

Sex, Gender and Regenerative Medicines: Multiple Sclerosis as a Disease Model

NASEM Workshop
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Disclosures

Research Support

- Weill Institute for Neuroscience
- Biogen, Roche Genentech, Novartis, Eli Lilly
- National Multiple Sclerosis Society Harry Weaver Award
- NIH
- DOD

Scientific Advisory Boards

- Alexion
- EMD Serono
- Horizon
- Janssen
- TG Therapeutics

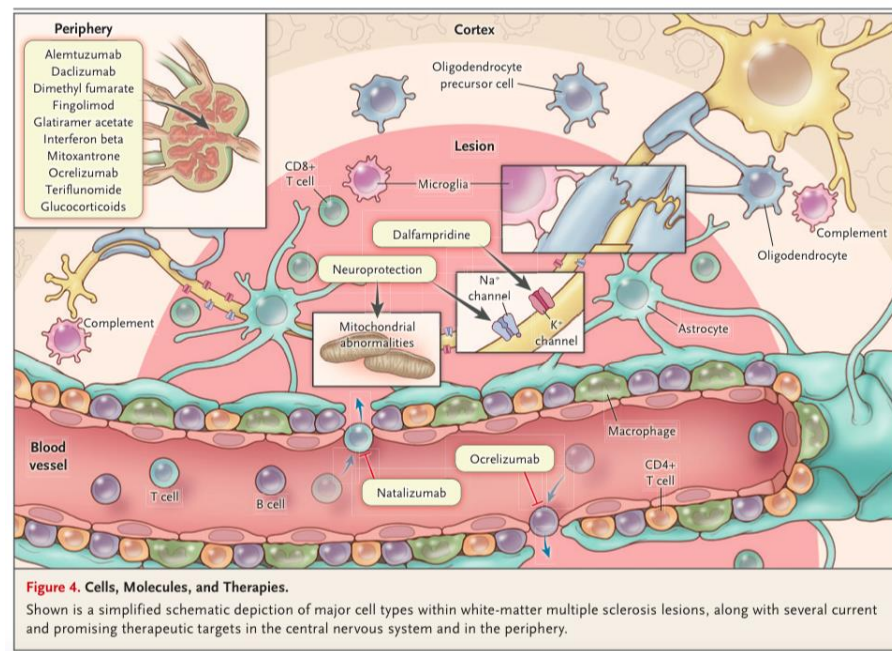
Sex Differences in Neuro/Psychiatric Conditions

| | Sex Ratio (F:M) | Onset | Notable clinical features |
|---------------------|---------------------------------------|-----------------------|---|
| Autism | 1 : 4-5 | same | M more social impairments; F affective symptoms |
| ADHD | 1 : 2-3 | same | M more hyperactivity/externalizing; F more intellectual impairments/internalizing |
| Parkinson's Disease | 1 : 1.6 | M 2 years before F | Development of symptomatic PD is delayed in F possibly due to oestrogens |
| ALS | 1 : 1.5 | Later in F | F bulbar, M limbs |
| Epilepsy | 1:1 | same | Semiologies/Types differ |
| Stroke | <85: M>F; >85: F>M | M 4 years before F | F longevity => increased strokes |
| Myasthenia gravis | 1:1 | Young F, older M | M more antiAChR antibodies |
| Alzheimer's Disease | 1.5-2 : 1 | earlier in F | More tangles and global pathology in F |
| Depression | 2 : 1 | same | Gender gap peaks in adolescence, then narrows and stable in adulthood |
| Anxiety | 2 : 1 | same | F show higher chronicity and comorbidity |
| Eating disorders | 3-4 : 1 | unknown | F show higher ED pathology |
| Migraine | 2-3 : 1 | same | F higher migraine symptoms and aura |
| Multiple sclerosis | 3 : 1 | ? slightly later in M | F more relapses; M faster progression |
| NMOSD | 9:1 | unknown | unknown |

Multiple Sclerosis (MS) as a Model Condition

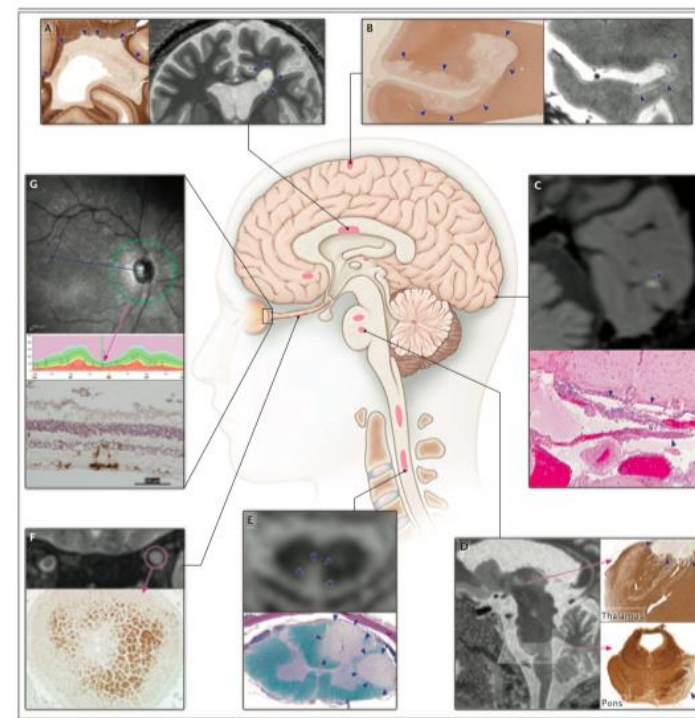
Disease Processes:

Inflammation *and* neurodegeneration



Reich et al, *NEJM* 2018

Disease Manifestations



Fatigue
Cognition
Mood
Vision
Facial
Brainstem

Motor
Sensory
Gait
Pain

Bowel
Bladder
Sexual

Neurological conditions, Sex/Gender, Cultural Changes

The New York Times

Women Are Calling Out 'Medical Gaslighting'

Studies show female patients and people of color are more likely to have their symptoms dismissed by medical providers. Experts say: Keep asking questions.

Give this story   2.7K



Marta Monteiro

By Melinda Wenner Moyer

Published March 28, 2022 Updated March 31, 2022

JAMA Neurology

Viewpoint

ONLINE FIRST

FREE

July 13, 2022

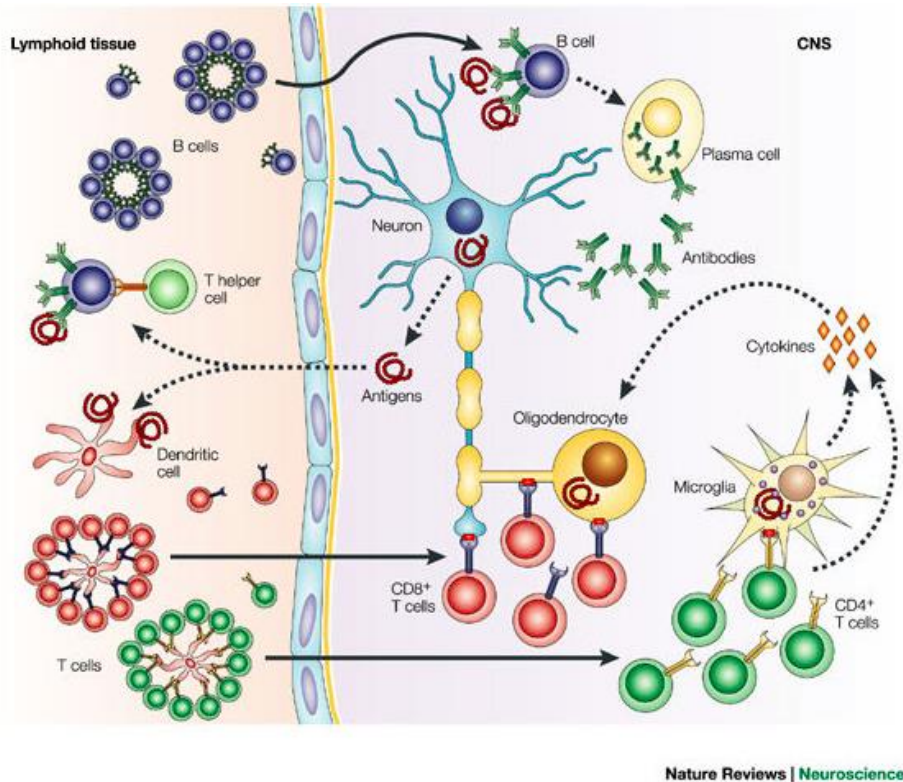
Reproductive Rights in Neurology—The Supreme Court's Impact on All of Us

Sara C. LaHue, MD^{1,2}; Dawn Gano, MD, MAS^{1,3}; Riley Bove, MD, MSc^{1,2}

What is happening societally? Representation in science => inclusive medicine

Gaps in SABV approaches from Bench to Bedside: How do we deliver Precision Medicine, or even Safe Medicine?

Bench



Some questions are narrow

Bedside

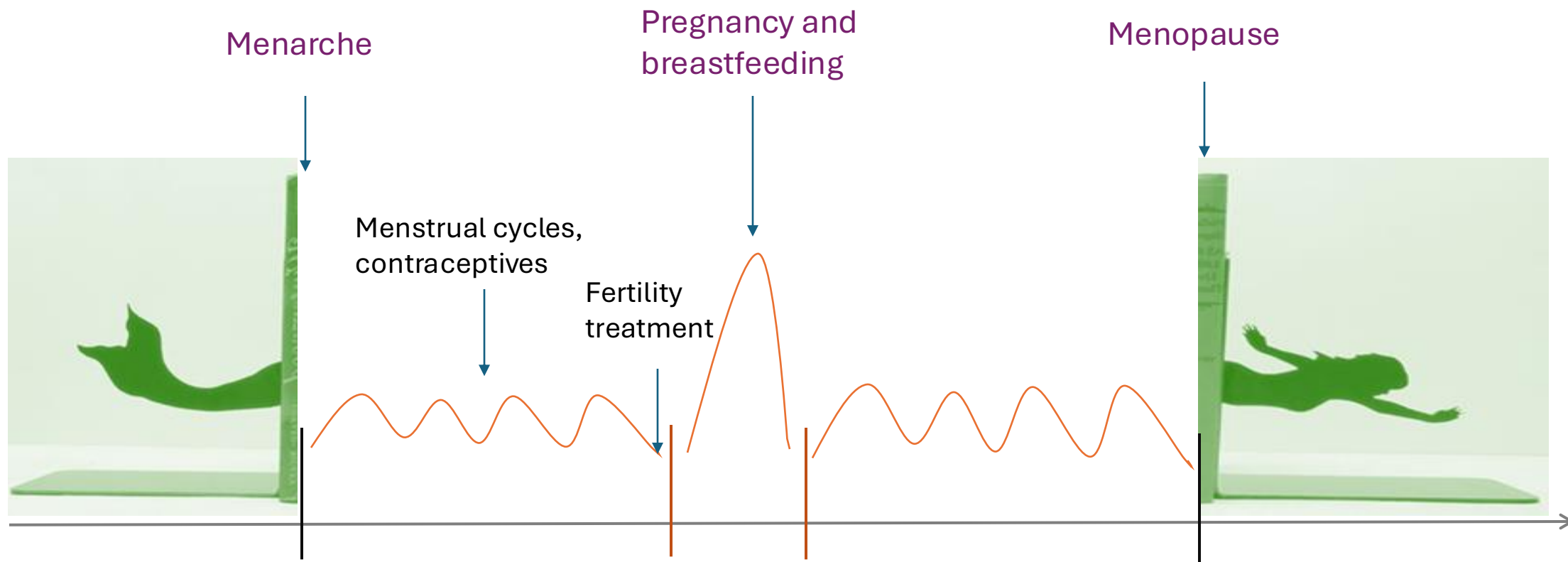
| BEST PRACTICES CRITERION ² | PRE 2017 (n=31) | POST 2017 (n=9) |
|--|--------------------|--------------------|
| Comparison of male and female participants' baseline demographic and clinical features | 0 (0%) | 0 (0%) |
| Pre-specified stratification by sex for primary trial efficacy outcomes | 10 (32%) | 4 (44%) |
| Post hoc analyses of primary trial efficacy outcomes by sex | 9 (29%) | 2 (22%) |
| Described or planned statistical power to identify sex differences in efficacy or safety | 0 (0%) | 0 (0%) |
| Pre-specified stratification by sex for adverse events or safety concerns | 0 (0%) | 1 (11%) |
| Post hoc analyses of adverse events by sex | 3 (10%) | 1 (11%) |
| Mentions of sex differences in the product's FDA labels | 6 (46%) | 5 (100%) |
| Inclusion of postmenopausal females (50+) | 5 (16%) | 3 (33%) |
| Additional: information about inclusion of diverse gender identities | 0 (0%) | 0 (0%) |

Balan et al, AAN 2024

Common medications and gynecological health

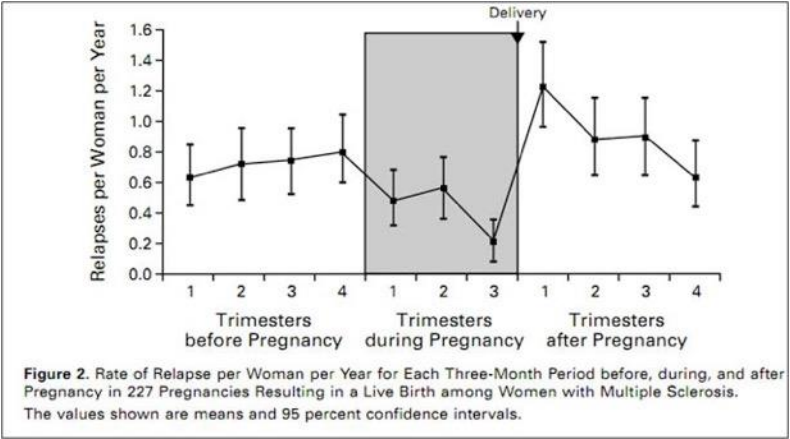
Some questions aren't asked

Sex-Specific Windows Across the Lifespan: Opportunities for Targeted Care

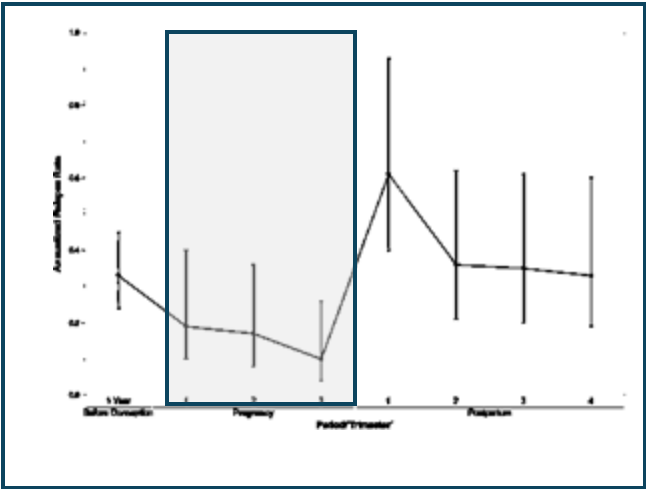


Reproductive transitions in a cis-woman's life

MS and Pregnancy



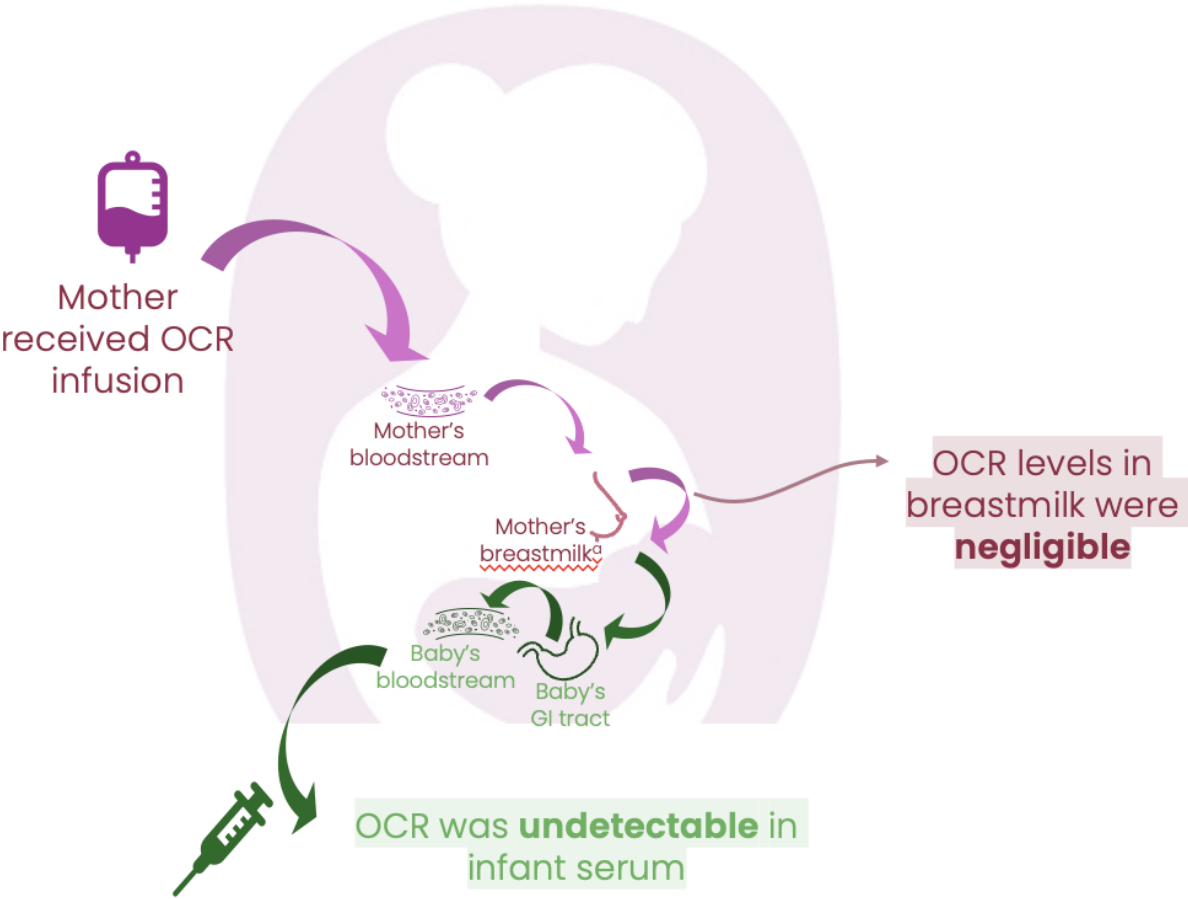
Confavreux et al, NEJM. 1998 339(5):285-91



Houtchens et al, N2 2020; Anderson et al, N2 2021

>50% patients have new lesions

MS Medications are Protective
Breastfeeding is Protective,
so...



Bove et al, ECTRIMS 2024

CAR-T Cells in MS

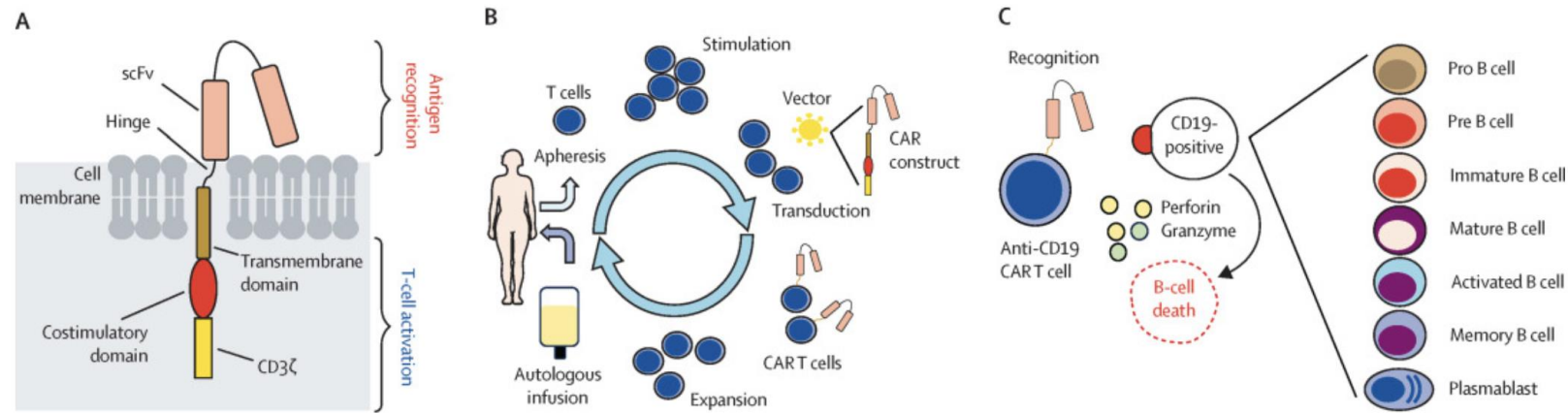


Figure 1 Design, production, and mode of action of CAR T cells

Haghikia et al, Lancet Neurol 2024

CAR-T Cell treatment



Vertical transfer across placenta of a T cell by 13 wks gestation

Longevity of a typical T cell (50-130d)

Potential persistence of a T cell including via clonal populations (decade)

Menopause and the Brain: A societal gap.

Welcome to the Menopause Gold Rush

Venture capitalists, former magazine editors and Goop have all converged on the new frontier in women’s wellness.

[Share full article](#)

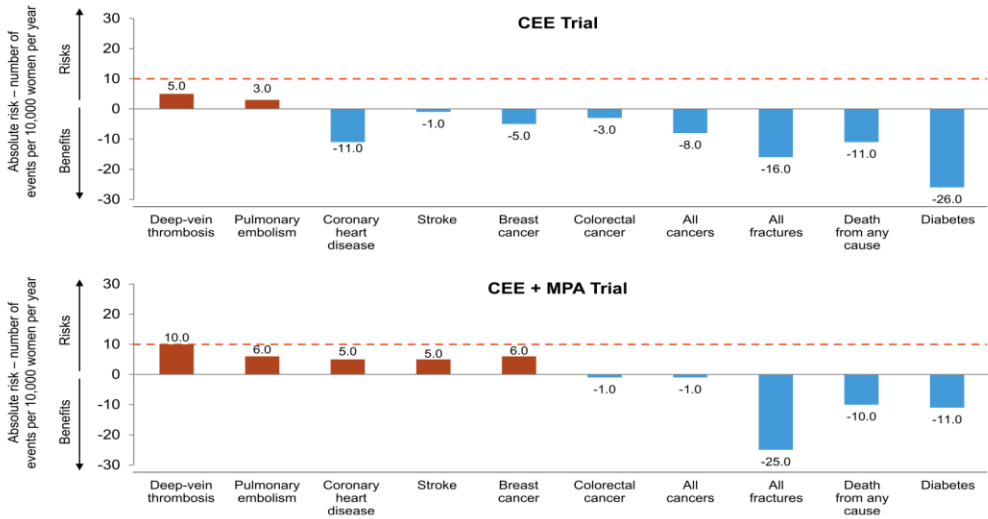


FIG. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA), evaluated in the Women’s Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line). Adapted from Manson JE, et al.⁹

NAMS, Menopause, 2022



For a 50th-birthday photo shoot, Gwyneth Paltrow covered the sun’s “celestial fingerprints” with piles and piles of gold powder. Goop, her wellness company, is jockeying for its share of the menopause market. Andrew Yee

Experiences with MS in Peri- and Post-Menopause

Median age: 51.4

| | | | | | | | | | | |
|--------------------------------------|---------------------|---------|------------|--------------------------------|---|-------------------------------------|--------------------------------|-----|------------------------------------|---|
| | Menarche | | | | FMP (0) | | | | | |
| Stage | -5 | -4 | -3b | -3a | -2 | -1 | +1 a | +1b | +1c | +2 |
| Terminology | REPRODUCTIVE | | | | MENOPAUSAL TRANSITION | | POSTMENOPAUSE | | | |
| | Early | Peak | Late | | Early | Late | Early | | | Late |
| | | | | | Perimenopause | | | | | |
| Duration | variable | | | | variable | 1-3 years | 2 years (1+1) | | 3-6 years | Remaining lifespan |
| PRINCIPAL CRITERIA | | | | | | | | | | |
| Menstrual Cycle | Variable to regular | Regular | Regular | Subtle changes in Flow/ Length | Variable Length Persistent ≥7- day difference in length of consecutive cycles | Interval of amenorrhea of >=60 days | | | | |
| SUPPORTIVE CRITERIA | | | | | | | | | | |
| Endocrine FSH AMH Inhibin B | | | Low Low | Variable* Low Low | ↑ Variable* Low Low | ↑ >25 IU/L** Low Low | ↑ Variable Low Low | | Stabilizes Very Low Very Low | |
| Antral Follicle Count | | | Low | Low | Low | Low | Very Low | | Very Low | |
| DESCRIPTIVE CHARACTERISTICS | | | | | | | | | | |
| Symptoms | | | | | | Vasomotor symptoms Likely | Vasomotor symptoms Most Likely | | | Increasing symptoms of urogenital atrophy |

COMPREHENSIVE PREVENTIVE CARE

Aging and Neurodegeneration

- Disability progression
- Risk factors and co-morbidities

Common Concerns

- GUS: Genitourinary syndrome of menopause
- Bone density loss
- Joint stiffness and pain

Sociocultural
Context

VMS: Vasomotor Symptoms

Common Concerns

- Sleep
- Cognition
- Mood
- Libido
- Energy/Fatigue

COMPREHENSIVE SYMPTOM MANAGEMENT

Post-Menopausal Brain Health: Analytical challenges

- Chronological aging: Menopause occurs in all females as they age
- Biological aging: Aging in the brain will correlate with aging in other organs including ovaries
 - *Ages 44 and 60 as specific inflection points*
- Reproductive aging: Does loss of gonadal hormones at menopause induce a change in brain health?
 - **Indirect** effects (e.g. cardiovascular)
 - **Direct** effects (e.g. neuronal targets, myelin repair)

Exposures

Comorbidities

Outcomes

Sociocultural context

Earlier life exposures (stress, trauma, education)

Behaviors
(eg exercise, smoking)

Genes

HT use
Oophorectomy

Menopause – loss of
gonadal hormones

Metabolic (DM, BMI)

Musculoskeletal
Hematologic
Immunologic
Cardiovascular

Age

Brain health

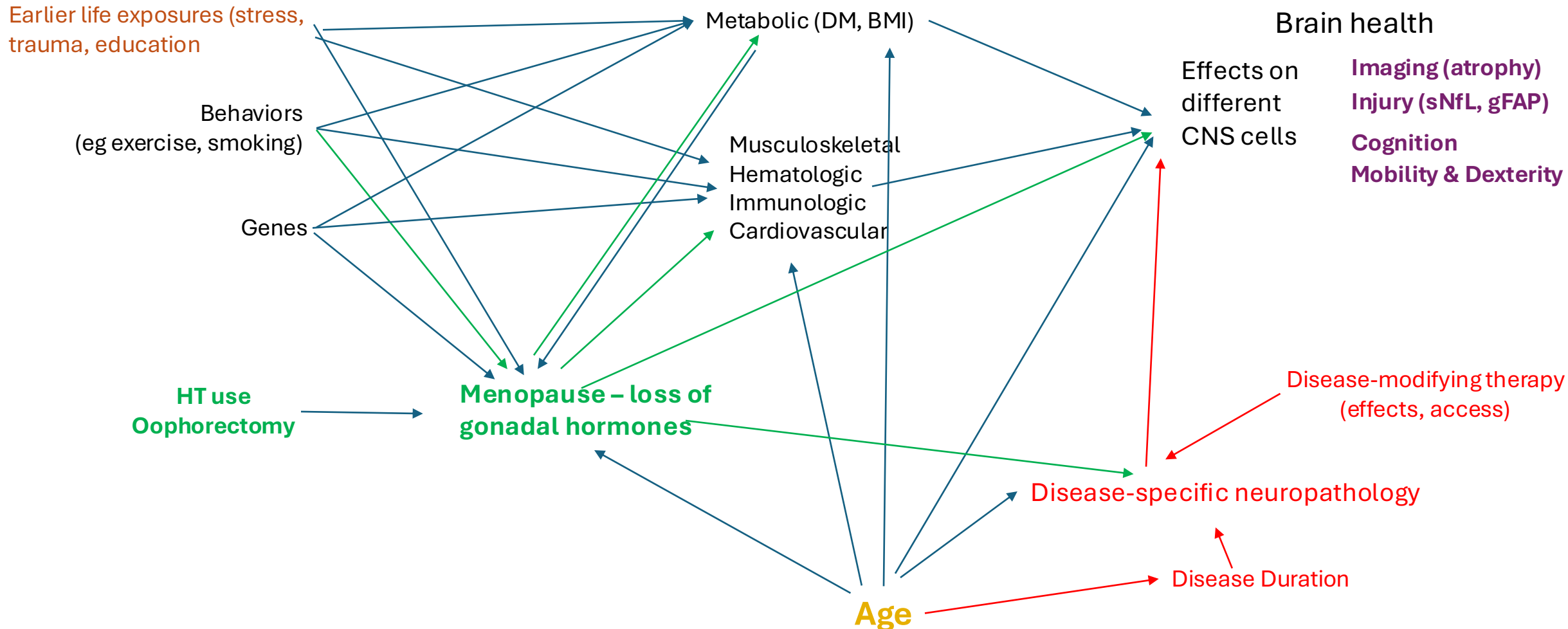
Effects on
different
CNS cells

Imaging (atrophy)
Injury (sNfL, gFAP)
Cognition
Mobility & Dexterity

Disease-modifying therapy
(effects, access)

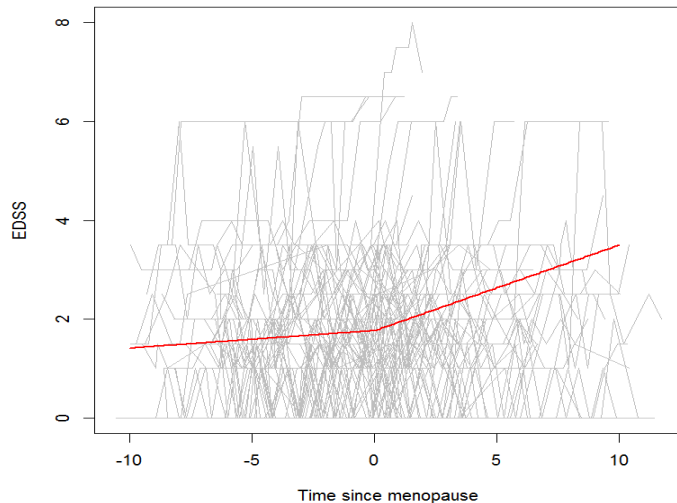
Disease-specific neuropathology

Disease Duration



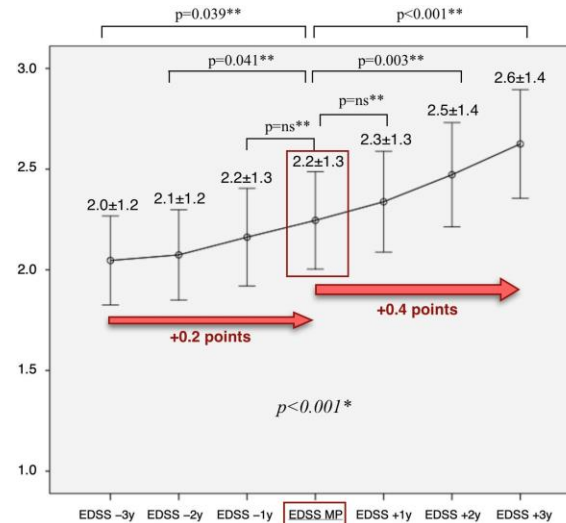
Approaches to measuring effect of menopause on brain health

- Cross-sectional comparison of outcomes between cycling, perimenopausal and postmenopausal groups
- Comparison of slopes between males and females before/age 50-52
- Early/surgical menopause as an “experimental” condition
- Regressions linking Age of menopause and specific outcome
- **Within-person changes before, during and after the menopausal transition**



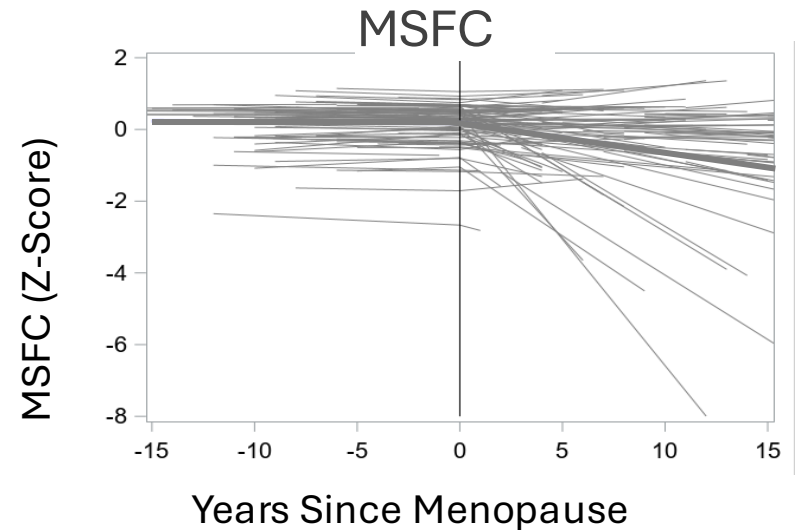
Change in EDSS slope at menopause, inflection point analysis (N=124, $p=0.024$)

Bove et al, MSJ 2018



ANOVA of annual EDSS score (mean±SD) 3Y pre, 3Y post FMP (n=108 patients)

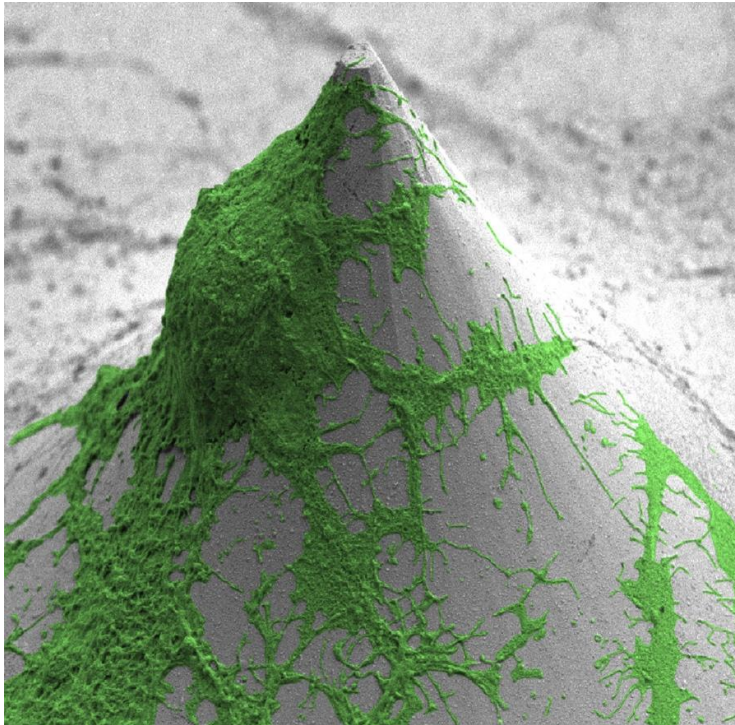
Baroncini et al. JNNP doi:10.1136/jnnp-2019-320587



Silverman et al, AAN 2023; Nylander et al, ECTRIMS 2023

Regenerative Therapy Use Case: Remyelination

Screening with BIMA
(Binary Indicant for Myelination using
Micropillar Arrays)



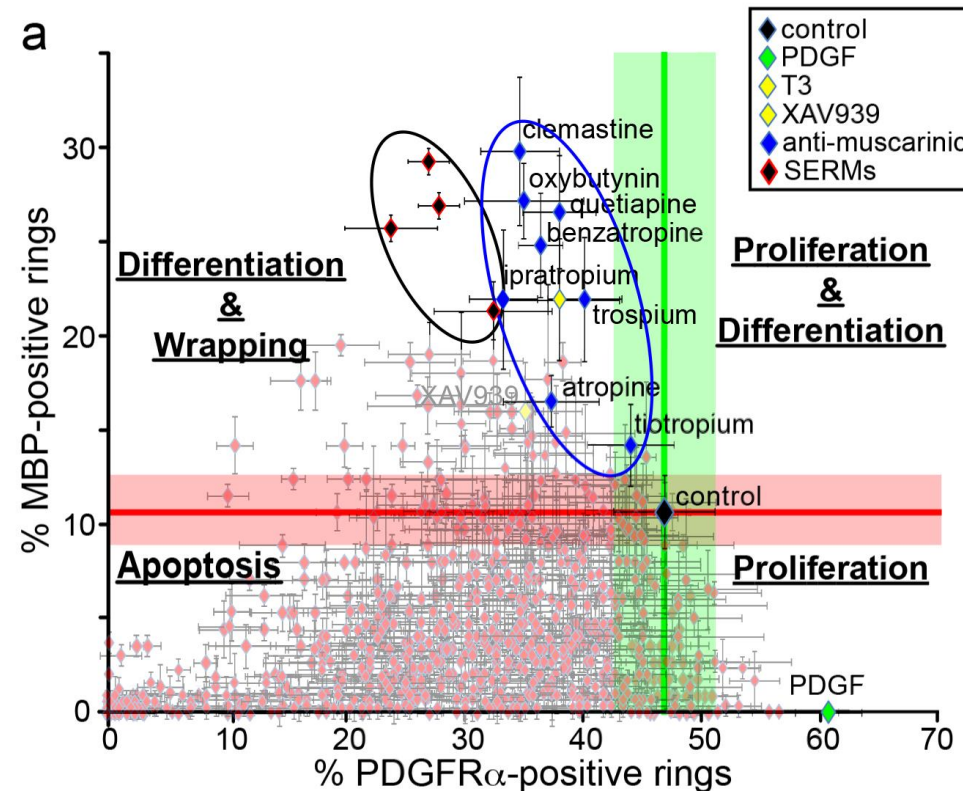
Selective Estrogen Receptor Modulators (SERMS)



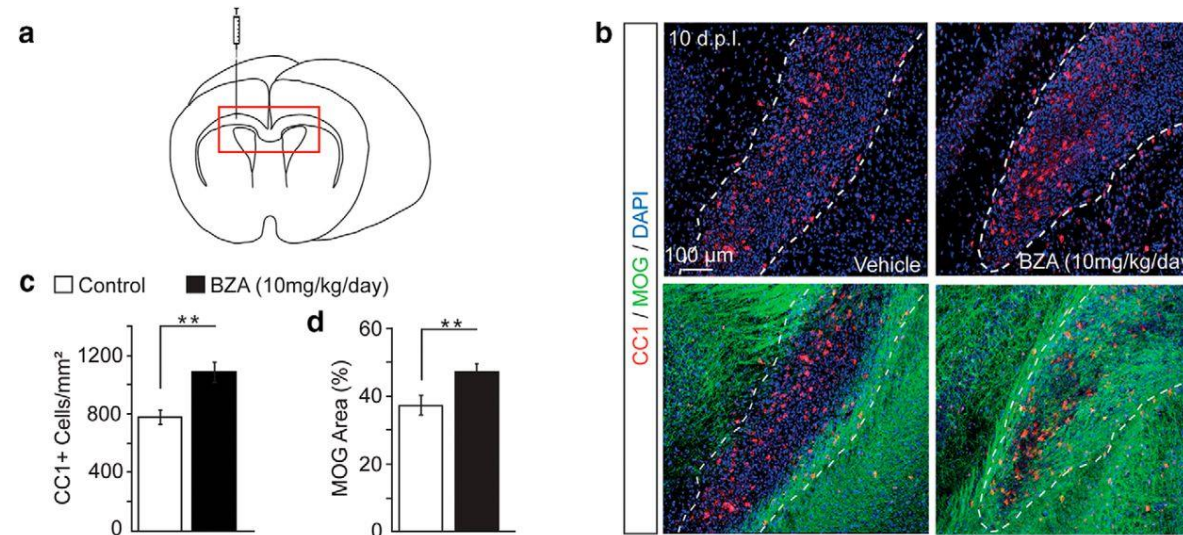
Dr Jonah
Chan

Dr. Ari
Green

Kelsey
Rankin

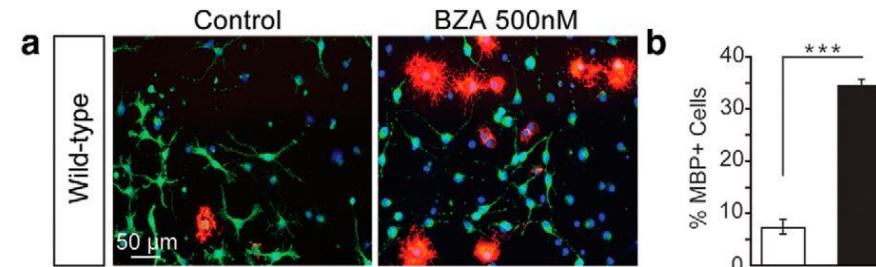


BZA promotes remyelination after demyelination ...



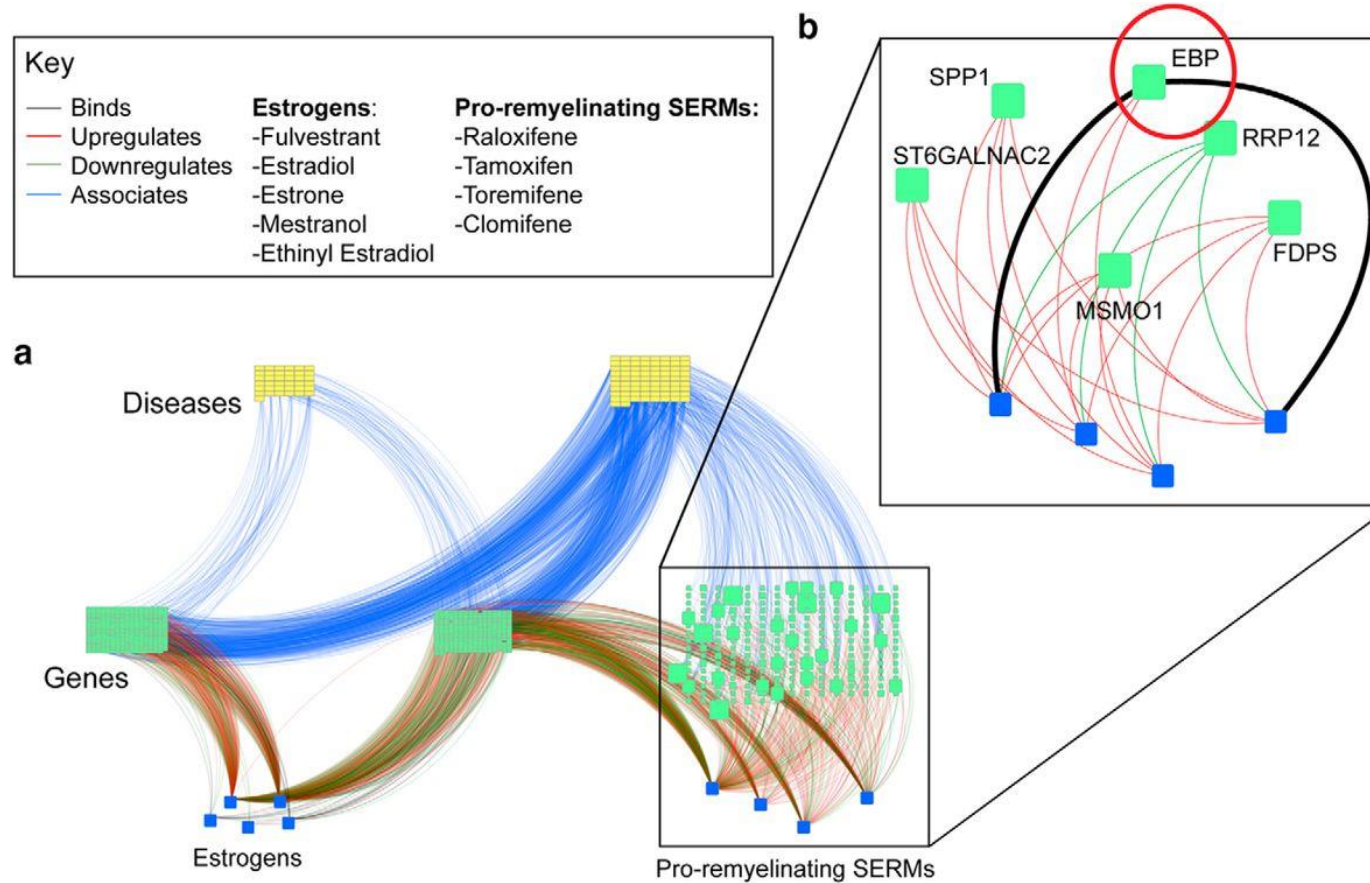
BZA enhances and accelerates remyelination in an in vivo focal demyelination model a, Schematic showing location of lysolecithin injection into the corpus callosum at the position: AP: -1.04, ML: 1, and DV: -1.75 from bregma. b, Representative images of les...

... independently of the estrogen receptors



BZA enhances OPC differentiation independently of the ER α , Representative images of control and BZA-treated (500 nm) WT, ER α , and ER β KO OPCs, treated for 2 d and immunostained for MBP (red) and PDGFR α (green).

Bioinformatics profiling implicates set of candidate targets posing unique pathway for SERMs
a, Network of first-degree (genes/proteins; green squares) and second-degree (diseases; yellow squares)
neighbors of select FDA-approved pro-remyelinating and non...

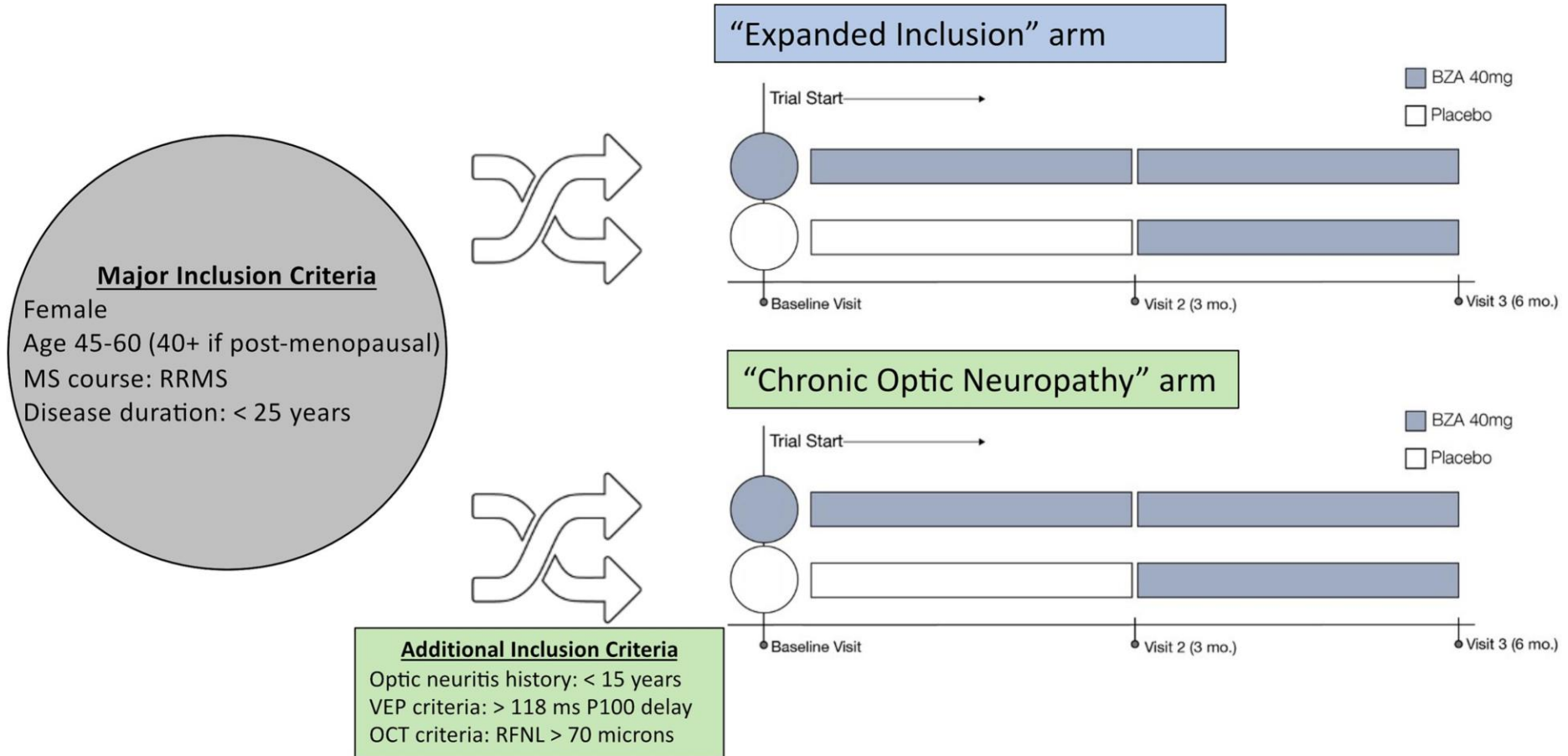


Kelsey A. Rankin et al. J. Neurosci. 2019;39:2184-2194

Sex-Specific Interventions:

Re-WRAP (Remyelination for women at risk of axonal loss and progression):

A phase II randomized placebo-controlled delayed-start trial of Bazedoxifene (SERM) for myelin repair in MS



Sex and Gender Enriched Neurology

NINDS GENDER R25

PI: Riley Bove, MD FAAN

Co-I: Sara LaHue, MD

SPECIFIC AIM 1. Develop and implement a **clinical best practices core curriculum that accelerates the translation of SAGE principles into neurology clinical practice.**

SPECIFIC AIM 2. Develop and implement a **scientific best practices core curriculum to train the next generation of clinician-scientists to conduct and interpret research using SAGE principles.**

SPECIFIC AIM 3. Promote active generation and dissemination of new knowledge through **mentored inquiry workshops.**

Summary

- Chronic conditions: a **lifespan** and **systems** approach to analyzing sex/gender effects
- Reproductive transitions are windows into **mechanisms** of disease and resilience
- Some science is hard, *but some is easy*
- **Treatments**
 - Must consider both *individual* and *intergenerational* safety
 - Even Phase III RCTs continue to lack scientific rigor for SABV/Gender analyses
- **Caution** about even “canonical” knowledge about hormones

THANK YOU

Bove Lab



UCSF MS Group



SUPPORT

