MULTIPLE SCLEROSIS JOURNAL | MSJ

Future Perspective

Landscape of MS patient cohorts and registries: Recommendations for maximizing impact

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Multiple Sclerosis Journal
1–8
DOI: 10.1177/1352458517698250

Abstract:

Background: There is a growing number of cohorts and registries collecting phenotypic and genotypic data from groups of multiple sclerosis patients. Improved awareness and better coordination of these efforts is needed.

Objective: The purpose of this report is to provide a global landscape of the major longitudinal MS patient data collection efforts and share recommendations for increasing their impact.

Methods: A workshop that included over 50 MS research and clinical experts from both academia and industry was convened to evaluate how current and future MS cohorts could be better used to provide answers to urgent questions about progressive MS.

Results: The landscape analysis revealed a significant number of largely uncoordinated parallel studies. Strategic oversight and direction is needed to streamline and leverage existing and future efforts. A number of recommendations for enhancing these efforts were developed.

Conclusions: Better coordination, increased leverage of evolving technology, cohort designs that focus on the most important unanswered questions, improved access, and more sustained funding will be needed to close the gaps in our understanding of progressive MS and accelerate the development of effective therapies.

Keywords: Progressive MS, cohort study, registries, data collection, patient-reported outcomes, biospecimens

Date received: 26 December 2016; revised: 10 February 2017; accepted: 12 February 2017

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Introduction

Although clinical trials are the gold standard for obtaining rigorous clinical data, their focus on individual agents and their relatively short duration limit their value for answering critical questions related to the evolution of multiple sclerosis (MS), particularly as it transitions into the progressive phase. For most individuals with MS, the progressive course can take more than 10 years to develop and then evolves over many decades, thus much longer follow-up is needed. Registries and cohorts that follow patients over a long time in a real-world environment have the potential to identify factors contributing to disability progression, individuals who are likely to benefit from early treatment, and the most effective treatment approach. Furthermore, if detailed physician- and patient-reported data are accompanied by both magnetic resonance imaging (MRI) of the central nervous system (CNS) and biological samples, significant insight into the pathophysiology of progressive MS could be achieved, which would likely accelerate development of disease-modifying treatments.

Substantial investments are being made in a growing number of efforts collecting detailed phenotypic and genotypic data from groups of MS patients. Improved awareness of existing and planned cohorts and registries is needed to better coordinate these efforts and maximize the impact of the limited resources available to support them. Greater coordination will reduce duplication, enhance scientific credibility, and sharpen the focus on the most critical unanswered questions in MS. The purpose of this report is to provide a landscape of the current and planned longitudinal MS patient data collection efforts and propose recommendations for increasing their impact.

Landscape

MS cohort and registry studies have provided fundamental information about MS prevalence and incidence, rates of disability progression, and life expectancy. More contemporary studies of correlations between outcome and demographic/clinical data,[1] the presence or absence of associations between exposure and MS risk,[2–4] disease-modifying therapy use and disability progression,[5] and a proposed algorithm defining secondary progressive MS[6] have added to our understanding of the natural history of MS.

A growing number of data collection efforts are underway (Table 1). These efforts differ in their genesis, recruitment criteria, types and frequencies of data collected (clinical, patient-reported outcomes, biospecimens, imaging), catchment area, and duration of follow-up, among others.

The Swedish MS Registry (EIMS) is an example of a clinical data set that has contributed to our understanding of the impact of disease-modifying therapy. The effort has enrolled approximately 80% of patients with MS in Sweden. Due to the use of a national personal ID in Sweden, data can be linked with other Swedish databases to investigate associations between MS and factors such as employment-related factors, co-morbidities, and other epidemiological factors. Similarly, the Danish Multiple Sclerosis Registry (DMSR) has enrolled nearly all patients with MS in Denmark and has advanced the understanding of MS epidemiology.

MSBase is a physician-driven observational registry that is based in Australia and has recruited more than 42,000 participants from 38 countries. Although this collection does not include biospecimens or imaging data, its large size and broad catchment area position it to address critical questions concerning the impact of disease-modifying treatment on the natural history of MS.

Other cohorts have been prospectively designed primarily for research purposes. The Expression, Proteomics, Imaging and Clinical (EPIC) study, which is based at the University of California, San Francisco, is an observational cohort of over 500 people with MS who have been carefully studied since 2004. The Comprehensive Longitudinal Investigation of Multiple Sclerosis (CLIMB) is a large-scale, long-term study of about 1500 MS patients based at Harvard's Brigham and Women's Hospital. Recently, these two groups have combined efforts to form the Serially Unified Multi-center Multiple Sclerosis Investigation (SUMMIT) with the purpose of building an open platform to elucidate risk factors that affect disease progression. The New York State MS Consortium is another research effort that collects numerous types of data including patient-reported outcomes, quality of life measures, co-morbidities, insurance information, and disease-modifying therapy use, among others.

The North American Research Committee on MS (NARCOMS) and iConquerMS are voluntary patient-driven registries that collect data from MS patients about treatments, quality of life, and other factors related to living with MS.

Strengths and limitations of existing cohorts

Existing cohorts have amassed large collections of data, and several have also established accompanying biospecimen repositories. Several cohorts are working toward standardization of data and the methods for biospecimen, imaging, and data collection.[7] Others are working toward creating standardized imaging protocols. Some registries are able to link to other databases (i.e. payor databases), which should enhance their ability to advance knowledge of the natural history of MS and address critical questions related to response to therapy and disability progression.

Many (but not all) efforts have been designed without a specific hypothesis and participant selection criteria. This "convenience cohort" approach allows the flexibility to ask different questions, but is limited by the unknown generalizability of the observations and conclusions. In addition, harmonizing data from different cohorts is often difficult due to the use of different data elements as well as incompatible platforms and standards (often developed "in house"). Changes in technology can also make comparisons challenging. Many cohorts are not readily accessible to other qualified investigators. Inconsistencies can result from different and evolving criteria used for diagnosing and defining MS subtypes, time to an event such as progressive disease, follow-up times, terminology, data collection methods, and physician perceptions and opinions. Unlike clinical trials, randomization is not possible, which introduces a risk for biases and confounders that can make interpretation of the results challenging. Cohorts that rely on patient-reported outcomes may also contain recall and referral bias.

Recommendations

In February 2016, the US National Institute of Neurological Disorders and Stroke (NINDS) and the National Multiple Sclerosis Society convened a

Table 1. Sample of major MS cohorts and registries underway.

Cohort	URL	Primary contact-email	Key attributes	Open Access	No. of active participants/ registrants	Enrollment dates	Geographic catchment	CIS/ relapsing/ progressive	Plasma/ serum/cells	DNA/RNA	MRI imaging data/frequency	Physician-reported outcomes	Patient-reported outcomes
Accelerated Cure Project	www.acceleratedcure.org	sloud@acceleratedcure.org	High-quality biospecimens with extensive associated data	Yes	3220 total (1787 MS+controls)	2006–2012	10 MS clinics in the United States	Yes/yes/yes	Yes/yes/yes	Yes/yes	No images, only descriptors	Yes	Yes
British Columbia MS Database	http://epims.med.ubc.ca/	helen.tremlett@ubc.ca	Longitudinal, clinical, linkable to population-based health administrative data	Upon request	Total (1980–present): 10,000+	August/1980–present	British Columbia, Canada	Limited/yes/yes	Study-specific collection only	Study-specific collection only	Study-specific collection only	Yes	Study-specific collection only
Centre d'Esclerosi Múltiple de Catalunya (Cemcat)	https://www.cem-cat.org/	xavier.montalban@cem-cat.org	Longitudinal deep phenotyping	No	2500	1995–present	Catalonia, Spain	Yes/yes/no	Yes/yes/yes	Yes/yes	Baseline, year 1, every 5 years	Yes	No
Cleveland Clinic Knowledge Program		COHENJ@ccf.org	Longitudinal follow-up of clinic population	No	4900	2007–present	Ohio/ Midwest, also national and international	Yes/yes/yes	No/no/no	No/no	Yes, ad hoc	Yes	Yes
Comprehensive Longitudinal Investigation of MS (CLIMB)	http://www.climbstudy.org	tchitnis@rics.bwh.harvard.edu	Longitudinal deep phenotyping	Upon request	2100	February 2000–present	Boston/ greater New England	Yes/yes/yes	Yes/yes/yes	Yes/derived	Yes, annual	Yes	Subset
Danish MS Registry (DMSR)	http://www.ms-research.dk/	melinda_magyari@dadlnet.dk	Longitudinal, nationwide, population based	Yes by application	25,000	Since 1956	Denmark	Yes/yes/yes	No/no/no only CSF	No	No	Yes	Yes
iConquerMS	https://www.iconquerms.org/for-researchers	iConquerMS@acceleratedcure.org	Patient-powered research; longitudinal; patient-reported outcomes	Yes	3200 and growing	February 2015–present	Primarily US-based with no geographic limitations (worldwide)	Yes/yes/yes	Not yet	DNA collection piloted; expansion with funding	No	No, in development	Yes
Italian MS Register		registroitalianosm@aism.it	Longitudinal prospective cohort	Upon request	36,200	2014–present	Italy	Yes/yes/yes	No/no/no	No	Yes/annual	Yes	No
Kaiser Permanente, SoCal		Annette.M.Langer-Gould@kp.org	Multi-racial/ ethnic population representative of geographic region. Incident cases with complete health record; matched controls for >600 participants in the MS Sunshine Study	No	~1500 total; MS Sunshine Study >600 incident cases with detailed environmental exposures, genetic information, and stored sera/plasma	January 2008–present entire incident cohort; subgroup 2011–2015	Southern California	Yes/yes/yes (total cohort and MS Sunshine study; also includes NMO)	Yes/yes/no from MS Sunshine Study	Yes/yes for MS Sunshine Study	Yes, standard of care, all cases	Yes	Subgroup

(Continued)

Table 1. (Continued)

Cohort	URL	Primary contact-email	Key attributes	Open Access	No. of active participants/ registrants	Enrollment dates	Geographic catchment	CIS/ relapsing/ progressive	Plasma/ serum/cells	DNA/RNA	MRI imaging data/frequency	Physician-reported outcomes	Patient-reported outcomes
MS Clinic Database and Registry, Health Sciences Centre, Winnipeg		rmarrie@exchange.hsc.mb.ca	Clinical registry for recruitment for research studies; core data can be used for record review/linkage studies	No	2061	April 2011–present	Manitoba, Canada/ northwestern Ontario	Yes/yes/ yes	No/no/no	No/no	MRI reports could be reviewed/ clinical judgment	Yes	Yes
MS genetics-expression, proteomics, imaging clinical (EPIC)	http://msepicstudy.com/	hausers@neurology.ucsf.edu	Longitudinal deep phenotyping with 85% at 10+ years	Upon request	530	June 2004–present	San Francisco, CA	Yes/yes/ yes	Yes/yes/yes	Yes/yes	Yes, annual	Yes	Yes
MSBASE	https://www.msbase.org	info@msbase.org	Longitudinal, multinational. Min. dataset = demographics, EDSS, relapses, DMT exposure, diagnostic test info	Access within collaborative group	42,248 (as of 11 October 2016)	January 2004–present	Global—38 participating countries	Yes/yes/ yes NMO	Yes/yes/no in subsets	Yes/no in subsets	No images, only descriptors	Yes	Subset
NARCRMS	http://narcrms.org/	krammohan@med.miami.edu, dj9d@virginia.edu	Longitudinal registry, clinician collected, soon to include MRI. Eventual interface with NARCOMS	Yes	Currently 15, but goal of 1000 in 5 years	June 2016 to present	North America	Yes/yes/ yes	Eventually, RFP in development	No/no	Yes, annual	Yes	Yes
North American Research Committee on MS (NARCOMS)	http://narcoms.org/	MSregistry@narcoms.org	Longitudinal self-reporting	No	11,000	1996–present	Global, mainly the United States	Yes/yes/ yes	No/no/no	No/no	No	No	Yes
Norwegian MS Registry & Biobank	https://helse-bergen.no/avdelinger/nevroklinikken/nevrologisk-avdeling/nasjonal-kompetansetjeneste-for-multippel-sklerose/norsk-ms-register-og-biobank	kjell-morten.myhr@helse-bergen.no	Longitudinal follow-up phenotyping	By application	ca 8000	2001	Norway	No/yes/yes	No/yes/no	Yes/no	Yes, prospectively for 2016	Yes	Yes from 2017

Table 1. (Continued)

Cohort	URL	Primary contact-email	Key attributes	Open Access	No. of active participants/ registrants	Enrollment dates	Geographic catchment	CIS/ relapsing/ progressive	Plasma/ serum/cells	DNA/RNA	MRI imaging data/frequency	Physician-reported outcomes	Patient-reported outcomes
NY State MS Consortium	http://www.nysmsc.org/nyregistry.asp	BWeinstock-Guttman@KaleidaHealth.org	Longitudinal data collection, historical cohort with no DMT use, patient-reported and clinical outcomes	Yes for affiliated centers	9650 enrolled/18,000 follow-ups	1996–present	New York, some Northwestern Pennsylvania	Yes/yes/yes	Subset	Subset	Subset	Yes	Yes
OFSEP (Observatoire Français de la Sclérose en Plaques)	www.ofsep.org	sandra.vukusic@chu-lyon.fr	Longitudinal clinical and MRI follow-up of French MS patients	Yes	58,000	2011 (but many local databases using the EDMUS software started before)	France	Yes/yes/yes (+RIS and NMOSD)	Yes/yes/yes only in subgroups	Yes/yes only in subgroups	Yes, standardized acquisition, frequency according to local prescription	Yes	No, in progress
OPTIMISE	http://www.optimise-ms.org/	p.matthews@imperial.ac.uk	Clinical data entry portal/database allows DICOM image upload with data management option in transMART platform	Yes	1000 and growing	Retrospective–present	UK	Not formally audited, all types	No/no/no but intended with future accrual	Limited transcriptomics	Partial	Yes	Wikihealth tool being added 2017
PROMOPRO-MS		giampaolo.brichetto@aism.it	Longitudinal, population-based, collected every 4 months, demographic, disease course, onset, treatments, physician-reported and patient-reported outcomes	For research, by application	2000 and growing	Longitudinal every 4 months from 2014	Italy	No/yes/yes	No/no/no	No/no	No, but intended with future integration with Italian NeuroImaging Network Initiative	Yes	Yes
SMSC (Swiss MS Cohort)	https://smsc.rodano.ch/	jens.kuhle@usb.ch claudio.gobbi@eoc.ch	Prospective, observational, standardized demographic, clinical, MRI data and biospecimens, focus on newer disease-modifying drugs	No, open for nested projects with a member of Scientific Board	1040/1102	June 2012–present	7 Swiss MS Centers	Yes/yes/yes	Yes/yes/yes selection	Yes/no	Yes, annual	Yes	No
Sonya Slifka Longitudinal Multiple Sclerosis Study		sminden@partners.org	Longitudinal, population-based, collected every 6–12 months, demographic, disease, health care use, costs, QOL; some on care providers, biospecimens for 150 newly dx	Yes with permission	4634	2000–2010	United States	No/yes/yes	Yes/yes/no for subset	Yes/yes for subset	No	No	Yes

(Continued)

Table 1. (Continued)

Cohort	URL	Primary contact-email	Key attributes	Open Access	No. of active participants/ registrants	Enrollment dates	Geographic catchment	CIS/ relapsing/ progressive	Plasma/ serum/cells	DNA/RNA	MRI imaging data/frequency	Physician-reported outcomes	Patient-reported outcomes
SUMMIT	www.summit.org	summit@partners.org	Longitudinal deep phenotyping; enriching with newly dx, rx naive cohort	Yes	1028	2000–present	Boston/ greater New England and greater San Francisco area	Yes/yes/ yes	Yes/yes/yes	Yes/yes	Yes, annual	Yes	Yes
Swedish MS Registry	http://www.neuroreg.se/en.html/multiple-sclerosis-research	Jan.hillert@ki.se	Longitudinal data on >80% of the prevalent patient population, mean 6 years follow-up	For research, by application	15,974 at 61 centers	1995–present +1000 patients annually	Sweden	Some/yes/ yes	In separate overlapping projects, 10,000 patients	In separate overlapping projects, 10,000 patients	High level info on #lesions and #Gd+ and #new lesions or MS-indicative yes/no on 32,000 scores, that is, 2–3 per contributing patient	Yes	Yes
US Network of Pediatric MS Centers: Pediatric MS and other Demyelinating Diseases Database	http://usnpmsc.org/	charlie.casper@hsc.utah.edu	Pediatric, longitudinal	No	1700	May 2011–present	USA (participating centers)	Yes/yes/no	No/no/no	No/no	Yes, as clinically ordered	Yes	No
Veterans Health Administration MS National Data Repository	http://www.va.gov/MS/index.asp	Steven.Leipertz@va.gov	United States VHA Medical Records	VHA Personnel and Affiliated	50,000	October 1998–present	United States	No/yes/yes	No/no/no	No	No	No	No

MS: multiple sclerosis; CIS: clinically isolated syndrome; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; NMO: neuromyelitis optica; EDSS: Expanded Disability Status Scale; DMT: disease-modifying drug therapy; QOL: quality of life; RFP: Request for Proposals; NMOSD: Neuromyelitis Optica Spectrum Disorder; RIS: Radiologically Isolated Syndrome; VHA: Veterans Health Administration.
This list of MS cohort studies and registries is not exhaustive, and additional cohorts are under development.

workshop that included over 50 thought leaders from around the world to evaluate how current and future MS cohorts might be better leveraged to answer urgent questions about progressive MS. The attendees included experts with academic, industry, and funders perspectives that developed the following recommendations.

Recommendation 1: create a federated network of cohorts

The landscape analysis revealed a significant number of largely uncoordinated parallel efforts. The participants recommended that strategic oversight and direction would greatly streamline and leverage existing and future efforts. This could be accomplished by creating a federated network of cohorts and engaging in regular activities that could be coordinated by the NINDS, industry, and advocacy organizations like the National MS Society. The first steps by this network should be to prioritize research questions and develop a data sharing model.

Recommendation 2: standardize data collection and management

Standardizing the collection and management of large data sets would greatly enhance the ability to share data and perform meta-analyses with aggregated data. The NINDS has developed common data elements for MS (https://www.commondataelements.ninds.nih.gov/MS.aspx#tab=Data_Standards) and recommends that MS cohorts incorporate this standard. The data standards established by the Clinical Data Interchange Standards Consortium (CDISC) for MS (http://www.cdisc.org/standards/therapeutic-areas/multiple-sclerosis) would also increase the likelihood that data sets could be confederated and used to answer clinically relevant questions in progressive MS. Additional standardization will likely be needed.

Recommendation 3: identify and prioritize research questions

Many cohorts were not designed to answer specific research questions; nonetheless, they should be mined to determine whether they can reveal significant insights into the natural history or pathogenesis of progressive MS or generate new hypotheses. Prioritizing research questions and focusing resources on high-priority research would likely accelerate progress and better leverage limited resources. Meeting participants identified several high-priority research topics including: (1) developing ways to measure progression, (2) developing proof-of-concept outcome measures, and (3) identifying prognostic factors. The participants recommended that meetings with a broader representation of stakeholders including patients be held to establish a consensus on the most critical research questions.

Recommendation 4: encourage collection of physician- and patient-reported outcomes

Patient- and physician-reported data should be integrated to provide a more complete picture of living with MS. Patient-reported outcomes are likely to better capture patient experiences with MS including psychosocial experiences, bladder/bowel/vision problems, employment, cognitive disability, quality of life, fatigue, and pain. Information from private practice is currently not being captured, but could also provide valuable additional data.

Recommendation 5: encourage technological innovation

Researchers should continue to utilize new technologies such as electronic health records and data collection methods. The utility of these approaches will be greatly enhanced by the creation of a minimum set of clinical and imaging standards to be used in all MS interactions. Likewise, investigators should incorporate guidelines for biospecimen collection,[7] and centralization of these repositories should be encouraged.

Recommendation 6: develop a universal informed consent process

Patient privacy and associated laws, including Health Insurance Portability and Accountability Act (HIPAA) in the United States, vary across countries, and consent forms should be developed to allow sharing of data with other countries. Restrictive consent forms can hamper research, but overly broad consent may make obtaining approval from local institutional review boards difficult.

Recommendation 7: provide sustainable funding

Cohorts are largely funded by grants with terms limited to 2–5 years. The most important unanswered questions in progressive MS will require following cohorts of patients for 10 years or longer, and thus, more sustained funding will be required. Better coordination and less duplication of data collection efforts should optimize the use of limited resources and allow for more sustained investments.

Conclusion

Despite significant investments in MS cohort studies, major gaps in our understanding of the natural history of MS progression remain. Better coordination, increased leveraging of evolving technology, a focus on the most important unanswered questions, improved access, and more sustained funding are key requirements for closing the gaps in our understanding of progressive MS. This knowledge will likely accelerate the development of effective therapies for progressive MS.

Acknowledgements

The authors thank Kristine De La Torre for medical writing assistance.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AJT has received honoraria/support for travel for consultancy from Eisai, Optum Insight, and Excemed. He received support for travel from the International Progressive MS Alliance, as chair of their Scientific Steering Committee and the National MS Society (USA) as member of their Research Programs Advisory Committee. He is Editor-in-Chief of *Multiple Sclerosis Journal*. RJF has received personal consulting fees from Actelion, Biogen, Genentech, Mallinckrodt, MedDay, Novartis, and Teva; has served on advisory committees for Biogen Idec and Novartis; received research grant funding from NIH, National MS Society, and Novartis; and receives salary support to Cleveland Clinic for his role as Managing Director of the NARCOMS registry. BFB, UU and KL have no conflicts to declare.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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