Future Perspective

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

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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

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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, the presence or absence of associations between exposure and MS risk, disease-modifying therapy use and disability progression, and a proposed algorithm defining secondary progressive MS 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. 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
| Cohort                                | URL                                      | Primary contact-email               | Key attributes                                                                 | Open Access | No. of active participants/registrants | Enrollment dates | Geographic catchment | CS/relapsing/progressive | Plasma/serum/cells | DNA/RNA | MRI imaging data/frequency | Physician-reported outcomes | Patient-reported outcomes |
|---------------------------------------|------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|-------------|---------------------------------------|------------------|------------------------|------------------------|------------------------|-----------------|----------------------------|--------------------------|--------------------------|
| Accelerated Care 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           | Yesyes          | 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/yesyes          | Yes/yesyes            | Yesyes          | Study-specific collection only | No                       | Study-specific collection only |
| Centre d’Eucrosi Multiple de Catalunya (Cemcat) | https://www.cemcat.org/ | xavier.monta@cem-cat.org | Longitudinal deep phenotyping                                                   | No          | 2500                                  | 1995–present      | Catalonia, Spain          | Yes/yesno            | Yes/yesyes           | Yesyes          | Baseline, year 1, every 5years | Yes                      | No                       |
| Cleveland Clinic Knowledge Program    | http://ohncms.org                        | COHENJ@ccf.org                      | Longitudinal follow-up of clinic population                                      | No          | 4900                                  | 2007–present      | Ohio/Midwest, also national and international | Yes/yesyes          | No/no/no             | No/0            | Yes, ad hoc              | Yes                      | Yes                      |
| Comprehensive Longitudinal Investigation of MS (CLIMB) | http://www.dimbstudy.org | tchkins@rcs.bwh.harvard.edu | Longitudinal deep phenotyping                                                   | Upon request | 2100                                  | February 2000–present | Boston/greater New England | Yes/yesyes          | Yes/yesyes           | Yes/herived    | Yes, annual              | Yes                      | Subset                   |
| Danish MS Registry (DMSR)             | http://www.ms-research.dk/              | melinda_magyar@dadmst.dk             | Longitudinal, nationwide, population based                                      | Yes by application | 25,000                                | Since 1956        | Denmark                | Yes/yesyes            | No/no/no             | No/0            | DNA collection piloted; expansion with funding | No                       | No                       |
| 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/yesyes          | No/yesyes             | Notyet           | No, in development       | Yes                       | Yes                      |
| Italian MS Register                   | registroitalianosm@asim.it              |                                     | Longitudinal prospective cohort                                                 | Upon request | 36,200                                | 2014–present      | Italy                   | Yes/yesyes            | No/no/no             | Yes/0            | 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/yesyes (total cohort and MS Sunshine study; also includes NMO) | Yes/yesyes or no from MS Sunshine Study | Yes/yesyes        | Yes/yesyes               | Yes, standard of care all cases | Yes                      |

(Continued)
| Cohort | URL | Primary contact-email | Key attributes | Open Access | No of active participants/registrants | Enrollement 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 | maurre@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 report could be reviewed/clinical judgment | Yes | Yes |
| MS genetics-expression, proteomics, imaging clinical (EPIC) | http://msepicstudy.com/ | | Upon request | 530 | June 2004–present | San Francisco, CA | Yes/yes/yes | Yes/yes/yes | Yes/yes/yes | Longitudinal deep phenotyping with 85% at 10+ years | Yes, annual | Yes |
| MSBASE | https://www.msbase.org | info@msbase.org | Access within collaborative group | 42,248 (as of 11 October 2016) | January 2004–present | Global—38 participating countries | Yes/yes/no in subsets | 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 | Currently 15, but goal of 1000 in 5 years | June 2016 to present | North America | Yes/yes/no in subsets | Yes/yes/no in subsets | Yes/yes/no in subsets | Eventually, RFP in development | Yes, annual | Yes |
| North American Research Committee on MS (NARCOMS) | http://narcoms.org/ | MSregistry@narcoms.org | Longitudinal self-reporting | 11,000 | 1996–present | Global, mainly the United States | Yes/yes/no in subsets | Yes/yes/no in subsets | Yes/yes/no in subsets | No | Yes | No | No | No | Yes |
| Norwegian MS Registry & Biobank | https://helse-bergen.no/avdelinger/neurologi/avdeling/national-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 | Yes/no | Yes/no | Yes/no | Yes, prospectively for 2016 | Yes | Yes from 2017 |
| Cohort                  | URL                          | Primary contact - email          | Key attributes                                                                 | Open Access | No of active participants/registrants | Enrollment dates | Geographic catchment | CS/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/registry.asp | BWeinstock-Guttman@KaleidaHealth.org | Longitudinal data collection, historical cohort with no DMT use, patient-reported and clinical outcomes | Yes for all listed centers | 9650 enrolled/18,000 follow-ups | 1996–present | New York, some Northwestern Pennsylvania | Yes/yes | Subset | Subset | Subset | Yes | No, in progress |
| 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 only in subgroups | Yes/yes only in subgroups | Yes | Yes | No, in progress |
| OPTIMISE | http://www.optimise-ms.org/ | pm.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 |
| PROMOPROMO-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 Neuro Imaging Network Initiative | Yes | Yes |
| SMSC (Swiss MS Cohort) | https://smsc.rodano.ch/ | jens.kuhle@usb.ch claudio.gobbi@ege.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 selection | Yes/no | Yes | 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 | Yes/yes | Yes/yes/no for subset | Yes/yes for subset | No | No | Yes |

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| 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 | 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             | Yes         | Yes, annual                  | Yes                         | Yes                         |                               |                             |                             |
| Swedish MS Registry          | http://www.neuroreg.se/en.html/multiple-sclerosis-research | Jan.hillert@ki.se          | Longitudinal data on >90% 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           | Yes/no/no/no            | Yes/no/no/no            | Yes         | 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/no/no/no             | No/no/no/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.Lei@pea.va.gov | United States VHA Medical Records | VHA Personnel and Affiliated | 50,000                              | October 1993–present | United States | Noyes/yes             | No/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 federated 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, 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.

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