

Abstract
Book

21st

State of the Art
Symposium

21st State of the Art Symposium

«Challenges in MS Treatment and Research»

Dear Colleagues,

It is with great pleasure that we invite you to this year's 21st State of the Art Symposium, organized by the Swiss MS Society and its Scientific Advisory Board. Multiple Sclerosis (MS) is a very heterogeneous and to a certain extent not clearly tangible disease, and the 21st State of the Art Symposium is dedicated to discussing «**Challenges in MS Treatment and Research**».

In the plenary morning sessions, five experts in the field will address individual topics on this theme. In the first session, **Bernhard Hemmer** will discuss the output from genetic studies in MS, while **Ari Waisman** will display the mechanisms of CNS inflammation. Finally, **Melinda Magyari** will address MS and old age. The second morning session will be dedicated to MS treatment. **Andrew Chan** will present the «Treatment Consensus for MS», a joint collaboration of members of the Scientific Advisory Board and other MS clinical experts. Long term risks of MS treatment will then be addressed by **Michael Linnebank**. In a final podium discussion these two speakers, together with **Christian Kamm** and **Ludwig Kappos**, will debate on the future challenges of MS treatment.

MS Researcher Poster Viewing: During the coffee and lunch breaks you will have the opportunity to view posters of the researchers currently funded by the Swiss MS Society, and discuss their projects.

The afternoon session, with two sets of two parallel workshops, will address specific topics relevant to daily practice. In Workshop A the speakers will present challenges in the management of **Pediatric MS**. Workshop B will discuss the role of **Biomarkers for MS**. Later, you will have the opportunity to discuss your own cases and questions with the MS experts from our Scientific Advisory Board in the workshops C and D «**Meet the Experts**». These workshops are offered in German and French/Italian. Updated information about the Symposium can be found on www.ms-state-of-the-art.ch

In the name of the organisers and speakers, we sincerely hope that the programme meets your interest and that you will be able to attend and actively take part in the discussions. We wish you an interesting symposium.



PD Dr. Chiara Zecca
President of the
Scientific Advisory Board



Patricia Monin
Director of the
Swiss MS Society

General Information

Date

Saturday, January 26th, 2019, 10.00-16.00

Venue

KKL Luzern, Europaplatz 1, CH-6005 Lucerne
www.kkl-luzern.ch

Programme Committee

Pasquale Calabrese, Basel
Andrew Chan, Bern
Tobias Derfuss, Basel
Renaud Du Pasquier, Lausanne
Britta Engelhardt, Bern
Christian Kamm, Lucerne
Doron Merkler, Geneva
Chiara Zecca, Lugano

Organisation

Swiss Multiple Sclerosis Society and its Scientific Advisory Board

Contact

Swiss Multiple Sclerosis Society, Josefstrasse 129, CH-8031 Zürich
symposium@multiplesklerose.ch, www.ms-state-of-the-art.ch

Credits

The Swiss Neurological Society will award **5 credit points**.

The Swiss Society of General Internal Medicine (SGAIM/SSMIG/SSGIM) will award **4 credit points**.

Contacts 2019

Programme Committee and Chairpersons

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Behavioral Neurology & Neuropsychology

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University Hospital Bern
Department of Neurology

Tobias Derfuss, Basel

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Renaud Du Pasquier, Lausanne

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Neurocenter of Southern Switzerland

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Bernhard Hemmer, Munich (DE)

Technical University Munich
Department of Neurology

Christian Kamm, Lucerne

Luzerner Kantonsspital
Neurocenter

Ludwig Kappos, Basel

University Hospital Basel
Department of Neurology

Michael Linnebank, Hagen (DE)

University Witten/Herdecke
Clinic Hagen-Ambrock

Melinda Magyari, Copenhagen (DK)

University Hospital Rigshospitalet Copenhagen
Danish Multiple Sclerosis Center

Ari Waisman, Mainz (DE)

University Medical Center Mainz

Speakers (Workshops)

Sandra Bigi, Bern

University Children's Hospital Bern

Department of Pediatrics

Pasquale Calabrese, Basel

University of Basel

Behavioral Neurology & Neuropsychology

Tobias Derfuss, Basel

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Departments of Neurology and Biomedicine

Jens Kuhle, Basel

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MS Researcher Poster Presentations

Thorsten Buch, Zurich

University of Zurich

Institute of Laboratory Animal Science

Lukas Enz et al., Basel

University of Basel & University Hospital Basel

Neurobiology, Department of Biomedicine

Andrea Glässer et al., Zurich

University of Zurich

Biomedical Ethics and History of Medicine

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Research and Development, Physiotherapy

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Diagnostic and Interventional Neuroradiology

Matthias Weigel, Oliver Bieri, Basel

University Hospital Basel

Department of Radiology, Radiological Physics

Programme on Saturday, January 26th, 2019

«Challenges in MS Treatment and Research»

Chairpersons	Session 1: Britta Engelhardt, Bern Doron Merkler, Geneva
	Session 2: Tobias Derfuss, Basel Caroline Pot, Lausanne
Moderation	Chiara Zecca, Lugano
09.30–10.00	Welcome with Coffee and Gipfeli
10.00–10.15	Christoph Lotter, Zurich Welcome from the Swiss MS Society
10.15–10.40	Bernhard Hemmer, Munich (DE) What have we learned from Genetic Studies in MS?
10.40–11.05	Ari Waisman, Mainz (DE) Mechanism of CNS Inflammation
11.05–11.30	Melinda Magyari, Copenhagen (DK) Facing Challenges with MS and Old Age
11.30–11.50	Coffee Break with MS Researcher Poster Presentation*
11.50–12.15	Andrew Chan, Bern A Swiss Treatment Consensus for MS
12.15–12.40	Michael Linnebank, Hagen (DE) Long Term Risks of MS Treatment
12.40–13.00	Podium Discussion on MS Treatment: the Challenges ahead! with Andrew Chan, Bern; Michael Linnebank, Hagen (DE); Christian Kamm, Lucerne and Ludwig Kappos, Basel
13.00–14.15	Lunch with MS Researcher Poster Presentation*
14.15–15.00	Workshops A and B
15.00–15.15	Coffee Break
15.15–16.00	Workshops C and D – Meet the Experts
16.00	Farewell Aperò

* MS Researcher Poster Presentation – During the coffee and lunch breaks you will have the opportunity to view selected posters from MS research projects that have been financially supported by the Swiss MS Society.



Bernhard Hemmer

What have we learned from Genetic Studies in MS?

The increased heritability within families and the directly proportional decrease in risk with degree of relatedness argue that genetic factors play a prominent role in the pathogenesis of multiple sclerosis (MS).

Over the last decade major progress has been made in identifying genetic factors that are associated with MS risk. Besides the Human Leukocyte Alleles (HLA)-DRB1*1501, DRB1*1303 and DRB1*0301, more than 200 genetic variants have been identified that are associated with MS. HLA alleles and the majority of genetic variants are related to immune cells supporting the concept that MS is primarily an immune mediated disease. With the discovery of an increasing number of genetic variants it has become possible to identify pathways in the immune system that are related to disease pathogenesis providing the basis for the development of new treatment strategies. Moreover, it has become evident that particular phenotypes or even treatment responses are influenced by genetic factors. Likewise, the extent of intrathecal IgG synthesis, the development of antibodies to biopharmaceuticals or the risk of side effects of MS drugs were shown to be associated with genetic factors.

Currently major efforts are underway to understand the impact of genetic factors on disease progression. The results of these studies will help to better understand the molecular mechanisms underlying disease progression and possibly pave the way for new strategies to treat progressive MS.

*Bernhard Hemmer, Munich (DE)
Technical University Munich
Department of Neurology*



Ari Waisman

Mechanism of CNS Inflammation: The role of IL-17 and the microbiota

IL-17A and IL-17F are two cytokines with similar biological activities which bind the same receptor and are produced by T cells called Th17. A clear role for IL-17A was shown in different autoimmune diseases, including psoriasis and rheumatoid arthritis, but their role in multiple sclerosis (MS) and in experimental autoimmune encephalomyelitis (EAE), the animal model of MS, is controversially discussed. We have previously shown that mice lacking IL-17A or IL-17F are only partially, if at all, protected from EAE, suggesting that these cytokines are not critical for disease pathogenesis.

We could show now that the role of IL-17 in EAE is critically dependent on the gut microbiota. We show that the main pathogenic role of IL-17 is mediated in the gut and is transmitted via the gut microbiota. Mice lacking IL-17A and IL-17F are resistant to EAE, but can be made susceptible to the disease if supplemented with the microbiota of wild type animals. Moreover, we could show that ectopic expression of IL-17A in the gut, but not anywhere else, is sufficient to regain susceptibility to the disease via regulating the microbiota. Our data suggest that IL-17 is a major regulator of gut microbiota and that it contributes to disease pathogenicity by affecting the microbiota and not directly the cells of the body.

*Ari Waisman, Mainz (DE)
University Medical Center Mainz*



Melinda Magyari

Facing Challenges with MS and Old Age

The incidence, prevalence and the average age of persons with multiple sclerosis (MS) is increasing. This is a result of increased life expectancy of the general population as well as the availability and effectiveness of disease-modifying therapies (DMT).

However, aging with MS presents great challenges. With advancing age, the disease transitions towards a less inflammatory and more neurodegenerative course. Aging with MS, as in the general population, is accompanied by the development and accumulation of comorbidities. This complicates the medical management of MS.

The currently approved therapies to treat MS are not as effective in preventing the disability progression associated with higher age and progressive disease as they are in preventing relapses. Trials of existing DMTs generally were not designed for persons with age higher than 55 years. Since a substantial portion remains in the relapsing phase, information on the safety and efficacy of DMTs in this population is greatly needed. The vast majority of therapies approved in relapsing-remitting MS have failed clinical trials in progressive MS and there are only few options for DMTs in individuals with progressive MS, who represent the majority of persons with MS over age 65.

Because clinical trials for existing DMTs have purposefully excluded aging persons with MS, there is insufficient knowledge on safety and efficacy of DMTs in elderly populations. Real-world studies are needed to identify the impact that DMTs have in elderly persons with MS.

Cognitive decline is a particular issue in the elderly population with MS, but studies evaluating symptomatic therapies for cognition in elderly persons MS have been largely negative.

Besides medical treatment, an emphasis should be more holistic, including social support and cognitive training, in order to improve quality of life for the aging population with MS.

*Melinda Magyari, Copenhagen (DK)
University Hospital Rigshospitalet Copenhagen
Danish Multiple Sclerosis Center*



Andrew Chan

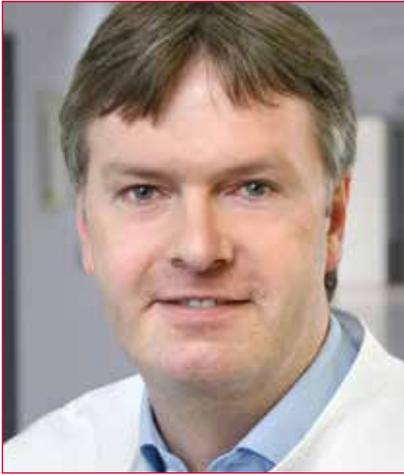
A Swiss Treatment Consensus for MS

More than a dozen substances are meanwhile available for the disease-modifying immunotherapy of multiple sclerosis (MS). However, for some substances there is a clear difference between approval in Switzerland (Swissmedic) and neighbouring countries (European Medicines Agency, EMA). In addition, limitations imposed by the Swiss Federal Office of Public Health (FOPH) in the specialties list (SL) have significant effects on use in daily clinical practice.

We will present consensus recommendations which were reviewed and agreed upon by the Scientific Advisory Board of the Swiss Multiple Sclerosis Society and the Swiss Neurological Society. We explicitly focus on practice-relevant differences in the approval of MS immunotherapies in Switzerland compared to the EMA area and discuss further limitations (SL) and their impact on the use in clinical practice.

Immunotherapies with the same approval in Switzerland and the EMA area and symptomatic therapies will not be discussed.

*Andrew Chan, Bern
University Hospital Bern
Department of Neurology*



Michael Linnebank

Long Term Risks of MS Treatment

The recent years yielded an increasing spectrum of symptomatic as well as disease modifying therapies for relapsing and progressive MS. It is dangerous not to treat MS, but also treatment strategies are associated with several known and possibly yet unknown risks.

Current disease modifying therapies include classic immunomodulators, drugs that target immune trafficking, drugs which interfere with immune cells on the DNA level and medications that attack defined types of immune cells. There seems to be some correlation between drug efficacy and adverse events, but the distinct products exhibit specific risks, which need to be addressed in patient counselling.

Concerning the new drugs, not all relevant risks are known today. Also dietary strategies or intake of vitamins and other supplements implicate several adverse effects especially in long-term applications. Symptomatic therapies that aim, for example, at improving fatigue, spasticity, bladder dysfunction or walking impairment, are associated with adverse events and risks, too. Valuing risks and benefits of the different therapies poses an important challenge of current patient care. This talk will provide an update of knowledge about the details of long term risks of MS treatment.

*Michael Linnebank, Hagen (DE)
University Witten/Herdecke
Clinic Hagen-Ambrock*



Andrew Chan



Michael Linnebank



Christian Kamm



Ludwig Kappos

Podium Discussion on MS Treatment: the Challenges ahead!

In this Podium Discussion the participants will elaborate on the most important questions raised in the plenary speeches. The focus is on the currently available treatment options and the challenges in MS treatment that lie ahead.

*Andrew Chan, Bern
University Hospital Bern
Department of Neurology*

*Michael Linnebank, Hagen (DE)
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*Christian Kamm, Lucerne
Luzerner Kantonsspital
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*Ludwig Kappos, Basel
University Hospital Basel
Department of Neurology*

Workshops

Saturday, January 26th, 2019

	<p>Clinical Case Management</p> <p>The workshops focus on aspects relevant to the daily management of MS patients. In «Meet the Experts», you will have the opportunity to discuss your own cases with the MS experts and receive first-hand answers to your questions. These workshops are offered in German and French/Italian.</p>
14.15 –15.00	<p>Workshop A: «MS in Children: the specific Challenges» <i>Sandra Bigi, Bern and Pasquale Calabrese, Basel</i></p> <ul style="list-style-type: none"> – Pediatric Onset Multiple Sclerosis (POMS) is characterised by a high relapse rate and rapid accrual of inflammatory brain lesions. – Substantial early cognitive impairment is in contrast to the excellent recovery from early relapses. – Treatment requires an individually tailored approach. <p>Workshop B: «Biomarkers for MS – ready for Clinical Practice?» <i>Jens Kuhle, Basel and Nicholas Sanderson, Basel</i></p> <p>Biomarkers have the potential to help the clinician in many areas from diagnosis to predicting disease course and drug response. Monitoring of neurofilament light chain offers a direct biological readout of neuronal damage to the entire nervous system.</p>
15.00 –15.15	Coffee Break
15.15 –16.00	<p>Workshop C – in German: «Meet the Experts» <i>Tobias Derfuss, Basel</i>, is a clinical neurologist with a specialisation in neuroimmunology. He is professor and senior physician at the University Clinic in Basel.</p> <p><i>Sven Schippling, Zurich</i>, is consultant neurologist at the University Hospital Zurich and Deputy Head of the Department of Neuroimmunology and Clinical Multiple Sclerosis Research (nims).</p> <p>Workshop D – in French and Italian: «Meet the Experts» <i>Caroline Pot, Lausanne</i>, is a clinician-scientist specialised in neuroimmunology with a strong expertise multiple sclerosis (MS). She is assistant professor at the CHUV in Lausanne.</p> <p><i>Chiara Zecca, Lugano</i>, is a neurologist at the Regional Hospital in Lugano, where she is co-chair of the Multiple Sclerosis Center.</p>
16.00	Farewell Aperero



Sandra Bigi



Pasquale Calabrese

Workshop A

«MS in Children: the specific Challenges»

Pediatric onset multiple sclerosis (POMS) is a rare disease in the pediatric age group with a reported incidence of 0.04-2.9/100'000; approximately 3-5% of MS patients experience their first attack before the age of 18 years. Low vitamin D level, remote EBV infection and HLA-DRB1*1501 are associated with POMS.

The first attack – an acquired demyelinating syndrome – is clinically heterogeneous and neurological symptoms can be highly variable; especially younger children may present with polyfocal neurological deficits. Therefore, a high index of suspicion is needed for the timely diagnosis of POMS. Diagnosis of POMS requires both the exclusion of MS mimics and the presence of dissemination in space and time.

A primary progressive disease course is not typical for POMS and prompts the neuropediatrician to look for hereditary diseases such as leukodystro-

phies, mitochondrial or other metabolic diseases. POMS is characterized by a high relapse rate in the early disease course, rapid accrual of inflammatory brain lesions – especially in the infratentorial area – and an excellent, often full recovery from first relapses. The time from first attack to permanent disability (EDSS 4) takes approximately 20 years, i.e. 10 years longer compared to adult onset MS. However, POMS patients are 10 years younger when they reach an EDSS of 4 compared to adult onset MS patients. In contrast to adult onset MS, POMS hits a still developing brain and negatively impacts on academic performance and vocational achievement. The early cognitive impairment and marked brain atrophy becoming obvious in the adolescent MS patient are highly worrisome.

There is consensus that pediatric patients with a diagnosis of MS need to be treated. However, the choice of the appropriate treatment remains a challenge despite the variety of MS therapeutics on



Jens Kuhle



Nicholas Sanderson

Workshop B

«Biomarkers for MS – ready for Clinical Practice?»

An ideal biomarker would be a simple measurement, from a sample obtained non-invasively, that gave reliable information, not easily obtained from other routine diagnostics, that would help treatment decisions in individual patients. The ease of discovering biomarker candidates is dependent on our understanding of the biology of the disease. At present, we have limited understanding of the causes of MS, hampering the development of biomarkers useful for differential diagnosis. Our understanding of the pathological process causing disability is relatively better, enabling the selection and development of useful biomarkers for monitoring disease activity and drug response:

1. Biomarkers have the potential to help the clinician in the following areas:
 - diagnosis
 - monitoring disease activity or worsening
 - monitoring drug response
 - monitoring drug side effects
 - predicting disease course

2. Biomarkers will be useful only if superior to MRI in one of the following:
 - offering different or additional information
 - cost
 - invasiveness or feasibility
 - temporal sensitivity
3. State-of -the-art monitoring of neurofilament light chain has come closest to meeting some of these criteria
 - direct biological readout of neuronal damage to entire nervous system
 - useful in monitoring disease activity and drug response
 - low cost
 - low invasiveness

*Jens Kuhle, Basel
University Hospital Basel
Neurologic Clinic and Policlinic*

*Nicholas Sanderson, Basel
University of Basel
Department of Biomedicine*



Tobias Derfuss



Sven Schippling

Workshop C

«Meet the Experts» – in German

This workshop is a lively, interactive question and answer round. Participants have the unique opportunity to discuss their own clinical cases with two renowned experts. They will receive first-hand answers to their questions concerning treatment of their patients.

Tobias Derfuss is a clinical neurologist with a specialisation in neuroimmunology. He received his clinical training at the Department of Neurology, Klinikum Grosshadern in Munich. His research at the Max-Planck Institute for Neurobiology, Department of Neuroimmunology, was focused on the discovery of new autoantigens in Multiple Sclerosis and the characterization of the immune response against latent herpesviruses. After training in neuromuscular diseases at the Friedrich-Baur Institute and in psychiatry at the Max-Planck Institute for Psychiatry in Munich he was appointed head of the out-patient department and MS clinic at the Department of Neurology of the University Clinic in Erlangen.

Since 2010 he is professor and senior physician at the Department of Neurology and research group leader at the Department of Biomedicine of the

University Clinic in Basel. His main research focus is the discovery of biomarkers and analyzing the mode of action of disease modifying treatments in MS. Especially the role of B cells in the pathogenesis of MS and the interaction of B cells with their target cells is explored in cell culture as well as in in vivo models. Tobias Derfuss is also involved in the design and conduct of clinical trials for newly emerging therapies in MS. Tobias Derfuss is committee member of the MS Society Scientific Advisory Board.

*Tobias Derfuss, Basel
University Hospital Basel
Departments of Neurology and Biomedicine*

Sven Schippling is currently Deputy Head of the Department of Neuroimmunology and Clinical Multiple Sclerosis Research (nims) at the University Hospital Zurich, Switzerland. He is the Co-Director of the Clinical Research Priority Program MS (CRPPMS) and Consultant Neurologist at the Department of Neurology at the University Hospital Zurich. He is a Senior Group Leader at the Neuroscience Center Zurich of the Federal Institute of Technology Zurich (ETHZ) and



Caroline Pot



Chiara Zecca

Workshop D

«Meet the Experts» – in French and Italian

This workshop presents a lively, interactive question and answer round. Participants have the unique opportunity to discuss their own clinical cases with two renowned experts. They will receive first-hand answers to their questions concerning treatment of their patients.

Caroline Pot is a clinician-scientist specialized in neuroimmunology with a strong expertise multiple sclerosis (MS). She has been trained as a neurologist at the Geneva University Hospitals, Switzerland. In parallel to her clinical expertise, she completed her MD-thesis in the laboratory of Prof. M.E. Schwab at the University of Zurich and further performed a research fellowship in the laboratory of Prof. V.K. Kuchroo at Harvard Medical School in Boston. Since 2011, she combines clinical work with basic and translational research in neuroinflammation. In 2015, she joined the Department of Clinical Neurosciences at the Lausanne University Hospi-

tal (CHUV), awarded by a Swiss National Science Foundation Professorship. She focuses her current research on establishing the role of lipid metabolism, mucosal immunology and nutrition in driving MS and its animal model. Caroline Pot is member of the MS Society Scientific Advisory Board.

*Caroline Pot, Lausanne
Lausanne University Hospital
Department of Clinical Neuroscience*

Chiara Zecca received her certificate as neurologist from the University of Milan in 2006. Since 2007 she has been working at the Neurology Department of the Neurocenter of Southern Switzerland, Regional Hospital in Lugano, where she is now Co-Chair of the Multiple Sclerosis Center and Head of the Headache Center. After obtaining her medical degree, she engaged in academic research in the field of neuromuscular disorders. Later, her inter-

MS Researcher Poster Presentations

Every year, the Swiss MS Society supports research projects in the field of Multiple Sclerosis with considerable financial contributions.

A selection of current projects will be displayed at the KKL during the coffee and lunch break of the State of the Art Symposium. Do not miss out on the opportunity of viewing these posters and discussing the projects with the researchers.

Quality of Life and Treatment

Talking About Life with Multiple Sclerosis. A Qualitative Study of Patient Experiences

Introduction: Listening to patients' voices is increasingly being recognized as an important factor for continuous improvement in health care. Integrating patients' stories about their experiences with Multiple Sclerosis (MS) seems paramount considering the relatively high prevalence of MS and its life-changing consequences for those affected and their families. The Swiss database of patient narratives provides a systematic and methodologically rigorous collection of interviews about the real-life experiences with health issues and presents them as video- and/or audio-sequences on a website.

Objective of this study is to describe a wide range of people's individual experiences of health and disease, to understand what matters to them and to provide a rich information resource for people with MS and for those who look after them.

Relevance of the study: To present the Swiss perspective of patients' experiences with MS via this platform. We want to show that learning about patients' perspectives based on qualitative research can be beneficial in a variety of ways:

- A) Improving health care: Narratives provide a valuable source of information on patients' perspectives that can help improve health care.
- B) Self-help and patient engagement: People facing similar issues benefit from consulting the website by gaining information and cope with MS more effectively.
- C) Education: The database of patients' voices can also be used as a resource in teaching medical and health professionals to better understand MS patients' needs and priorities.
- D) Research: The project contributes to health-related narrative research and offers the opportunity to get involved in the growing field of interprofessional research.

Methodology: The project is part of the international DIPEX network, represented by fourteen countries, led by UK (www.healthtalk.com). DIPEX works with a well-established and rigorous qualitative research methodology developed by the University of Oxford in 2000.

Results: Out of 10 cantons 32 participants with MS were interviewed concerning their personal experiences of health and illness. The recruitment was mainly supported by the Swiss MS Registry.

Conclusion: Understanding what is important for patients when they are ill is a crucial prerequisite for the development of patient-relevant outcomes, quality measures, and for identifying opportunities for improvement and best-practice models. In 2019, these patients' voices will be presented by www.DIPEX.ch.

*Andrea Glässer, Nina Streeck, Corine Mouton Dorey, Dana Briegel,
Giovanni Spitale, Jürg Kesselring, Nikola Biller-Andorno
University of Zurich
Institute of Biomedical Ethics and History of Medicine (IBME)*

Quality of Life and Treatment

Impact of In-Patient Rehabilitation on Walking in Daily Life

Clinical and laboratory based examinations with persons with MS (pwMS) have shown that rehabilitation can result in a faster, more regular gait with a reduced risk of falls, and an improved ability to walk longer distances. The patients usually report that these improvements have a significant impact on their daily life and enhance their participation.

However, the impact of rehabilitation on daily life is difficult to measure because there is no objective observer such as a doctor or a therapist. So far, our knowledge about the impact on daily life is based mostly on reports from pwMS, i.e. by using questionnaires e.g. about mobility at home or quality of life. Although relevant, this information is subjective and may not reflect the reality.

We use miniature wearable sensors fixed on the body to gather objective information of patient's physical activity and mobility in real life before and after in-patient rehabilitation. Preliminary data of this ongoing study are presented.

*Roman Gonzenbach
Rehabilitation Centre Valens
Clinic of Neurology and Neurorehabilitation*

Quality of Life and Treatment

Feasibility Study of a three-week Inpatient Fatigue Management Education (IFME) Protocol for Persons with MS-Related Fatigue

Background: Multiple sclerosis (MS)-related fatigue limits participation in everyday activities (Krupp, 2006) and has considerable impact on quality of life, thereby affecting productivity and employment (Flensner et al., 2008). Outpatient education interventions with energy conservation strategies and cognitive behavioural therapy techniques are helpful (Asano and Finlayson, 2014). However, no inpatient programme is currently available. The inpatient energy management education (IEME) programme is a novel group intervention, 6.5 h in duration that is conducted by a trained occupational therapist (OT) during a three-week period of inpatient rehabilitation. Persons with MS (pwMS) and OTs have previously evaluated the IEME positively after a test run (Hersche et al., 2018). The aim of this study was to evaluate the feasibility of a research protocol and collect preliminary data about the IEME effect size.

Methods: Design: Feasibility of a randomised clinical trial. Sampling: pwMS-related fatigue during a three-week period of inpatient rehabilitation at a rehabilitation centre. Interventions: Six IEME (experimental) group sessions or progressive muscle relaxation (PMR, control) group sessions comprised part of a personalised rehabilitation programme. Data collection: evaluation of recruitment and assessment procedures, dropout and follow-up rate, treatment fidelity, compliance with therapy and six telephone interviews with IEME participants after returning home. Outcomes were fatigue impact, occupational performance, self-efficacy in using energy conservation strategies and quality of life at baseline (BL), discharge (T1) and 4 months (T2). Statistical analysis: Paired and independent t-tests for within- and between-group effects. Effect sizes were estimated with Cohen's d.

Results: Between August and November 2017, 47/83 pwMS were included and randomised. The dropout rate (4.2%) was low and the samples were balanced. The PMR was a well-accepted control intervention. The IEME participants confirmed the adequacy of the proposed programme. The OTs reported no problems in conducting the IEME, and treatment fidelity was high. Both interventions alleviated the impact of fatigue, and improved partial occupational performance and some dimensions of quality of life at discharge. The IEME alone resulted in significant improvements in self-efficacy in performing energy conservation strategies and perceived physical functioning dimension of quality of life with large effect sizes at T2. A sample size of 192 participants would guarantee sufficient power. Considering the recruitment rate, 369 potential participants should be sought for a further study.

Conclusion: This feasibility study has been successfully concluded and provided important information about all open issues. The IEME is a promising and cost-friendly intervention for pwMS during inpatient rehabilitation. The self-efficacy for performing energy conservation strategies assessment and the occupational self-assessment should be employed to determine the primary outcome measures at T1 and T2; whereas the SF36 should preferably be employed at T2. The modified fatigue impact scale may be used as secondary outcomes, as it captures the effects of multidisciplinary rehabilitation of all patients. The IEME improved the use of fatigue management strategies and behaviour. It seemed to positively influence the perception of competence in performing daily activities and reduced the perceived influence of MS-fatigue on physical functioning.

Ruth Hersche
University of Applied Sciences and Arts of Southern Switzerland
Rehabilitation Research Laboratory 2rLab,
Department of Business Economics, Health and Social Care

Quality of Life and Treatment

Markers of Quality of Life in Multiple Sclerosis: The Impact of Nonverbal Communication

Multiple sclerosis is the most common neurological disease of young adulthood leading to physical disability and reduced quality of life.

In particular, good vocational status and social functioning contributes to quality of life, which extends beyond health-related quality of life, which focusses on disease-associated symptoms. In MS, symptoms such as disability and fatigue contribute to impairment, whereas good self-efficiency and high social support are, in turn, associated with higher levels of quality of life. Actual gold standard of fatigue assessment is based on different questionnaires.

In this ongoing project, we aim to measure motor fatigue and quality of life by means of 24 hours wrist actimetry as well as a digital video analysis of a standardized conversation. Further, the effect of fatigue on the ability to make a conversation should be evaluated.

Preliminary analysis demonstrated that in our cohort of 28 patients with multiple sclerosis the FSMC score for motor and cognitive function correlated nicely with the «Fatigue Questionnaire» as well as the «Fatigue Severity Scale». Higher fatigue scores were mildly associated with depressive symptoms as assessed by BDI-11, whereas no correlation was found with assessments of sleepiness. Interestingly, a moderate association between cognitive fatigue and the negative symptom scale was present. This scale is commonly used in psychiatric research to evaluate the negative symptoms of schizophrenia, which have a major impact on conversation and social interaction of the affected persons. While cognitive fatigue demonstrated a link with negative symptoms, motor fatigue was negatively correlated with motor speed (km/h) as measured with the wrist worn actimetry during a two minute walk test. This association remains significant even after exclusion of the two MS patients who need unilateral assist to perform the two minute walk test. Finally and most importantly, the fatigue measurements correlated robustly with MS related physical and mental quality of life.

The results presented here are results of an ongoing project. At the time of abstract writing 30% of the intended MS patients (28/96) have been recruited. Analysis of 24-hour actimetry and video sequences will follow. Thus, we expect this project to provide further insights into how MS related fatigue could be measured.

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Quality of Life and Treatment

Evaluation of upper Extremity Motor Function with Tablet-PC Tests

Background: Many persons with multiple sclerosis (pwMS) experience difficulties in activities of daily living as a consequence of impaired arm and hand coordination. We developed five touchscreen tablet-PC based tests for the evaluation of arm-hand coordination:

- 1) finger individuation («playing the piano»);
- 2) dysmetria test («targeted index finger movement»);
- 3) rapid index finger tap;
- 4) Finger-nose test; and
- 5) rapid lower arm pro- and supination.

Methods: Cross sectional study in 36 pwMS (EDSS median 5.5, range 2-8; age 53.8±11.6, range 25-87) and 120 healthy persons (age 50±15, range 20-80). PwMS performed tablet as well as conventional versions of these tests rated on a 4 or 5 point ordinal scale. For the tablet tests we evaluated velocity, movement precision and the number of hits, floor and ceiling effects, the ability to distinguish healthy persons and PwMS, test-retest stability, the association with clinical tests and the effect of age and hand dominance.

Results: The effect of age and hand dominance was negligible. Floor and ceiling effects were generally lower in tablet based tests compared with clinical tests. In pwMS, the dysmetria test had the strongest association with clinical tests. In all tests, movement velocity and accuracy clearly distinguished healthy persons and pwMS.

Discussion and conclusion: All tests can be used for the evaluation of arm-hand coordination. Patients can perform tests online at home and results can be sent to the physician, physical or occupational therapist and support monitoring of symptoms as well as the effect of interventions. This would allow evaluating performance more frequently without additional consultations. The tablet based dysmetria tests can be used instead of the clinical test. We will present more detailed results at the State of the Art poster session.

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Quality of Life and Treatment

A Single-Center, Prospective, Cross-Sectional Study to Evaluate the Reliability and Validity of the Modified Manual Muscle Test for Persons with Multiple Sclerosis

Background: In MS patients, testing muscle function can be confounded by many factors, such as spasticity and ataxia, which are not considered by the existing tests and may cause biased test results. Steinlin Egli described a Modified Manual Muscle Test (MMMT) that considers spasticity and may provide a more reliable and valid muscle function test for MS patients.

Aim of the study: We evaluate the inter- and intra-rater reliability of the Modified Manual Muscle Test in MS and the validity of the Modified MMT according to the criteria of the Neurostatus EDSS manual muscle test and the microFET2 handheld dynamometer.

Methods: This is a single-centre, prospective cross-sectional study with a test-retest design. The primary endpoint is the ordinal MMMT level. The intra-class correlation coefficient (ICC) of the ranked MMMT levels will be estimated. We aim to show that the MMMT results are clinically relevant with a high level of ICC.

The secondary endpoints include the Neurostatus EDSS levels, the muscle strength as measured by the microFET2 dynamometer, fatigue using a numeric rating scale (NRS) and spasticity with the Modified Tardieu scale. Subgroup analyses will determine whether the MMMT is less sensitive to the influence of spasticity than the Neurostatus.

We will test 28 patients with MS in 3 days. Six examiners, three MS-therapists and three neurologists will test the patients. The examiners will be blinded to the results of the other examiners. All test persons will be blinded to their test results. The order of the examiners and the test they use (MMMT or Neurostatus) is randomized.

Results: First results will be available in January 2019. We expect the MMMT for MS to be a reliable and valid manual muscle function test that can be used in the evaluation of the long-term treatment of MS patients with physical therapy.

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Quality of Life and Treatment

Evaluation of a Powered Exoskeleton with 6 Degrees of Freedom for Multiple Sclerosis Patients

Locomotion and mobility is a serious issue in numerous people suffering from multiple sclerosis (MS). Gait training with exoskeleton has proven its impact at different levels on people with MS. However, the access to stationary devices is limited to clinics (i.e. Lokomat), while wearable devices (i.e. ReWalk) were designed for people with paraplegia and they only fit a limited group of people with MS. AUTONOMYO is a novel architecture of wearable exoskeleton that is meant to be used without crutches for people with poor residual walking activity.

The current investigation consists in performing a clinical feasibility study in partnership with the CHUV. This study will include about 5 people with MS, with an EDSS between 4.5 and 7.5 and a control group. The participants will be tested on a 6 minutes walking test with and without the exoskeleton after two to four training sessions. The muscular activity and kinematics will also be compared in both conditions but over a short gait path. Results should assess the safety and comfort of use of the wearable exoskeleton and its physiological impact on gait.

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Quality of Life and Treatment

Feasibility of a Videogame Based Virtual Reality Dexterity Training in Multiple Sclerosis: a Pilot Study

Background: Videogame based training might be a feasible training tool to improve dexterity in MS patients. A device which is able to combine gamification and Virtual reality (VR) is the Leap Motion Controller (LMC). The aim of this study is to investigate if VR LMC training, focused on dexterity, is feasible in patients with MS.

Methods: The out- and in-patients participate in a dexterity VR LMC training program, which consists of 8 sessions of 30 minutes, twice a week for four weeks.

The following measurements are performed at baseline and four weeks later:

- System Usability Scale (SUS)
- Pittsburgh Rehabilitation Participation Scale (PRPS)
- Nine Hole Peg Test (9HPT)
- Arm Function in Multiple Sclerosis Questionnaire (AMSQ)
- Multiple Sclerosis Impact Scale 29 (MSIS 29)

Results: Preliminary results with regard to the usability of the VR LMC training are presented at the State of the Art poster session.

Discussion: Impaired dexterity is a common problem in many MS patients. The use of a new VR videogame based LMC dexterity training seems to be a feasible training method to improve dexterity in MS.

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Quality of Life and Treatment

Automatic Segmentation of MS Lesions, Brain Volumetry and Morphometry: Proposal of a Diagnostic Tool for Disease Monitoring; Part II

During the current project, we have updated the anonymized control database from the outdated FreeSurfer version 5.3 to the current version 6.0, requiring to re-run the analysis on all datasets. In this process, we were able to substantially extend the database from 323 to 422 subjects who have participated in earlier studies at our institute. This closed an earlier existing gap at adolescents and young adults. Further, now a five-year follow-up is available for healthy adolescents. Both very relevant for MS research.

In a first application of the longitudinal analysis pipeline to five MS patients under therapy with natalizumab and very long follow-up series on our 3T scanners (average follow-up time was ≈ 5 years, 10 to 13 MRIs) we found patient specific atrophy patterns and regions with pronounced progression of atrophy and structural reorganization (3). Thereafter, we investigated how many subsequent MRI exams (follow-up interval ≈ 0.5 years) are needed in order to reliably detect the progression pattern observed from the full follow-up series. It turned out that depending on the patient 4 to 7 MRIs are sufficient.

In parallel to the improvements made to the morphometric pipeline, we have continued to improve our lesion segmentation software, by modernizing the neural network architecture, and by expanding the number of tissue classes predicted to reduce the number of false positive and false negative lesion identifications. A major difficulty in developing MS lesion segmentation algorithms is the avoidance of false positives. Three major sources of false positives are cortical grey matter, the choroid plexus, and physiological changes in the periventricular regions (so-called «caps and bands»), all of which appear bright in FLAIR imaging, and may therefore be mistaken for MS lesions. Human raters may also label these structures as being lesion tissue, in particular if lesions are being marked by examining a single 2-dimensional plane.

A thorough re-labelling of the dataset was carried out with particular attention to the periventricular region. In addition, the lesion labels were enriched by labels derived from FreeSurfer, which had already been calculated as part of our morphometric pipeline. These extra labels include cortical grey matter and white matter, but also subcortical structures, hippocampus, amygdala and choroid plexus. We used these new labels to train a classifier, which we call DeepSCAN, which can provide lesion segmentations in two modes: binary segmentation and softmax segmentation. We have been able to demonstrate, on a cohort of 32 test subjects, that both versions of DeepSCAN are a significant improvement over NAbla net.

By our improvements to the ground truth and the classifier, we have been able to show substantial improvements in lesion segmentation over our NAbla net. Wilcoxon signed rank tests show that the Dice coefficients between the human consensus and NAbla-net are significantly different to those between DeepSCAN (binary) and the human consensus ($p < 1e-5$) and to those between DeepSCAN (softmax) and the human consensus ($p < 1e-5$). In terms of Dice coefficient comparisons with the human consensus, no significant difference was found between the two segmentations of DeepSCAN, or between the segmentations of DeepSCAN and the individual human raters.

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Pathogenesis and Preclinical Studies

Dissecting the Role of Pattern Recognition in Initiation of Anti-Myelin Autoimmune Responses

As the animal model of multiple sclerosis, experimental autoimmune encephalomyelitis can be actively induced in C57BL/6 mice by co-administration of myelin oligodendrocyte glycoprotein peptide and complete Freund adjuvant, together with pertussis toxin. The requirement of adjuvant components for successful EAE induction suggests that there may be a role for pattern recognition receptors (PRR) in the onset of this disease. PRR recognise pathogen- or damage-associated molecular patterns, engaging the innate and adaptive immune systems. Even though there is abundant literature implicating PRR and their downstream signalling molecules in the development of EAE, no molecule or receptor has yet been identified as a major player in this model.

It is known that MyD88 knockout mice are resistant to EAE. Surprisingly, studies in our lab show that this effect is not due to TLR signalling, the main upstream signalling pathway of MyD88, as in our hands TLR23479 knockout mice develop EAE to the same extent as control mice. Thus, we hypothesise that there are alternative pathways involved in EAE development. In order to study these pathways, we have generated knockout mice for key molecules of other PRR pathways: Mavs (RLR pathway), Tram (TLR pathway), Card9 (CLR, NLR and TLR pathways) and Sting (CDS pathway). These knockout mouse lines develop EAE, with variable levels of delay in onset and severity than their littermate controls.

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Pathogenesis and Preclinical Studies

Functional Impact of Genes potentially involved in De- and Remyelination in cultured Oligodendrocytes on Nanofibers

Multiple sclerosis is a chronic inflammatory, demyelinating disease of the central nervous system with diverse clinical presentations and a heterogeneous histopathology. A major characteristic of MS is the formation of the so-called plaques or lesions, areas of demyelination, inflammation and axonal damage. Demyelination occurs in the white and grey matter and can lead to chronic inactive demyelinated lesions or, if remyelination occurs, to remyelinated lesions, the so-called shadow plaques. Understanding the mechanisms of de- and remyelination is essential to comprehend multiple sclerosis pathogenesis and to develop improved therapies. Until today several factors promoting or inhibiting remyelination have been described and identified in de- and remyelinating multiple sclerosis lesions (Zeis et al., 2018; PMID: 29596844). However, the overall nature and timing of molecular signaling necessary for remyelination in human brain tissue is still not fully understood.

Primary co-culture systems are suitable to investigate specific questions on myelination, but due to their complexity, direct effects on oligodendrocytes and oligodendrocyte precursor cells proliferation, differentiation and myelination can hardly be differentiated from indirect effects. Moreover, quantitative approaches are often handicapped due to the cell heterogeneity in these co-culture systems.

In 2012, the research group of Jonah Chan demonstrated that oligodendrocytes are capable of myelinating engineered nanofibers (Lee et al., 2012; PMID: 22796663). This technique has enormous potential to evaluate the effect of single molecules on oligodendrocyte myelination, and to identify potential therapeutic targets. In this study, we have successfully optimized this method and combined it with the protocol of Pedraza et al. (Pedraza et al., 2008; PMID: 18512250) to reliably differentiate between effects on proliferation, differentiation and myelination in a single experiment. This makes this in vitro model ideal for testing the effect of different factors on oligodendrogenesis and furthers high-throughput screening possibilities.

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Pathogenesis and Preclinical Studies

Treatment of Autoimmune Encephalomyelitis

Autoimmune encephalomyelitis can occur when an initial unknown trigger results in recognition of self-antigens expressed in the nervous system as «foreign», resulting in activation of T lymphocytes thereby destroying the myelin sheath and severely damaging the nervous system. In humans, such T cell activation is believed to be implicated in the establishment of multiple sclerosis, while in mice, several model systems exist that can be used to study the etiology as well as test potential treatment options for autoimmune encephalomyelitis. The exact etiology of the disease remains unknown. Current treatments are largely based on disease-modifying therapies aimed at reducing the number of relapses and extending remissions through modulation of the immune system. However, a major drawback for all of these treatments is the occurrence of side effects since the targets of these therapies are either expressed ubiquitously or in all immune cells, therefore also greatly increasing susceptibility towards infections and potentially increasing the risk of cancer.

Whether it is possible to block autoimmune responses while maintaining immunity towards infectious agents and tumor cells remains largely unknown. Our work as well as that from other laboratories over the past decade has pointed towards a novel target, coronin 1, that is specifically required for the generation of encephalomyelitic T lymphocytes and dispensable for the activation of immunity against a wide variety of infectious agents.

In our current project, we are exploring the possibility to block and/or inactivate coronin 1 or the coronin 1-dependent pathway as a mean to suppress or prevent the development of autoimmune encephalomyelitic responses in mice. Our preliminary results suggest that coronin 1 can indeed be modulated pharmacologically. Additionally, we have defined both upstream as well as downstream targets of the coronin 1 signaling pathway that may represent targets for immune suppression. Together our results suggest that modulation of the coronin 1 signaling pathway may be useful for the treatment of autoimmune encephalomyelitis.

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Pathogenesis and Preclinical Studies

Rapid and Reliable, Fully-Automated Brainstem Segmentation for Application in Multiple Sclerosis

Introduction: Atrophy is a hallmark of neurodegeneration in Multiple Sclerosis (MS) that can be quantified by MRI in vivo. Brainstem (BS) atrophy is under-investigated in MS.

Objective: To assess accuracy and reproducibility of a fully-automated deep learning-based segmentation method for BS volumetry in 3D high-resolution T1w MRI data of healthy controls (HC) and MS patients.

Methods: Segmentation was done using multi-dimensional gated recurrent units (MD-GRU; Andermatt et al., 2016 (DOI 10.1007/978-3-319-46976-8_15), Andermatt et al., 2018 (DOI 10.1007/978-3-319-75238-9_3)) a deep learning-based, fully-automated semantic segmentation approach employing a convolutional adaptation of gated recurrent units (GRU; Cho et al., 2014 (<http://arxiv.org/abs/1409.1259>)). The respective neural network was trained for 100,000 iterations on 67 scans (17 HC, 50 patients). The segmentations showing the highest mean Dice score with respect to an expert-labeled manual ground truth were used as a final training state for evaluation. Expert-labeled manual BS segmentations were then used to validate the accuracy of the automated segmentation in another independent set of 30 patients' scans using Dice scores and mean surface distances (MSD). The reproducibility of the segmentations was assessed in 11 HC that underwent a MR test-retest experiment with repositioning in-between. The mean %-change betw. test and retest and the respective intra-class correlation coefficients (ICC) were calculated.

Results: Accuracy: In the validation set, the mean Dice scores comparing automated to the manual segmentations were (mean/SD): 0.97/0.005 (total BS), 0.94/0.015 for the mesencephalon (M), 0.98/0.007 for the pons (P), 0.95/0.015 for the medulla oblongata (MO); the MSD were all < 0.32mm. Reproducibility: The mean %-change/SD between test-retest scans was 0.48%/0.004 for the automated and 0.83%/0.005 for the manual segmentation of the total BS. The ICC of the automated test-retest segmentations of the total BS, M and P were all >0.99, of the MO 0.97.

Conclusions: This fully-automated BS segmentation provides accurate, reproducible segmentations in HC and MS patients in 200s/scan on an Nvidia GeForce GTX 1080 GPU and has potential for use in longitudinal studies.

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Pathogenesis and Preclinical Studies

A new MRI Approach for Rapid Spinal Cord Imaging Using Multi-Slice Averaged Myelom Inversion Recovery Acquisitions

Pathologies of the spinal cord are a significant contributor to the accrual of disability in MS. While focal inflammatory lesions have long been regarded as the main culprit, atrophy – in particular grey matter atrophy – was shown to better correlate with MS related physical disability. However, the reliable assessment of spinal cord atrophy, and grey matter and white matter atrophy in particular, can be extremely challenging.

Recently, we have developed a novel MRI based approach dedicated to spinal cord morphometry termed AMIRA (averaged magnetization inversion recovery acquisitions). AMIRA acquires several images of notable different contrast simultaneously that can be combined to facilitate an enhanced grey to white matter contrast in the spinal cord. In the fastest approach, high quality AMIRA images of $0.67 \times 0.67 \times 8 \text{ mm}^3$ can be acquired in 51 secs per slice.

To further increase the acquisition efficiency of AMIRA, an interleaved multi-slice scheme within the AMIRA sequence was developed (imsAMIRA). imsAMIRA typically experiences a boost factor of 2.0 regarding acquisition speed compared to the conventional approach. The present work illustrates the prerequisites and optimizations that were performed to develop imsAMIRA. Furthermore, spinal cord imaging results of the optimized imsAMIRA approach are demonstrated.

With the advance of our suggested approach, reliable assessments of disease progression and therapeutic considerations in MS patients should be easier in the future.

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We thank you for your participation and wish you a safe journey home.

See you next year at the
22nd State of the Art Symposium,
Saturday, January 25th, 2020.

Best regards
Swiss Multiple Sclerosis Society

Swiss Multiple Sclerosis Society

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