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Multiple Sclerosis

National Academies of Science, Engineering, and Medicine
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Outline

- Recent Update of the Prevalence of MS in the US
- Recent Research Advances in MS
- Existing Scientific and Research Gaps: *Pathways to Cures for MS*

Recent Update of the Prevalence of MS in the US

Timeline

- 2006: *Meetings between ALS, PD, and MS communities with ATSDR/CDC*
- 2008: *ALS Registry established* PUBLIC LAW 110-373—OCT. 8, 2008 122 STAT. 4047
- 2008: *MS and PD groups draft legislation for a neurological conditions surveillance system*
- 2008-2014: *Congress fails to pass NNCSS legislation*
- 2014: *NMSS decides to fund a national prevalence study*
- 2016: *Congress passes and President Obama signs legislation establishing NNCSS*
- 2019: *NMSS Prevalence Workgroup publishes first comprehensive prevalence study of MS since 1976*



Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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National Neurological Conditions Surveillance System (NNCSS)



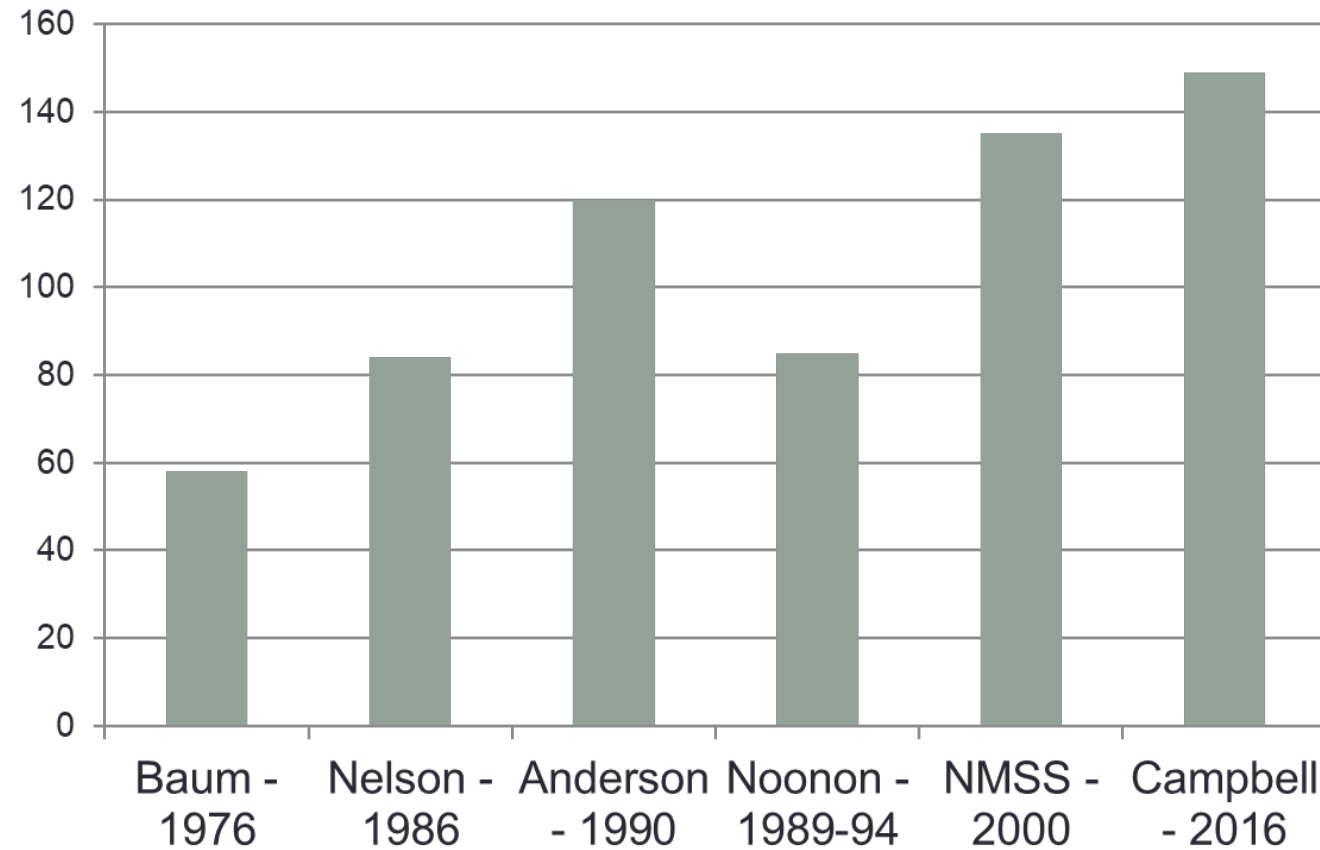
MS

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Together We Are Stronger.

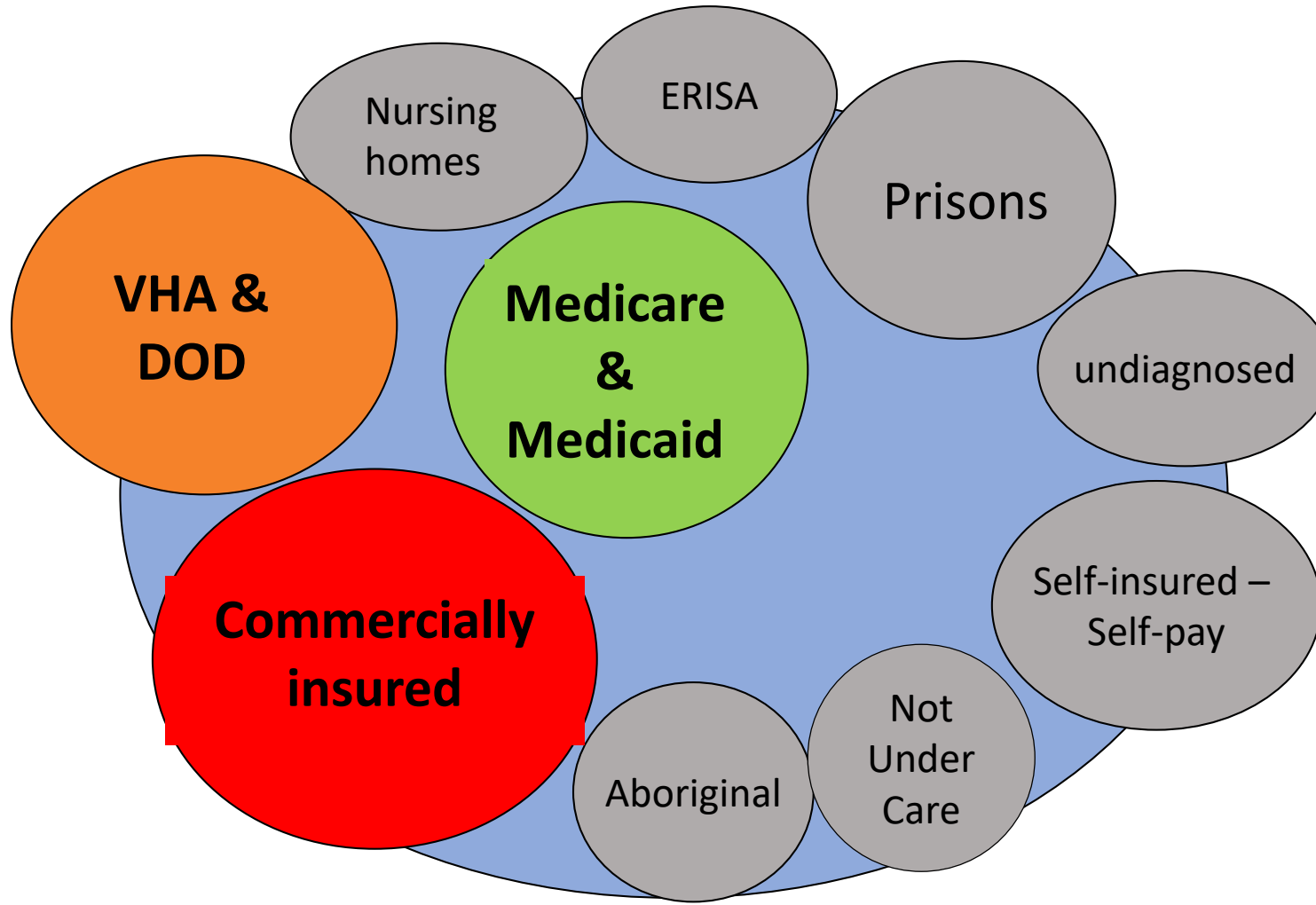
US MS Prevalence Rate Estimates 1976-2014 (cases per 100,000)



Challenges to a U.S. Study of MS Prevalence

- Previous estimate of 400,000 was based on revisions to estimates from 40-year-old data
- There is currently no surveillance system to track prevalence of neurological conditions in the US
- Lack of a unified health system makes it hard to identify and track patients

Finding MS Cases in the US: What are the Challenges?



What were Our Options?

- “Traditional” epidemiology – *not feasible?*
- Add on to an existing survey – *unreliable?*
- Use an existing registry or build a new one – *impractical and not feasible?*
- Use electronic medical records – *not ready for prime time?*
- Mine administrative data – *supported by ATSDR pilot studies.*
- Combination of the above – *unaffordable?*

The Approach We Took

- Develop and test several algorithms that could search existing health datasets and identify patients with MS in the adult population
- Select the most accurate of those tested
- Apply the algorithm to US administrative datasets for the 2008-2010 period (*“period prevalence”*)
 - Private insurance (Truven and Optum)
 - Medicare/Medicaid
 - Veterans Administration

89.8 Million records

Candidate Algorithms

Table 2 Description of candidate algorithms for MS^a

Case definition name	Number and type of claims
MS_A	≥ 2 IP or ≥ 3 OP
MS_B	≥ 2 IP or ≥ 4 OP
MS_C	≥ 2 IP or ≥ 5 OP
MS_D	≥ 2 IP or ≥ 3 OP or ≥ 1 DMT
MS_E	$(IP + OP + DMT) \geq 3$

Abbreviations: DMT = disease modifying therapy; IP = inpatient admission; MS = multiple sclerosis; OP = outpatient visit.

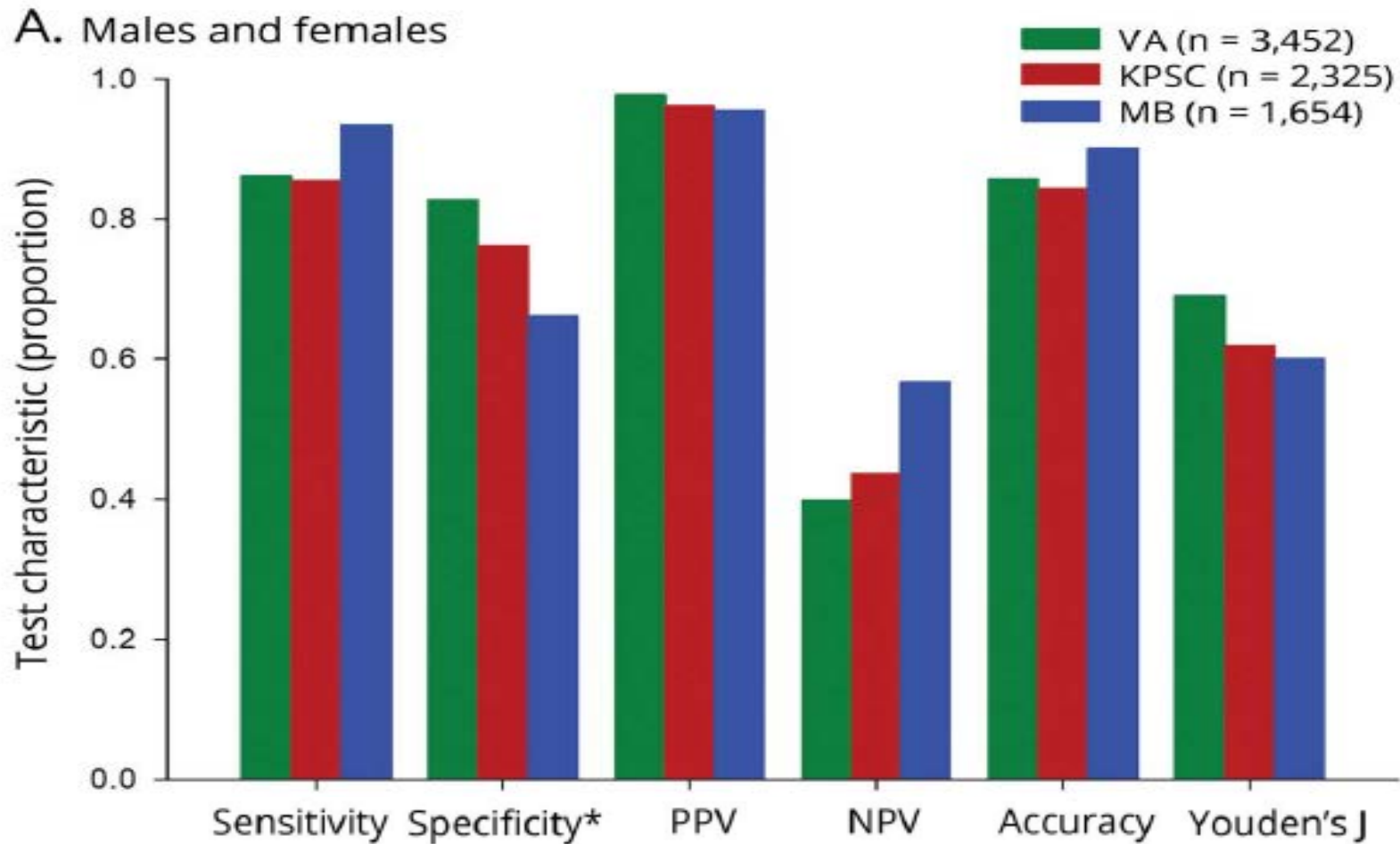
^a The performance of each algorithm was evaluated on the basis of both a 1-year and a 2-year time period.

Culpepper et al, 2019

The Algorithm Judged as Most Accurate

- A “case” is defined as an individual who has 3 or more of the following in any combination:
- An inpatient encounter
- An outpatient encounter
- A prescription for one of the MS disease modifying drugs

Performance of the Algorithm across 3 Datasets

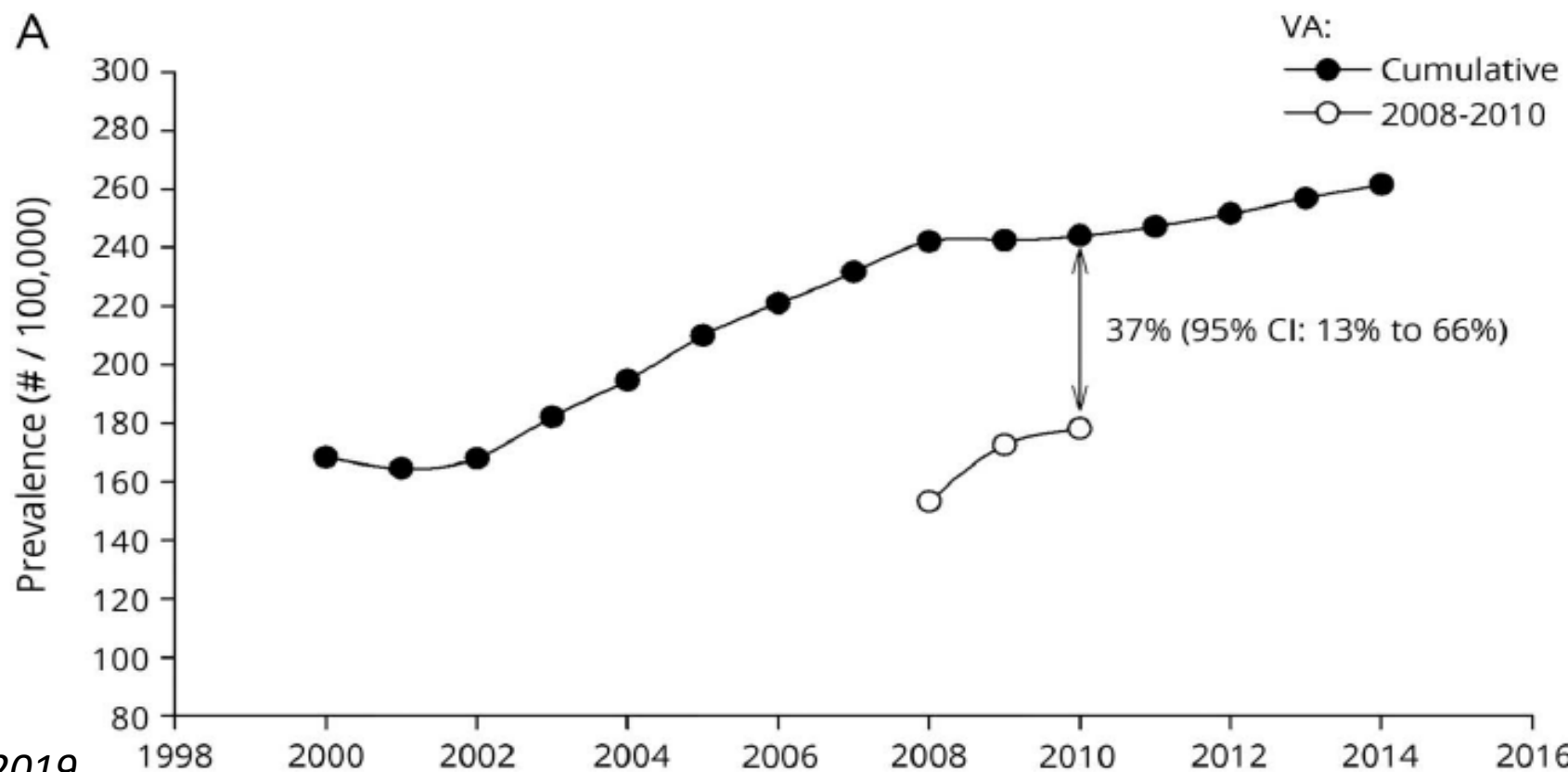


Putting the Algorithm to Work

- Assessed **period** prevalence for 2008, 2009, and 2010 in all datasets
- Assessed **cumulative** prevalence 2008 through 2010 in all datasets
- Merged and adjusted the estimates
 - Extrapolated to 10-year **cumulative** prevalence adjusted for population growth till 2017

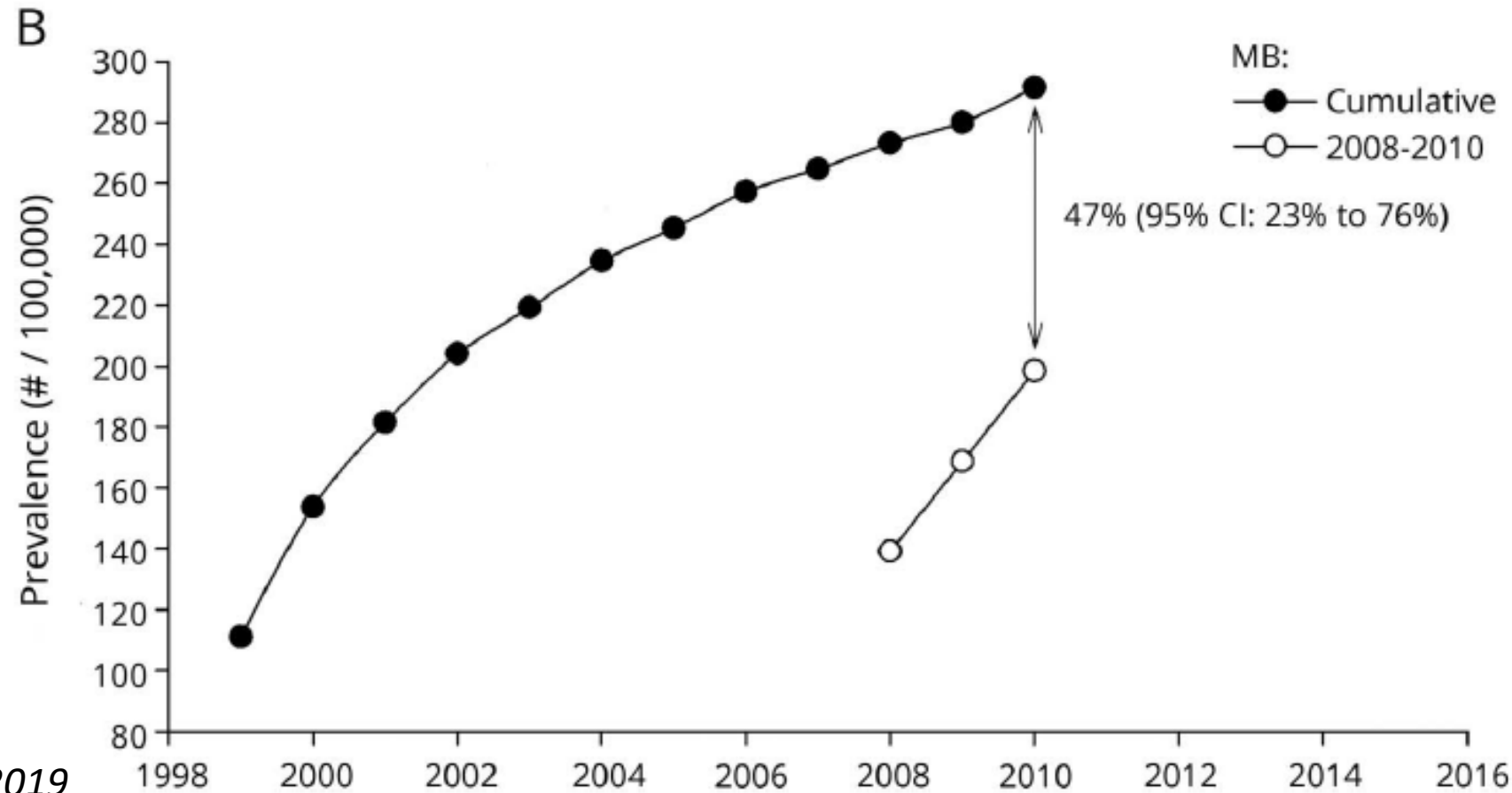
Culpepper et al, 2019

Comparison of Prevalence based on a 3 vs 10-Year Ascertainment Period as of 2010 in the VA Dataset



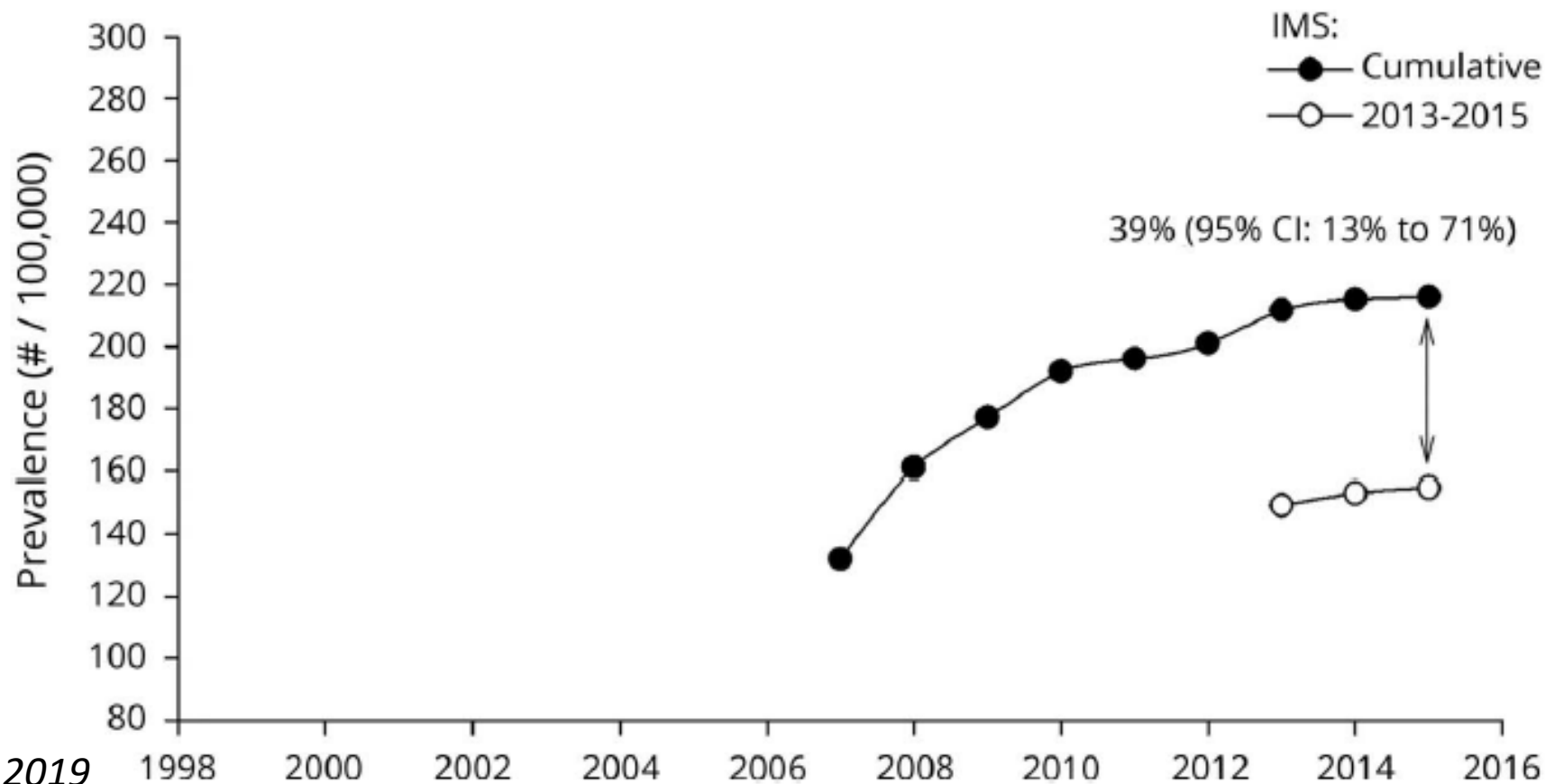
Culpepper et al, 2019

Comparison of Prevalence based on a 3 vs 10 Year Ascertainment Period as of 2010 in the Manitoba Dataset



Culpepper et al, 2019

Comparison of Prevalence based on a 3 vs 10-Year Ascertainment Period as of 2015 in the IMS (PharMetrics) Dataset



Culpepper et al, 2019

Cumulative MS Prevalence Estimate as of 2017 (*“period prevalence”* for 2008-2010 Adjusted for Population Growth from 2010 to 2017)

Estimated Range = 851,749 – 913,925

Wallin et al, 2019

Why is this Estimate so much Higher than Prior Estimates?

- Population growth
- The aging of the U.S. population means there are more people in the age groups with higher prevalence
- Increasing life expectancy for the MS population
- Improved diagnostic criteria and procedures
- Availability of effective MS therapies provides a strong incentive to diagnose MS

Wallin et al, 2019

Prevalence: *It takes a Village*

Mitchell Wallin

William J. Culpepper

Jonathan Campbell

Lorene Nelson

Annette Langer-Gould

Ruth Ann Marrie

Gary Cutter

Wendy Kaye

Laurie Wagner

Helen Tremlett

Steven Buka

Barbara Topol

Lie Chen

Albert Lo

Olelg Muravov

Robert McBurney

Bari Talente

Leslie Ritter

Tim Coetzee

Weyman Johnson

Ted Thompson

Jennifer Sheridan

Plyameth Dilokthornsakul

Nicholas LaRocca

Recent Research Advances in MS

Stopping MS

- Development of effective immunomodulatory treatments
- Neuroimaging including prognostic indicators for disease progression
- Progress toward biomarkers for disease activity and treatment response
- Documenting the impacts of co-morbidities and aging
- Improvements in the diagnostic methods for MS
- Impact of diet/gut microbiome on CNS immune activity

Restoring Function

- Impacts of rehabilitative and wellness interventions
- Identifying mechanisms for neural and myelin repair and inhibitory factors
- Recognition of the heterogeneity of MS and its course
- Impacts of aging on myelin repair

Ending MS forever

- Evidence for the genetic and epigenetic underpinnings of MS
- Identification of the role of environmental and life-style risk factors in MS
- New understanding of subclinical and prodromal phases of MS
- Revised understanding of the epidemiology of MS
- Improved understanding of pediatric MS

Existing Scientific and Research Gaps in MS

Pathways to Cures for MS: Stop – Restore – End

STOP: Goal: No More Disease Activity

Target #1

PRECISION MEDICINE

Achieve no worsening of daily living or quality of life, and no change in disease manifestations, *for each individual with MS*

- Factors that determine the heterogeneity of MS pathology
- Precisely which biomarkers identify who will respond to a particular therapy and when a therapy is no longer effective
- Which therapies pose an increased risk to an individual
- The relationship between inflammation and neurodegeneration
- How to measure the transition to secondary progressive MS

STOP: Goal: No More Disease Activity

Target #2

EARLY DETECTION

Reduce or eliminate the impact of MS before neurological deficits accumulate *in an individual with MS*

- Exactly which biomarkers (fluid/imaging/genetic) identify an individual likely to develop MS prior to expression of overt clinical manifestations required to confirm diagnosis
- A full understanding of the early pathological events that lead to the initiation of MS
- Whether interventions targeted at the very earliest stages of MS will stop disability progression

RESTORE: Goal: Reverse symptoms and disabilities to enable full participation in society

Target #1

REMYELINATION

Tissue repair/regeneration, includes better understanding of mechanisms related to remyelination

- The key pathways/targets needed to overcome repair failure
- How neuron-glial and glial-glial interactions impact repair
- How oligodendroglia may act as antigen presenting cells and contribute to axonal pathology
- How to limit damage, induce full repair and maintain myelin stability
- To what degree regional differences in CNS impact repair
- How age, sex, and genetics impact repair

RESTORE: Goal: Reverse symptoms and disabilities to enable full participation in society

Target #2

RESTORE ACTIVITY

Rehabilitation and symptom management include better understanding of rehabilitation approaches and wellness behaviors

- Mechanistic understanding of the effects of rehabilitation on the central nervous system
- How to enhance tissue regeneration with rehabilitation
- Proper dosing of intervention to facilitate optimal change
- Best outcome to measure symptoms
- Mechanisms to improve fatigue, bowel and bladder function
- The extent that exercise can facilitate remyelination processes

END: Goal: No New Cases of MS

Target #1

PRIMARY PREVENTION

To prevent MS before it occurs by limiting exposure to MS risk factors in the *general population*

- Whether any risk factors are necessary /sufficient to cause MS
- The critical time frame for exposure to an MS risk factor
- The complete genetic/epigenetic contribution to MS etiology in all human populations and how they interact with environmental risk factors
- Which public health interventions will reduce risk for MS

END: Goal: No New Cases of MS

Target #2

SECONDARY PREVENTION

To reduce or eliminate the impact of MS before onset of signs/symptoms by identifying pre-clinical MS in the *high-risk population*

- Precisely which biomarkers (fluid/imaging) identify risk for developing MS, when they become elevated, and what thresholds identify an individual as being at increased risk
- Which interventions are going to delay or stop the further development of MS in an individual
- What particular aspects of a medical history and/or neurological test will contribute significantly to identifying people at high risk for MS.
- A full understanding of the early pathological pathways/events that lead to the initiation of MS
- Whether interventions targeted at the very earliest stages of MS will slow down or stop disability progression

National MS Society

- <https://www.nationalmssociety.org>
- MS Navigator Program: 1-800-344-4867

Citations

Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, Cutter GR, Kaye WE, Wagner L, Tremlett H, Buka SL, Dilokthornsakul P, Topol B, Chen LH, LaRocca NG; US Multiple Sclerosis Prevalence Workgroup. **The prevalence of MS in the United States: A population-based estimate using health claims data.** *Neurology*. 2019 Mar 5;92(10):e1029-e1040. doi: 10.1212/WNL.0000000000007035. Epub 2019 Feb 15. Erratum in: *Neurology*. 2019 Oct 8;93(15):688. PMID: 30770430; PMCID: PMC6442006.

Culpepper WJ, Marrie RA, Langer-Gould A, Wallin MT, Campbell JD, Nelson LM, Kaye WE, Wagner L, Tremlett H, Chen LH, Leung S, Evans C, Yao S, LaRocca NG; United States Multiple Sclerosis Prevalence Workgroup (MSPWG). **Validation of an algorithm for identifying MS cases in administrative health claims datasets.** *Neurology*. 2019 Mar 5;92(10):e1016-e1028. doi: 10.1212/WNL.0000000000007043. Epub 2019 Feb 15. PMID: 30770432; PMCID: PMC6442008.

Institute of Medicine (US) Committee on Multiple Sclerosis: Current Status and Strategies for the Future, Joy JE, Johnston RB Jr., eds. **Multiple Sclerosis: Current Status and Strategies for the Future.** Washington (DC): *National Academies Press (US)*; 2001.