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Myositis registries and biorepositories: powerful tools to advance clinical, epidemiologic and pathogenic research

Lisa G. Rider[a], **Katalin Dankó**[b], and **Frederick W. Miller**[a]

[a]Environmental Autoimmunity Group, Program of Clinical Research, National Institute of Environmental Health Sciences, National Institutes of Health (NIH), DHHS, Bethesda, MD

[b]Division of Immunology, 3rd Dept. of Internal Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary

Abstract

Purpose of review—Clinical registries and biorepositories have proven extremely useful in many studies of diseases, especially rare diseases. Given their rarity and diversity, the idiopathic inflammatory myopathies, or myositis syndromes, have benefited from individual researchers' collections of cohorts of patients. Major efforts are being made to establish large registries and biorepositories that will allow many additional studies to be performed that were not possible before. Here we describe the registries developed by investigators and patient support groups that are currently available for collaborative research purposes.

Recent findings—We have identified 46 myositis research registries, including many with biorepositories, which have been developed for a wide variety of purposes and have resulted in great advances in understanding the range of phenotypes, clinical presentations, risk factors, pathogenic mechanisms, outcome assessment, therapeutic responses, and prognoses. These are now available for collaborative use to undertake additional studies. Two myositis patient registries have been developed for research, and myositis patient support groups maintain demographic registries with large numbers of patients available to be contacted for potential research participation.

Summary—Investigator-initiated myositis research registries and biorepositories have proven extremely useful in understanding many aspects of these rare and diverse autoimmune diseases. These registries and biorepositories, in addition to those developed by myositis patient support groups, deserve continued support to maintain the momentum in this field as they offer major opportunities to improve understanding of the pathogenesis and treatment of these diseases in cost-effective ways.

Correspondence to: Lisa G. Rider, MD, Environmental Autoimmunity Group, National Institute of Environmental Sciences, National Institutes of Health, DHHS, Clinical Research Center Room 4-2352, 10 Center Drive, MSC 1301, Bethesda, MD 20892-1301, USA, Phone: +1 301 451- 6272, Fax:+1 301 451-5588, riderl@mail.nih.gov.

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INTRODUCTION

Clinical registries, which are organized databases of information about certain diseases, along with biorepositories, which are catalogued collections of biological specimens from subjects, have been developed by many different groups for a number of purposes. Clinical registries include national administrative efforts and health care systems' tracking of medical utilization, costs, and outcomes, including such databases as the Social Security Death Index, from which mortality information may be gleaned [1**;2] or national health care registration systems that can be used to estimate disease prevalence in epidemiologic research [3*]. Registries may also include those that involve investigator-initiated research, with data collection that may include epidemiology, clinical features, outcomes, disease activity and damage assessments, and assessment of responses to therapies. When such clinical data are linked to biospecimens, including serum, DNA, or tissue biopsy samples, they become powerful tools to explore and define disease pathogeneses, biomarkers, and genetic and environmental risk factors. Such collections of information and specimens have had a major impact in understanding the epidemiology and prognosis of various disorders, especially the rare diseases, in which progress for an individual researcher at a single center could be slow and inadequately powered, hampered by a lack of adequate patient information and specimens.

MYOSITIS REGISTRIES AND BIOREPOSITORIES

In the case of the idiopathic inflammatory myopathies, or myositis syndromes, some of the early investigator-initiated efforts in this area involved collections of systematic data on larger numbers of patients allowed some of the first careful phenotypic descriptions of these diseases and their clinical [4] and serologic [5] classifications. More recently, registries have greatly assisted in better appreciating the incidence and prevalence of myositis phenotypes in different areas [6–9, 10*], as well as their costs and resource usage [11;12].

For this review, we queried myositis researchers from multiple specialties and across the globe in order to develop a catalog of clinical research registries and biorepositories that are currently available for collaborative research. Although this list of 46 myositis registries may not be comprehensive, we nevertheless hope that it will be helpful to myositis investigators and enhance collaborative research efforts toward better understanding of these rare autoimmune disorders. In this regard, the principal investigator(s) and their contact information are provided for each registry.

The number and scope of myositis registries have grown substantially over the past several decades. This is leading to larger studies to enable approaching research questions with adequate statistical power. The multicenter national and international registries and their

linkage to large biorepositories allow new research questions to be evaluated. Among the 46 registries, we estimate that there are currently more than 30,000 myositis patients involved, although there may be overlap in the enrollment of patients among some studies.

We have categorized this listing of myositis research registries into different groups (see Tables 1, 2, and 3) [13**,14,15*,16–28,29*,30*,31–37,38*,39–42,43* 44,45,46*,47–60,61**,62,63*,64*,65, 66*,67,68**,69*,70*,71,72*,73–82,83*,84–90,91*,92–107,108*, 109,110**,111** 112–115,116*,117, 118*,119–121, 122**,123–129, 130*,131–133,134*, 135,136*, 137–149,150*,151,152,153*,154*] based on the types of myositis included, as well as whether the registries are regional, national, or international in scope. Thirteen registries are international and 33 are national or regional registries. Sixteen registries include all types of myositis, with a predominance of adult forms of myositis (Table 1), 19 include only adult forms of myositis (Table 2), and 11 registries have only juvenile forms of myositis (Table 3). For the registries in which adult and juvenile types of myositis are included, adults generally outnumber juveniles. Registry sizes vary from fewer than a hundred patients to several thousand. A number of the registries are continuing to enroll patients; thus, the enrollment numbers reflect those at the time this article was prepared for publication. The scope and research questions being asked vary considerably, with the most common research focusing on clinical features, phenotype definitions, epidemiology, outcomes, assessment of disease activity, treatment responses, and pathogenesis. The majority of registries (37 of 46) also have associated biorepositories. Sera or plasma samples are the most common specimens collected, but DNA and muscle biopsies are often banked, and skin biopsies, calcinosis specimens, and RNA are available in some.

The largest myositis registry to date, Euromyositis (https://www.euromyositis.eu/), was established in 2008 as a registry for myositis patients, with support from a European Union project “Autocure” by three European centers with interest in clinical myositis research involved in the Autocure project.. The registry has expanded globally through the network Myonet (http://www.myonet.eu) to include 3000 myositis patients, primarily with dermatomyositis and polymyositis, but also including inclusion body myositis (IBM), juvenile dermatomyositis (JDM), statin-associated myopathy, anti-synthetase syndromes, necrotizing myopathies, and other myopathies. The registry includes demographics, clinical features, treatment, and longitudinal outcome data, as well as core set activity and damage outcome assessment measures, as defined by the International Myositis Assessment and Clinical Studies Group (IMACS) [13**]. To date, the registry has enhanced our understanding of myositis-specific autoantibody (MSA) phenotypes [14, 155] and contributed a large number of samples to the myositis genetics consortium that completed a genome-wide association study [15*] in dermatomyositis patients of European descent. Future anticipated work includes the development of prognostic biomarkers, improved serologic testing for myositis autoantibodies, studies of gene–environment interactions, and facilitation of multicenter myositis therapeutic trials.

RESEARCH ADVANCES THROUGH MYOSITIS REGISTRIES AND BIOREPOSITORIES

The development of large myositis registries has led to extensive efforts among a number of studies to carefully phenotype patients based not only on clinical features, but also based on the presence of myositis autoantibodies. These registries have been helpful in refining our knowledge of the spectrum of traditional clinicopathologic [98,110,*** 129,137,144,154*]] and MSA phenotypes [5,14,34,59,60,64*,78,79,85,110**,111**, *130] and in understanding how such phenotypes differ among populations around the world. In studies [98,110**,129,137,144,154*] of JDM, for example, the criteria used to diagnose patients, clinical features at illness onset, and initial medications used for treatment have been documented in several national registries, with some differences between countries.

Studies in several different investigator-initiated and national myositis registries have led to a rapid appreciation of the association of recently identified myositis autoantibodies with serious illness features and outcomes: the association of anti-TIF1γ autoantibodies with photosensitive skin rashes and a chronic illness course in juvenile dermatomyositis (JDM) and with cancer-associated dermatomyositis in adults [29*,49,50,112]; of anti-MJ autoantibodies with calcinosis in JDM and adult dermatomyositis [29*,51,131,132]; of anti-MDA-5 autoantibodies with rapidly progressive interstitial lung disease, cutaneous ulcerations, and a high mortality in dermatomyositis [16,30*,44,49,52,53,87,88]; and an immune-mediated necrotizing myopathy associated with autoantibodies to hydroxymethylglutaryl-coenzyme A reductase [31–33,61*,65, 86]. These registries should also lead to the recognition of phenotypes not currently known.

A study of myositis phenotypes has been undertaken through a large registry that is attempting to define new classification criteria for myositis and its clinicopathologic phenotypes, known as the International Myositis Classification Criteria project. Through the collection of a large number of clinical, demographic, and laboratory variables on almost a thousand myositis patients from around the world, and through use of novel statistical approaches, promising new criteria are emerging to classify myositis and its subgroups that should improve inclusion criteria for natural history and treatment studies and improve our understanding of pathogenesis by using common definitions of these illnesses that have higher sensitivity and specificity [18].

Through large international collaborative research networks, such as IMACS and the Pediatric Rheumatology International Trials Organisation, new measures have been developed and validated to assess myositis disease activity, manifestations related to reversible inflammatory changes, and damage, that is, the chronic long-term changes associated with previously active disease, as well as illness sequelae and adverse reactions to medications. Core set measures of myositis activity have been agreed upon to be assessed in all therapeutic trials for dermatomyositis, polymyositis, and JDM [101,119,123–126], and these have been combined to provide preliminary definitions of improvement that represent clinically meaningful change to be used as therapeutic trial endpoints [19,120,127]. These core set measures have also been utilized in preliminary definitions of moderate and major response clinical response, representing larger degrees of clinical improvement, and of

clinically inactive disease for JDM [121,122**]. Consensus in the conduct of myositis clinical trials and standardized therapeutic approaches has also been achieved [99,156]. These developments have led to standardized reporting of outcomes in therapeutic trials [24] and an increase in the number of myositis therapeutic trials, including trials of new biologic therapies for myositis [80,102,103,120,133,157, 158].

Attention to outcomes beyond the core set measures is a recent development [123]. Standardized assessment of skin activity and damage in myositis through cutaneous assessment tools [20,72*,73,74] has been developed, and assessment of muscle dysfunction, including exercise intolerance [145,150*], and pulmonary and cardiac involvement [71,146–148], is emerging with the use of new, more sensitive radiographic measures. A focus on capturing patient-reported outcomes, including the severe impact of myositis on health-related quality of life, is now beginning [75,96]. Development of measures for IBM is also receiving attention, as well as standardized muscle biopsy scoring, as a useful adjunct in therapeutic trials or in studies of prognosis [134*].

Tools such as the Myositis Damage Index have enabled further understanding of long-term outcomes and the appreciation that most adult and juvenile myositis patients have moderate to severe damage on long-term follow-up as well as ongoing active disease [81,148;,149,151, 152,159,160]. Interest in long-term outcomes and prognosis has also received attention more generally, including the recognition of risk factors for chronic illness course in JDM [35,104], associated malignancies or autoimmune overlap syndromes [36,37,66*], or certain sequelae of disease, such as calcinosis, lipodystrophy [100,104,113], premature cardiovascular disease, and metabolic syndrome [38*,69*,147]. A large French national natural history study [62] of IBM revealed progressive functional disability but no overall increase in mortality. Predictors of mortality for polymyositis, dermatomyositis, and JDM have been determined and were found to be similar in different parts of the world and among phenotypes, with interstitial lung disease and the anti-synthetase autoantibodies among the risk factors predicting greater mortality [1**,37,67,82]. Classic epidemiologic investigations have been performed, deriving estimates of incidence and prevalence in national registries [3*,58], with documented increases in incidence over time for IBM in Australia and an increased prevalence of polymyositis and dermatomyositis in urban regions of Canada, for example [9,10*,97,129,138].

Larger registries and repositories have also allowed for adequate statistical power to assess other risk factors for myositis. The human leukocyte antigen (HLA) 8.1 ancestral haplotype —A1, B8, DRB1*0301, DQA1*0501—has been found to be the strongest immunogenetic risk factor identified to date for all major clinical subgroups of myositis for patients of European ancestry [21,90,91*,92,93,114,139,161]. Nonetheless, MSA phenotypes and some clinical subgroups have distinct HLA risk and protective factors [21,22,26,88,94,162]. Through candidate gene studies, additional immune response genes have been identified as risk factors, including PTPN22 [135], STAT4 [89], NF-kappaB [27], pro-inflammatory cytokine polymorphisms of TNFa and IL-1a [115;140], immunoglobulin heavy chain phenotypes in JDM, dermatomyositis, and polymyositis, and NOTCH4 polymorphisms in IBM [95]. A genome-wide association study [15*] that combined specimens from several

registries has confirmed the HLA region as strongest region of risk, but found additional autoimmune loci to be risk factors for dermatomyositis.

Regarding environmental risk factors, ultraviolet radiation has been found to be a risk factor for dermatomyositis and JDM, and its associated autoantibody phenotypes (Mi-2 and anti-TIF1), especially in females [54,116*]. Documented infections and other exposures proximal to illness onset, which differ among phenotypes, also suggest environmental factors [141,163]. For example, the finding, by geospatial clustering analyses, that anti-MDA5 autoantibodies are non-randomly distributed suggests that environmental factors play a role in this phenotype [49].

Seasonality in onset and birth distributions suggests other environmental factors may be important in pathogenesis [117]. A lack of association with enteroviruses has been documented [139]. A gene-environment interaction study suggested an interaction of smoking with the DRB1*03 risk factor in patients with anti-synthetase autoantibodies [17], and the DRB1*1101 allele has been associated with hydroxymethylglutaryl-coenzyme A reductase autoantibodies that may follow statin use [31]. Additional work on gene-environmental interactions should be possible through large registries of carefully phenotyped patients (with biospecimens) for whom common environmental data are also collected, as is being done in Euromyositis, UK Myonet, and other registry studies.

Collections of detailed clinical data and associated biospecimens by investigators have been invaluable in helping us understand many aspects of pathogenesis and in developing biomarkers of disease. Examples include the discovery of the primary role of plasmacytoid dendritic cells and the interferon signature in the pathogenesis of dermatomyositis and JDM muscle and skin disease in several populations [40,45,46*,47,55,142,164] and that pro-inflammatory cytokines and chemokines, including TNFa and IL-6, as well as macrophage activation markers, are biomarkers of active disease [41,42,136*,143]. A role for antigen-restricted T cells in IBM [60,63*], and the pathogenesis of endothelial activation [105], muscle regeneration [106] and calcifications [107] in JDM have also been examined.

MYOSITIS PATIENT SUPPORT GROUP REGISTRIES

Myositis patient support groups also maintain registries of patients and data, primarily consisting of demographic information, diagnoses, and contact information. Such patient databases are potentially valuable resources to enable patients to be contacted to inform them of newly approved research studies for which they may be eligible to participate. The Myositis Association (www.myositis.org), a US-based, international patient support group for all forms of myositis, maintains a database of almost 8000 patients with dermatomyositis, polymyositis, IBM, and JDM, which also includes basic demographic and contact information. The Cure JM Foundation (www.curejm.org), a US-based support group for juvenile myositis, maintains an electronic database with demographic information for more than 1300 juvenile myositis patients. Cure JM has epidemiologic research goals, including examining possible geographic clustering of cases. The Muscular Dystrophy Association has initiated a research registry program for neuromuscular diseases through their clinics. Starting with 25 pilot clinics and several neuromuscular disorders (amyotrophic

lateral sclerosis, Duchenne muscular dystrophy, and spinal muscular atrophy), they plan to register up to 3500 patients in an initial phase and expand this to additional neuromuscular disorders, including myositis, and involvement of all their clinics in a national network [165*]. The research goals of the Muscular Dystrophy Association's neuromuscular registry program include understanding the course of illness through the collection of longitudinal data, benchmarking best clinical practices, implementing a quality improvement program, collecting data about genotype-phenotype correlations to allow for better prediction of disease progression, and to facilitate clinical trial recruitment.

Recently, two large national (United States) myositis patient research registries have been established, which include some patients from other countries, particularly Canada. The Myositis Association has established a registry called MYOVISION, which contains information from almost 2000 patients with dermatomyositis, polymyositis, IBM, and JDM. Demographic, clinical, and treatment information, associated environmental exposures and quality-of-life information were obtained in a recent patient questionnaire. A second registry, the Yale University IBM Registry, led by Dr. A. David Paltiel, has enrolled 950 patients with IBM from the United States and Canada, capturing patient-reported demographic and clinical features as well as activities of daily living information. Although the data collection has been retrospective, the investigators hope this information will serve as the basis for a prospective patient registry, as well as inform the development of basic information about disease progression and other issues of interest to patients, caregivers, and physicians. Both registries are currently analyzing their findings.

CHALLENGES AND BENEFITS OF REGISTRIES AND BIOREPOSITORIES

Myositis registries have become tremendous resources and have provided a wealth of new research findings and opportunities for future research. Myositis researchers may collaborate with existing registries, including the possibility of depositing their data with some registries, such as Euromyositis or the IMACS Outcomes Repository. New registries may examine genetic and/or environmental factors of geographically isolated populations that may provide insights into the geoepidemiology of myositis. Much work remains to be done within existing registries to bring to fruition new research findings from the large volumes of data and samples already gathered.

The proliferation of registries and biorepositories for myositis has also generated a number of challenges. Inconsistencies in the classification and diagnostic criteria of myositis and its subgroups among studies, lack of use of standardized terms and variables for the databases, collection of varying data elements and biobank specimens, and variations in assays for myositis autoantibodies and other biomarkers - all make comparisons of the findings among various studies difficult and complicate combining data among registry studies to enhance statistical power for research questions. Use of appropriate standards to maintain biorepositories [166] and appropriate informed consent for new genetic testing, as well as differences in national and international rules for data sharing between studies are some other noted challenges. While myositis registries have become tremendous resources and have provided a wealth of new research, more stable funding is required to maintain and expand these databases and biorepositories. The involvement of patient support groups and

other private foundations and donors is needed, with recognition of the importance of these resources for future efficient research in myositis.

CONCLUSION

The establishment of larger collections of patients with detailed clinical, outcome, and other data, often linked to biospecimens, has enabled more rapid progress in myositis clinical and translational research over the past several decades. We expect the further growth of these national and international registries to lead to expanded understandings of myositis phenotypes, outcomes and prognoses, genetic and environmental risk factors, including gene–environment interactions, and pathogenesis, all of which could lead to more effective new therapies, and even the prospect of preventing some forms of myositis in the future. The era of single investigator research has yielded great advances in many areas of myositis, but future studies will require collaborations not only among multiple investigators within a single registry, but also among multiple registry studies, to allow for the most cost-effective and timely advances in our understanding of myositis.

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KEY POINTS

- More than 45 myositis research registries, often with associated biorepositories, have enrolled more than 30,000 myositis patients around the world, providing opportunities for collaborative research.
- Myositis research registry studies have greatly enhanced our understanding of the clinical and autoantibody phenotypes, outcome assessment, long-term outcomes and prognoses, genetic and environmental risk factors, and pathogenesis of the idiopathic inflammatory myopathies.
- Challenges include enhancing the interactions of current myositis registries and biorepositories, developing standards for their maintenance, and obtaining adequate funding to preserve and expand them.

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Table 1

Registries that include all forms of myositis

Project name (website) principal investigator(s) and e-mail, type of registry	Total number and types of myositis[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
International Registries					
EuroMyositis (http://euromyositis.eu/) Ingrid Lundberg, Ingrid.lundberg@ki.se, Jiri Vencovsky, Hector Chinoy, Hector.Chinoy@manchester.ac.uk, Retrospective and Prospective, Multicenter	3000: DM, PM, IBM, JDM, JPM, SAM, Other	BioM, Outcomes, Natural history, Assess, clinical trial patient identification/More than 3000 patients from throughout Europe and the globe have been registered. MSA phenotypes and genetic risk factors have been further defined.	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat	N/A	[13**,14,15*,16,17]
International Myositis Classification Criteria Project Principal Investigator: Ingrid E. Lundberg, Ingrid.Lundberg@ki.se (Project Coordinator: Anna Tjärnlund, anna.tjarnlund@ki.se) Retrospective, Multicenter	974: DM, PM, IBM, JDM, JPM, ADM, HMDM, IMNM, Other	Classification criteria/Developed new classification criteria for myositis and its major subgroups	Demo, Clin, MSA, Lab, Treat	N/A	[18]
NIAMS studies on the natural history and pathogenesis of PM, DM and related diseases James D. Katz, James.katz@nih.gov, Adam Schiffenbauer, and Paul Plotz Prospective, Single center	800: DM, PM, IBM, JDM, Other IIM	Phenotype definitions, Pathogen, Genetics, Assess/ Epidemiology, extraskeletal muscle involvement, prognostic factors in response to immunosuppressives and immunologic abnormalities	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen	S, DNA, RNA[e], MuscBx[e], SkBx[e]	[5,19–23]
IMACS Outcomes Repository (http://www.niehs.nih.gov/research/resources/imacs/researchguidelines/index.cfm) Lisa Rider, riderl@mail.nih.gov and Frederick Miller Prospective, Multi-center	200: DM, PM, IBM, JDM, JPM, Other	Collection of nine clinical trials and three natural history studies. Assess, Outcomes, Repository for future research/Patient profiles for new myositis response criteria	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat[e]	N/A	[20,24]
PANLAR Myositis Registry Ignacio Garcia de la Torre, igdlt@aol.com Retrospective, Multicenter	120: DM, PM, JDM	Env factors, Phenotype definitions/Findings N/A	Demo, Clin, MSA, Lab, Outcomes, Treat, Env	S, MuscBx[e]	[20]
National or Regional Registries					
MYOVISION Bob Goldberg, goldberg@myositis.org Hermine Brunner, hermine.brunner@cchmc.org Retrospective, Single center, USA	1956: DM, PM, IBM, JDM, JPM, HMDM, Other	Patient registry, Epidemiology, Phenotype definitions, Env factors, QoL, Repository for future research/Demo and Clin appear to be similar to other clinic and registry populations	Demo, Clin, Treat, QoL, Env	N/A	[25]
UKMYONET Robert G. Cooper, Robert.g.cooper@manchester.ac.uk and William Ollier, bill.ollier@manchester.ac.uk Prospective, Multicenter, United Kingdom	1111: DM, PM, IBM JDM, JPM, CTM, ADM, SAM	Phenotype definitions, Pathogen/ Myositis genotype and serotype correlate with and are predictive of disease progression/outcome. Association of A1, B8, DR3, DQA1*0501 as major immunogenetic risk factor	Demo, Clin, MSA, Genet	Plasma, DNA, MuscBx[e]	[15*, 17,26–28]

Project name (website) principal investigator(s) and e-mail, type of registry	Total number and types of myositis[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
Hopkins Myositis Research Database Lisa Christopher-Stine, lcs@jhmi.edu Retrospective and Prospective, Single center, National	1071: DM, PM, IBM, JDM, IMNM, CTM	Phenotype definitions, Treat/ Determined MSA phenotype associations, including anti-HMGCR, anti-TIF1γ, anti-NXP2, and anti-MDA5	Demo, Clin, MSA, Lab, Outcomes, Genet	S, DNA, MuscBx	[29*,30*,31–33]
Hungarian Myositis Workgroup Katalin Dankó, katalin.danko@gmail.com Retrospective and prospective, Multicenter, Hungary	475: DM, PM, IBM, JDM, JPM, ADM	Epidemiology, Clin and Lab features, Pathogen, Outcomes, Natural history, Assess, Treat/Incidence and prevalence of IIMs in Hungary are similar to other intl findings. Risk factors for mortality, disease course, associated cancers, and CTM defined	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen, Env	S[e], DNA[e], MuscBx[e]	[15*,20,34–37,38*,39]
SweMyoNet (http://srq.nu/) Ingrid E. Lundberg, Ingrid.lundberg@ki.se Prospective, Multicenter, Sweden	454: DM, PM, IBM, JDM, ADM	Quality care registry, identify prognostic BioM/PM/DM patients have reduced grip strength at diagnosis. Men respond better than women to treatment (grip force)	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat	MuscBx, linked to S and DNA biobanks	N/A
Immunopathology of IIM (IL-17 and IFN pathways in disease)/Biomarker discovery for IIM Ann Reed, Reed.ann18@mayo.edu and Floranne Ernste, Ernste.Floranne@mayo.edu Prospective, Single center, USA	350: DM, PM, IBM, JDM, JPM, Other	Pathogen, BioM/ IL-6 and IFN pathways are key to disease pathogen and as BioM	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet[e], BioM, Pathogen	S, DNA, RNA, MuscBx[e], SkBx[e], PBMCs	[40–42,43**]
Molecular and pathologic studies in autoimmune skin disease David Fiorentino, Fiorentino@stanford.edu Prospective, Single center, Regional	183: DM, PM, JDM, Cutaneous lupus, SSc	Pathogen DM skin disease, Outcomes, Assess, Phenotype definitions/Most cancer-associated DM patients have Abs to TIF-γ or NXP2. Defined anti-MDA5 cutaneous phenotype. Described an IFN signature in DM skin	Demo, Clin, MSA, Lab, Assess (CDASI), Pathogen	S, DNA, RNA, SkBx	[29*,44,45,46*, 47,48]
Predictors of muscle function in myositis Beatriz Y. Hanaoka, byhanaoka@uky.edu Retrospective and prospective, Single center, Regional	98: DM, PM, IBM, JDM, CTM	Strength-Pathogen correlates, Outcomes/ Findings N/A	Demo, Clin, MSA, Lab, Assess, Outcomes, Pathogen	S	N/A
Risk Factors for IIM in Guatemala Abraham Garcia-Kutzbach, abraham@garciakutzbach.org, postgradoagar@gmail.com Retrospective, Single center, Guatemala	64: DM, PM, JDM, IIM	Risk factors, Demo, Clin, Epidemiology/ Findings N/A	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, BioM	S, MuscBx	N/A
Clinical Significance of AutoAbs in Myositis Yoshinao Muro, ymuro@med.nagoya-u.ac.jp Retrospective and prospective, Single center, Japan	50: DM, PM, JDM, CTM	Phenotype definitions /Identified the clinical significance of MDA5, TIF-1γ, and NXP2 Abs, incl illness severity and epidemiology. Developed ELISAs measuring anti-MDA5, TIF1α/β/γ, Mi-2 and SAE1/2	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, BioM, Pathogen[e]	S, SkBx[e]	[49–53]

Abbreviations: AutoAbs, autoantibodies; CALIPER, computer-aided lung informatics for pathology evaluation and rating; EUSTAR, European Scleroderma Trial and Research; IMACS, International Myositis Assessment and Clinical Studies Group; NIAMS, National Institute of Arthritis, Musculoskeletal, and Skin Disease; NIH, National Institutes of Health; SCTC, Scleroderma Clinical Trial Consortium; PRINTO, Pediatric Rheumatology International Trials Organization; SCTC, Scleroderma Clinical Trial Consortium.

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[a] Types of myositis abbreviations: ADM, amyopathic dermatomyositis; CTM, overlap (or connective tissue) myositis; DM, dermatomyositis; HMDM, hypomyopathic dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PM, polymyositis; SAM, statin-associated myopathy; sIBM, sporadic inclusion body myositis.

[b] Key objectives/key findings abbreviations: Abs, autoantibodies; ASS, anti-synthetase syndrome; CDASI, Cutaneous Disease and Activity Severity Index; CK, creatine kinase; DMARDs, disease-modifying anti-rheumatic drugs; ELISA, enzyme-linked immunosorbent assay; HLA, human leukocyte antigen; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HR-QoL, health-related quality of life; HRCT, high-resolution computed tomography; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILD, interstitial lung disease; i.v., intravenous; MDI, Myositis Damage Index; MHC, major histocompatibility complex; MITAX, Myositis Intention to Treat Index; MRI, magnetic resonance imaging; MSA, myositis-specific autoantibodies; Pathogen, pathogenesis; SF-36, Short Form 36; SNPs, single-nucleotide polymorphisms; SRP, signal recognition particle; SSc, system sclerosis; Th, T-helper cells; TIF1, transcriptional intermediary factor; TNFα, tumor necrosis factor alpha; Treg, T-regulatory cells; UVR, ultraviolet radiation.

[c] Features captured abbreviations: Assess, outcome assessment/Outcome measures; ADLs, activities of daily living; BioM, biomarkers; Clin, clinical features; Demo, demographics; DXA scan, dual-energy X-ray absorptiometry scan; Env, environmental factors; Gen, genetic data; Lab, other laboratory tests; MSA, myositis autoantibodies; Outcomes, disease outcomes; Pathogen, pathogenesis evaluation; PFT, pulmonary function test; QoL, quality of life; Treat, treatment response data.

[d] Biospecimen abbreviations: Calc, calcifications; MuscBx, muscle biopsy; N/A, not available; P, plasma; PBMCs, peripheral blood mononuclear cells; S, serum; SkBx, skin biopsy.

[e] Partial data set.

Table 2

Registries that include only adult-onset forms of myositis

Project name (website), principal investigator and e-mail, type of registry	Total number and types of myositis[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
International Registries					
Myopathy in patients with systemic sclerosis (SSc): EUSTAR-SCTC project (http://www.eustar.org) Britta Maurer, Britta.Maurer@usz.ch, Veronika Jäger, Lorinda Chung, Vivien Hsu, Ulrich Walker, Oliver Distler, EUSTAR-SCTC Retrospective and prospective, Multicenter	~3,000–4,000: PM and DM overlap with SSc	Predictors of severe muscle disease and diagnosis of SSc-overlap myositis /In EUSTAR, ~30% have weakness and 10% have CK elevation	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Pathogen	S[e], DNA[e], MuscBx[e], SkBx[e]	N/A
NIH Myositis Cohort Frederick Miller, millerf@mail.nih.gov Retrospective and Prospective, Single center	~1300: DM, PM, IBM	Phenotype definitions, Genetics, Env factors, Outcomes, Treat/Clinicopathologic and myositis Ab phenotypes have unique presentations, risk factors and prognoses, incl distinct immunogenetic associations. Association of A1, B8, DR3, DQA1*0501 as major immunogenetic risk factor for myositis. UVR intensity predicts relative distribution of DM and anti-Mi-2 Abs in women	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen	S, DNA, RNA[e], MuscBx[e], SkBx[e]	[5,15*,19,21,54–57]
Yale University IBM Survey A. David Paltiel, david.paltiel@yale.edu Retrospective, Single center	950: IBM	Patient registry, Demo, Clin and Social features/ Findings N/A	Demo, Clin, Outcomes, ADL	N/A	N/A
National or Regional Registries					
A nationwide registration system for patients with intractable diseases (http://www.mhlw.go.jp/english/) National Ministry of Health, Labour and Welfare, Japan (www-admin@mhlw.go.jp); Hitoshi Kohsaka, kohsaka.rheu@tmd.ac.jp Retrospective and Prospective, Multicenter, Japan	20 000: DM, PM	Epidemiology, Clin, Lab, Natural History, Outcomes/ Incidence and clinical features	Demo, Clin, Lab, Outcomes	N/A	[3*,58]
Myositis AutoAbs specific classification Olivier Benveniste, Olivier.benveniste@psl.aphp.fr Retrospective and Prospective, Multicenter, France	942: DM, PM, IBM, IMNM, Other	Classification, Phenotype definitions, Natural history, Outcomes, Treat/Refined pathological diagnostic criteria for IBM. Defined natural history of IBM, and defined quadriceps strength as best clinical outcome for future IBM clinical trials. Examined immune responses in IBM (Treg deficiency and Th-1 signature), showed oligoclonal expansions of cytotoxic CD8+ cells in peripheral blood and muscle	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen	S, DNA, RNA, MuscBx, PBMCs	[59,60,61**,62,63*]

Project name (website), principal investigator and e-mail, type of registry	Total number and types of myositis[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
A South Australian database for patients with biopsy-proven myositis Vidya Limaye, Vidya.limaye@health.sa.gov.au Retrospective and prospective, Multicenter, South Australia	468: DM, PM, IBM, IMNM, Other	Epidemiology, Clin, Genetics/Mortality and associated cancers were increased, and risks identified. Immunogenetic associations with MSAs. The staining patterns of MHC Class I and II of muscle have been identified	Demo, Clin, MSA, Lab, Assess[e], Outcomes, Genet	S[e], DNA[e], MuscBx	[10* 64*,65,66*,67, 68**]
Metabolic syndrome in DM and PM Samuel Katsuyuki Shinjo, samuel.shinjo@gmail.com Retrospective and Prospective, Single center, National – Brazil	250: DM, PM, IBM	Clin, Treat, Metabolic syndrome in IIM / Prevalence and risk factors for metabolic syndrome in DM and PM	Demo, Clin, MSA, Lab, Outcomes, Treat, Genet, BioM	S[e], DNA[e], RNA[e], MuscBx[e]	[69*,70*]
Use of CALIPER software in HRCT in IIM with ILD Floranne Ernste, Ernste.floranne@mayo.edu Retrospective, Single center, Regional	165: DM, PM, ASS	Assess ILD activity and progression in IIM/IIM patients with ILD showed parenchymal improvement at 1 and 3 years by CALIPER	Demo, Clin, Lab, Assess, Outcomes, HRCT scan	N/A	[71]
REGAS (REGistry of Antisynthetase Syndrome) Albert Selva-O'Callaghan, aselva@vhebron.net Retrospective, Multicenter, Spain	142: DM, PM, ILD only without myositis	Phenotype definitions, including cancer association and mortality/ 10-year survival is near 75% in anti-Jo1 Ab patients. Myositis and ILD are most frequent findings	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat	DNA[e]	[15*]
DM Database Victoria P. Werth, werth@mail.med.upenn.edu Prospective, Single center	135: DM, ADM, HMDM	Assess (cutaneous, CDASI), QoL, Pathogen/ Validation of the CDASI, QoL is decreased in DM, translational studies in DM skin	Demo, Clin, MSA, Lab, Assess (incl skin tools), Outcomes, Treat, BioM, Pathogen	S, DNA, RNA, SkBx[e], PBMCs	[72*,73–77]
Seoul National Univ Hospital Myositis Registry Yeong Wook Song, ysong@snu.ac.kr Retrospective, Single center, Regional	110: DM, PM	Phenotype definitions/Findings N/A	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat	S, DNA, MuscBx[e]	[20]
CHUM Myositis Registry Jean-Luc Senécal, MD, and Yves Troyanov, jl.senecal@umontreal.ca Retrospective, Multicenter, Canada	101: DM, PM, IBM, Anti-SRP + IMNM	Classification, Phenotype definitions/Overlap myositis is the dominant subset in IIM. Proposed new classification of IIM	Demo, Clin, MSA, Lab, Outcomes, Treat, Genet, Pathogen	S, DNA[e], RNA[e], MuscBx[f]	[78,79]
Univ College London Myositis Registry David Isenberg, d.isenberg@ucl.ac.uk Prospective, Single center, Regional	~100: DM, PM, IBM, CTM	Clin, Outcomes, Assess, Treat/Natural history. Developed MITAX and MDI assessment tools. Treat to rituximab	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat[e], Genet, BioM	S, DNA, MuscBx	[15*,80–82,83*,84]
Study of treatment approaches in myositis (http://www.chictr.org/cn/proj/show.aspx?proj=4172) Guochun Wang, guochunwang@hotmail.com Prospective, Multicenter, China	97[g]: DM, PM	Treat, remission among different immunosuppressives if clinically improved at week 24/Findings N/A	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, BioM	S[e], MuscBx[e]	N/A
Neuromuscular Database Project Richard Barohn, rbarohn@kumc.edu, Mazen M. Dimachkie, mdimachkie@kumc.edu Retrospective, Single center, Regional	86: DM, PM, IBM, PM CTM, Other	Database of candidate patients for future neuromuscular studies/Identified unusual phenotypes in IBM, incl dysphagia as first symptom years before weakness in 15% of IBM cases. Large case series of statin-associated	Demo, Clin	N/A	[85,86]

Project name (website), principal investigator and e-mail, type of registry	Total number and types of myositis[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
		necrotizing autoimmune myopathy in which weakness progresses 2 months after statin cessation			
Tokyo Women's Medical Univ Myositis Database Takahisa Gono, tgono@ior.twmu.ac.jp, Yasuhiro Katsumata Prospective, Single center, Regional	76: DM, PM	Epidemiology, Phenotype definitions, Genetics, BioM, Pathogen/Ferritin predicts disease severity and prognosis for patients with anti-MDA5 Ab. STAT4 polymorphism a risk factor for PM/DM	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet[e], BioM[e]	S[e], DNA[e], MuscBx[e]	[87–89]
TIF1γ Proteins and Paraneoplastic DM Ernesto Trallero-Araguas, etrallero@vhebron.net and Albert Selva O'Callaghan, aselva@vhebron.net Prospective, Single center, Regional	72: DM, PM	Longitudinally assess changes anti-TIF1γ levels in DM, TIF1γ expression in skin and muscle, capillaroscopic pattern in DM/Findings N/A	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen	S, DNA, MuscBx, SkBx, Cancer	N/A
Clinical, Epidemiological and Genetic Studies into sIBM Merrilee Needham, Merrilee.needham@health.wa.gov.au and Frank Mastaglia Retrospective, Multicenter, Western Australia	65: IBM	Epidemiology, Clin, Muscle involvement, Genetics/Prevalence of sIBM in Western Australia is 14 cases/million. Most severely affected muscles are forearm flexors and knee extensors, but some patients present with foot drop and dysphagia. Confirmed HLA-DR3 risk factor, and found stronger association with HLA-DR3/DR1	Demo, Clin, MSA, Lab, Outcomes, Treat, Genet, Pathogen	S[e], DNA	[90,91*,92–95]
Immunoapheresis for Refractory DM or PM Hans Kiener, hans.kiener@meduniwien.ac.at Retrospective, Single center, Regional	42: DM, PM, IBM, IMNM	Treat/Preliminary findings suggest beneficial effect of immunoapheresis	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat	S[e], DNA[e], MuscBx[e], SkBx[e], Lung biopsy[e]	N/A
Canadian Inflammatory Myopathy Study Marie Hudson, Marie.hudson@mcgill.ca and Murray Baron Prospective, Multicenter, Canada	20[h]: DM, PM, ADM, SAM, CTM	Research, Training, Exchange, and Patient advocacy in IIMs/Among subjects with incident systemic rheumatic diseases, those with IIM had the worst physical and mental health-related QoL scores at disease onset	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet[e], BioM, Pathogen	S, DNA[e], RNA[e], MuscBx, SkBx, PBMCs[e]	[9,12,96,97]

Abbreviations are given in Table 1.

[f] Collected but not available for further studies.

[g] 564 planned.

[h] 200 planned.

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Table 3

Registries that include only juvenile-onset forms of myositis

Project name (website), principal investigator and e-mail, type of registry	Total number and types of myositis cases[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
International, Multicenter Registries					
The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry (https://www.carragroup.org) Norman Ilowite, Christy Sandborg, Laura Schanberg, Carol Wallace, and Kelly Mieszkalski, research@carragroup.org Retrospective and prospective	631: JDM	Natural history, Epidemiology, Clin, Treat/Clin, Demo, incl frequency of diagnostic tests and initial therapy. Corticosteroids and methotrexate are first-line medications used by United States and Canadian pediatric rheumatologists for JDM	Demo, Clin, Lab, Assess, Outcomes, Treat	N/A	[98–100]
Northwestern's Juvenile Myositis Registry Lauren Pachman, Pachman@northwestern.edu Prospective, Single center	496: JDM, JPM, Other	Pathogen, Clin, Treat, Long-term outcome /Studies of IFN and endothelial activation in peripheral blood, muscle, and skin. Altered methylation of homeobox genes. Mast cells present in unaffected skin of JDM. The association of A1, B8, DR3, DQA1*0501 and the TNFα-308A allele with JDM was confirmed. TNF-α strong component of JDM inflammatory response. Predictors of outcome and Treat	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen, Nailfold capillary	S, Plasma PBMCs, DNA, MuscBx, RNA, SkBx, Calc[e]	[15*,20,101–107,108*,109]
Childhood Myositis Heterogeneity Study Lisa Rider, riderl@mail.nih.gov and Frederick Miller Retrospective	480: JDM, JPM, CTM, ADM, Other	Phenotype definitions, Genetics, Env, Outcomes, Treat, Pathogen/ Defined major clinical and Ab phenotypes of juvenile IIM. HLA alleles, TNFα and IL-1α SNPs as risk and severity factors. UVR associated with JDM and the anti-TIF1 antibody	Demo, Clin, MSA, Lab, Outcomes, Treat (in progress), Genet, BioM, Pathogen, Env	S, DNA, RNA[e], MuscBx[e], Urine[e], Calc[e]	[1**,15*,110**, 111**,112–115,116*,117, 118*]
PRINTO JDM Trial (www.printo.it) Nicola Ruperto, nicolaruperto@ospedale-gaslini.ge.it Prospective randomized trial in new onset JDM	294: JDM, JPM	Assess/Developed and validated PRINTO JDM core set disease activity measures and preliminary response criteria. Criteria for clinically inactive disease defined	Demo, Clin, Lab, Assess, Outcomes, Treat	N/A	[119–121;122**]
JDM Disease Activity Study Lisa Rider, riderl@mail.nih.gov and Frederick Miller Prospective	120: JDM, JPM, CTM	Assess/Developed and validated core disease activity measures for JDM, part of IMACS and PRINTO. A cutaneous assessment tool was developed and validated. Several biomarkers (macrophage activation markers and muscle	Demo, Clin, MSA[e], Lab, Assess, Outcomes, Treat[e]	S[e], Plasma[e], Urine[e]	[19,20,23,123–128]

Project name (website), principal investigator and e-mail, type of registry	Total number and types of myositis cases[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
		metabolites) correlate with activity and damage. The studies of this group were succeeded by IMACS			
National or Regional Registries					
UK JDM Cohort & Biomarker Study & Repository (http://www.juveniledermatomyositis.org.uk/) Lucy Wedderburn, l.wedderburn@ucl.ac.uk or info@jdrg.org.uk Retrospective and prospective, Multicenter, UK	444: JDM, JPM, CTM, Other	Demo, Phenotype definitions, Assess, Treat, BioM, Genetics, Pathogen, future clinical trials/ Defined Ab phenotypes; HLA haplotype and MSA associations; standardized biopsy score assessment method; evidence for use of anti-TNF and cyclophosphamide in JDM	Demo, Clin, MSA, Lab, Assess, Outcomes, Treat, Genet, BioM, Pathogen	S, DNA, RNA, MuscBx, SkBx[e], PBMCs	[15*,129,130*, 131–133,134*,135, 136*]
NIH-NIAMS New Onset JDM Registry Lauren M. Pachman, pachman@northwestern.edu Prospective, Multicenter, USA	323: JDM	Epidemiology, Env, Demo and Clin at diagnosis/Incidence of JDM in the US was established by 'capture-recapture' methodology. Frequent history of infection in the 3 months prior to first JDM symptom. Gene expression profile data documented a very strong Type 1 IFN-induced gene pattern in JDM muscle. Increased duration of untreated disease is associated with vascular remodeling	Demo, Clin, Lab, Genet, BioM, Pathogen, Parent interviews	S[e], MuscBx[e], SkBx[e], Calc[e]	[28,104,137–143]
A Brazilian Registry of JDM Claudia Saad Magalhães, claudi@fmb.unesp.br Retrospective, Multicenter, São Paulo State, Brazil	189: JDM, JPM, CTM, ADM	Clin, Classification, Treat, describe co-morbidities, incl calc, CTM, and malignancy/Diagnosis, Clin at onset, classification criteria, and standard treatment	Demo, Clin, Lab, Assess, Outcomes	S[e], MuscBx[e], SkBx[e]	[144]
JDM in Norway Helga Sanner, helga.sanner@medisin.uio.no Retrospective and prospective, Single center, Norway	70: JDM	Assess, long-term Outcomes, BioM/After median 16.8 years, 90% had cumulative organ damage by MDI, 51–73% of JDM patients had active disease. Adult patients with JDM had reduced HR-QoL. Abnormalities in muscle, pulmonary, and cardiac function also frequent	Demo, Clin, MSA, Lab, Assess, Outcomes, Genet, BioM, Cardiac function	S, DNA, RNA, MuscBx	[145–149]
JDM in Denmark Pernille Mathiesen, permat@dadlnet.dk Retrospective, Single center, Denmark	53: JDM, JPM	Long-term Outcome, identify outcome predictors/60% of JDM patients had disease damage on long-term follow-up, with severe damage in 25%. Longer disease duration was the most important predictor of damage, calc, and impaired muscle function	Demo, Clin, MSA, Lab, Assess, Outcomes, Genet, Exercise test, PFT, DXA scan	S, DNA, RNA, MB[e]	[150*,151,152, 153*]

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Project name (website), principal investigator and e-mail, type of registry	Total number and types of myositis cases[a]	Key objectives/key findings[b]	Features captured[c]	Bio-specimens[d]	Key references
JDM in Japan Takayuki Kishi, takayuki@ped.twmu.ac.jp Retrospective, Single center, Regional	50: JDM	Clin, Prognosis, Treat /i.v. methylprednisolone resulted in fewer disease flares than oral prednisone alone. IgE levels were higher in patients who developed generalized calc	Demo, Clin, Lab, Assess, Outcomes, Treat	S, MuscBx[e], SkBx[e]	[154*]

Abbreviations are given in Table 1.

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