The International Multiple Sclerosis Visual System Consortium (IMSVISUAL): Advancing visual system research in multiple sclerosis

Running title: IMSVISUAL

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Abstract

Background: The International Multiple Sclerosis Visual System Consortium (IMSVISUAL) was formed November 2014 with the primary goal of improving research, care and education regarding the role of the visual system in multiple sclerosis (MS) and related disorders.

Methods: In this review, we describe the formation, goals, activities, and structure of IMSVISUAL, as well as the relationship of IMSVISUAL with the Americas Committee for Treatment and Research in MS (ACTRIMS). Finally, we provide an overview of the work IMSVISUAL has completed to date, as well as an outline of research projects ongoing under the auspices of IMSVISUAL.

Results: IMSVISUAL has 140 members worldwide and continues to grow. Through IMSVISUAL related work, optical coherence tomography (OCT) derived peri-papillary retinal nerve fiber layer (pRNFL) thinning has been established as a predictor of future disability in MS. IMSVISUAL has also developed guidelines for reporting OCT studies in MS. Moreover, a systematic review performed by IMSVISUAL found that not only are pRNFL and ganglion cell + inner plexiform layer (GCIPL) thicknesses reduced in MS patients [particularly in eyes with prior optic neuritis (ON)], but that inner nuclear layer (INL) measures may be higher among MS ON eyes, relative to healthy control eyes. Currently, there are several ongoing IMSVISUAL projects that will establish a role for visual outcomes in diagnosing MS; and, quantifying the effects of emerging therapies in clinical trials.

Conclusions: The development of IMSVISUAL represents a major collaborative commitment to defining the role of visual outcomes in high-quality, large-scale studies which generate definitive and instructive findings in the field of MS. As a consortium, IMSVISUAL has completed several international collaborative projects, is actively engaged in numerous ongoing research studies, and is committed to expanding the role of vision research in MS and related disorders.

Introduction

The international multiple sclerosis visual system consortium (IMSVISUAL) was formed in November 2014 (www.imsvisual.org) following a series of international meetings recognizing the need for a platform to ensure high quality in research, share data, provide clinical guidance and promote research and teaching in the field[1, 2]. Currently, IMSVISUAL has 140 members located worldwide, including the United States, Canada, Europe, Middle East, South America, and Australia, and continues to grow. A membership survey is provided to all IMSVISUAL members upon joining. As of August, 12th 2018, of the 47 members who responded to the survey (each are from unique/distinct sites), 33 were neurologists, 13 neuro-ophthalmologists, 5 researchers, and 3 ophthalmologists (of these respondents, 8 indicated having 2 specialties). Collectively, across just this small subset of IMSVISUAL members there are approximately 60,000 multiple sclerosis (MS) patients being actively followed, the majority of whom have relapsing remitting MS (RRMS), followed by progressive MS, then clinically isolated syndrome (CIS), and finally NMO spectrum disorder (NMOSD) (figure 1). Almost all IMSVISUAL members have published at least one paper in the last three years pertaining to the visual system in MS (or a related disorder), and are participating in ongoing studies. Areas of research include, but are not limited to the expanding roles of optical coherence tomography (OCT) high and low-contrast visual function, and electrophysiology (visual evoked potentials) in MS patients. A large proportion of IMSVISUAL investigators also report routinely using OCT in considering the diagnosis of MS, as well as for monitoring disease progression and drug efficacy...

Goals and activities of IMSVISUAL

The overarching goal of IMSVISUAL is to improve care, research and education in MS and related neuroinflammatory disorders by advancing our understanding of how the visual system is affected by these conditions. Specifically, IMSVISUAL's goals are as summarized below.

1. To promote and foster vision research, with the purpose of furthering our understanding of disease mechanisms in MS and other neuroinflammatory disorders. With respect to this, the consortium is interested in all stages and types of MS, including progressive MS and pediatric MS. The consortium aims to determine how structural, clinical and functional measures of the visual system over time are related to other surrogate endpoints, including cognition, biomarkers of inflammation and neurodegeneration, conventional and non-conventional magnetic resonance imaging (MRI), as well as genomic, proteomic and metabolomic profiles, in MS, and related disorders, and healthy controls of all ages.

2. To establish the visual system as a model within which to monitor neurodegeneration and disease progression, as well as neuroregeneration and neuroplasticity in MS and related disorders, both for the purpose of tracking patients clinically, as well as outcomes in clinical trials. Although the consortium is committed to all aspects of the visual system in MS and its related conditions, IMSVISUAL is particularly interested in ocular imaging, progressive MS, pediatric MS, relating the visual system to the global MS disease process, and optic neuritis (ON). The

consortium aims to achieve this through the creation of a shared repository of data, including, but not limited to, demographic, OCT, MRI, visual electrophysiology, genetic, diagnostic, therapeutic, immunologic, and cerebrospinal fluid (CSF) data. All members can access central repositories by submitting formal project proposals to the consortium.

3. To improve upon existing, as well as develop new techniques for assessing the visual system in MS and related disorders. With respect to this, the consortium has a particular interest in ocular imaging techniques, including but not limited to OCT.

4. To promote education regarding all facets of the visual system in MS and related disorders. This objective will be achieved by holding IMSVISUAL meetings at least twice per year, to coincide with the annual Americas Committee for Treatment and Research in MS (ACTRIMS) and European Committee for Treatment and Research in MS (ECTRIMS) Forum meetings. In 2018, IMSVISUAL members worked in concert with ECTRIMS to host….was also , as well as teaching (such as the ECTRIMS 2018 summer school, Budapest, Hungary).

Structure of IMSVISUAL

Membership to IMSVISUAL is free and open to anyone with an interest in the aims of the consortium. Currently, this only includes non-commercial members with an academic, educational, clinical or personal interest. Membership can be requested via the consortium's website (http://imsvisual.org).

IMSVISUAL is governed by an executive committee and a working committee. Together they form the steering committee. The executive committee supervises the overall strategy and activities of IMSVISUAL. The working committee is responsible for coordinating and managing all IMSVISUAL operations. Both committees hold monthly phone conferences, in order to jointly decide over ongoing proceedings, and currently consist of the founding members of IMSVISUAL.

It is envisaged that IMSVISUAL will become incorporated as a not-for-profit organization in the foreseeable future. In addition, restructuring of IMSVISUAL governance will likely take place, which will also include elected committees.

IMSVISUAL and ACTRIMS

ACTRIMS is a not-for-profit organization dedicated to providing leadership in the field of MS and related disorders. One of the core missions of ACTRIMS is to focus on knowledge dissemination, education, and collaboration (www.ACTRIMS.org). Over the past two years, ACTRIMS has taken steps in this regard by supporting IMSVISUAL. One avenue in which ACTRIMS fulfills its mission is by holding an annual conference. In 2016, ACTRIMS hosted its first annual stand-alone Forum, “Progressive MS: Bench to Bedside and Back Again”, which surpassed expectations regarding attendance and abstract submissions. Subsequent ACTRIMS Forums held in have built on this success with nearly 1000 attendees in 2018. The ACTRIMS Forum offers a single track of scientific and clinical presentations in an interactive environment, and includes platform presentations by young investigators and poster sessions. Junior faculty, fellows, and students are eligible for educational grants to support their attendance at the meeting.

Moreover, trainees (including residents and medical students) learn about career paths by participating in a pre-conference resident summit. In accordance with ACTRIMS commitment to providing opportunities to other MS related groups, ACTRIMS partnered with IMSVISUAL in 2017 and 2018. This support has provided IMSVISUAL with programming opportunities, including a dedicated IMSVISUAL symposium during each Forum as part of the ACTRIMS program, in addition to supporting separate IMSVISUAL member meetings during the Forums. ACTRIMS and IMSVISUAL aim to continue their collaboration and are interested in finding synergies and establishing consensus procedures to carry out exceptional education opportunities and other jointly-supported activities. Currently, there is an affiliate understanding in place between ACTRIMS and IMSVISUAL, such that IMSVISUAL will continue to have an ongoing symposium at the annual ACTRIMS Forum until 2021. Moreover, ACTRIMS and IMSVISUAL leadership have been discussing additional ways to partner outside of the ACTRIMS annual Forum. This relationship has been critical to helping advance and promote IMSVISUAL, provide support to IMSVISUAL, and give IMSVISUAL the unique opportunity to disseminate visual system research findings in MS, consistent with one of the central goals of IMSVISUAL.

Summary of key findings from IMSVISUAL work to date

1. Assessing the role of a single measurement of retinal thickness by spectral domain (SD)-OCT as a marker of disability worsening in MS

By 2010, several studies suggested an inverse association between disability and retinal thickness in MS[3]. However, most of these studies utilized time-domain (TD)

OCT and were cross-sectional. In order to definitively assess the utility of retinal thickness measures as surrogate markers of disability worsening in MS, we conducted a multi-center study of 15 sites in Europe and North America. This study included data prospectively collected between 2008 and 2013 from 879 patients with MS[4]. SD-OCT were performed with Spectralis® (Heidelberg Engineering, Heidelberg, Germany) or Cirrus HD-OCT™ (Carl Zeiss, Dublin, CA, USA). We used the mean value of peri-papillary retinal nerve fiber layer (pRNFL) thickness and macular volume (MV) in eyes unaffected by prior MS related ON (MSON), or the value from unaffected eyes in cases of prior unilateral MSON, as predictors of disability worsening, estimated by expanded disability status scale (EDSS) scores. If available, MSFC assessments following standard criteria for disability worsening were also assessed[5-7]. Patients with a pRNFL thickness ≤ 87 μm or ≤ 88 μm (measured with Cirrus and Spectralis OCT respectively) had approximately double the rate of disability worsening at any time after the first and up to the third years of follow-up (HR=2.06, 95% CI (1.36-3.11), and the rate was increased by nearly four times after the third and up to the fifth years of follow-up (HR=3.81, 95% CI (1.63–8.91). We did not find significant associations for MV, and ganglion cell + inner plexiform layer (GCIPL) thicknesses were not available for inclusion in this study[4].

2. The Advised Protocol for OCT Study Terminology and Elements (APOSTEL) recommendations

A critical aspect of OCT research is the underlying quality of imaging data. For example, pRNFL thickness measurements vary according to OCT signal quality[8]. Likewise,

different segmentation techniques or investigated areas of interest differ greatly in reliability and thus utility to investigate specific scientific questions[9, 10]. In 2012, OCT quality criteria, termed OSCAR-IB criteria, were developed[1]. These criteria were validated in a multi- center approach, with free online training provided by a website and the need for a regular networked revision recognized[11]. Today, the OSCAR-IB criteria are routinely used for assessing OCT image quality in MS studies. However, OCT studies in MS to date have been generally lacking sufficient information to reproduce their settings and potential quality issues. Accordingly, IMSVISUAL aimed to define reporting guidelines for OCT studies, which would not only serve to support the assessment of a study's quality, but would also act as a guideline for OCT researchers, including which factors to control or account for in OCT studies. The recommendations were formed by expert consensus involving the steering committee of IMSVISUAL, several members of IMSVISUAL, as well as collaborating ophthalmologists, and were published in 2016 as the Advised Protocol for OCT Study Terminology and Elements (APOSTEL) recommendations [12]. The APOSTEL recommendations suggest not only reporting image quality analysis procedures, but also OCT relevant elements of the study protocol, acquisition device, acquisition settings, scan protocols, fundus imaging, data analysis and statistical approaches. The APOSTEL recommendations also made suggestions to harmonize the use of nomenclature and abbreviations among OCT studies.

The initial expert consensus-based APOSTEL recommendations are currently undergoing revision as part of a structured Delphi process, in order to gain broader input, awareness and support among colleagues who were not involved in the

development of the initial APOSTEL recommendations. This Delphi process is currently in its late stages, and a revised version of the APOSTEL recommendations is expected to be available in 2019.

3. Meta-analyses of retinal layer thicknesses and the effect of ON

In 2010, a meta-analysis demonstrated that MSON causes substantial pRNFL atrophy [3]. Importantly, pRNFL atrophy was also present in eyes of patients without MSON. All studies included in this meta-analysis used earlier TD-OCT technology. The reliability of these early OCT measures has been determined by a second meta-analysis based on new SD-OCT data from new patient cohorts, performed as part of an IMSVISUAL collaboration[13]. A total of 40 studies investigating retinal layer thickness in MS using SD-OCT were included. In addition to peri-papillary and macular RNFL, data was obtained for the GCIPL, inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL). New important findings from the SD-OCT meta-analysis were that consistent with pRNFL atrophy, there is inner retinal layer (RNFL, GCL, IPL) atrophy in the macula reproducing similar patterns for MSON and non-MSON eyes. In contrast with the reductions in pRNFL and GCIPL thicknesses relative to control eyes, MSON eyes demonstrated INL thickening[13]. Trans-synaptic axonal degeneration may halt at the level of INL, with thickening of the INL and deeper retinal layers potentially representing signs of inflammation, as previously suggested[14].

Ongoing IMSVISUAL projects

1: Determining optimal thresholds for inter-eye differences in pRNFL and GCIPL thickness for predicting a history of unilateral ON

Despite high prevalence (50%) of acute MSON[15] and nearly ubiquitous optic nerve disease post-mortem[16, 17] in MS, the optic nerve is not currently considered an imaging lesion site in MS diagnostic criteria[18]. Consistent with the data from our meta-analyses prospective studies have suggested an inter-eye pRNFL thickness difference of 5-6 µm[19] or a 5% inter-eye difference in GCIPL thickness[20] as useful thresholds for identifying prior ON affliction. As part of IMSVISUAL, a multi-center, international study of 11 sites was conducted to evaluate inter-eye differences in pRNFL and GCIPL thickness in people with MS to determine optimal thresholds for predicting a history of unilateral MSON. In addition to SD-OCT, high- and low-contrast acuity and vision-specific quality of life (VS-QOL) were also performed and correlated with inter-eye SD-OCT differences. A total of 368 healthy controls and 1,530 MS patients were recruited. Preliminary results show good agreement with previous studies in a single-center cohort evaluating a 5µm threshold in pRNFL thickness as optimal for predicting a history of unilateral MSON and that inter-eye differences above this threshold also correlate with visual dysfunction. Further results from this study will be forthcoming in due course.

2. Assessing the relationship of INL volume changes with inflammatory disease activity in MS

Whereas the pRNFL and GCIPL consistently demonstrate thinning in MS, thought to predominantly relate to retrograde degeneration caused by either overt or occult optic neuropathy, the INL may not be susceptible to this mechanism or degree of injury. In

2012, Gelfand et al. first described the presence of microcystic macular edema in the INL and demonstrated that its presence was associated with increased disability[21]. In 2012, Saidha et al. reported that increased INL thickness at baseline in MS was predictive of clinical and radiological disease activity in the future, as well as disability worsening, suggesting that INL thickness may reflect global inflammatory activity in MS[22]. In order to further investigate the potential of the INL as a biomarker for inflammatory processes, an ongoing IMSVISUAL collaborative project is focusing on the effect of inflammatory disease activity on INL volume changes. Because of the relatively small effect size[13], this has only become possible by pooling data from a large group of well-established centers in the field, as part of the IMSVISUAL consortium.

In this longitudinal multi-center study, data was pooled from 11 centers worldwide, resulting in a sample of almost 800 MS patients. This study demonstrated a significant increase in INL volume in eyes with new episodes of MSON or other clinical relapses. Although the underlying mechanism responsible for thickening of the INL remains unknown, the INL seems to reflect some degree of global disease activity and may play a role in capturing inflammatory disease activity. Indeed, Knier and colleagues have previously reported the potential for INL measures to capture the anti-inflammatory effects of disease modifying therapies in MS[23].

3. Measuring neuroprotection in the visual pathway: identifying best outcomes in randomized clinical trials in patients with acute ON

The prominent short-term structural and functional changes that can be measured and tracked by SD-OCT and visual evoked potentials (VEPs) respectively after acute MSON

support the use of acute MSON as a model to test drugs that putatively promote neuroprotection and/or myelin repair[24-30]. Despite some promising results, the conduction of these studies has raised important methodological concerns regarding inclusion/exclusion criteria, as well as the precise definition and utilization of the SD-OCT, VEP and visual outcomes assessed. Through IMSVISUAL and in collaboration with other institutions, we have thus far collected data from 212 patients with acute MSON including SD-OCT, low-contrast vision, and VEPs. Recruitment in this study is ongoing and we expect to generate a highly informative and enriched study population, forming the basis for determining the most accurate outcomes for measuring chronological damage following acute ON using SD-OCT, VEPs and visual outcomes. This study will also evaluate the role of other demographic and prognostic factors during the course of acute MSON.

4. Identifying occult visual system involvement in CIS/early MS

IMSVISUAL is currently collecting OCT and VEP data from patients after their first CIS suggestive of MS to investigate the utility of OCT and VEP for establishing optic nerve involvement in patients with a clinical syndrome other than of the afferent visual system. Smaller scope studies have previously shown that retinal and electrophysiological changes can be detected even in the earliest stages of MS/CIS[31] and are predictive of future disease activity[32]. In this multicenter study, the utility of OCT and VEP in these earliest disease stages in regard to establishing dissemination in space and an MS diagnosis will be further determined [33].

5. SD-OCT in Progressive MS

Progressive MS (PMS) is a clinical form of MS characterized by a steady and gradual accumulation of disability over time[7]. There are two principal subtypes – SPMS and PPMS. Although some PMS patients may exhibit superimposed relapses and/or inflammatory activity (on MRI), the majority of PMS patients with do not exhibit any evidence of overt inflammatory activity (clinically or radiologically), yet demonstrate ongoing clinical decline[34].

OCT has emerged as a complementary tool to MRI with particular utility for tracking neurodegeneration (and accordingly neuroprotection) in MS[35]. It has been shown that GCIPL thickness correlates with high- and low-contrast letter acuity, as well as EDSS scores[36]. It has also been shown that GCIPL atrophy mirrors whole brain atrophy over time, in particular gray matter atrophy, and that rates of GCIPL atrophy are differentially modulated by different disease modifying therapies in RRMS[37, 38]. However, the vast majority of OCT studies in MS have been performed in RRMS, with a paucity of examination in PMS. Currently, we have an incomplete understanding of the pathobiology of PMS. Moreover, there is also a lack of validated outcomes to identify/distinguish PMS and therefore track as well as measure treatment effects in PMS (since the disease may be predominantly non-inflammatory), thereby hindering the identification of effective medications for PMS. While non-conventional MRI techniques, such as whole brain and brain sub-structure volumetrics have a role in PMS[39, 40], such techniques have not identified MRI signatures specific for PMS. Moreover, non-conventional MRI may be costly, lack sensitivity, and has been challenging to implement into clinical practice[41]. Lack of sensitivity to change over time is also a limitation of clinical outcome measures such as the EDSS in PMS[42]. An ongoing

IMSVISUAL endeavor aims to address these gaps in PMS, helping to elicit if there are distinct differences in retinal changes over time in PMS relative to RRMS, leading to the development of more specific PMS outcomes, and potentially shedding light on the pathophysiology of PMS. Currently, as part of this study, there are 242 people with PMS being tracked with OCT. Preliminary results of this study are expected in early 2019.

Conclusions

Through IMSVISUAL, neurologists, neuro-ophthalmologists, and ophthalmologists, among other researchers and scientists have the opportunity to join efforts to develop high-quality scientific evidence to better understand the role of the visual system in MS and related disorders. The development of IMSVISUAL is a testament of the importance and interest in the visual system in MS, and represents a concerted, wide-scale, international, collaborative commitment to its study. IMSVISUAL facilitates extremely powerful, high-quality, large-scale studies of the visual system in MS that generate definitive and instructive findings. As such, IMSIVUSAL enables broad-scale studies to be performed in a timely fashion, serving as a driving force for major advancements in visual system research in MS. Several instructive, novel and important studies have already been completed under the umbrella of IMSVISUAL. Moreover, IMSVISUAL has numerous other ongoing research projects as outlined above. IMSVISUAL has formed an important affiliation with ACTRIMS over the last number of years and is committed to virtually all aspects of visual system based research in MS and related disorders.

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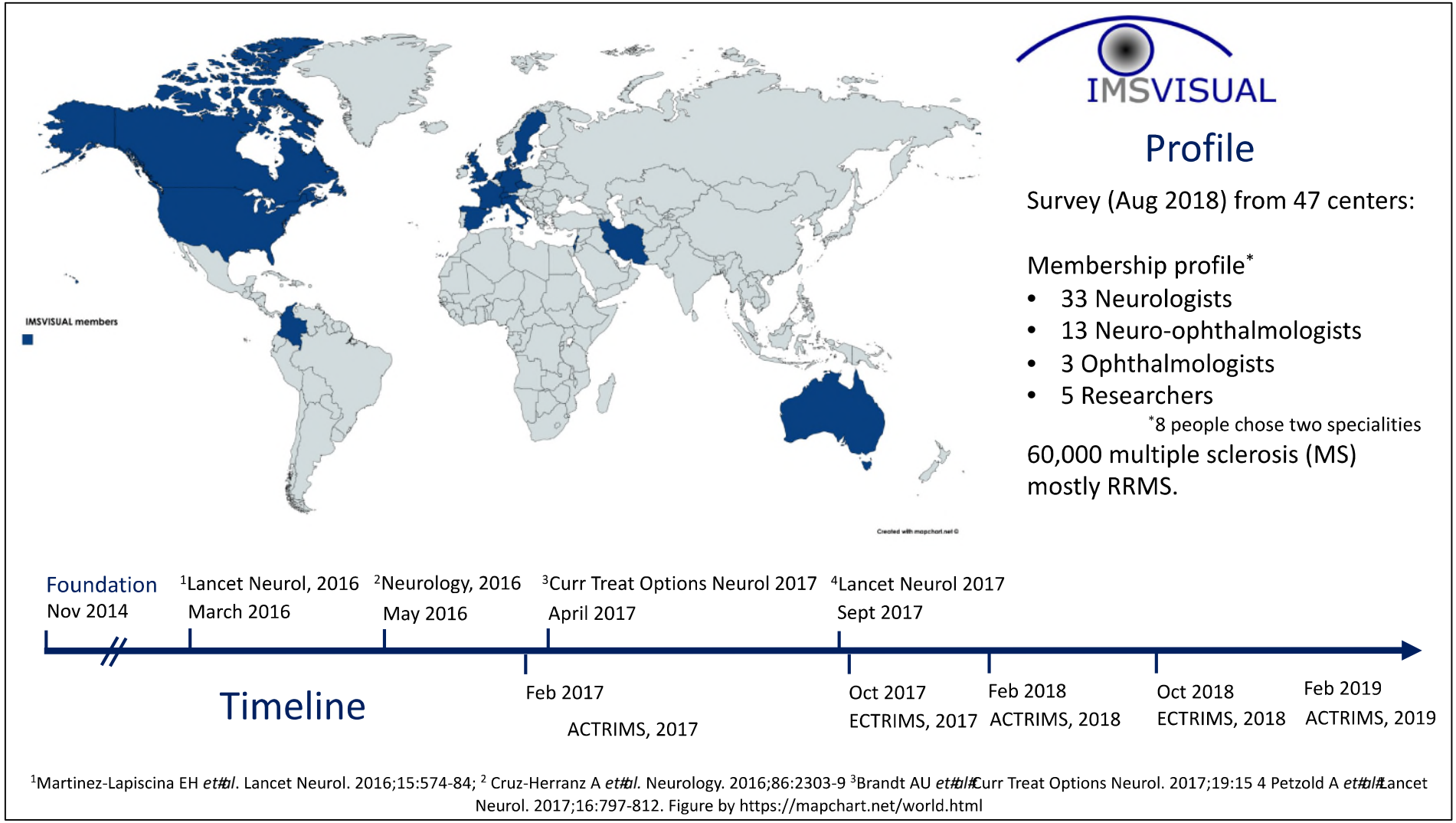
Figure 1 IMSVISUAL Overview



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