

Pediatric Multiple Sclerosis Research Agenda

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This research agenda was developed in collaboration with members of the pediatric multiple sclerosis (MS) community, including children, teens, and young adults diagnosed with pediatric MS, their parents, guardians, and grandparents, and siblings. We are grateful to them for sharing their insights about and experiences with pediatric MS and for their assistance in shaping this agenda around their priorities. We are also grateful to the researchers and clinicians who provided their professional expertise to the project and creation of this document.

For more information or to engage with the iConquerMS Kids & Teens initiative, please contact Sara Loud, Accelerated Cure Project, at kidsandteens@iConquerMS.org.

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Research Agenda for Pediatric Multiple Sclerosis

Background

Children and adolescents with multiple sclerosis (MS) and their families face a great deal of uncertainty resulting from the diagnosis of a chronic and unpredictable disease. MS is less commonly diagnosed in children than in adults, with the prevalence of MS in people 0-18 years old estimated as 5,000 in the US and 10,000 worldwide, compared to estimates of 900,000 total MS cases in the US and 2.3 million worldwide^{1,2,3}. Because of the comparatively smaller pool of pediatric MS patients, and because research with children requires additional steps to ensure their care and protection, the vast majority of MS research focuses solely on adult populations. There is, therefore, a lack of information available as to the long-term impact of pediatric MS on overall health, quality of life, emotional impact, and family systems. The safety and effectiveness of MS interventions, including lifestyle interventions, in this age group is also poorly understood.

Accelerated Cure Project (ACP), a nonprofit organization with the mission to improve the health, healthcare, and quality of life for those affected by MS through the creation and deployment of resources to facilitate research, launched the iConquerMS™ people-powered research network in 2014. iConquerMS is a research initiative developed to bring together adults diagnosed with MS and researchers, healthcare providers, funders, and others, to work in collaboration to design and conduct research on the topics that matter most to those living with the disease. Members of iConquerMS participate in the initiative's activities via an online platform (<https://www.iconquerms.org/>) and engage in research and research-related activities including sourcing research questions, contributing their insights to the design of research studies, participating in research through the sharing of data and biospecimens, and assisting in the dissemination of research evidence.

ACP launched iConquerMS Kids & Teens (<https://kidsandteens.iconquerms.org/kidsandteens>), a research initiative similar in concept to iConquerMS, but focused exclusively on the needs, preferences, and priorities of children and teens diagnosed with pediatric MS and their family members, in 2023. iConquerMS Kids & Teens was designed in collaboration with the pediatric MS community, including youths with MS and their family members, to address their unique

¹ Clinical trials of disease-modifying agents in pediatric MS: Opportunities, challenges, and recommendations from the IPMSSG. *Neurology*. 2019;93(14):647. doi:10.1212/WNL.00000000000008186.

² The prevalence of MS in the United States: A population-based estimate using health claims data. Mitchell T. Wallin, William J. Culpepper, Jonathan D. Campbell, Lorene M. Nelson, Annette Langer-Gould, Ruth Ann Marrie, Gary R. Cutter, Wendy E. Kaye, Laurie Wagner, Helen Tremlett, Stephen L. Buka, Piyameth Dilokthornsakul, Barbara Topol, Lie H. Chen, Nicholas G. LaRocca. *Neurology* Mar 2019, 92 (10) e1029-e1040; DOI: 10.1212/WNL.00000000000007035.

³ Atlas of MS 2013. Multiple Sclerosis International Federation. <http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf>

needs, and to enable them to participate as research partners in every phase of research from concept development through to dissemination and impact on care.

iConquerMS Kids & Teens is well-suited to enable the conduct of two important types of research in pediatric MS: patient-centered outcomes research (PCOR) and comparative effectiveness research (CER). PCOR emphasizes the health outcomes that matter most to patients and their families, such as quality of life, daily functioning, and overall well-being. This research approach incorporates patient preferences, experiences, and values when assessing the effectiveness of various treatments and healthcare interventions. CER aims to evaluate the benefits and risks of different therapeutic options, pharmacological interventions, or healthcare strategies to determine which approaches yield the most favorable outcomes for specific subpopulations of pediatric MS patients in real-world settings. Together, PCOR and CER provides patients, families, and healthcare professionals with the necessary evidence to make informed, individualized treatment decisions for children and adolescents with MS, optimizing care and outcomes for this unique patient population.

Importance of Developing a People-Centered Research Agenda

While iConquerMS Kids & Teens provides the platform and opportunities for engagement of youths diagnosed with pediatric MS in research, it does not currently have the capacity to allow its members to source the research questions of importance to them. Moreover, the majority of MS research is investigator-initiated. People affected by MS have unanswered questions on a wide variety of topics but do not have many opportunities to express and prioritize them. The lack of inclusion of the patient voice in the development of research agendas is even more pronounced for the pediatric MS population, who are infrequently, if ever, asked about their research priorities, which may differ significantly from those of adults living with MS. Therefore, even when research topics and questions are sourced from the MS patient and family communities, the resulting research studies may not reflect the priorities and needs of those living with pediatric MS, nor address the outcomes of greatest importance to them.

Identifying the research questions that matter most to youths affected by MS, and investigating their feasibility as future research studies, requires aligning the research interests of pediatric MS patients with those of researchers and funders. As such, we have developed this research agenda in collaboration with multiple stakeholders representing the patient, family, research, care, and funding communities, centralized on the experiences, insights, and questions of highest priority to those personally affected by the disease.

Process

This research agenda has been developed in collaboration with more than 25 youths and family members affected by pediatric MS, and 5 researchers and/or healthcare providers with expertise in the disease, over the course of a 12-month period.

The project's activities, including the design and hosting of two gatherings held via Zoom, with additional engagement of stakeholders in the interim, have been guided by a multi-stakeholder

steering committee. A planning committee, representing a subset of the steering committee and consisting of a professional facilitator, 2 staff members from ACP, the founder of the pediatric MS nonprofit Mr. Oscar Monkey, and a staff member from the National MS Society, developed the desired outcomes, processes, and agendas for each of the virtual gatherings.

The first convening, held in December 2023, included 8 youths living with pediatric MS, 2 siblings, and 15 parents or guardians. This gathering focused exclusively on the patient and family communities in order to provide an open space for the sharing of their lived experience with pediatric MS, and the sourcing of their insights, priorities, and needs. The themes and topics developed during this convening are found in Appendix A.

Following the first convening, the planning committee used meeting transcripts to document a list of 13 topics, raised by participants, for further exploration. The topics were presented, via survey, to our stakeholders, with the youths, parents, and siblings invited to identify their top 5 priorities. Researcher and clinician stakeholders were also invited to rank the topics but their responses were not included in the weighted rankings. The topics and resulting prioritization are found later in this document, as well as in Appendix B.

Using the prioritized list of topics, the planning committee identified 4 topics as the basis for further discussion at the second convening. The topics were selected based on their weighted ranking, the likelihood of producing a robust discussion at the convening to further source the research questions of highest importance to those affected by pediatric MS, and their alignment with PCOR and/or CER.

The second convening, held in March 2024, included 7 youths diagnosed with pediatric MS, 2 siblings, 10 parents or guardians, and 5 researchers/clinicians. Each of the 4 topics was discussed in greater detail, in small groups, with the use of breakout rooms. Each of the breakout rooms was staffed with a discussion facilitator and at least 1 researcher/clinician to provide their insights as to the current research underway for the topic, and to assist in shaping the research questions.

Following the second convening, the planning committee used meeting transcripts to document and refine the questions raised during the convening by meeting attendees. These research questions are found in Appendix C.

Research Agenda

Youths diagnosed with pediatric MS and their family members have unanswered questions on how to better diagnose, treat, and thrive while living with MS. The topics raised during our first convening ranged from the biology of MS (including genetics, remyelination, and impact of lesion location), addressing the most troubling symptoms (including the “silent” symptoms of fatigue, brain fog, and mental health), options for treatments (including non-pharmacological approaches), and how to engage in school, social, and other settings for better outcomes.

While research evidence may exist within some of these topic areas, providing answers for some of the questions raised by our families, the evidence may not be readily available to them, may not fit their particular circumstances, or may not exist at all.

As previously noted, our youth and family member participants have contributed to the ranking of the topics below as a reflection of their priorities and needs:

Weighted Ranking**	Topic
1	Mental health issues in kids with MS: how common are they and how to treat them
2	Impact of a lesion's location on MS symptoms
3	Diet, wellness, and other non-drug approaches to help kids and teens manage MS
4 (tie)	Factors that cause fatigue and brain fog in kids with MS, and how to treat them
4 (tie)	Understanding what triggers relapses and changes in symptoms in kids with MS
5	Repairing damage to myelin in kids with MS
6	New types of treatments including cord blood stem cells
7	Approaches for predicting future changes in a person's MS
8	Accommodations in school and other settings
9 (tie)	Which MS drug treatments can be used in kids, and how to choose the best one for yourself/your child
9 (tie)	Increasing public knowledge and understanding of pediatric MS
10	Genes and other factors that cause MS in kids and teens
11	How MS is diagnosed in kids and teens and factors impacting how long it takes to be diagnosed

** Rankings were calculated using a weighted approach based on the number of 1s, 2s, 3s, 4s, and 5s noted where 1 = highest priority: $\#1s*5 + \#2s*4 + \#3s*3 + \#4s*2 + \#5s*1$

Each of the topics above represents an opportunity for further exploration through patient-centered outcomes research in pediatric MS.

The 4 topics further explored in our second convening

1. Mental health issues in kids with MS
2. Diet, wellness, and other non-pharmacological approaches to help kids and teens manage MS
3. Factors that cause fatigue and brain fog in kids with MS, and how to treat them
4. Understanding what triggers relapses and changes in symptoms in kids with MS

are particularly well suited for CER.

Appendix C contains a list of questions, per topic, that could be explored through research studies, with the questions most aligned with CER highlighted . The questions listed include those that were expressed by meeting attendees during the 2nd convening, as well as additions made by the planning committee following the gathering. The committee used meeting transcripts to translate some of the ideas expressed by attendees into research questions.

Next Steps

The topics and questions identified through the development of this research agenda reflect the priorities and needs of the children, teens, and young adults, and their family members, who we have engaged throughout this project. Their insights, when aligned with the interests of pediatric MS researchers and funders, form the basis for a pathway forward for people-centered research in pediatric MS.

ACP, with its mission of accelerating research focused on the needs and priorities of those affected by MS, and through its iConquerMS Kids & Teens initiative, is eager to advance the research questions of highest priority to those affected by pediatric MS into funded PCOR/CER studies, and to generate the evidence needed by youths with pediatric MS and their family members to make decisions related to their health, healthcare, and quality of life.

ACP and iConquerMS Kids & Teens (<https://kidsandteens.iconquerms.org/kidsandteens>) are available as resources and research partners to facilitate this work. We will disseminate this research agenda to our community of researchers and funders to identify topics around which collaborative projects could be developed. We will also seek to disseminate the agenda development process and results at conferences and in publications.

We look forward to deepening our collaborative partnerships and relationships with the patient and family communities, other advocacy organizations, and researchers, healthcare providers, funders, and others with interests in and commitment to pediatric MS. We will continue to build capacity within the iConquerMS Kids & Teens initiative to enable those affected by pediatric MS to engage as research partners throughout the entire research continuum, from the sourcing of research questions through to the dissemination of evidence and impact on care, and welcome partnership from all to advance this work.

To discuss this agenda, our development process, or other topics related to advancing PCOR/CER research in pediatric MS, please contact Sara Loud, at ACP, via email at kidsandteens@iConquerMS.org.

Appendix A - Topics Raised by People Affected by MS during the 1st Convening

Participant Group	Themes and Topics
<p>Youths diagnosed with pediatric multiple sclerosis</p>	<p>Living with MS can be isolating, tiring, overwhelming, and anxiety-provoking. It makes youth feel different from their peers.</p>
	<p>Unanswered questions include understanding and treating symptoms and side effects, how treatments work, non-pharmaceutical treatments, remyelination, and a cure.</p>
	<p>Invisible symptoms like brain fog, fatigue, and mental health issues are very impactful but often not understood by others. Teachers and friends don't always grasp the extent of the symptoms.</p>
	<p>Youth wish for more understanding of pediatric MS among the general public. They want their experiences to be validated.</p>
	<p>Unanswered questions include understanding and treating symptoms and side effects, how treatments work, non-pharmaceutical treatments, remyelination, and a cure.</p>
	<p>The most pressing symptoms discussed were brain fog, fatigue, mental health issues, mobility limitations, and sensory issues. The symptoms really impact their daily lives.</p>
<p>Parents, guardians, or grandparents of youths diagnosed with pediatric multiple sclerosis</p>	<p>Mental health challenges are a major issue. Many parents reported that dealing with their child's mental health struggles related to having MS has been very difficult. Depression and anxiety are common. Finding mental health support and resources is a major need.</p>
	<p>Navigating treatments and medications is complex, especially since many are not approved for use in children. Parents want help understanding the options and side effects. Access, insurance coverage, and costs are also challenges.</p>
	<p>Connecting with other families facing pediatric MS is extremely valuable. Groups like iConquerMS provide important community, information sharing, and support. Events like family weekends are also impactful but not always accessible.</p>

	<p>Parents feel urgency around finding a cure and want research priorities to focus on understanding causes and underlying mechanisms. They believe clues may come from studying children since they have less lifetime environmental exposure.</p>
	<p>Raising awareness is important so children with mostly invisible symptoms are understood. Schools and others often lack knowledge about pediatric MS. Success stories should also be shared.</p>
	<p>The diagnosis experience is scary and overwhelming. Clear guidance on next steps and access to resources like National MS Society support is needed immediately. Better crisis intervention for newly diagnosed families could help significantly.</p>
<p>Siblings of youths diagnosed with pediatric multiple sclerosis</p>	<p>Siblings can feel overlooked compared to the sibling with MS who requires more attention. They want equal attention.</p>
	<p>Siblings were young when their sibling was diagnosed and did not fully grasp MS at the time. Learning more helped over time.</p>
	<p>Siblings wish for more awareness that MS affects youth, not just adults. They want their sibling's experiences validated.</p>
	<p>Questions around genetics were brought up - why their sibling got MS and not them. Also long diagnosis times were a frustration.</p>
	<p>Fatigue and its impact was a big topic of discussion. As well as school accommodations and participation.</p>
	<p>The value of connecting with other siblings and families affected by MS was emphasized.</p>

Appendix B – Prioritized Topics

Weighted Ranking**	Topic
1	Mental health issues in kids with MS: how common are they and how to treat them
2	Impact of a lesion's location on MS symptoms
3	Diet, wellness, and other non-drug approaches to help kids and teens manage MS
4 (tie)	Factors that cause fatigue and brain fog in kids with MS, and how to treat them
4 (tie)	Understanding what triggers relapses and changes in symptoms in kids with MS
5	Repairing damage to myelin in kids with MS
6	New types of treatments including cord blood stem cells
7	Approaches for predicting future changes in a person's MS
8	Accommodations in school and other settings
9 (tie)	Which MS drug treatments can be used in kids, and how to choose the best one for yourself/your child
9 (tie)	Increasing public knowledge and understanding of pediatric MS
10	Genes and other factors that cause MS in kids and teens
11	How MS is diagnosed in kids and teens and factors impacting how long it takes to be diagnosed

** Rankings were calculated using a weighted approach based on the number of rankings (1-5) where 1 = highest priority: $\#1s \cdot 5 + \#2s \cdot 4 + \#3s \cdot 3 + \#4s \cdot 2 + \#5s \cdot 1$

Appendix C - Questions Raised in Conversation Among People Affected by MS and Researchers During the 2nd Convening

Bolded topics/questions are particularly well suited to be studied via PCOR/CER.

Theme	Questions Raised
<p data-bbox="226 756 709 873">Mental Health Issues in Kids With MS: How Common Are They and how to Treat Them</p>	How many kids living with pediatric MS also experience mental health issues?
	How can we understand the origins of mental health issues of kids living with MS? How do we differentiate between symptoms that might be “normal” or unrelated to MS, those that are triggered by getting the diagnosis of a lifelong, chronic illness, versus those that are triggered by the physical symptoms of MS (i.e. created as a result of lesions)
	How do we best treat mental health issues in kids living with MS? What types of therapy are most effective? What is the impact of seeing a general pediatric provider versus a pediatric provider who specializes in chronic illness versus an adult provider who specializes in chronic illness? Are there certain medications meant to treat mental health issues more effective in the population of kids living with MS?
	What is the impact of having a sibling living with MS in relation to mental health? What about the impact of having a family member living with MS?
	Mental health changes and how they correspond with developmental milestones. How does MS contribute to this? Are mental health issues related to a development age influenced by or heightened because of MS?
	As we look at infectious diseases as a possible trigger for an MS diagnosis, is there a correlation to those same infectious diseases and mental health issues, too? Are these things related in any way?
<p data-bbox="212 1239 724 1356">Diet, Wellness, and Other Non-drug Approaches to Help Kids and Teens Manage MS</p>	What contributes to supporting and/ or advancing the overall health and wellness of kids and teens with MS? How does community connection, recreational activities and resources accessible to kids with MS, etc. support wellness?
	What do we know about what it takes to engage kids and teens in listening to their bodies and engaging with available resource/ opportunities? What supports/ increases buy-in from young people and families?

	<p>With diet and nutrition, what do we know about the kinds of foods that contribute to physical well-being and/or symptom regulation? What do we know about what foods are less helpful and/or should be avoided? What do we know about food allergies and MS – might food allergies jump-start an overactive immune system or start a MS flareup? How can we distinguish between underlying issues and/or other challenges (like a dairy issue)?</p>
	<p>With diet and nutrition, how does diet contribute to physical stamina and/ or fatigue? How much does consistency in diet matter?</p>
	<p>What are effective ways to promote physical activity or diet changes in youths with MS? How do we attend to diet and physical activity in personalized ways (not one size fits all – e.g., activity coach, dietician in clinic visits? What might be the role of technology – e.g., phone app (that is individualized and allowed young people the interplay of things like diet, exercise, etc. and could make individualized recommendations)?</p>
	<p>What do we know about herbal remedies, vitamins and other supplements, holistic medicine/ traditions beyond western medicines? How might vitamins, herbal remedies, etc. interact with drugs used to treat MS? What about vitamin B12 and/or other vitamins, and specifically in managing fatigue and pain?</p>
	<p>How/ when might we bridge the differing perspectives of medical/ clinical guidance and holistic/ alternative/ natural/ traditional medicines?</p>
	<p>With exercise and physical activity, what do we know about how much and how often? How physically active do young people living with MS need to be? Are there certain exercises that should be encouraged and/or avoided? Depending on other factors that kids are dealing with, how do we modulate our recommendations for physical activity?</p>
	<p>What do we know about the benefits/ efficacy of yoga and meditation?</p>
	<p>How do we build awareness about pediatric MS at schools and how symptoms might show up at different times of day and impact ability to participate? How might schools enable kids to get credit for their activity outside of school, enable physical/ occupational therapy to be substituted for a PE credit in school?</p>
<p>Factors That Cause Fatigue and Brain Fog in Kids With MS, and How to Treat Them</p>	<p>What are the underlying biological mechanisms of fatigue in pediatric MS? Can studies using brain imaging, biomarkers or other objective measures shed light on what is happening in the body during fatigue episodes?</p>
	<p>How can we better distinguish between MS-related fatigue and normal tiredness in teenagers? What criteria or assessment tools could help differentiate these?</p>

	<p>What is the relationship between fatigue, cognition, mood and sleep in pediatric MS? Does treating one symptom (e.g. improving sleep) have a positive impact on the others? Investigating these interconnections could inform a more holistic treatment approach.</p> <p>What pharmacological treatments might be effective for fatigue and cognitive issues in pediatric MS? Controlled studies on medications and comparing their efficacy to non-pharmacological approaches would provide valuable guidance.</p> <p>How do lifestyle factors like diet and exercise impact fatigue and cognition in youth with MS? Intervention studies promoting healthy eating, physical activity, sleep hygiene etc. could assess their potential for symptom management.</p> <p>Can non-pharmacological interventions like cognitive behavioral therapy, mindfulness, and meditation help with managing fatigue, brain fog and mood issues? Randomized controlled trials could test the feasibility and efficacy of these approaches in the pediatric MS population.</p> <p>For very young children with MS, how can we better capture their fatigue and cognitive challenges since they may not have the language or self-awareness to describe them? Developing age-appropriate measures and assessment strategies is needed.</p> <p>What educational supports and accommodations are most helpful for students with MS experiencing fatigue and cognitive issues? Studies partnering with schools to implement and evaluate different strategies (e.g. OT services, executive function coaching) could inform best practices.</p>
<p>Understanding What Triggers Relapses and Changes in Symptoms in Kids with MS</p>	<p>What impact could a change in diet have on symptoms/ relapse prevention? What techniques work best in getting young people with MS to eat a healthier diet?</p> <p>What triggers relapses/worsening of existing symptoms (e.g., stress, weather, other illnesses)? Can relapses/worsening be prevented?</p> <p>How can young people optimally manage their symptoms/relapses across different life stages (without parental support; post-high school with less institutional support)?</p> <p>How to tell if a new symptom (e.g., foot numbness) is due to MS or something else? How to communicate about/get help with new symptoms that nobody else can see?</p> <p>How can young people be supported in coping when they're experiencing limitations due to their symptoms (e.g, fatigue)? This includes dealing with their own feelings of frustration as well as setting expectations with friends.</p> <p>What can be expected after stopping DMT for a young person? How to monitor or predict whether disease activity is at risk of returning?</p>