The therapeutic benefits of fingolimod, siponimod, and ozanimod are thought to be largely mediated by their modulation of sphingosine 1-phosphate receptor subtype 1, inhibiting lymphocyte trafficking and possibly directly targeting neurons. Impacts on oligodendrocytes (via sphingosine 1-phosphate receptor subtype 5) have also been proposed, but although all three therapies do have activity on this subtype, its importance is not known.[1] Ongoing trials of ponesimod, a sphingosine 1-phosphate receptor modulator that acts exclusively on receptor subtype 1,[1] might help to answer this question. Regardless, the results of the SUNBEAM[9] and RADIANCE[10] ozanimod trials provide reassurance about the clinical efficacy and safety outcomes of sphingosine 1-phosphate modulators.

*Ellen M Mowry, *John R Corboy*
Johns Hopkins University, Baltimore, MD, USA (EMM); University of Colorado, Aurora, CO 80045, USA (JRC)
john.corboy@cuanschutz.edu

EMM reports serving as site principal investigator for clinical trials or studies sponsored by Biogen and SunPharma; research support from Sanofi Genzyme and Biogen for investigator-initiated trials; free medication for a clinical trial, of which she is principal investigator, from Teva Neuroscience; and royalties for editorial duties from UpToDate. JRC reports grants from MedDay, Novartis, the Patient Centered Outcomes Research Institute (also as coordinating center), and the National Multiple Sclerosis Society; and personal fees from Mylan, Prime Continuing Medical Education, Medical Logix, and the American Academy of Neurology.

1 Chaudhry BZ, Cohen JA, Conway DS. Sphingosine 1-phosphate receptor modulators for the treatment of multiple sclerosis. *Neurotherapeutics* 2017; **14:** 859–73.
2 Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 402–15.
3 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.
4 Kappos L, Cohen J, Collins W, et al. Fingolimod in relapsing multiple sclerosis: an integrated anaylsis of safety findings. *Mult Scler Relat Disord* 2014; **3:** 494–504.
5 Selmaj K, Li DKB, Hartung HP, et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomized, phase 2 study. *Lancet Neurol* 2013; **12:** 756–67.
6 Kappos L, Bar-Or A, Cree BAC. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomized, phase 3 study. *Lancet* 2018; **391:** 1263–73.
7 Food and Drug Administration. MAYZENT (siponimod) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209884s000lbl.pdf (accessed June 21, 2019).
8 Kappos L, Li DKB, Stuve O, et al. Safety and efficacy of siponimod (BAF312) in patients with relapsing-remitting multiple sclerosis: dose-blinded, randomized extension of the phase 2 BOLD study. *JAMA Neurol* 2016; **73:** 1089–98.
9 Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol* 2019; **18:** 1009–20.
10 Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol* 2019; **18:** 1021–33.
11 Berger JR, Cree BA, Greenberg B, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. *Neurology* 2018; **15:** e1815–21.
12 Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service. *Brain* 2012; **135:** 1778–85.

The dawn of robust individualised risk models for dementia

Published **Online**
September 13, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30353-9

See **Articles** page 1034

Mild cognitive impairment (MCI) typically represents a holding pattern for individuals who live for many years without knowing their long-term prognosis. Such uncertainty between improvement or remaining stable versus progressing to a diagnosis of dementia is unsatisfying. Scarcity of specific information or advice compounds this issue. People with MCI do not have access to treatments such as cholinesterase inhibitors or memantine, they usually cannot partake in therapeutic trials, and the absence of a path forward can add to their anxiety and that of family members.[1]

In *The Lancet Neurology*, Ingrid van Maurik and colleagues[2] attempt to clarify this situation. They provide a method for individualised prognosis by indicating which of the participants with MCI in their study were most likely to progress to dementia over 1, 3, and 5 year timeframes. They assessed four separate prognostic models: first, a model incorporating age, sex, and the Mini-Mental State Examination (MMSE); second, a model of age, MMSE, and hippocampal volume; third, a model of MMSE, CSF amyloid β (1–42), and CSF total tau;[3] and fourth, the ATN model[4] of CSF amyloid β (1–42), CSF phosphorylated tau, and hippocampal volume. These models were applied to 2611 MCI participants across the European Medical Information Framework for Alzheimer's disease (EMIF), the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Amsterdam Dementia Cohort (ADC), and the Swedish BioFINDER studies. Of these 2611 MCI participants, 1007 (39%) progressed to dementia within a mean follow-up period of 3 years (SD 2). 808 (80%) participants progressed to dementia due to Alzheimer's disease.

Van Maurik and colleagues had to overcome many difficulties in harmonising the data from so many participants and to ensure that robust and appropriate analyses

were conducted. To validate the harmonisation of these data, they first considered the alignment of the study based on the demographics age and sex; however, *APOE* ε4 allele status was not included in the models, despite the known impact on conversion rates.[5] The successful data harmonisation was validated with no difference between models with or without controlling for centre via Harrell's C statistic, a rigorous statistical analysis step to ensure alignment across studies. Nevertheless, the use of large sample sizes allows for increased confidence in the results presented.

Results from van Maurik and colleagues indicate that, of the four models tested, the ATN model provided the highest efficacy for predicting likelihood of progression to dementia. As most participants that progressed to dementia specifically progressed to Alzheimer's disease, it might be fairer to say that the ATN model had the highest efficacy for predicting progression to Alzheimer's disease. These findings align with the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework,[4] based upon a biological definition using ATN criteria for the diagnosis of Alzheimer's disease. The partial regression coefficients of the amyloid deposition, tauopathy, and neurodegeneration categories in the ATN model presented by van Maurik and colleagues were of similar magnitude, indicating that the three measures were of equal importance. However, it would have been interesting to evaluate the efficacy of different combinations of the markers, such as whether amyloid deposition and neurodegeneration was enough to confer the likelihood of progression as indicated in previous contributions across MCI and cognitively normal participants,[6,7] as well as to understand the contribution of *APOE* ε4 allele status and other genetic constructs such as polygenic risk scores. Or, furthermore, to understand the contribution of the biomarkers to a demographics model by combining the demographic and biomarker variables.

An increasing number of different models of progression to Alzheimer's disease have been reported in the literature.[8–10] However, rather than clarifying information for people with MCI as well as their clinicians, the availability of many different models might confound the issue. The findings of van Maurik and colleagues provide plausible estimates for time to progression and a good benchmark for future studies. It is likely that the choice of which algorithm, tool, or framework to adopt will not only be at the discretion of the individual clinician but will also be limited by the information available to them. The biomarkers required (genetics, CSF, or imaging) for the precision algorithms are not readily available to every clinician. With the advent of accurate and sensitive blood-based biomarkers for amyloid β (1–42), phosphorylated tau, and neurofilament light chain (a measure of neurodegeneration) on the horizon, the clinical utility of these algorithms will increase substantially, especially if the blood-testing can be performed and analysed on the day of the clinical visit.

Although the process of informing people that they meet MCI criteria is difficult for the clinician, these individuals, and their families,[11] research suggests that most people would like to know their diagnosis, especially if they are in the early stages of Alzheimer's disease.[12] A tool capable of receiving data—such as an individual's CSF biomarker levels and hippocampal volume—and translating them into meaningful risk percentages or time to event information would have a substantial impact. As most people agree it is better to know than not know, studies like this will move this field closer to a time when it is possible to remove the uncertainty surrounding the prognosis of people with MCI.

**Samantha C Burnham, Samantha M Loi, James Doecke, Victor Fedyashov, Vincent Dore, Victor L Villemagne, Colin L Masters*

The Australian e-Health Research Centre, CSIRO Health & Biosecurity, Parkville, VIC 3052, Australia (SCB, VD); Centre of Excellence for Alzheimer's Disease Research & Care, School of Medical Sciences, Edith Cowan University, Joondalup, WA, Australia (SCB); Neuropsychiatry Unit, NorthWestern Mental Health, Royal Melbourne Hospital, Parkville, VIC, Australia (SML); Department of Psychiatry (SML), Florey Institute of Neuroscience and Mental Health (VF, CLM), ARC Training Centre in Cognitive Computing for Medical Technologies (VF), and Department of Medicine(VLV), The University of Melbourne, Parkville, VIC, Australia; The Australian e-Health Research Centre, CSIRO, Herston, QLD, Australia (JD); and Department of Molecular Imaging & Therapy, Austin Health, Heidelberg, VIC, Australia (VD, VLV)
samantha.burnham@csiro.au

We declare no competing interests.

1 Gomersall T, Smith SK, Blewett C, Astell A. 'It's definitely not Alzheimer's': Perceived benefits and drawbacks of a mild cognitive impairment diagnosis. *Br J Health Psychol* 2017; **22:** 786–804.

2 van Maurik IS, Vos SJ, Bos I, et al. Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study. *Lancet Neurol* 2019; **18:** 1034–44.

3 van Maurik IS, Zwan MD, Tijms BM, et al. Interpreting biomarker results in individual patients with mild cognitive impairment in the Alzheimer's biomarkers in daily practice (ABIDE) project. *JAMA Neurol* 2017; **74:** 1481–91.

4 Jack CR Jr, Bennett DA, Blennow K, et al. Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; **14:** 535–62.

5 Liu C-C, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* 2013; **9:** 106–18.

6 Vos SJ, Verhey F, Frölich L, et al. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain* 2015; **138:** 1327–38.

7 Burnham SC, Bourgeat P, Doré V, et al. Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: a longitudinal study. *Lancet Neurol* 2016; **15:** 1044–53.

8 Li H, Habes M, Wolk DA, Fan Y. A deep learning model for early prediction of Alzheimer's disease dementia based on hippocampal magnetic resonance imaging data. *Alzheimers Dement* 2019; **15:** 1059–70.

9 Ehrensperger MM, Taylor KI, Berres M, et al. BrainCheck—a very brief tool to detect incipient cognitive decline: optimized case-finding combining patient- and informant-based data. *Alzheimers Res Ther* 2014; **6:** 69.

10 Bilgel M, Jedynak BM. Predicting time to dementia using a quantitative template of disease progression. *Alzheimers Dement (Amst)* 2019; **11:** 205–15.

11 Whitehouse P, Frisoni GB, Post S. Breaking the diagnosis of dementia. *Lancet Neurol* 2004; **3:** 124–28.

12 Marzanski M. Would you like to know what is wrong with you? On telling the truth to patients with dementia. *J Med Ethics* 2000; **26:** 108–13.