonia diagnosis and treatment (for example, botulinum toxin workshops): these could be implemented also in the context of movement disorders curricula or fellowship programs for residents and young fellows, which are however lacking in some countries (15). In the COST initiative, three "dystonia schools" (Bol, Croatia; Groningen, the Netherlands; London, UK) were organized for young neurologists and scientists. In addition, awareness in the general population may be increased by means of media campaigns at a European level, involving national patient associations through Dystonia Europe. DystoniaNet, in close collaboration with the ERN-RND, can play a significant role in this.

An Algorithm for the Diagnosis of Dystonia

Dystonia can be classified based on clinical characteristics (axis I, including age at onset, body distribution, temporal pattern, and associated features) and etiology (axis II) (1). Clinical characteristics form the basis for the etiological clinical suspicion and thereby give an indication of which supplementary laboratory tests or imaging should be performed.

The major developments in genetic testing, allowing us to analyze many genes in a relatively short time, make the case for a renewed diagnostic strategy: recently, a diagnostic algorithm has been proposed for dystonia occurring in children and adolescents (16). Similarly, we could envisage a diagnostic model for adults (see below). This should consider the availability of the diagnostic modalities in different countries and be open to continuous updates as knowledge increases and techniques become readily available and affordable. When a specific investigation (like genetic testing) is not available in one country, international collaboration may provide the solution to complete the diagnostic process. When all patients have undergone the same diagnostic process, larger groups of well-characterized rare dystonia subtypes can be collected, which would increase the statistical power of research at a pathophysiological and treatment level.

Genetics

In 1997, the TorsinA (*TOR1A*) gene was the first to be identified as the major cause for young-onset (primary) generalized dystonia (17). However, monogenic causes of dystonia can only be found in 1–2% of the patients in an average dystonia clinic (18, 19). The other subgroup of dystonia with a genetic background includes the hereditary disorders in which dystonia is part of the symptom spectrum. This list contains isolated, combined, and complex dystonias. Importantly, some of the hereditary forms include treatable (metabolic) diseases (16).

In clinical practice, the possibility of testing for a genetic background of dystonia has evolved rapidly. With the development of next generation sequencing (NGS), it has become possible to analyze thousands of genes simultaneously. One of the NGS techniques involves targeted gene panel analysis, in which a specific set of preselected genes is tested. Compared with other techniques like whole-genome and whole-exome sequencing, the costs of a gene panel analysis are lower, and there

TABLE 1 | Goals DystoniaNet Europe.

Priorities of action of DystoniaNet Europe	Highlights
Diagnostic process	
Improving dystonia awareness among patients and clinicians	• Organization of trainings for GPs, neurologists, physical therapists, with focus on diagnosis and treatment (for example botulinum toxin treatment).
Algorithm for diagnosis of dystonia	• Development of a diagnostic model for adult onset dystonia
Genetics	• Sharing of technical knowledge across gene banks • Pooling of data across existing genetic databases • Development of a European biobank
Neurophysiological diagnostic biomarkers dystonia	• Development of neurophysiological markers to discriminate dystonia from other movement disorders and to differentiate idiopathic, acquired, and functional dystonia • Gain knowledge of dysfunctional brain networks • Development of biomarkers for the effectiveness of DBS
Imaging biomarkers	• Gain knowledge about pathophysiological mechanisms • Development of automatic algorithms of image analysis
Endophenotypes	• Organization of large prospective studies of patients and relatives to prospectively study endophenotypes
Treatment	
Physical and occupation therapy	• Collection of evidence on different training programs and on cost effectiveness • Development of dystonia specific training programs, with a personalized approach • Collection of evidence about the effect of physical therapy and occupational therapy on pathophysiological mechanisms
Botulinum toxin treatment	• Collection of more evidence about some treatment aspects (e.g., use of polymyography and ultrasound in guiding injections) • Clinical studies aimed at improving the benefit/side effect ratio and reducing the number of non-responsive patients • Development of uniform European BoNT treatment guidelines • Improvement of access to treatment
Deep brain stimulation	• Development of an expert network across European countries for clinical consultation, sharing experiences, and outcomes • Development of European Dystonia DBS registry/biobank aimed to collect information about DBS outcomes in rare forms of dystonia and in children, rare side effects, and unexpected responses • Collection of evidence about biomarkers predictors of outcome
Non-motor symptoms	• Development of a non-motor symptom questionnaire for different dystonia subtypes • Improvement of treatment of non-motor symptoms • Development of a subjective goal outcome scale • Development of a multidisciplinary approach

BOX 1 | Patient's experience.

Dystonia patient: "Today I was diagnosed with dystonia after 18 years of having these awful shakes where everyone thinks I am saying no. I now have a name for it. It is not essential tremor, it is not in my mind, and it is a very real condition."

are fewer spurious findings (20). The panel approach results in a higher percentage of confirmed molecular diagnoses than a more classical clinical approach based on diagnostic hypotheses. In addition, the average costs and the time needed to reach an etiological diagnosis are lower when gene panel analysis is used compared to single gene analysis (20, 21).

Genetic testing should be considered mainly in young onset dystonia patients, patients with a positive family history, patients with paroxysmal dystonia, and patients with other (neurological) symptoms (18, 20, 21). The benefits of testing include diagnostic certainty for the individual patient, which then can avoid further unnecessary investigations, information about the risk of recurrence in the family (22), and prevention of transmitting the affected gene to the next generation. This of course comes together with ethical issues that need to be addressed. Although rare, a genetic diagnosis may, in some cases, also alter treatment.

Gene panel analysis is likely to play an important role in the future. However, at this time, it is not uniformly available, and there are differences in patient selection, counseling, and gene panel composition across different countries. In addition, the rapidly expanding genetic findings require a systematic update of the genes included in the gene panel. A uniform panel across Europe, with a centralized update system, could have major benefits. Knowledge could be exchanged across laboratories, and techniques for coverage and lab protocols can be shared and optimized. For research purposes, a uniform approach would

BOX 2 | Patient's experience.

Dystonia patient: "Much more needs to be done to raise awareness of this disease. General practitioners and nurses need to be educated on it. We get fed up hearing: "oh it is like Parkinson's then"."

make it possible to derive reliable epidemiological data across countries and to create large cohorts of patients and controls to test for variants of unknown significance. For this purpose, following the example of some national databases such as the German DysTract, bio banking at a European level could be pursued. Alternatively, a more open and easier sharing of regional or national gene banks would allow for a continuous actualization and implementation of clinical and genetic data. This would form the basis to identify new causative and disease-modifying genes or risk factors for dystonia and attribute clinical significance to variants of unknown pathogenicity for genes already identified. In the future, the discovery of more dystonia-related genes, and the unraveling of the highly complex network of cellular pathways, will eventually increase our understanding of the dystonia pathophysiology and hopefully create new treatment options (23). Moreover, a European network could facilitate the transfer of expertise and sharing of best practice can be implemented.

Neurophysiological Diagnostic Biomarkers Dystonia

Electrophysiological and sensory perceptual studies have supported the view of dystonia as a disorder of network dysfunction involving the basal ganglia, thalamus, cerebellum, and sensorimotor cortices (24).

Despite major advances that have provided a better understanding of dystonia pathophysiology by means of different neurophysiological techniques (25–28), the diagnosis mainly relies only on clinical features. It would be a major advantage if (1) neurophysiological testing could reliably discriminate dystonia from other movement disorders and (2) could support the etiological diagnosis (idiopathic, genetic, or functional) (for a patient's experience, see **Box 3**). To date, neurophysiological studies have been inconsistent in differentiating idiopathic from functional (29, 30) or genetic dystonia (31). Only recently, a few studies found between-groups differences using different neurophysiological techniques in subjects with different etiologies of dystonia (32–35). It has been possible to distinguish between children with acquired isolated genetic or idiopathic dystonias using a corticomuscular, intermuscular, and sensory perturbation paradigm (32). In small sample size studies in adults, the blink reflex recovery cycle (33) and the paired associative stimulation protocol (used to test sensorimotor plasticity) (34, 35) have been effective in discriminating, respectively, cranial and limb functional dystonia from idiopathic dystonia. However, sensorimotor plasticity has been shown to be highly variable across subjects with different phenotypes of idiopathic dystonia and also within the same phenotype (36). In addition, although it has been hypothesized that different phenotypes of dystonia reflect altered processing at different levels of a dysfunctional brain network (37), there is only preliminary supporting evidence for CD (38).

Confirmation by testing homogeneous cohorts of subjects is needed to define which neural networks may underlie different dystonic manifestations (tremor, tonic posturing, patterned movements), localization in different body parts, and associated non-motor symptoms, such as pain. Finally, as the discriminatory power at individual level for any of these neurophysiological paradigms have never been tested, it is crucial to design studies on large samples to test putative diagnostic biomarkers in idiopathic dystonia, which may aid the differential diagnosis primarily with functional dystonia, given the normality of structural neuroimaging in both conditions and the different therapeutic pathways.

From a methodological point of view, there are several technical challenges. One challenge is to investigate whether different components of the network are involved in generating the heterogeneous clinical picture of dystonia. Electrophysiological signals from the cerebellum have traditionally been viewed as inaccessible to magnetoenc ephalography (MEG) and electroencephalography (EEG). However, recent advances have allowed MEG and EEG to detect cerebellar activity using a high-resolution tessellation model of the cerebellar cortex constructed from repetitive high-field (9.4 T) structural MR imaging (39).

Transcranial magnetic stimulation (TMS) has been used extensively to study motor cortex physiology and plasticity in dystonia, as well as sensorimotor integration (25). However, reproducibility of results across studies has been difficult. Multimodal approaches integrating different neurophysiological techniques with neuroimaging are envisaged not only to support the diagnostic process (i.e., functional and genetic dystonias) but also to determine predictors of response to treatment, in particular DBS.

Another possible biomarker for the effectiveness of DBS in dystonia is intermuscular coherence analysis. In children, both idiopathic/genetic and acquired dystonia share an abnormal low-frequency intermuscular coherence, but their intermuscular coherence patterns respond differently to a sensory perturbation (32). In adult dystonia patients, low-frequency and beta band intermuscular coherence partly correlate with dystonia severity and improvement after DBS. This finding suggests that intermuscular coherence can function as a biomarker for DBS efficacy in dystonia, although confirmation in larger studies is needed.

BOX 3 | Patient's experience.

Dystonia patient: "A test to diagnose dystonia would help to reduce the time to a diagnosis and to increase its certainty."

Increased low-frequency activity (3–12 Hz) in the internal globus pallidus (GPi) of dystonia patients has also been reported as a potential biomarker (40) that is coherent with dystonic EMG discharges and correlates with symptom severity as assessed by dystonia rating scales in a large cohort of patients with CD (41). In patients that present predominantly with phasic components, DBS indeed decreases this pallidal low-frequency activity (42), and DBS contacts localized close to the highest low-frequency peak are clinically most effective (41), which could be useful for parameter selection for DBS or as a feedback signal for closed-loop stimulation in the future.

These specific neurophysiological tests require expertise and often need to be performed on expensive machines. This restricts research on neurophysiological markers to a few specialized centers. To this end, a European network such as DystoniaNet together with the ERN-RND could support the diffusion of a broader knowledge of specific techniques among neurophysiologists and the pooling of larger cohorts of patients for neurophysiological studies. Further developments in the neurophysiological field could aid the diagnostic process and form a powerful tool for guiding new treatment approaches with less side effects.

Imaging Biomarkers

Morphological and functional imaging currently offers no reliable markers that can be used in the differential diagnosis of dystonic syndromes. Some notable exceptions are dystonia syndromes caused by neurodegenerative disorders and disorders associated with focal lesions or with metal accumulation in the basal ganglia such as neurodegeneration with brain iron accumulation (NBIA) and Wilson's disease.

For the other forms of dystonia, limited local changes in gray matter volume or thickness, subtle changes in the organization of white matter, and aberrant functional connectivity affecting large-scale networks can be detected only on a large group basis. Knowledge in this field is still relatively scattered due to high phenotype variability. Most imaging studies concern focal dystonias, and relatively little is known about generalized dystonic syndromes.

Imaging findings have contributed to the understanding of dystonia as network disorders (nexopathies, circuitopathies) (43). The weakness of all imaging studies is the fact that they cannot distinguish between cause and effect (44). Usual findings include frequent structural changes and hyper-/hypoactive connections involved in somatosensory perception and its integration into motor circuits (45–47). These are mainly the cortico-striato-pallido-thalamo-cortical pathway and the cerebello-thalamo-cortical pathway, the dysfunction of which is manifested in both focal and generalized dystonias (48). The first one, which involve connections from the basal ganglia and thalamus to the primary sensorimotor cortex, is hyperactive and less responsive to regulatory feedback stimuli from the cortex and subthalamus (44) and thus probably associated with well-known hyperexcitability of the motor cortex (49). The latter causes insufficient inhibition of the motor cortex via hypofunctional connection projecting from the cerebellum through the thalamus (50). Interestingly, local changes in the SM cortex correspond to the cortical representation of body segments affected by task specific dystonias (51–53).

The variability of morphometric findings, functional activity, and connectivity of the motor network largely depends on the genotype of dystonia and, to some extent, on the genotype/phenotype interaction. Basal ganglia volume and activity differ not only among different mutations (DYT-TOR1A, DYT-THAP1) (54) but also between DYT-TOR1A patients and DYT-TOR1A asymptomatic carriers (55). However, there is no universal imaging picture on which a genetic mutation could be predicted.

Resting-state functional MRI (fMRI) (as opposed to a task-based fMRI), has the advantage of not being contaminated with the executive or sensory component of the voluntary movement and has shown that the dystonic motor network is abnormally connected even at rest. In task-specific dystonia, changes in basal ganglia, primary sensory cortex, and premotor and parietal cortices have been shown (56, 57). In CD patients, increased connectivity of the putamen and its connections with the cortex and other basal ganglia partially normalize after botulinum toxin injections (44). In addition, CD patients who can temporarily relieve dystonia using a sensory trick showed reduced resting connectivity of the SM network and increased cerebellar connectivity while imagining this trick (58). Thus, findings in focal dystonia are, to some extent, variable but limited to sensorimotor circuits, which has also been confirmed by multimodal studies (51, 59).

Imaging studies in dystonia have already had some practical consequences both in supporting the differential diagnosis of dystonia and in predicting DBS effect.

A meta-analysis of the anatomical position of the active contacts of implanted DBS leads allowed for the construction of a probabilistic map associated with the clinical benefit of pallidal DBS. The sweet spot was located at the ventrolateral margin of the GPi and sub-pallidal white matter (60). The volume of tissue activates also quantitatively affected the structural and functional connectivity of the premotor and motor cortices, thalamus, supplementary motor area (SMA), and cerebellum, proving the remote effects of pallidal DBS in dystonia patients (61). These results indicated that imaging could be used for optimal targeting and even to inform stimulation parameter choice.

Furthermore, great hopes are placed on automatic algorithms of image analysis based on neural networks and machine

learning. The automatic classification of resting-state fMRI has correctly detected patients with spasmodic dysphonia (SD) (62), CD (63), or alien-hand dystonia in corticobasal syndrome (64) with sufficient sensitivity and specificity. This approach seems promising also in the search for potential biomarkers predicting future clinical effects of DBS. For example, classification using a support vector machine based on the distribution of cortical atrophy within the associative, SM, and visuomotor areas resulted in 88% accuracy in estimating the pallidal DBS outcome in patients with segmental and generalized dystonia (65). The future use of these methods therefore seems promising.

Combining different techniques together, such as supervised machine learning applied to standard diagnostic brain MRI together with measuring central motor conduction times (CMCT) with transcranial magnetic stimulation (TMS), or -evoked potentials (SEPs) together with dystonia severity scales, can help counsel patients and families of dystonic children regarding the likely benefit of DBS in acquired dystonias as well as provide personal predictive and decision-making data using receiver operating characteristic (ROC) curves (66). This process applied internationally could rapidly build gene-specific and acquired disease-specific decision-making tools.

Endophenotypes

Temporal discrimination, the ability to determine two sequential stimuli as separate in time, is disturbed in a number of basal ganglia disorders. Abnormal temporal discrimination is not specific for idiopathic and genetic (67) dystonia but can also be found in functional dystonia, albeit being produced by a different mechanism (68). It is, however, a highly sensitive measure with 97% sensitivity in the most common form of adult onset focal dystonia: cervical dystonia. It shows age- and sex-related penetrance in unaffected first-degree relatives, being found in ∼50% of female first-degree relatives after the age of 40 years, indicating full (100%) penetrance; in male relatives, its penetrance is ∼40% (69).

Accumulating evidence over the last 15 years has indicated that abnormal temporal discrimination is a mediational endophenotype in adult-onset dystonia. The features of mediational endophenotypes are as follows: (a) they are an expression of a genetic mutation, necessarily present prior to disease onset; (b) they reflect disease susceptibility and are not altered by disease expression or severity; and (c) they are more penetrant than the phenotype (70). Mediational endophenotypes, found both in CD patients and, importantly, in their unaffected relatives, may illuminate pathogenetic mechanisms not obvious from the motor phenotype.

Further support of this endophenotype is that, in unaffected relatives with abnormal temporal discrimination (compared to relatives with normal temporal discrimination), it is associated with increased putaminal volume (71), reduced putaminal activity (72), and reduced activation in the superior colliculus in response to a looming stimulus (73).

It is proposed that abnormal temporal discrimination indicates a disturbance in the system involved in covert attentional orienting, involving processing of salient environmental sensory stimuli through the superior colliculus. The midbrain covert attentional network captures changes in the environment potentially important for survival, which requires inspection and action. It is likely that impaired inhibition, caused by defective GABAergic mechanisms at the level of the synapse, underlies both abnormal temporal discrimination and dystonia.

It is also likely that non-motor symptoms in dystonia, like mood disorders and abnormal social cognition, are also driven by disrupted subcortical mechanisms of covert attention. Salient environmental stimuli include emotional threats (visual or auditory) and require emotional threat detection by the medial amygdala. Social cognition (74) integrates cognitive processes, such as the ability to follow eye gaze, share attention, and recognize emotion, to distinguish between self and others' intentions. There are preliminary studies indicating disordered basic social cognition in patients with adult onset dystonia (75–77). It is suggested that abnormal basic social cognition (to emotional face and voice stimuli) in patients with CD reflects disrupted subcortical processing in the collicular–amygdala pathway for threat detection (basic social cognition). This may be linked to heightened levels of anxiety and depression.

The results from different studies on social cognition in focal dystonia have been often contradictory; a recent large study assessing all four major social cognition dimensions found that participants maintained generally intact social cognitive abilities (78). The authors did note reduced recognition of facial expressions of fear; some patients with CD showed defective empathy. In another study, higher anxiety and depression levels were associated with better performance on an Facial Affect Naming task, suggesting that patients with CD might overactivate perceptual processing of social stimuli to compensate for baseline increases in anxiety levels and lowered mood (79). Most of the, admittedly limited, research shows little evidence of deficits in complex social cognition in adult onset focal dystonia, but basic social cognition, including emotion recognition in facial expressions and prosody, may be impaired; this requires further investigation.

Given the high penetrance of abnormal temporal discrimination in unaffected female relatives, it may be worthwhile to examine the prevalence of mood disorder and impaired social cognition in this population (in comparison to female relatives with normal temporal discrimination) and to follow them up prospectively.

In addition, this purpose can only be achieved by means of collaborative studies collecting large populations of patients and their relatives.

TREATMENT CHALLENGES

Motor Symptoms

Nowadays, the treatment of dystonia consists of several possible strategies, depending on the age of the patient, dystonia subtype, or other specific factors. The effect of treatment can be monitored by several motor scales, although they frequently fail to observe small effects. In general, oral medication such as anticholinergics, physical therapy, botulinum toxin (BoNT) injections, or surgical treatment including DBS or ablative procedures can be considered. Here, in cooperation with the

ERN-RND, we will focus on the need for European guidelines for physiotherapy/occupational and BoNT therapy and the unmet needs for DBS.

Physical and Occupational Therapy

A specific physical therapy (PT) intervention for CD has been described by JP Bleton (80). It aims to strengthen the non-dystonic antagonist muscles and to learn or relearn motor skills. A recent single-blinded randomized controlled trial investigated the effectiveness of a specialized PT program on disability in CD, compared to a regular PT program (81). Both groups showed a significant improvement of motor symptoms after 12 months of treatment, but no difference between groups was found, as both programs were effective. However, the specialized therapy group showed significant improvement in general health perception and self-perceived improvement over the general therapy group (for a patient's experience, see **Box 4**). Importantly, total health-related costs were lower in favor of the specialized therapy group.

In the Netherlands, several physical therapists were trained for this study and continued treating patients with the specialized therapy after the successful results. Currently, it is crucial to widely spread the knowledge to physiotherapists across Europe and to provide them with adequate training. To this end, international training schools and active professional networks should be organized to promote exchange of experiences and the implementation of standardized physiotherapy programs across Europe.

This could result in an improvement of treatment with a reduction in motor symptoms and lower costs (for a patient's experience, see **Box 5**). Moreover, considering that many patients still consult a physical therapist first after the onset of dystonia symptoms, the delay in diagnosis could be improved.

Recently, a cognitive orientation for occupational therapy (COOP) approach has been successfully studied in children and adolescents with acquired and genetic dystonias, who, after DBS were not achieving their goals (riding a bicycle, applying mascara, catching and throwing balls, swimming, feeding, carrying, and pouring drinks) (82). COOP, previously used in stroke rehabilitation in adults with developmental coordination disorder, was shown effective in one study focused on three participant-selected goals. The trained COOP skills were transferable to two additional untreated goals, and the result was obtained over 10 1-h sessions compared to hundreds of hours of "conventional therapy practice" sessions in the past. Extension of this technique with multiple therapists has been studied, and the application of COOP to children and young people without DBS is now required.

The search for the most effective physical treatment program for dystonia patients is far from over. There is a need for different approaches for different kinds of dystonias, in both children and adults, taking into consideration the affected body region, the symptoms severity, the presence of comorbidities, and age, social life, and skills of the patients. Ideally, every patient should receive a personalized approach (such as COOP), based on the experience of the physiotherapist and the patient preferences.

To this end, new studies should be designed with sufficiently large populations, which would require multicenter efforts.

Future research should also focus on the effect of PT and OT on the pathophysiological mechanisms of dystonia and how this relates to the maladaptive neuroplastic changes (83). This would improve the understanding of pathophysiological mechanisms and possibly improve therapeutic strategies. Finally, a broad training program for physiotherapists should ideally rely not only on solid evidence of efficacy but also on data about feasibility and cost effectiveness: such studies are currently scarce.

Botulinum Toxin Injections

BoNT injections are the most important treatment choice for focal dystonias but can also be used in segmental or generalized dystonias to relieve symptoms. Extensive research resulted in class I evidence to support efficacy and safety of several BoNT formulations (83). Up to 70–85% of CD patients report a significant benefit on the motor symptoms but also on pain and quality of life (83).

However, there are still uncertainties, such as the optimal starting dose, the interval between injections, or the need for single or multipoint injections in dystonic muscles. Especially after long-time treatment, neutralizing antibodies can develop, with a negative effect on BoNT efficacy (84, 85). In addition, dystonia syndromes with tremor may require a different approach, which needs further investigation. The use of polymyography seems to be effective in guiding injections and improving patient satisfaction but needs confirmation in larger studies. In addition, the use of ultrasound to target muscles and reduce the episodes of dysphagia seems to be a promising option to improve botulinum toxin treatment (83, 86).

Uniform European BoNT treatment guidelines could improve treatment for patients and enable further research toward improving the benefit/side effect ratio of BoNT treatment and reducing the number of primary and secondary non-responsive patients. A standardized working definition of non-responsiveness should be developed, and dose finding and comparative studies across different BoNT toxins should be performed. In addition, the additional value of polymyography and ultrasound should be examined.

Another important need is to improve access to treatment uniformly. It is currently unclear how many patients who are candidates for treatment are not receiving it. Factors that explain under-referral should be investigated and addressed, including lack of knowledge among treating physicians, costs, and scarce availability of BoNT centers in some areas (15). The development of a multidisciplinary consultation were the patient visit the movement disorder specialist, directly followed by polymyography and treatment with BoNT, can also significantly improve the diagnostic and treatment process for the individual patient.

Deep Brain Stimulation

Dystonic symptoms can severely impair the patients quality of life, while the response of dystonia to oral medical treatment may be disappointing (87). DBS has been applied for different forms of dystonia since the late 1990s (88–90). Satisfactory results can be safely achieved in most patients—including very young children (91) who go through rigorous selection to identify and

BOX 4 | Patient's experience.

Dystonia patient: "I have had cervical dystonia for at least 2 years and was treated with botulinum toxin with little effect. When I finally came to a physical therapist specialized in dystonia, it was the turning point. From her I got tools such as special exercises and advice on how to manage my dystonia. It was nice to start to feel some control again. My family has also witnessed how much happier I was after I started seeing the physical therapist."

BOX 5 | Patient's experience.

Dystonia patient: "I have been suffering from cervical dystonia for 14 years. I am receiving botulinum toxin treatment. A few years ago my neurologist referred me to physiotherapy at a local hospital in the town where I live. On the first appointment, it turned out that my physiotherapist had never heard of dystonia, but said she would try to help me. She was stretching my muscles for an hour. I did not want to risk worsening my condition and did not continue this therapy. As far as I know there is a lack of physiotherapists in my country who are familiar with dystonia and can help patients with this condition."

characterize specific types of dystonia known to benefit most from DBS (92–94) (for a patient's experience, see **Box 6**).

DBS is a complex therapy that requires a team of highly specialized allied health professionals, neurologists and neurosurgeons, specific technical equipment, and expensive implantable materials. DBS management requires an intensive follow-up after surgery. This therapy may present with complications and rare and poorly understood side effects that need to be recognized and handled. In addition, the DBS field advances quickly, as new technological tools arrive on the market (95). The complexity of DBS treatment increases when different types of dystonia are concerned due to the availability of different targets (GPi, different thalamic targets, subthalamic nucleus), the wide range of possibilities with advanced stimulation options, and the variable response that can be observed. It is also worth mentioning that neurosurgical treatment of dystonia is not restricted to DBS alone but includes other options such as stereotactic lesioning, MRgFUS, or selective peripheral neurosurgery, which can be combined or may be proposed as an alternative or even as a rescue treatment in selected cases (96–100).

Unfortunately, not all patients experience the optimal benefit from DBS, and the response of different forms of dystonia, some of which are very rare, still needs to be adequately investigated. Finally, when severe forms of generalized dystonia needing surgical treatment concern children, the range of skills and expertise required becomes even wider (101, 102).

Regarding these considerations, it is evident that DBS for dystonia can only be offered in selected specialized centers. The geographical distribution of such centers is not uniform across Europe: some countries have no center at all (15), and some DBS centers do not treat dystonia patients or have a low volume of surgeries due to the lack of resources or qualified personnel. As a result, patients in some areas currently do not have access to this effective treatment (103) (for a patient's experience, see **Box 7**).

Moreover, while DBS centers with significant experience in this field can encounter difficulties in patient selection and postoperative management, such problems apply even more so to centers with less experience or smaller annual volume.

An expert network across European countries, gathering regularly in (virtual) meetings, could provide the needed infrastructure for clinical consultation in relation to challenging cases, exchange of experiences with the prevention and management of complications, and sharing of outcomes for the rarest forms of dystonia undergoing surgery. The virtual consultation infrastructure of ERN-RND as well as bilateral agreements between centers of different countries within the network could facilitate referral of patients to centers with specific expertise for treatment.

Such an initiative could have an immediate impact on daily practice, but it could also form the basis for the institution of a European Dystonia DBS registry, as it has been implemented already in some countries at a national level for special forms of dystonia in children (104). The registry could serve to collect information about DBS outcomes in rare forms of dystonia and in children, rare side effects, and unexpected responses.

At a subsequent stage, it could be supplemented with infrastructures for biobanking. Indeed, although a growing amount of data suggest that some patient characteristics may inform patient selection for surgery (105–108), at the moment, there are only tentative clinical, neuroradiological, genetic, or neurophysiological elements that could predict individual surgery outcome [as described above (66)]. Such much-needed biomarkers need to be rolled out across a wider population and pooled diagnostic subgroups, and this requires a collective effort, where different centers would not only contribute clinical data but also share infrastructures and expertise in the different fields.

Non-motor Symptoms

Recently, the importance of non-motor symptoms (NMS) associated to dystonia has been brought to light. The lifetime prevalence of psychiatric disorders can reach up to 91.4% in CD patients and mainly consists of depressive symptoms and anxiety disorders (3, 109). Besides psychiatric disturbances, other NMS such as fatigue, sleep disorders, and pain are also highly prevalent (4).

Recognition and correct evaluation of the NMS associated with dystonia is of paramount importance for the choice of

BOX 6 | Patient's experience.

Dystonia patient: "Recently I have had deep brain stimulation and right now I can look at you straight, so I feel amazing! My life … it is like being reborn … it is crazy … I can wake up, I can go to work, I can drive my car, I can do shopping, I can go around, I can go to a bar, I can talk to people. Last night I was in the bar here and I talked to everybody, whereas before that never happened. My confidence is back."

BOX 7 | Patient's experience.

Dystonia patient: "My doctor had even no idea that you can get deep brain stimulation for dystonia or whether that was a good option for me or not. Even when I asked to be referred he wouldn't know where to refer me to."

treatment approaches that would also target this important aspect (for a patient's experience, see **Box 8**).

Non-motor Symptom Questionnaire

The high prevalence of NMS and the impact on the patients' well-being demands a more structural screening toward NMS during the regular outpatient visits. For this purpose, a standardized, validated NMS questionnaire specific for dystonia patients is needed to identify the symptoms and to evaluate the effect of treatment.

Recently, a novel 14-item self-completed questionnaire has been introduced (110). This Dystonia Non-motor Symptoms Questionnaire (DNMSQuest) covers seven domains including sleep, autonomic functions, fatigue, emotional well-being, stigma, activities of daily living, and sensory symptoms, and was tested in craniocervical dystonia patients. It appeared robust and easy to apply in daily practice, with just 14 questions that could be answered in about 5 min with yes or no. A possible disadvantage is that it does not score the severity of symptoms, for which additional information is required from the patient. Furthermore, it has only been validated for CD, so further validation in other dystonia subtypes is required. A European network would facilitate larger studies to create a questionnaire also for NMS severity and to validate the NMS questionnaire in other dystonia subtypes ll.

Treatment of Non-motor Symptoms

Treatment of NMS is important not only to improve the significant impact that they have on the quality of life but also to investigate their effect on motor symptoms and pathophysiological networks.

Psychiatric symptoms like depression and anxiety disorders are associated with neurotransmitter disturbances and are treated with medications influencing neurotransmitter systems like serotonin, dopamine, and noradrenalin. Importantly, these systems are involved in dystonia as well (111, 112). Safety profiles of most medications are based on a healthy (or non-dystonia) population and need further investigation in dystonia patients. One study showed that prescribing selective serotonin reuptake inhibitors (SSRIs) to CD patients is safe, with no deterioration of motor symptoms, but the effect on non-motor symptoms needs to be examined in larger studies investigating higher dose and longer schedule (113).

Evidence regarding the best treatment for NMS such as fatigue, sleep disturbances, and cognitive problems are still at an even more rudimentary stage. Besides pharmacological interventions, an approach including PT, cognitive therapy, coping strategies, and caregiver support, possibly in the context of a multidisciplinary rehabilitation program, could possibly contribute to a better well-being and requires further investigation.

An integrated treatment approach of motor and non-motor symptoms aiming at improving quality of life requires further research, also considering that the several dystonia forms have their own pathopsychological mechanisms and related NMS spectrum. Especially for the rare dystonia subtypes, this cannot be realized without international collaboration.

Subjective Goals as Outcome Measures

In general, the goal of any treatment is to improve quality of life and patient's satisfaction. To date, the standard way of assessing the effect of dystonia treatments is to measure the reduction in motor symptoms and, more recently, non-motor symptoms, which can be objectively measured. However, current scales are often not fully capable of accurately reflecting changes that are relevant for the patients. Indeed, small changes in predefined scores can make a big difference in daily life in some cases, while, on the other hand, measurable improvements do not always translate in significant ameliorations in functioning or independence.

A different approach could be to aim directly for functional improvement in daily life, as defined by the patients themselves (114, 115). One previous study examined the effectiveness of GPi DBS in dystonia patients on preoperatively set of functional priorities in daily living (116), measured with the Canadian Occupational Performance Measure (COPM). Priorities varied between patients but showed a significant improvement in performance and satisfaction after DBS in all. Importantly, improvement was reported both by the motor responders and by several patients classified as non-responders based on the motor outcome. Such an approach focuses on important improvements for the individual patient that would not have been objectified

BOX 8 | Patient's experience.

Mother of 7-year-old girl with dystonia: "We were on a waiting list for a year and just recently we have started to go to regular psychologist meetings. I think it is so important for family, friends and professionals to be aware and to be educated that dystonia doesn't just affect people physically."

with a general motor or non-motor symptom rating scale only and could be applied also to other treatment such as BoNT, psychotherapy or PT, or even to potential new treatments being investigated in clinical trials (116, 117). A similar effect was also shown in other studies, were patients' perceptions in changes in life after DBS were studied with thematic interviews, instead of motor rating scales (118, 119).

A Multidisciplinary Approach

The diagnosis of dystonia motor symptoms, the recognition of the non-motor spectrum, and the identification of syndromes are very challenging. In addition, other factors can complicate the diagnostic process, like an abnormal development in children and the wide range of possible etiologies (120).

In other movement disorders, such as Parkinson's disease, a multidisciplinary approach has increasingly been shown to be beneficial (121). Also in children with movement disorders like dystonia, a multidisciplinary approach has already shown significant improvement in phenotyping, a high diagnostic yield and minimal diagnostic delay (120). Future research should investigate the additional value of a multidisciplinary approach also in the adult dystonia population.

The composition of a multidisciplinary team will vary at different levels. All patients may benefit from experienced Allied Health Professionals for support and specialized interventions (102) and application of the principles of the International Classification of Function (ICF). Children might require teams with a pediatrician, geneticist, or a specialist in metabolic diseases, although differences per center and per country can be expected. Adults may benefit from a multidisciplinary approach covering also the broad range of non-motor symptoms. A European network could advise on the specialists that would preferably be involved in the multidisciplinary team. When the optimal composition is not possible in a single center, multicenter collaboration can offer additional expertise. When highly specialized professionals are needed, international collaboration could be envisaged. In this way, multicenter collaborations could help overcome the shortcomings of the single centers, possibly also by implementing teleconsultation with external specialists.

For all dystonia patients, a dedicated multidisciplinary team may shorten the diagnostic delay, improve the classification and diagnostic yield, and play an important role in a timely and optimal treatment. In addition, genetic counseling may decrease the uncertainty for patients and families, not only concerning the cause of their symptoms but also about the consequence for next generations. Probably, this approach will result in reduced costs by reducing unnecessary investigations and, with a timely correct treatment, promoting faster participation in society.

Multicenter (international) collaborations pose several challenges, starting from identifying the correct specialists, allocating time, and solving technological communication issues while preserving data safety. The reality of the different countries with cultural and social differences, along with the geographical and technical disparities, must also be taken into account.

PATIENT AND CAREGIVER PERSPECTIVE

As mentioned above, the route to dystonia diagnosis can be very challenging, causing prolonged suffering for many dystonia patients.

The impact of dystonia motor and non-motor symptoms is also reflected in the patients' stories Dystonia Europe receives. The boxes within the text provide a short insight into patients' experiences.

Based on the evidence and reports collected, which reflect the patients' and caregivers perspective, there are some goals in the care of dystonia patients that should be prioritized.

These include the following:

- Improving education and training for (young) neurologists and for general practitioners to speed up diagnosis and initiation of treatment;
- Promoting specialized dystonia centers across Europe with expertise in diagnosing and treating patients with more severe forms of the disease;
- Building up multidisciplinary teams, including, among others, neurologists, physiotherapists, occupational therapists, and psychologists for the care of dystonia patients;
- Training of physiotherapists and occupational therapists specialized in the treatment of dystonia patients and facilitating access to physiotherapy across Europe;
- Increasing awareness by developing standardized dystonia information material translated to the different European languages.

There are still major gaps in public understanding of dystonia and the psychological and financial burden that it may bring, in medical knowledge, and in timing of diagnosis and access to treatment for dystonia patients across Europe. To close these gaps and uniformly improve care and quality of life for dystonia patients, we need to work together: the medical profession, researchers, policy makers, patients, and carers. Therefore, the establishment of a strong international European dystonia network is much advocated by the dystonia community. The opportunity to collaborate across borders on education (with specialized dystonia training schools), research projects, improvement of dystonia awareness, etc. is the base to achieve

the best care and improve quality of life for dystonia patients throughout Europe.

CONCLUSIONS

Although dystonia is the third most common movement disorder after tremor and Parkinson's disease, it is still relatively rare. The wide heterogeneity of dystonia presentations makes it difficult to collect large numbers of specific dystonia subtypes for research purposes. Previous studies tended to lump patients with different forms of dystonia together (whether these were about diagnosis, pathophysiology, or treatment), while there are multiple different pathophysiological processes leading to different dystonia phenotypes. This may have affected the results.

DystoniaNet Europe is born with the aim of connecting dystonia experts and patients all over Europe in a network that can form the basis for leveling care at an upper level and for supporting large multicenter research project to advance knowledge. Such a network could also lay the foundations for a European registry to support future dystonia studies by the collection of data from different countries.

Leveraging existing infrastructure, we will be collaborating and interconnecting with the ERN-RND; however, we will also reach out to other networks such as the American Dystonia Coalition, aiming at a continuous fruitful interchange, which can enrich both associations and further advance knowledge through collaboration.

With joined forces, dystonia research can reach an important next level to further improve dystonia care and treatment.

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AUTHOR CONTRIBUTIONS

MS: organization, design, and writing the manuscript. AA, ME, and HG: manuscript reviewing and critique. MB, MH, RJ, JK, FM, RR, and MT: manuscript writing and critique. MC: design and writing the manuscript and critique. MAJT: design and manuscript reviewing and critique. All authors in the Appendix reviewed the manuscript for important intellectual content.

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The ARCA Registry: A Collaborative Global Platform for Advancing Trial Readiness in Autosomal Recessive Cerebellar Ataxias

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Autosomal recessive cerebellar ataxias (ARCAs) form an ultrarare yet expanding group of neurodegenerative multisystemic diseases affecting the cerebellum and other neurological or non-neurological systems. With the advent of targeted therapies for ARCAs, disease registries have become a precious source of real-world quantitative and qualitative data complementing knowledge from preclinical studies and clinical trials. Here, we review the *ARCA Registry*, a global collaborative multicenter platform (>15 countries, >30 sites) with the overarching goal to advance trial readiness in ARCAs. It presents a good clinical practice (GCP)- and general data protection regulation (GDPR)-compliant professional-reported registry for multicenter web-based capture of cross-center standardized longitudinal data. Modular electronic case report forms (eCRFs) with core, extended, and optional datasets allow data capture tailored to the participating site's variable interests and resources. The eCRFs cover all key data elements required by regulatory authorities [European Medicines Agency (EMA)] and the European Rare Disease (ERD) platform. They capture genotype, phenotype, and progression and include demographic data, biomarkers, comorbidity, medication, magnetic resonance imaging (MRI), and longitudinal clinician- or patient-reported ratings of ataxia severity, non-ataxia features, disease stage, activities of daily living, and (mental) health status. Moreover, they are aligned to major autosomal-dominant spinocerebellar ataxia (SCA) and sporadic ataxia (SPORTAX) registries in the field, thus allowing for joint and comparative analyses not only across ARCAs but also with SCAs and sporadic ataxias. The registry is at the core of a systematic multi-component ARCA database cluster with a linked biobank and an evolving study database for digital outcome measures. Currently, the registry contains more than 800 patients with almost 1,500 visits representing all ages and disease stages; 65% of patients with established genetic diagnoses capture all the main ARCA genes, and 35% with unsolved diagnoses are targets for advanced next-generation sequencing. The ARCA Registry serves as the backbone of many major European and transatlantic consortia, such as PREPARE, PROSPAX, and the Ataxia Global Initiative, with additional data input from SPORTAX. It has thus become the largest global trial-readiness registry in the ARCA field.

Keywords: ataxia, registry, network, natural history, trial readiness

ARCA REGISTRY: THE OVERARCHING GOAL

Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of ultrarare multisystemic neurodegenerative diseases affecting the cerebellum and/or its afferent tracts, often accompanied by damage to other neurological (e.g., corticospinal tract, basal ganglia, vestibular system, and peripheral nerves) or non-neurological systems (e.g., muscle, heart, and pancreas) (1, 2). The number of ARCA genes is continuously expanding, extending far above >100 genes, and the first ARCAs now come into reach of targeted treatment options (2).

Disease registries have been important for identification, characterization, and aggregation of rare neurological diseases. However, the real-world quantitative and qualitative evidence in registries and registry-based natural history and outcome measure studies have now also become a precious source for planning of treatment trials and modeling trial designs and endpoints, thereby complementing the knowledge available from

preclinical studies and clinical trials (3). The *ARCA Registry* was launched in 2013 in order to apply this concept to the field of ARCAs, and it remains the only multicenter registry fully dedicated to ARCAs and early-onset ataxias (EOAs), which are known to be enriched but not exclusive for ARCAs (1, 2). The overarching goal of the *ARCA Registry* is to become a key facilitator enabling trial readiness by

- providing an easily accessible, web-based, good clinical practice (GCP)-conforming, and general data protection regulation (GDPR)-compliant multicenter multi-trial registry infrastructure platform as a backbone for global trial-readiness efforts in ARCAs;
- building cohorts of sufficient size for trial-readiness studies and upcoming treatment trials through aggregating ARCA patients in an accessible, standardized, multicenter fashion around the world;
- characterizing the phenotypic spectra for ARCAs, which will inform treatment trial design and especially outcome selection for future treatment trials;
- collecting real-world natural history data for ARCAs acquired during daily clinical life across a large range of centers across the world, thereby informing design, planning, and modeling of treatment trials; and
- providing a continuous database backbone for trial-readiness ataxia consortia around the world, e.g., the German DZNE ARCA-EOA network (4), the PREPARE consortium (5), PROSPAX (6), and ARCA GLOBAL (7).

In this overview, we will describe the main methodological features and assets of the *ARCA Registry*, with examples on how it is already being utilized to improve trial readiness in the field of ARCAs, including its current use by multiple research networks. It will also illustrate the registry's potential for expansion to other partners worldwide to promote trial readiness for ARCAs.

A GOOD CLINICAL PRACTICE- AND GENERAL DATA PROTECTION REGULATION-COMPLIANT GLOBAL WEB-BASED REGISTRY: DATA CAPTURE, DATA ACCESS, AND DATA SHARING

The *ARCA Registry* is built on WebSpirit (2mt Software, Ulm, Germany), a web-based electronic data-capture system currently used in a variety of national and international medical research consortia (**Figure 1**). The web-based implementation allows direct access by registered clinicians and study teams from any computer worldwide, as required for easy access in a global multicenter setting. The fact that it uses the same technical registry platform (WebSpirit) as one of the largest autosomal dominant ataxia registries, namely, the spinocerebellar ataxia (SCA)/ESMI registry (8, 9) and SCA Global (10), as well as the large sporadic ataxia registry (SPORTAX) (11, 12) and the Hereditary Spastic Paraplegia (HSP) Registry, allows for cross talk and joint analysis not only across the manifold ARCAs captured in the ARCA Registry itself but also with SCAs, sporadic ataxias, and even HSPs. This is further facilitated by aligning all key electronic case report forms (eCRFs) between these major ataxia registries. The registry platform is GCP-compliant: an audit trail is maintained to track changes to recorded data, a detailed rights and role management system limits access to entered data for each individual system user, and quality assurance is supported by an integrated online-monitoring system. Moreover, it is fully compliant with the European Union GDPR based on the following features: use of unique pseudonyms generated with a secure one-way hash function to restrict the use of personally identifiable data to local sites; separation of processing activities through assignment of user roles (e.g., data entry, monitoring, and data management) and restriction of access to data; record and transfer only of pseudonymized data; all access to data through encrypted connections; and servers located within the EU. Participating sites maintain access to their data entered in the *ARCA Registry*, with the possibility to easily export and systematically analyze locally aggregated datasets. Access to full multisite datasets is provided for specific projects upon request by a standardized project template and provided to the project submitter after evaluation of the request.

The physician-reported multidomain datasets in the *ARCA Registry* are the core of a larger systematic multi-component ARCA database cluster (**Figure 1**). For longitudinal collection of biomaterials, the *ARCA Registry* is linked to an *ARCA biomaterial database* built on REDCap. To facilitate whole-exome and whole-genome sequencing in all patients with unsolved ARCA, the ARCA Registry is moreover linked to next-generation sequencing (NGS) data on the genomics research platform GENESIS (13, 14). GENESIS is a user-friendly collaborative cloud-based analysis and matchmaking platform that encompasses the largest ataxia NGS dataset collection worldwide (>2,000 ataxia NGS datasets), aggregated via the PREPARE consortium (*PREPARE-GENESIS*) (see below). While the ARCA Registry and the GENESIS platform are two distinct databases, subjects from the registry are linked to the GENESIS platform via an ID generated by the ARCA biomaterial database. Ongoing developments of this multi-component ARCA database cluster will include an *ARCA multi-study database* as a repository for features of digital outcomes such as magnetic resonance imaging (MRI), digital-motor sensors (APDM, Q-Motor), and optical coherence tomography and for patient-driven entry of patient-reported outcome measures (PROMs).

Abbreviations: ADLs, activities of daily living; AGI, Ataxia Global Initiative; ARCA, autosomal recessive cerebellar ataxia; DZNE, German Center for Neurodegenerative Diseases; ESMI, European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative; eCRF, electronic case report form; EMA, European Medicines Agency; EOA, early-onset ataxia; ERDRI, European Rare Disease Registry Infrastructure; ERN-RND, European Reference Network for Rare Neurological Diseases; FARS, Friedreich Ataxia Rating Scale; GCP, good clinical practice; GDPR, general data protection regulation; HSP, hereditary spastic paraplegia; INAS, Inventory of Non-Ataxia Signs; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PGI-C, Patient's Global Impression of Change; PHQ-9, patient health questionnaire on depression and anxiety; PROM, patient-reported outcome measure; SARA, Scale for the Assessment and Rating of Ataxia; SPORTAX, Consortium "Sporadic Degenerative Ataxia with Adult Onset"; PREPARE, Consortium "Preparing for therapies in autosomal recessive ataxias"; PROSPAX, Consortium "An integrated multimodal PROgression chart in SPastic atAXias"; SCA, spinocerebellar ataxia.

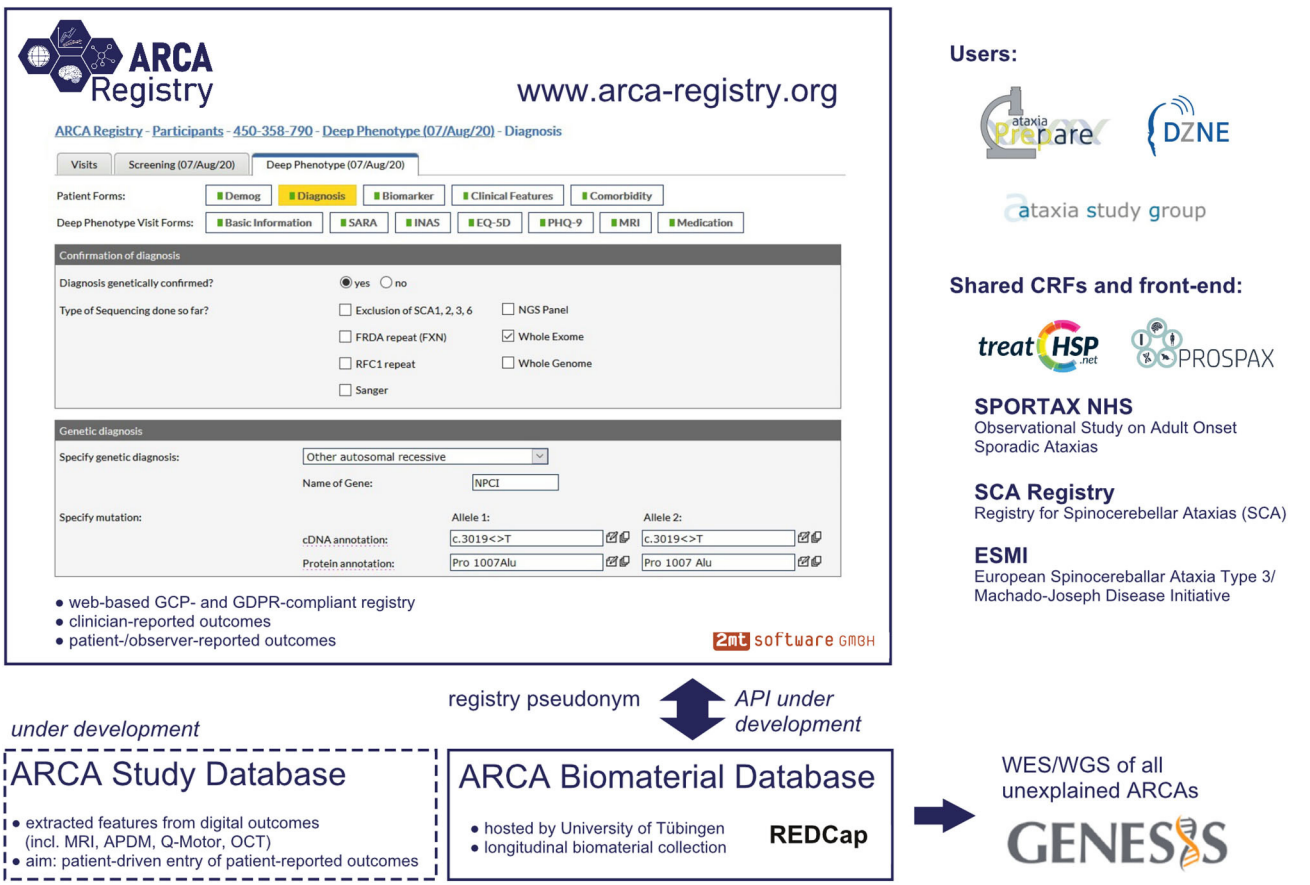

FIGURE 1 | Platform and database infrastructure of the ARCA Registry. Graphical user interface of the web-based ARCA Registry, with display of a representative electronic case report form (eCRF) and embedding in the larger database infrastructure. The front-end of the software and the main core of eCRFs are shared with other major ataxia and rare disease registries (e.g., the HSP registry used by the TreatHSP network), making the ARCA Registry user friendly and convenient for joint analysis of data across genetic ataxias, sporadic ataxias, and hereditary spastic paraplegia (HSP) registries.

CAPTURING PHENOTYPIC SPECTRA, PHENOTYPIC EVOLUTION, AND DISEASE PROGRESSION OF AUTOSOMAL RECESSIVE CEREBELLAR ATAXIAS: THE ELECTRONIC CASE REPORT FORMS

The eCRFs of the *ARCA Registry* are designed to characterize the clinical heterogeneity of phenotypic spectra and natural history phenotypic evolution of ARCAs, thus helping in the selection of outcomes and planning of upcoming treatment trials (sample size calculation, trial duration, etc.) as well-modeling of trial endpoints and treatment effects. Different degrees of eCRFs details—characterized as "core," extended," and "optional" datasets—allow data capture tailored to the participating site's variable interests and resources (**Table 1**). In brief, the eCRFs include clinical scales and composite measures, clinician-reported outcome measure and PROMs, biomarker outcomes, and quantitative performance measures:

- The core dataset in the *ARCA Registry* comprises demographic data (with ethnic background), genetic diagnosis (with types of sequencing performed), different scores to measure disease severity like the Friedreich Ataxia Rating Scale (FARS) Functional Stage (15), the Scale for the Assessment and Rating of Ataxia (SARA) (16), systematic phenotyping using the Inventory of Non-Ataxia Signs (INAS) (17) with customized amendments (e.g., bradykinesia, ptosis, or the head impulse test), the presence and onset of typical clinical ARCA features (e.g., ataxia, epilepsy, cognitive impairment, and diabetes), ARCA biomarkers (serum and neurophysiology), and relevant comorbidities (including alcohol intake).
- The extended dataset adds questionnaires on health status and depression (EQ-5D and PHQ-9) (18, 19), disease-relevant medication and treatment effects, and a summary of MRI findings.
- Optional datasets include the possibility to report pediatric features (e.g., pregnancy and birth or developmental milestones), and the ARSACS Disease Severity Index as a disease-specific outcome measure (20).

The Patient's Global Impression of Change (PGI-C; core dataset) (21, 22) and the FARS Activity of Daily Living (ADL; extended datasets) (15) have recently been implemented as "anchor

TABLE 1 | Case report forms in the ARCA Registry.

Case report form	Items/description	Dataset
Demographics	Sex, year of birth, dexterity, ethnic background, consanguinity, siblings	Core
Diagnosis	Genetic diagnosis, type of sequencing so far, mutation/repeats (optional)	Core
Biomarkers	Biosampling for research, biochemical markers (e.g., AFP and Vit E), neurophysiology (e.g., NCS and MEP)	Core
Clinical features	Onset, course (progressive, episodic), multisystemic involvement (e.g., eyes, epilepsy, diabetes, heart, and kidney), cognition, behavior, and mainstream school	Core
Comorbidity	Alcohol, CNS/PNS unrelated to ARCA, psychiatric, and review of systems; with possible contribution to impairment	Core
SARA	Scale for the Assessment and Rating of Ataxia	Core
INAS	Inventory of Non-Ataxia Signs	Core
FARS Stage	functional staging, mobility milestones (e.g., cane, walker, and wheelchair)	Core (since 2020)
PGI-C	Patient's Global Impression of Change since last visit	Core (since 2021)
EQ-5D/EQ-5D-Y	Self-rated assessment of health status	Extended
PHQ-9	Patient health questionnaire on depression and anxiety	Extended
MRI	Summary of imaging features (e.g., atrophy and signal abnormalities)	Extended
Medication	Disease-specific; generic name, dose, target symptom, and outcome (optional)	Extended
FARS ADL	Activities of daily living	Extended (since 2021)
Pediatric features	Pregnancy, gestation, weight, head circumference, and development/walking	Optional
ARSACS DSI	Disease severity index for ARSACS	Optional

AFP, alpha-fetoprotein; MEP, motor-evoked potential; NCS, nerve conduction studies; CNS, central nervous system; PNS, peripheral nervous system.

measures," i.e., measures reflecting the patient's subjective experience of disease progression and functional impairment, which serve as reference measures helping to evaluate the significance of changes and effect sizes observed for the longitudinal clinical and biomarker data in the registry.

CROSS-CONTINENTAL MULTICENTER CAPTURE AROUND THE WORLD: THE CONTRIBUTING CENTERS

The *ARCA Registry* captures ARCAs from centers around the world (**Figure 2**). While initially mainly capturing centers from countries across Europe, the scope of the *ARCA Registry* has continuously grown in the last 5 years currently to now more than 30 sites from 15 countries. The registry has an active strategy to recruit centers from underrepresented countries to strengthen its global representation of ARCAs, regarding both disease prevalence and variable genetic/ethnic backgrounds. Participation is possible upon request. Minimum requirements are the commitment to contribute CRFs of at least the basic phenotype (see above) and to aim for longitudinal follow-ups.

FIGURE 2 | Contributing centers. The ARCA Registry is a growing, cross-continental multicenter registry, with more than 30 contributing sites in 15 countries by the end of 2020.

CURRENT DATA IN THE ARCA REGISTRY: A DESCRIPTIVE OVERVIEW OF 800 PATIENTS AND 1,500 VISITS

From its foundation in 2013 until now, more than 800 patients with almost 1,500 visits have been recruited to the *ARCA Registry*. In the past 5 years, there has been a considerable increase in longitudinal data, currently reaching up to eight annual follow-up visits in the first patients (**Figure 3A**). Follow-up core datasets including SARA or INAS from at least two visits and 13 sites are available in >300 patients. Follow-up extended datasets such as MRI summary data or the self-rated assessment of health status by EQ-5D from at least two visits are available from >200 patients. In addition to its longitudinal coverage, the *ARCA*

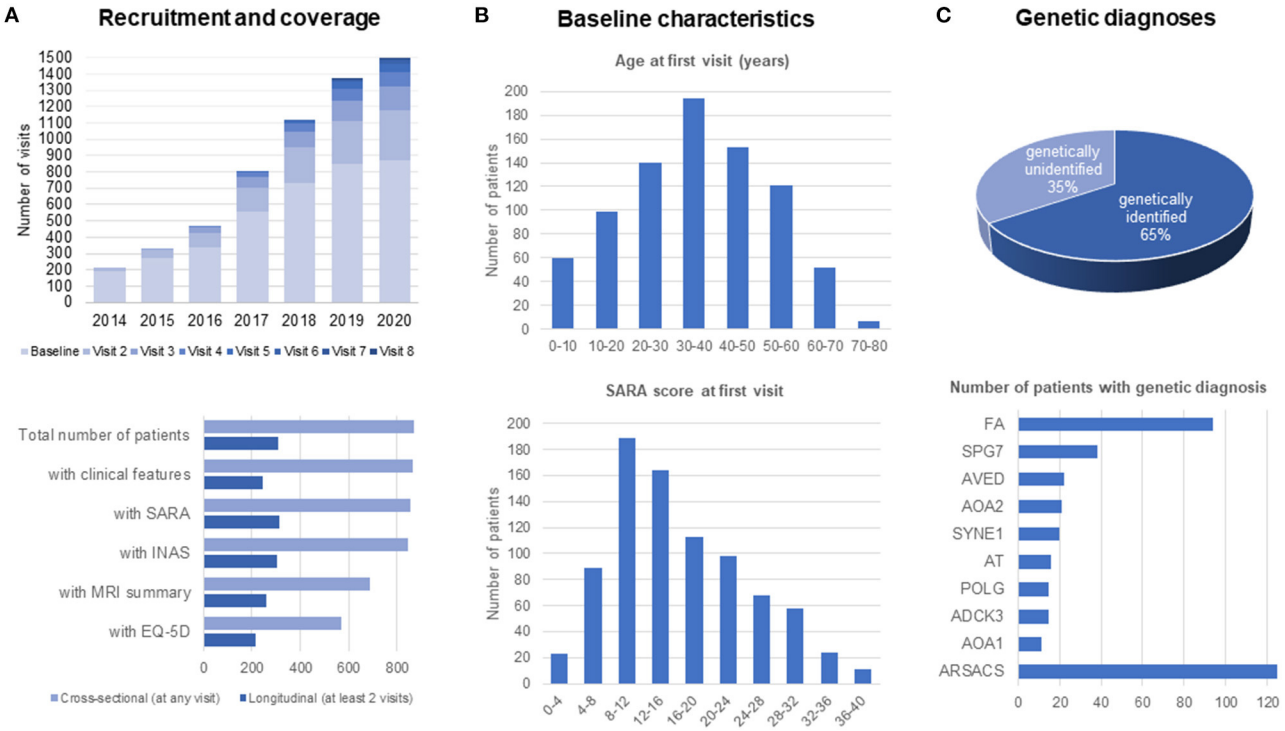

FIGURE 3 | Recruitment and patient characteristics in the ARCA Registry. **(A)** Recruitment and coverage. Recruitment of patients is continuous since 2013, reaching more than 800 patients with up to eight longitudinal assessments by the end of 2020. Longitudinal data with at least two assessments are available in about 200–300 patients. **(B)** Baseline characteristics of patients. Patients in the ARCA Registry span the full range of ages and disease stages. **(C)** Genetic diagnoses in the ARCA Registry, with a list of the 10 most frequent genetic causes.

Registry also captures patients with a broad range of ages and disease stages (**Figure 3B**). While—in keeping with the early onset of ARCAs (1, 2) −60% of patients have symptom onset before 40 years of age, 40% of patients have later onset, up to 80 years of age. Ataxia severity at baseline visits have been recorded as mild (SARA: ≤8), moderate (8–16), and severe (>16) in 16, 41, and 43% of patients, respectively. Sixty-five percent of patients have an established genetic diagnosis. The most frequent diagnoses in the *ARCA Registry* are ARSACS (∼120 patients, 14%), Friedreich ataxia (∼90 patients, 11%), and SPG7 (∼40 patients, 4%; see **Figure 3C** for the 10 most frequent ARCAs). Except for the enrichment of ARSACS—which is an overrepresentation due to the major contribution of participating sites in Quebec—the *ARCA Registry* provides prevalence data that are generally consistent with expectations from the literature (1, 23). Patients in the ARCA Registry who do not have a genetic diagnosis yet (currently 35%) are included in a coordinated NGS effort on a continuous basis to make a diagnosis or to identify novel genes, via the PREPARE-GENESIS platform (see above).

The *ARCA Registry* with its phenotypic and longitudinal data has enabled large clinico-genetic cohort studies to delineate the phenotypic spectrum and longitudinal disease progression of major and novel ARCAs. It thus fulfills the requirements of primary datasets that can be used to describe natural history progression models and plan treatment trials in almost all of the most frequent ARCAs, including pharmacometric modeling of outcome measures and treatment effects. For example, for *RFC1*-ataxia, it has helped to reveal multisystemic phenotypes mimicking cerebellar type multiple system atrophy and progressive supranuclear palsy, and hyperkinetic movement disorders such as chorea and dystonia, and provided first sample size calculations based on longitudinal SARA assessments (24). For *COQ8A/ADCK3*-ataxia, the *ARCA Registry* facilitated the delineation of clinico-genetic associations, and the longitudinal analysis of SARA scores has provided the first systematic, group-based evidence for a possible treatment effect of coenzyme Q10 (25). Similarly, the *ARCA Registry* has enabled the natural history of *POLG*-related ataxia to be documented through longitudinal SARA and INAS assessments (26). The systematic assessment of patients with as-yet-unknown genetic molecular diagnoses means that—when the underlying gene is discovered—there are already established longitudinal progression data, as exemplified for patients found to carry pathogenic variants in the novel ARCA gene *PRDX3* (27).

MEETING CRITERIA OF THE EUROPEAN RARE DISEASE REGISTRY INFRASTRUCTURE AND OF THE EUROPEAN MEDICINES AGENCY GUIDELINES FOR REGISTRY-BASED STUDIES

European authorities including the European Medicines Agency (EMA) have highlighted the potential of disease registries to provide real-world evidence that can complement preclinical,

clinical, and even post-marketing data especially for rare diseases (3). At the same time, however, they have also put forward clear standards for data collection and quality criteria for disease registries that aim to meet this goal.

European Medicines Agency Registry Standards for Data Collection

The *ARCA Registry* captures the key EMA data elements (3), including administrative information (e.g., site, contact dates, registry entry and exit dates, and reason for registry exit), patient data (e.g., age, sex, and alcohol as lifestyle factor), disease features (including diagnosis, disease duration, severity/staging, genetic information, and biochemical tests if appropriate), relevant comorbidities, and disease-related or relevant concomitant medical treatment (**Table 2**). The *ARCA Registry* is also enrolled in the European Directory of Registries of the European Rare Disease Registry Infrastructure (ERDRI.dor). As a constituent registry of the evolving Rare Neurological Disease Registry of the European Research Network on Rare Neurological Diseases (ERN-RND) (28), the *ARCA Registry* will provide the common data elements defined by the ERDRI (29), which adds more systematic coding of diagnosis (Orpha code), genetic diagnosis (HGVS) or phenotype (HPO), resources for research (e.g., biosampling and link to biobank), and a classification of disability (**Table 3**). As a *cross-disease database*, the ERN-RND registry collects general information on demographics, genetics, and phenotype, which allows the identification of centers that look after specific (and often genetically defined) patient groups. By contrast, as a *disease-group specific* database, the *ARCA Registry* collects complementary in-depth data to enable trial readiness in recessive ataxias. Both registries are well-interconnected, as the common ERN dataset can be easily extracted from the ARCA Registry and imported into the ERN-RND registry. This link with the ERN-RND registry also adopts the FAIR principles in the *ARCA Registry*, ensuring that its data are *f*indable, *a*ccessible, *i*nteroperable, and *r*eusable between countries (30).

European Medicines Agency Standards for Data Quality

In line with the EMA standards of data quality (3), the *ARCA Registry* aims for consistency, completeness, accuracy, and timeliness. Consistency of data is facilitated by common standardized eCRFs, by clearly defined variables and selection of questions with binary outcomes, and by the implementation of clinical scales with high interrater reliability, especially SARA, INAS, and FARS stage or ADL (15, 16, 31). Completeness of data in core datasets is automatically checked online as the first step of a continuous database-embedded monitoring process; this resulted in 95% (e.g., for clinical features of ARCAs) to 99% (e.g., for SARA or INAS) CRF completion rate. Following automated online control of data plausibility and consistency within and between different CRFs at the time of data entry, accuracy of data is afterwards controlled offline in the second monitoring step. Recruitment numbers including availability and completeness are regularly disseminated in systematic, standardized reports of networks that use the *ARCA Registry*.

TABLE 2 | Implementation of EMA guidelines on patient registries.

Data element	Data items	ARCA registry
Administrative information	Name of center	✓
	Availability of informed consent	✓
	Registry entry date	✓
	Registry exit date and circumstances	✓
	Dates of encounters	✓
Patient data	Age or birthdate	✓
	Gender	✓
	Lifestyle factors (alcohol, smoking, employment)	✓
Disease characteristics	Diagnosis	✓
	Date of clinical diagnosis or first consultation	✓
	Genomic information	✓
	Severity/stage	✓
	Milestones/outcomes/functional status	✓
Comorbidities	Relevant comorbidities (past/current)	✓
Disease-related and relevant concomitant treatments	Substance	✓
	Dose	✓
	Start date	(✓) *
	End date	(✓) *
	Route	✓
	Schedule	×
	Brand name	×
Pregnancy	Pregnancy status/outcome	×
PROMs	Patient-reported outcomes in clinical practice	• **
Safety reporting	adverse events/reactions	• ***

EMA, European Medicines Agency.
**Indirect assessment by longitudinal capture of current treatment; **planned; ***once closer to monitoring of drug treatments.*

NETWORKS USING THE ARCA REGISTRY AS THEIR INFRASTRUCTURE BACKBONE

The ARCA Registry is being used not only by more than 30 single sites but also by several leading ARCA networks in Europe and worldwide.

German Autosomal Recessive Cerebellar Ataxias/Early-Onset Ataxia Network

The German network on ARCAs and EOAs, launched in 2013 by the German Center for Neurodegenerative Diseases (DZNE), comprises five major German ataxia sites (Tübingen, Bonn, Munich, Magdeburg, and Rostock). The network has established the first version of the ARCA Registry, which was co-hosted by the Ataxia Study Group. Every effort was made to ensure that the Registry is fully aligned in its data fields and database system with other major SCA and sporadic ataxia registries (32), likewise hosted by the Ataxia Study Group. Since then, the German ARCA/EOA network has contributed >400 subjects to the ARCA

TABLE 3 | Implementation of common data elements of the EU Rare Disease platform.

Common data element	Data items	ARCA/ERN-RND registry
Pseudonym	Patient's pseudonym	✓
Personal information	Date of birth	(✓)*
	Sex at birth	✓
Patient status	Alive or dead	✓
	Date of death	✓
Care pathway	First contact with specialized center	✓
Disease history	Age at onset of first symptoms/signs	✓
	Age at diagnosis or first consultation	✓
Diagnosis	Diagnosis of rare disease in Orpha code	✓
	Genetic diagnosis in HGVS	✓
	Undiagnosed case in HPO terms	✓
Research	Agreement to be contacted for research	✓
	Consent to reuse data for other research	✓
	Biological sample available	✓
	Link to biobank where biosample is stored	✓
Disability	Classification of functioning/disability	✓

Restricted to year of birth.

Registry and provides monthly reports on its recruitments to the ARCA Registry.

PREPARE

PREPARE (Preparing for therapies in autosomal recessive ataxias) was launched in 2016 as an EU-funded (E-RARE JTC 2015) rare disease network; it was one of the first dedicated ARCA trial-readiness networks. Utilizing the complementary expertise from many ARCA centers and international ARCA networks, it was established to facilitate all crucial translational steps from genetic profiling (including discovery of new genes) to standardized preclinical trials, developing FDA-compliant outcome measures, and registry-inventoried transnational trial-ready cohorts, hereby fully building on the ARCA Registry as its backbone. The network began with seven centers from across Europe and Canada and has now expanded to >13 centers including centers in Turkey, Iran, and New Zealand. Using the extended site network and longitudinal dataset provided by the ARCA Registry, PREPARE has run phenotype and natural history studies on several ARCAs, e.g., RFC1 (24), COQ8A/ADCK3 (25), RFC1, POLG (26), and PRDX3 (27).

PROSPAX

The network PROSPAX (An integrated multimodal PROgression chart in SPastic atAXias), launched in 2020 and funded by the European Joint Program on Rare Diseases (EJP RD), will establish a paradigmatic integrated trial-ready model of disease progression and mechanistic evolution in spastic ataxias. It hereby builds on a rigorous trial-like multicenter natural history center study on the two flagship recessive ataxias ARSACS and SPG7, combining longitudinal clinician- and patient-reported digital and molecular outcomes for these spastic ARCAs. It unites all major European ARCA and HSP networks and includes Canadian ARCA centers (>7 centers) to run this transatlantic natural history study. PROSPAX hereby utilizes a "spin-off" study registry version, which directly builds on the ARCA Registry, with fully compatible pseudonymization procedure and eCRFs, and where datasets will be integrated into the ARCA Registry (and equally the HSP registry) at the end of the study. PROSPAX also draws on all the other components of the multi-component ARCA database cluster described above (ARCA biomaterial database, GENESIS, and ARCA multi-study database). By sharing the same core eCRFs and front-end with the HSP Registry used by the TreatHSP network (33), this spin-off version of the ARCA Registry enables direct cross talk with the HSP registry and joint analysis with HSPs, which is of high importance given the large genetic, molecular, and clinical overlap between ataxias and HSPs (34).

ARCA Global

ARCA GLOBAL and its sister platform SCA GLOBAL together comprise the Ataxia Global Initiative (AGI). The AGI presents a worldwide multi-stakeholder (academia, industry, and patient organizations) platform coordinating and preparing all necessary steps for trial readiness in autosomal-dominant (SCA GLOBAL) and autosomal recessive (ARCA GLOBAL) ataxias (7, 10). With establishing trial-ready cohorts and cross-center harmonized clinician-reported outcome measures and PROMs as one of its key tasks, the AGI uses the ARCA Registry as one of its key registries. This reflects the fact that the ARCA Registry already captures all outcome measures that were stipulated by the AGI as the common core set of clinical outcome measures to be used by ataxia centers worldwide. Moreover, the AGI builds on the ARCA Registry as one of its major trial-readiness resources, as this registry readily allows data-download and dataset preparation for further workup, e.g., by the Critical Path to Therapeutics for the Ataxias (CPTA) consortium of the Critical Path Institute (C-Path), which aims to prepare regulatory approval by the FDA and the EMA for clinical endpoints in genetic ataxias.

In addition, the SPATAX network, which includes all types (i.e., not only autosomal recessive) of ataxias and HSPs, has contributed subsets of data to the ARCA Registry.

LIMITATIONS AND OUTLOOK

The ARCA Registry faces several limitations and open challenges that remain be to be addressed:

- The sustainability of the ARCA Registry depends on strong commitment by the contributing centers as well as project-based funding, with fluctuations in patient recruitment, participating sites, and monitoring performance. Technical improvements and new software implementations often come along with variable latencies. Even the "core dataset" may exceed the possibilities of a clinical appointment in many ataxia centers, but further minimization of the core dataset

would need to be carefully weighed against the minimal required data necessary to really help in preparing trial readiness as well as against registry standards put forward by public authorities. The timeliness of monitoring is governed by batch monitoring of each site by site, which provides the opportunity for focused local revision of data and files but also leads to periodic delays for those sites that had just been monitored.

- Patients with the same genetically defined ARCA are still dispersed in different ataxia registries, e.g., because of identification of novel autosomal recessive genes in sporadic late-onset ataxia patients (e.g., RFC1) who have so far been collected in a sporadic ataxia registry (e.g., the SPORTAX registry).
- The ARCA Registry does not cover all aspects of each ARCA disease, or may cover it with measures that are too broad for clinical trial design in a specific ARCA disease. While the global phenotype or the progression of ataxia as measured by the SARA score is assessed, more fine-grained motor (e.g., walking speed) and especially a larger array of non-motor features (e.g., the cerebellar cognitive-affective syndrome) are not captured. Moreover, selected eCRFs and non-ataxia scales like the INAS were primarily implemented to systematically capture disease phenotypes but might show less responsiveness to change. Thus, for capturing the natural history of certain ARCAs, the ARCA Registry might need to be complemented by additional eCRFs. Registry spin-offs such as PROSPAX registry, however, exemplify that the registry infrastructure can indeed be readily adapted to meet the needs of such natural history studies.
- Finally, recruitment into the ARCA Registry is still biased toward patients from Europe or of European descent, which leads to an underrepresentation of ARCAs with other ethnic/genetic as well as sociocultural backgrounds. Structural disadvantages (especially availability of local person and funding resources for data-entry) and language barriers may hamper a more global dissemination of the ARCA Registry. The eCRFs, the registry software, and templates for an application to a local institutional review board are all available in English language, but additional translations and country-specific adaptations may help to increase the scope.

CONCLUSIONS

The ARCA Registry has (i) enabled the harmonization of clinical outcomes across ataxia centers around the world; (ii) has demonstrated its capacity to act as a centralized database for genotype–phenotype and natural history studies in the >100 ARCAs, already exemplified for *COQ8A*-, *RFC1*-, and *POLG*-related ataxias; and (iii) aggregates the necessary large-scale longitudinal progression datasets for calculating sample sizes, modeling trial designs and randomization procedures, and running pharmacometric models simulating treatment effect sizes for anticipated clinical trials. Given its adoption by many international ARCA sites and networks; its GCP, GDPR, and EMA compliance; its web-based data capture; and its connections to a constantly growing multi-component ARCA database cluster, the ARCA Registry is well-placed to become a global trial-readiness registry for ARCAs.

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AT and MS have designed and conceptualized the review and analyzed the data. All authors have contributed data to the ARCA Registry and/or drafted or revised the manuscript for intellectual content, contributed to the article, and approved the submitted version.

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REVIEW
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Enroll-HD: An Integrated Clinical Research Platform and Worldwide Observational Study for Huntington's Disease

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Established in July 2012, Enroll-HD is both an integrated clinical research platform and a worldwide observational study designed to meet the clinical research requirements necessary to develop therapeutics for Huntington's disease (HD). The platform offers participants a low-burden entry into HD research, providing a large, well-characterized, research-engaged cohort with associated clinical data and biosamples that facilitates recruitment into interventional trials and other research studies. Additional studies that use Enroll-HD data and/or biosamples are built into the platform to further research on biomarkers and outcome measures. Enroll-HD is now operating worldwide in 21 countries at 159 clinical sites across four continents—Europe, North America, Latin America, and Australasia—and has recruited almost 25,000 participants, generating a large, rich clinical database with associated biosamples to expedite HD research; any researcher at a verifiable research organization can access the clinical datasets and biosamples from Enroll-HD and nested studies. Important operational features of Enroll-HD include a strong emphasis on standardization, data quality, and protecting participant identity, a single worldwide study protocol, a flexible EDC system capable of integrating multiple studies, a comprehensive monitoring infrastructure, an online portal to train and certify site personnel, and standardized study documents including informed consent forms and contractual agreements.

Keywords: Huntington's disease, disease network, registry, clinical research platform, longitudinal observational cohort study, Enroll-HD

INTRODUCTION

Enroll-HD is a worldwide integrated clinical research platform that has, at its core, an observational study that has recruited almost 25,000 participants. In concert, the platform and study are designed to meet the clinical research requirements necessary to successfully develop and evaluate therapeutics for Huntington's disease (HD) (1). Enroll-HD is supported—financially, scientifically, and managerially—by CHDI Foundation, a nonprofit biomedical research organization solely

dedicated to collaboratively developing therapeutics that will substantially improve the lives of those affected by HD. Here, we outline the Enroll-HD platform's objectives, scope, operational infrastructure, associated research studies, clinical trial recruitment and site feasibility services, advisory/educational outreach, and governance structure, and provide an overview of the Enroll-HD observational study, including the cohort dataset and associated biosamples and how any researcher can access these resources.

HD is a rare, adult-onset, autosomally-dominant neurodegenerative disorder caused by the dynamic expansion of a polymorphic CAG repeat in exon 1 of the *huntingtin* (*HTT*) gene that encodes the mutant huntingtin (HTT) protein (2), with an estimated prevalence of 5–17 individuals per 100,000 (3, 4). CAG-repeat length is inversely related to age of onset; a CAG-repeat length between 8 and 26 is normal, whereas CAG-repeat lengths of 40 or more are fully penetrant. CAG repeats of 36–39 have reduced penetrance, and CAG-repeat lengths of 27–35 are considered intermediate alleles that do not cause pathology in the carrier but could expand to pathogenic length after transmission through the germline (5).

Clinically, HD is a prototypic monogenic neurodegenerative disease with a protracted but relentlessly progressive course. Although fluctuating and often worsening psychological manifestations are notable early on (6, 7), progressive involuntary movement disorder (predominantly chorea) is the definitive manifestation, with a simultaneous decline in cognitive function that, together, lead to severe morbidity, disability and, ultimately, death (8, 9). Classically, the appearance of motor dysfunction defines the clinical onset of disease, usually termed "motor onset" or "motor diagnosis." The CAP score (CAG-Age-Product, i.e., the product of excess CAG length and age) is a commonly used predictor of disease states in HD, including motor onset, and a reference for disease progression statistics (10). Currently, there are no disease-modifying therapeutics for HD but extensive ongoing research into HTT-lowering agents holds promise despite recent trial setbacks (11), as do gene-therapy approaches to silence the mutant gene.

ENROLL-HD PLATFORM

The Enroll-HD platform has been designed with the benefit of experience gained from several foundational HD studies—REGISTRY, PREDICT-HD, COHORT, and TRACK-HD/Track On-HD (12–16). Enroll-HD's main objectives are to improve the design and expedite the recruitment and execution of clinical trials and studies, improve our understanding of HD and the factors that influence disease progression, and promote good clinical care to improve the health of individuals with HD (**Figure 1** and **Table 1**). The platform was designed as a low-burden entry for participants into HD research, and provides a large, well-characterized, research-engaged cohort with associated clinical data and biosamples to facilitate recruitment into interventional trials and other research studies. The platform infrastructure and HD-expert network is available to trial/study sponsors from industry and academia to prospectively assess trial/study-design feasibility, identify clinical sites with eligible participants and appropriate resources, and assist with key operational aspects.

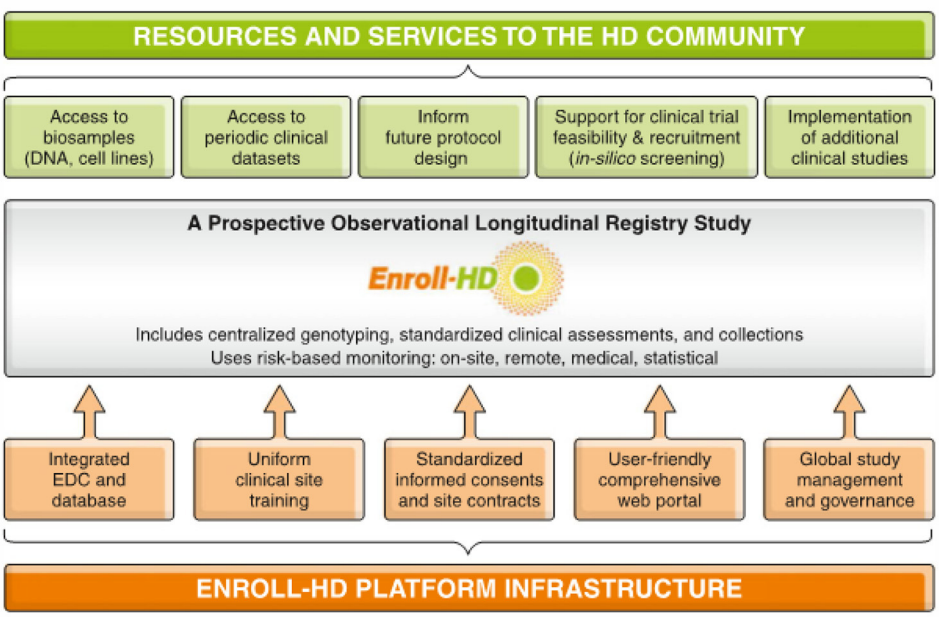

FIGURE 1 | Schematic outlining the Enroll-HD clinical research platform.

TABLE 1 | Objectives of the Enroll-HD observational study.

1. To provide a platform to support the design and conduct of hypothesis-testing clinical trials and studies by:

- identifying and developing novel assessment tools, clinical endpoints, and biomarkers,
- collecting longitudinal participant data to inform disease modeling studies,
- using "run-in" data to estimate rates of disease progression and inform the selection of potential trial participants.

2. To improve the understanding of the dynamic phenotypic spectrum and the pathobiological mechanisms of HD by:

- collecting observational data covering the cognitive, behavioral, and motor domains to estimate rates of progression and give insight into the neurobiology of HD,
- collecting data and biosamples to identify genetic and environmental factors that can alter disease progression and the HD phenotype,
- promoting exploratory studies that can give further insight into HD pathogenesis.

3. To promote the development of evidence-based guidelines to inform clinical decision making and improve health outcomes for those affected by HD by:

- identifying beneficial interventions (clinical, pharmaco-therapeutic, non-pharmacologic),
- facilitating the dissemination and implementation of current best clinical practice,
- providing a platform to conduct outcome research,
- promoting exploratory data analysis projects to identify processes to improve the healthcare of affected individuals and their families.

ENROLL-HD OBSERVATIONAL STUDY

Central to the clinical research platform is the Enroll-HD study (NCT01574053), a prospective longitudinal observational study that collects natural history data in HD gene-expansion carriers (HDGECs) and non-HDGEC controls. Established in July 2012, the Enroll-HD study has generated a large and rich clinical database with associated biosamples to support research, including developing disease-progression and prognostic biomarkers, identifying clinically relevant phenotypic characteristics, and establishing endpoints for interventional trials. As of January 1, 2021, Enroll-HD is operating worldwide in 21 countries at 159 sites across four continents—Europe, North America, South America, and Australasia—and has recruited 24,854 participants, 20,159 of whom are still currently enrolled, and 19,311 are currently active.

Two HD observational studies, REGISTRY and COHORT, were precursors to Enroll-HD. REGISTRY, a longitudinal observational cohort study conducted in Europe between 2004 and 2017 with >14,000 participants, was the result of strong collaboration and trusted partnership among preclinical and clinical investigators, patients and families in forming the European Huntington's Disease Network (EHDN). Enroll-HD has recruited 6,247 participants from REGISTRY who reconsented to continue participation and transfer their data.

Currently there is an emphasis on recruiting premanifest HDGEC participants into Enroll-HD, especially younger adults, to identify early biological and clinical characteristics with a view to designing clinical trials earlier in the disease course. Planning is now ongoing for a digital study, SelfEnroll, that will allow remote data collection and encourage younger participants to join.

PATIENT RECRUITMENT AND INFORMED CONSENT

Participants are recruited at specialized HD clinics following a written informed consent that includes research genotyping. Donating biosamples (venous blood) for banking purposes, pedigree charting and family history, linking of data collected across other studies, and willingness to be contacted to consider participation in future trials/studies are additional optional components that require specific participant consent.

STUDY POPULATION

The study population comprises HDGECs (CAG expansion ≥36 on the longer allele) classified as:

1. Manifest HD: HDGECs age 18 or older who are deemed to have diagnostic HD clinical features in the opinion of the site investigator (and confirmed at each subsequent visit).
2. Premanifest HD: HDGECs age 18 or older who are deemed not to have diagnostic clinical features of HD.
3. Juvenile HDGECs: HDGECs under the age of 18 years who are clinically diagnosed with juvenile HD.

The control population comprises individuals who do not carry the *HTT* gene expansion (CAG expansion <36 on the longer allele) and includes three categories:

1. Genotype negative: first- or second-degree relative of an HDGEC, who has undergone predictive testing and does not have the CAG expansion.
2. Family control: family member or other individual not genetically related to an Enroll-HD HDGEC participant (e.g., spouses, partners, and caregivers).
3. Community control: individual not genetically related to an HDGEC, who did not grow up in an HD-affected family and does not have a concurrent neurological disorder.

Individuals from known HD families who are at risk of inheriting the *HTT* CAG expansion but do not wish to know their genetic status can enter the study as "genotype unknown" (see below).

ENROLL-HD CLINICAL DATA AND BIOSAMPLE COLLECTION

At their annual study visit, each participant is required to complete a core battery of assessments; extended and optional assessments are completed at the discretion of the PI and participant, respectively (**Table 2**). Visits vary between 45 min (core battery only) and 2.5 h (core battery plus extended and optional assessments), and data are collected regarding demographics, medical history (including comorbidity and pharmacotherapy), and clinical assessment of four HD domains—motor, cognition, behavior, and function. The Unified Huntington's Disease Rating Scale (UHDRS) is a widely used

TABLE 2 | Enroll-HD data elements and assessments.

Data element/assessment	Core[a]	Extended[b]	Optional[c]
General			
Investigator determined classification of participant	X		
Sociodemographic data	X		
HD clinical characteristics	X		
Medical history	X		
Comorbid conditions	X		
Current therapies (pharmacotherapies, non-pharmacologic therapies, and nutritional supplements)	X		
Reportable event monitoring	X		
Motor			
UHDRS '99 Motor	X		
UHDRS '99 Diagnostic Confidence Index	X		
Timed Up and Go		X	
30 second Chair Stand Test		X	
Function			
UHDRS '99 Total Functional Capacity	X		
UHDRS '99 Function Assessment Scale	X		
UHDRS '99 Independence Scale	X		
Behavior			
Problem Behaviors Assessment (Short)	X		
Hospital Anxiety and Depression Scale		X	
Snaith Irritability Scale		X	
Columbia Suicide Severity Rating Scale		X	
Cognition			
Symbol Digit Modality Test	X		
Stroop Word Reading Test	X		
Verbal Fluency Test (Category)	X		
Stroop Color Naming Test	X		
Stroop Interference Test		X	
Trail Making Tests (Parts A and B)		X	
Verbal Fluency Test (Letters)		X	
Mini Mental State Examination		X	
Global assessment			
Clinical Global Impression		X	
Quality of Life			
Short Form Health Survey 12v2		X	
Caregivers Quality of Life Questionnaire		X	
Health Economics			
Client Services Receipt Inventory		X	
Work Productivity and Activity Impairment-Specific Health Problem		X	
Genotyping			
Research CAG genotyping	X		
Local CAG genotyping (predictive/diagnostic) (if applicable)			
Family history			X
Biosample donation			X

[a]Completed or updated at each annual visit. [b]Completed at the discretion of the principal investigator. [c]Completed at the discretion of the participant.

standardized clinical assessment that has been extensively evaluated for reliability and internal consistency (17). The UHDRS motor and diagnostic confidence index subscales characterize the clinical HD motor phenotype and capture the rater's diagnostic confidence regarding HD motor onset in participants, respectively. Total Functional Capacity, Functional Assessment and Independence Subscales of the UHDRS '99 assess participants' functional status, and cognition is assessed using the Categorical Verbal Fluency Test, Symbol Digit Modality Test, and Stroop Color, and Word Reading Test.

Identity is protected by assigning an HDID code to each participant, generated *via* a secure system; no personally identifying information is stored in the EDC system, and a participant's data from another study can be linked using their HDID. Additionally, all participants are assigned both a lab ID and a research ID for use by the biorepository and other service providers (such as travel reimbursement), respectively, to avoid widespread sharing of their HDID. Similarly, a recoded participant ID, not the HDID, is used in publicly available dataset releases to further reduce risk of identification.

Research CAG genotyping is conducted at a central laboratory in Italy for every participant following their baseline visit, including those designated as "genotype unknown." The CAG-repeat length defined in this research genotyping is used for all data analysis but is not reported back to the site investigator or participant. Participants who enroll as "genotype unknown" are reassigned to the appropriate HDGEC or genotype negative category at the time of data release under the recoded participant ID; the genetic status of these participants is not linked to their HDID as an extra protection. Data on reportable events—suicide attempts, completed suicide, mental health events requiring hospitalization, death from any other cause—are also captured. Most participants consent to donate biosamples; family history (pedigree) may also be recorded, subject to participant consent. The Data Dictionary and annotated eCRF at https://enroll-hd.org/for-researchers/technical-support/ contain a complete list of variables.

ENROLL-HD STUDY COHORT

Data extracted from the database in October 2020 was released in December 2020 as periodic dataset 5 (PDS5; details below). This dataset contains data on 21,116 Enroll-HD participants (16,120 HDGECs and 4,996 non-HDGECs) from 71,682 visits (baseline and follow-up visits); 55,975 of these were Enroll-HD visits, with the remainder from REGISTRY ($N = 14{,}737$) and *ad hoc* sources such as unscheduled visits ($N = 970$). Participant sociodemographic distribution and disease characteristics (**Table 3**), the longitudinal data available (**Figure 2**), and the geographic distribution (**Figure 3**) and HD category distribution at baseline (**Figure 4**) of the Enroll-HD cohort are summarized. A detailed overview of the Enroll-HD PDS5 dataset is available at https://enroll-hd.org/for-researchers/technical-support/.

ENROLL-HD SUPPORTED STUDIES

Studies that use Enroll-HD platform services—clinical support and/or infrastructure services—are referred to as supported studies. Studies built into the platform and that recruit participants within the large Enroll-HD cohort (utilizing their annual-visit data and the extensive network of sites and investigators) and that involve additional assessments are referred to as nested studies; currently, these studies are investigating biomarkers and clinical or patient-reported outcomes. These arrangements reduce participant burden while allowing biomarker and outcome-related data to be linked. Ongoing and proposed supported and nested studies included below.

TABLE 3 | Enroll-HD participant characteristics - sociodemographic and basic disease variables (PDS5 dataset; release 2020-10-31v1).

	Total participants	HDGECs	Controls
Number of participants	21,116	16,120	4,996
Sex, female; *N* (%)	11,783 (56%)	8,727 (54%)	3,056 (61%)
Age at baseline; mean (SD)	47.9 (14.0)	48.7 (14.0)	46.7 (14.8)
Education level (ISCED[a]; 0–3); *N* (%)	10,119 (48.1%)	8,130 (50.7%)	1,989 (40.0%)
Mean CAG length (SD)	N/A	43.6 (4.1)	20.2 (3.6)
CAP score[b] at baseline; mean (SD)	N/A	97.2 (24.0)	N/A

[a] *ISCED education level dichotomized into binary variable: 0–3 and 4–6. Precise definitions for these categories vary by country. In the UK, 0–3 captures everything up to and including sixth form (i.e., further education), 4–6 captures university and beyond (i.e., higher education).* [b] *CAP score calculated using the formula CAP = AGE × (CAG−30)/6.49, which is standardized such that CAP = 100 at estimated age of disease onset.*

HDClarity

HDClarity (NCT02855476) began in 2016 as a prospective nested annual CSF and blood (serum and plasma) collection initiative recruiting HDGECs and control participants from Enroll-HD. The large longitudinal cohort and the comprehensive phenotypic data linked to each CSF biosample are advantageous in validating potential biofluid biomarkers that were previously assessed in cross-sectional or longitudinal studies (18, 19), and to date more than 600 participants have donated CSF and blood biosamples at 24 study sites.

ImageClarity

ImageClarity is a proposed nested study that will recruit eligible HDClarity participants to undergo an annual multisequence structural and functional modality brain magnetic resonance imaging (MRI). The goal is to expedite identification of biomarkers relevant across the full spectrum of pathological events, especially those occurring in very early stage HD, to evaluate disease progression in interventional trials.

iMagemHTT

iMagemHTT (11C) (NCT03810898) is an ongoing nested PET-imaging study evaluating the binding and kinetic properties of the radioligand [^{11}C]CHDI-180R and its suitability to measure aggregated mutant HTT in the brain, especially the basal ganglia, of HDGECs compared to non-HDGEC controls. This is an adaptive study that includes five go/no-go decision points dependent on the radioligand's promise that is being conducted at three sites in Belgium and the Netherlands.

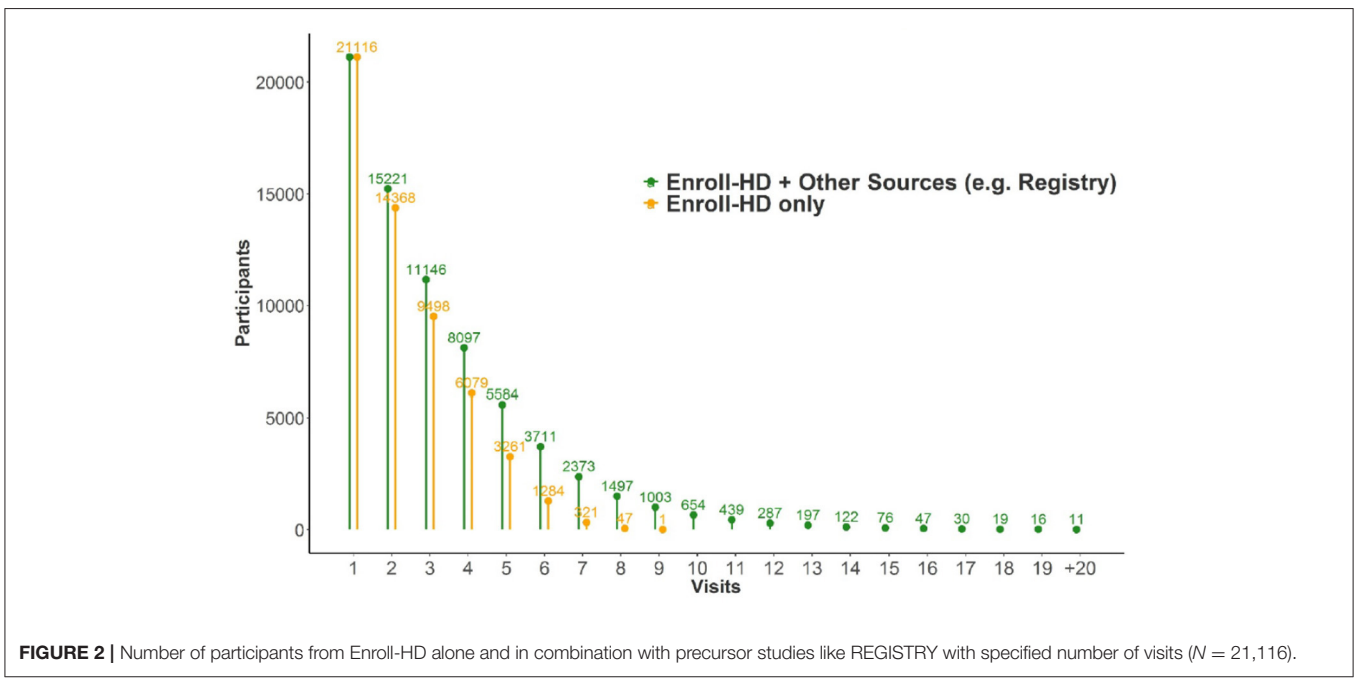

FIGURE 2 | Number of participants from Enroll-HD alone and in combination with precursor studies like REGISTRY with specified number of visits (*N* = 21,116).

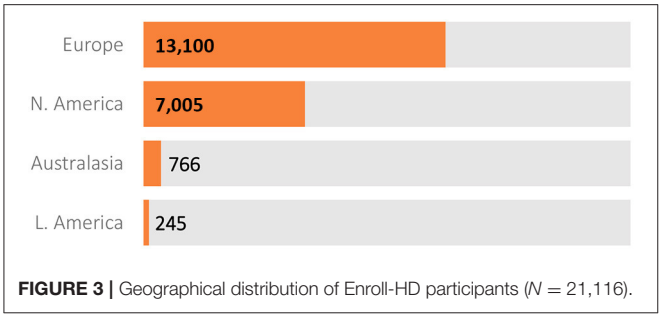

FIGURE 3 | Geographical distribution of Enroll-HD participants ($N = 21,116$).

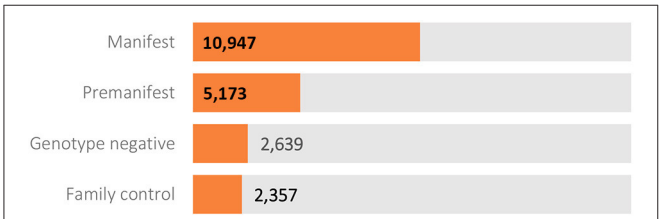

FIGURE 4 | Participant category at Enroll-HD baseline visit ($N = 21,116$).

iMagemHTT (F-18) is a proposed nested study currently in late-stage preclinical development that will comparatively evaluate multiple ^{18}F-labeled, next-generation mutant HTT-targeting PET tracers. This first-in-human study will be conducted at a single site at Johns Hopkins University.

Origin-HD

Origin-HD is a proposed nested cross-sectional, multi-site, observational study to investigate differences in germline and somatic *HTT* CAG-repeat instability and identify genetic modifiers of intergenerational CAG instability. Semen and blood biosamples from at least 1,000 male HDGECs will be collected at a single visit at around 40–50 sites.

Later Stage HD Assessments

LSA is a nested study developing two assessments to measure critical milestones during advanced HD when travel is especially burdensome to participants; importantly, these assessments need to be conducted with the assistance of a participant companion, either in-person or remotely. The two-part study will evaluate the internal consistency, reliability, validity and clinimetric properties of the two assessments in development, initially at four sites and subsequently at 20 sites in the US and UK.

FOCUS-HD

The proposed FOCUS-HD nested study aims to longitudinally validate FuRST 2.0—a patient reported outcome assessment sensitive to early functional changes in premanifest HDGECs—and HD-CAB—the only available fit-for-purpose HD cognitive assessment battery (20)—to define effect-size estimates of cognitive decline for power analyses in interventional trials. Cognitive pretesting for FuRST 2.0 was conducted at four Enroll-HD sites with eligible candidates and required resources.

PACE-HD

PACE-HD (Physical Activity and Exercise Outcomes in Huntington's Disease; NCT03344601) is an ongoing interventional supported study conducted in about 120 HDGEC participants (21) that uses several aspects of the Enroll-HD platform—including core assessment data, onsite monitoring, and participant eligibility—to significantly reduce participant and site burden and speed study start-up by simplifying EDC system development.

ENROLL-HD DATA AND BIOSAMPLE AVAILABILITY

To accelerate HD therapeutic research and development, the platform provides any verified researcher access to the high-quality datasets and biosamples from Enroll-HD and nested studies. Enroll-HD clinical data are shared with the research community through periodic datasets (PDS) and specified datasets (SPS). PDSs are prepared from the Enroll-HD study database every 1–2 years and include a large majority of the collected variables. Prior to release each PDS undergoes stringent QC and coding procedures during which certain variables are transformed, aggregated, or suppressed (excluded) to protect participant identity. Access to non-transformed, non-aggregated, or suppressed data may be obtained through SPS request, subject to approval by the Scientific Review Committee (SRC) that weighs the scientific merit of the proposed project against the increased risk for participant identification. Renewable biosamples (lymphoblastoid cell lines, and DNA from such) can be obtained without review but non-renewable biosamples from Enroll-HD (DNA from whole blood, peripheral blood monocytes, EDTA plasma) or HDClarity (LiHep plasma, serum, CSF, cells from CSF) require merit review by the SRC.

Any researcher employed by a recognized research organization can open an Enroll-HD access account to obtain data and biosamples from Enroll-HD (or nested studies that make such resources available), subject to the researcher's employer/institution signing the appropriate data/biosample use agreement(s). Datasets with online click-through agreements, such as PDSs, are accessible immediately, whereas SPS and non-renewable biosample requests require SRC approval. All biosample requests require completion of a material transfer agreement (MTA) with wet ink signature. More detailed access information is available at https://enroll-hd.org/for-researchers/access-data/.

RESEARCH USING ENROLL-HD DATA AND BIOSAMPLES

Enroll-HD datasets and biosamples have been used by researchers in academia, industry, and healthcare around the world to advance HD research. Enroll-HD PDSs have been downloaded 632 times and 124 SPS requests fulfilled. Further details on data users and their projects can be found at https://enroll-hd.org/for-researchers/current-enroll-hd-data-projects/, and a list of the publications using Enroll-HD data and/or

biosamples is at https://enroll-hd.org/for-researchers/scientific-publications/. A series of articles providing useful advice on Enroll-HD data analysis is at https://enroll-hd.org/analysis-tools/.

Genome-wide association studies (GWAS) have already been conducted using biosamples from over 9,000 (soon to be 14,000) HDGEC participants, most of them from Enroll-HD as well as other HD clinical studies (22, 23). Using the difference between the CAG-length-predicted and actual age at motor onset as the predictor, three modifier signals at two loci within the *FAN1* and *MLH1* genes (involved in DNA maintenance and mitochondrial regulation) were found that affect motor onset. Drug development programs investigating genes involved in DNA mismatch repair are now underway.

Predictive and causal modeling for predictors of HD progression has also been undertaken using Enroll-HD data. Given the large number of healthy controls it was possible to establish cognitive and motor norms to determine the effects of natural aging and contrast these with HD progression. Normative curves by age, sex, and education have been estimated for the 0.05, 0.25, 0.50, 0.75, and 0.95 quantiles from the distribution of observed cognitive, motor and functional scores. Extreme quantile estimates for each measure can be considered as boundaries for natural aging, outside which can be attributed to HD pathology (24). Propensity score weighting to examine the effects of educational level, employment status, and tobacco, alcohol, recreational and prescription drug use on HD progression within the Enroll-HD cohort found that light and moderate alcohol use were not significantly linked to HD progression (25), contrary to a previous report (26). However, participants treated with antidepressants were likely to progress faster than non-users (27). A probabilistic machine learning-driven disease progression model that quantitatively describes complex changes around the time of clinical diagnosis has recently been developed; it has identified nine disease states within HD and can estimate the anticipated duration of each state (28). Further ongoing work to determine the likelihood that a participant will transition to the next state within a certain time period may assist in participant stratification to improve clinical trial design.

ENROLL-HD PLATFORM SERVICES

Scientific and operational support services are available to industrial and academic sponsors of HD interventional clinical trials and research studies. The Clinical Trial Committee (CTC) provides sponsors an opportunity to consult with highly experienced HD clinicians and researchers through all stages of protocol development regarding study design, endpoint strategy, and study population. CTC members review the study design, including the proposed assessments and endpoints, and ensure that participant interests are protected. Provided the protocol is rational and reasonable, the CTC issues a letter of acceptance that the sponsor can present to IRBs/ERBs.

The CTC also manages the HD Clinical Trial Site Certification program that uses an industry-standard framework to determine whether sites have the appropriate infrastructure to support clinical trials. Sites that are not part of Enroll-HD can apply for site certification to enable participation in other HD-related studies.

The Enroll-HD operational infrastructure also offers trial/study start-up and conduct to sponsors, with site feasibility assessment, country and site selection, eligible participant availability (in silico feasibility assessment), and liaison with local IRB/ERBs if requested.

ENROLL-HD OPERATIONAL INFRASTRUCTURE

Enroll-HD operates under a single study protocol worldwide and is supported by a comprehensive operational and oversight management infrastructure. Data quality and integrity is fundamental, and quality control and assurance measures designed to maximize data consistency, completeness, and accuracy are implemented and monitored at the participant, site, and study level. Enroll-HD's governance structure includes the CTC and SRC (see above), the Scientific Oversight Committee—which provides overall scientific strategy, ensures adherence to study and platform goals, and reviews non-interventional study protocols—and the Data Safety Monitoring Committee that reviews reportable events and addresses safety concerns. Together these committees ensure effective oversight of the platform and guidance to study site investigators and staff, regulatory authorities, researchers, and trial/study sponsors.

Centralized EDC System

Enroll-HD uses a centralized multi-study electronic data capture (EDC) system that hosts Enroll-HD and supported/nested study data, providing a common data collection and reporting framework for every study site. This ensures the format and definitions of data entered are consistent on an intra- and inter-site level, cross-sectionally and longitudinally, in turn facilitating the application of centralized data QC procedures. System prompts, guidance documents, automated data validity checks, and automated field completion built into the EDC help ensure that accurate information is entered.

Data Monitoring and Site Management

Remote centralized statistical monitoring (CSM) of data is conducted at the participant and site level by the data monitoring team. Participant-level data are subject to remote QC that checks cross-sectionally and longitudinally for consistency, completeness, and plausibility. Site-level CSM of compliance, performance, and data quality involves outlier analyses targeting site-specific operational performance metrics and clinical data, which may result in follow-up action (communication and training) with sites. All Enroll-HD sites are routinely monitored to review source data and ensure compliance with the study protocol, Good Clinical Practice (GCP), and other applicable regulations.

Sites also receive quarterly bulletins, semi-annual site metrics cards, and other communications. Tailored feedback and support

are provided to improve underperforming sites and corrective action plans implemented when appropriate.

Training

Investigators undergo standardized site-initiation training regarding the protocol, data entry and informed consent. To ensure consistency and accuracy in data collection, assessment-specific rater training and online certification is conducted through the Enroll-HD Clinical Training Portal (UHDRS motor certification and GCP), interactive webinar training (PBA-s), *ad hoc* training (in response to site-specific training needs), and self-study of online training materials. Onsite monitors also undergo standardized training to ensure consistency.

Informed Consent and Participant Confidentiality

Recoded participant-level data and biosamples from Enroll-HD are made available to the research community under three stipulations: data and biosamples are shared subject to participants' informed consent and in accordance with GDPR (EU) and HIPAA (US) laws; a data use agreement (DUA) and/or material transfer agreement (MTA) must be signed and adhered to by any requester; and the risk of identification from their clinical data is assessed for all participants before data release and remedial steps taken for those above a predetermined risk threshold.

Participant identification recoding uses two data safety methods: the safe harbor method that removes 18 variables that may directly identify individuals (e.g., birth date, visit date, and site location), and the expert determination method where statisticians assess all individuals' risk of identification.

Engagement With HD Advocacy Organizations

Enroll-HD works closely with HD patient advocacy organizations to engage their constituents in ongoing clinical research and provide updates on new developments in Enroll-HD. *Enroll!*, the Enroll-HD newsletter, features articles about ongoing HD research and clinical trials/studies, including Enroll-HD platform studies, as well as human interest stories from various stakeholders, and is translated into all the languages within Enroll-HD. The Enroll-HD platform also functions as a hub that enables collaborative projects with patient advocacy organizations.

DISCUSSION

Since its launch 9 years ago, Enroll-HD has developed into a multi-faceted clinical research platform that can support various clinical studies and interventional trials and has recruited almost 25,000 participants into the core worldwide longitudinal observational study, amassing a rich clinical database that is made available to any researcher. Enroll-HD has successfully incorporated all the required functionalities and provides a dynamic environment that supports clinical research to identify and develop biomarkers and clinically-relevant endpoints, validate novel patient-reported outcome measures, facilitate clinical trial recruitment and site feasibility, and provide expert scientific input on trial/study protocols. Enroll-HD is meeting its remit to better enable the clinical research needs required to develop HD therapeutics.

In addition to being a clinical research platform and observational study, Enroll-HD is also a patient registry, defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose" (29). Such registries, particularly those for rare diseases, are especially useful when they make the collected longitudinal data widely available for research purposes, including to assess disease course (30).

In recent years there has been a drive to recruit more premanifest individuals, particularly young ones, into Enroll-HD to further understand this phase of the disease in preparation for clinical trials in, and subsequent treatment of, such individuals as early as possible. CHDI is now actively planning a companion study, SelfEnroll, that will remotely monitor premanifest participants' disease continuously rather than once a year.

Despite the demonstrated commitment of academic researchers, funding agencies, pharmaceutical companies, and patient advocacy groups, drug development for rare disorders has been hindered by sequestered research with insufficient collaboration (31) that often leads to duplicative and uncoordinated work. Enroll-HD is a cohesive endeavor to consolidate HD clinical research—thereby minimizing costs and patient burden while maximizing collaboration—that is designed to initiate, support and maintain additional studies planned by CHDI or other industrial/academic sponsors that can capitalize on the assembled research infrastructure, including the centralized EDC system, study site and participant selection, feasibility assessments, online training portal, standardized operating procedures, and access to a comprehensive network of HD clinicians and researchers.

AUTHOR CONTRIBUTIONS

SS and CS initially developed the manuscript concept and outline. SS wrote the first draft. JW, JL, and EN wrote sections of the manuscript. SN edited the manuscript throughout and added some further sections. All authors contributed to manuscript revision and have read and approved the submitted version.

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