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$50M Wellcome Leap Program

CARE: Cutting Alzheimer's Risk through Endocrinology

Worldwide, someone develops Alzheimer's disease every 3.2 seconds. Nearly two-thirds of all patients are women. CARE aims to cut the lifetime risk of Alzheimer's among women by half, reducing risk for 330 million women globally – and, given current conversion rates, preventing 54.5 million Alzheimer's cases by 2050.

Alzheimer's disease is the most common form of dementia worldwide, affecting over 55 million individuals. As the population ages, the number of affected individuals is expected to triple by 2050, reaching an estimated 130 million patients globally[1].

We have known since the 1990's that, after advanced age, being a woman is the second strongest risk factor for Alzheimer's disease[2,3]. Women outnumber men ~2:1 in the Alzheimer's population, with postmenopausal women constituting over 60% of all those affected[1]. The estimated lifetime risk for Alzheimer's for a 45-year-old woman is 1 in 5, twice as high as the 1 in 10 risk for a man of the same age[1]. While the risks for both sexes are slightly higher at age 65, the ratio remains stable – 21% for women and 11% for men.

These statistics raise questions about the specific factors that contribute to this disparity and how best to mitigate the higher lifetime risk in women.

For many years, Alzheimer's disease was considered an inevitable consequence of aging or genetics—or a combination of both. However, this perspective has shifted as research has uncovered the significant role of *modifiable factors* in Alzheimer's risk. Today, we understand that while age and genetics cannot be modified, other factors can be intervened upon—such as lifestyle, health behaviors, and socioeconomic conditions—that account for a cumulative 45% of Alzheimer's risk[4,5].

This means that 55% of Alzheimer's risk remains unexplained. Current estimates are *sex-aggregated*, meaning they do not account for differences in risk profiles between men and women. Female-specific risks remain unquantified in available population-attributable risk (PAR) models. These gaps highlight the need for a deeper comprehension of Alzheimer's mechanisms linked to sex-specific biology; robust, sex-specific risk biomarkers; and tailored interventions to support cognitive function and prevent neurodegeneration in women.

Emerging evidence of blood-based biomarkers of Alzheimer's along with advancements in neuroimaging and machine learning techniques, coupled with more detailed mechanistic understanding of estrogen action in the brain, means that we can identify at-risk individuals with unprecedented accuracy, develop tailored prevention strategies, and intervene earlier to significantly reduce the burden of the disease – at scale.

We have the tools. Now is the time. CARE is focused on women, beginning in midlife, when the potential for preventing Alzheimer's is greatest. Deep phenotypic identification of female-specific risks, coupled with rapid stratification and patient-specific matching to the most promising

treatment options, has ***the potential to cut Alzheimer's risk in the female population in half.*** In the United States alone, this would result in $4.56 trillion USD in savings. The global implications would be multiples of this number. Therefore, the program will also emphasize advances that increase access and reduce cost.

What needs to change? New considerations of neuroendocrine effects.

It's not 'just' aging. A prevalent but reductive explanation for the higher representation of Alzheimer's in women has been that Alzheimer's is a disease of old age, and women live longer than men. In actuality, the difference in life expectancy between women and men is small — 4.5 years in the US and 5 years globally. More importantly, there is now consensus that Alzheimer's is not a disease of old age, but a disease *of midlife*, with symptoms that start in old age[6].

Alzheimer's begins with a lengthy "silent" (prodromal) phase, during which brain pathology develops in the absence of overt symptoms[6]. Notably, the early phase of Alzheimer's coincides with the neuroendocrine aging transition of menopause for women, pointing to a critical window of vulnerability and highlighting the impact of female-specific neuroendocrine (hormonal) risks.

Increasing evidence implicates neuroendocrine aging as a driver of neuropathological aging[7-14]. In particular, many studies implicate a longer reproductive span and longer lifetime exposure to sex-steroid hormones — chiefly estrogen — as female-specific protective factors against Alzheimer's[11,15]. Estrogen (17β-estradiol) is a neuroprotective hormone that promotes neuronal resilience by reducing inflammation, tau phosphorylation, and amyloid beta (Aβ)-induced neurotoxicity[12,13]— all hallmarks of Alzheimer's. Conversely, estrogen deprivation following menopause is associated with accelerated neuronal aging and an increased risk of neurodegenerative insults[16-19]. In mechanistic analyses, changes in hormonal concentrations and associated neuroendocrine function resulting from the surgical removal of the ovaries (oophorectomy) with or without the uterus (hysterectomy) are a trigger for Alzheimer's pathology.[9,12-14] Clinical studies have confirmed that an earlier age at menopause, particularly due to surgical menopause, is associated with a higher risk of Alzheimer's and all-cause dementia[8,20-22].

Currently, approximately one in nine women undergoes hysterectomy, often leading to surgical menopause. Another one in eight women develops breast cancer and may experience 'medical menopause' following endocrine therapy. These women represent an important target population for prevention strategies.

There is also observational evidence that women undergoing spontaneous menopause exhibit increased biomarker indicators of Alzheimer's risk compared to premenopausal women and age-controlled men[23-30]. These findings suggest an earlier onset of Alzheimer's pathology in women than in men, possibly resulting from the loss of neuroprotective effects of endogenous sex steroid hormones. In this scenario, the postmenopausal Alzheimer's risk increase presents a window of opportunity for extension of neuroprotection through hormonal interventions.

The controversial role of hormone therapy. While preclinical research has demonstrated estrogen's neuroprotective potential, the clinical application of menopausal hormone therapy (MHT) for reducing Alzheimer's risk remains a subject of active debate.

A major hindrance has been the lack of randomized controlled trials (RCT) evaluating MHT as a preventative against Alzheimer's. The only RCT examining MHT's impact on dementia risk is the Women's Health Initiative Memory Study (WHIMS), which was conducted in 1996-2002[31,32]. The study investigated oral conjugated equine estrogens (CEEs) both alone and with medroxyprogesterone acetate (MPA) compared to placebo in postmenopausal women ages 65 and older[31,32]. The trials concluded with an approximately doubled dementia rate in the CEE+MPA group, and a non-significant increase in the CEE-only group. A general critique to the WHIMS is that these were late intervention trials of older women without active menopausal symptoms, possibly missing the therapeutic window for estrogen efficacy[33,34].

Findings from WHIMS are not applicable to contemporary clinical practices where MHT is typically initiated close to menopause for symptom relief, and often involves different formulations such as micronized estradiol, frequently administered transdermally, with or without a progestogen other than MPA.

By contrast to WHIMS, recent meta-analyses of observational and natural history studies, along with retrospective analysis of electronic records from midlife women (likely in the critical window for MHT action), indicate a reduced risk of Alzheimer's and all-cause dementia with overall use[35,36]. MHT efficacy appears to be influenced by several factors, primarily timing of initiation and formulation[35,36]. MHT use in midlife was associated with 22% reduced risk of Alzheimer's and dementia compared to late-life use. Estrogen-only therapy for women who have undergone hysterectomy was associated with 19% reduced risk compared to combined therapy. Additionally, geographic location may play a role as studies conducted outside Northern Europe reported a 32.4% risk reduction with MHT use[36]. Apolipoprotein E (APOE) epsilon 4 genotype, the strongest genetic risk factor for late-onset Alzheimer's[2,39,40], may also influence outcomes. MHT was associated with a 35.2% Alzheimer's risk reduction for non-carriers, and neutral effects for APOE-4 carriers[36].

As of today, professional societies recommend estrogen therapy for support of cognitive function for women with early and surgical menopause[37]. The value of MHT for women undergoing spontaneous menopause remains controversial.

The lack of detailed, state-of-the-art data surrounding the use of estrogen therapy for Alzheimer's prevention is limiting our ability to make clear clinical decisions regarding effective therapies that are female-specific, time-sensitive, and formulation / dose appropriate to reduce Alzheimer's risk. Key will be quantitative stratification using genetic, medical, neuroendocrine and biomarker assessments to determine who may benefit most from hormonal interventions, so as to develop targeted preventive protocols.

We need better answers. If successful, CARE could offer a path to prevention in midlife for millions of women, when the potential for preservation of cognitive function is greatest.

Program goal.

Our ultimate goal is to cut women's lifetime risk of Alzheimer's in half. CARE is focused on the intersection of neuroendocrine risks and neurodegeneration so as to identify personalized preventative strategies and treatments. This approach utilizes an individualized medicine framework — leveraging biomarkers, advanced imaging, genetic profiling— to tailor interventions to the specific needs of women at risk for Alzheimer's due to neuroendocrine aging.

How do we get there?

To achieve a 50% risk reduction by 2050, we must optimize each step in the funnel: ensure high biomarker accuracy for effective screening, expand outreach, and maximize treatment efficacy and optimize frequency.

The CARE program includes three primary thrust areas designed to achieve this overall goal, designed to stratify at-risk individuals into progressively specialized diagnostic pathways. This tiered approach optimizes resources and widespread application, while ensuring comprehensive risk assessments and cost-effective prevention strategies:

- **Screening**: The foundation of the model involves broad-based, easily implementable tests designed to identify 80% of at-risk individuals. These may include clinical measures and blood-based hormone tests that provide a first-pass screening for neuroendocrine and cognitive risk.
- **Assessment**: For individuals flagged as at risk, a more detailed layer of assessment is added. This may include neurological and cognitive evaluations, as well as biomarkers of Alzheimer's pathology. These tests provide deeper insights into disease progression risk and refine the pool of individuals needing further evaluation.
- **Diagnostic Confirmation and Treatment Optimization**: The final tier focuses on the women at the greatest risk, identified through earlier stages of the model. These individuals will ideally undergo brain imaging to measure neuroendocrine function directly in the brain and in relationship with Alzheimer's risk.

Each thrust will provide key elements to each tier, as described below, with the goal of systematically reducing Alzheimer's risk in women on a global scale. Thrusts 1 and 2 will provide the clinical and biological markers for risk assessment and patient stratification, and novel imaging probes of neuroendocrine risk. Thrust 3 will develop female-specific predictive models of Alzheimer's risk, integrate data across thrusts, and develop tools for widespread outreach.

Thrust Area 1. Identify high-precision female-specific neuroendocrine targets and therapies for Alzheimer's risk reduction.

Biomarker screening accuracy and outreach (percentage of the at-risk population reached) must combine to identify at least 330 million women globally who are both at risk and reachable for treatment. Additionally, the impact of preventative efforts depends on treatment efficacy and frequency. As an example, if we had a test with 80% screening accuracy, and outreach just above

60%, it would be possible to reach over 330 million women at risk to initiate treatment. If treatment were at least 60% effective, 3 rounds of treatments spaced ~8 years apart could reduce risk for the target population of 330 million women by 2050. Because of this combined effect, preference will be given to screening techniques with outreach that are cost-effective and scalable, and to effective therapies that require minimal infrastructure, which are easy to administer, and can be widely accessible across diverse populations.

For Thrust 1A-C, priority will be given to analyses of existing and/or ongoing datasets such as:

- Longitudinal or large-scale cross-sectional examinations of women undergoing spontaneous menopause, stratified by age, menopause status, and hormone therapy status, as appropriate.
- Longitudinal (before vs. after surgery or treatment initiation) or large-scale cross-sectional examinations of patients receiving hysterectomy / oophorectomy and/or endocrine therapy, stratified by age, menopause status, and hormone or endocrine therapy status, as appropriate.

For longitudinal studies, a minimum follow-up of one year is required. Leveraging existing data, whether from proprietary or publicly available databases and repositories, is welcome as it provides a head start while new data collection is underway. For ongoing datasets, we're interested in proposals that also address retention and the wellbeing of their participants and include strategies for doing so.

1A. Develop high-performance neuroendocrine predictors of Alzheimer's risk in women.

Develop ***neuroendocrine*** biomarkers for risk identification, prevention, and/or delay of Alzheimer's disease onset by evaluating their predictive power for Alzheimer's diagnosis (Alzheimer's vs. controls) and/or biomarker positivity (e.g. Aβ and/or tau levels within vs. below Alzheimer's range) in clinically normal midlife and older women (without dementia or mild cognitive impairment). We're particularly interested in analysis of neuroimaging data, cerebrospinal fluid (CSF), and blood samples from existing or ongoing biobanks, epidemiological cohorts, medical repositories, and research datasets. fMRI, rsfMRI, NIRS, DTI connectivity studies, or -omic studies alone are not of interest, unless combined with hormone and Alzheimer's-specific biomarkers.

Biomarkers with an **accuracy of ≥80%** fall into the target zone for high clinical utility, as determined via an ROC (Receiver Operating Characteristic) curve analysis. This threshold ensures that the biomarker reliably distinguishes between at-risk and non-at-risk individuals with both high probability of detection (P_d, e.g., clinical sensitivity) and low probability of false alarms (P_{fa}, e.g. clinical specificity). Established Alzheimer's biomarkers like Aβ and phosphorylated tau in CSF or PET imaging demonstrate high accuracy levels (~90%). This sets a precedent for neuroendocrine biomarkers, which aim to complement or augment these existing tools by focusing on risk prediction early in life.

- Develop multivariable prediction models that combine brain-based and blood hormone levels neuroendocrine markers (e.g., estrogen, progesterone, FSH, LH) with menopause-related clinical measures [such as age at menopause and menarche, menopause type (surgical, spontaneous, medically induced), frequency of vasomotor symptoms (e.g. hot flashes, night sweats), presence of 'brain fog' (e.g. subjective cognitive/memory fatigue), and hormone therapy use (type, dose, duration)], as well as estrogen-dependent cognition (e.g. memory, attention, fluency). Estrogen receptor polymorphisms are also of interest. Integration with risk factors for Alzheimer's such as a first-degree family history and Apolipoprotein E (APOE) epsilon 4 allele is warranted.
- Alone or in aggregate, these measures should demonstrate an **accuracy of ≥80%** in predicting Alzheimer's risk, as defined above. Multivariable models reduce noise and improve predictive performance while allowing the development of predictive tools for clinical practice.

1B. Identify the 'window of opportunity' for neuroendocrine intervention in women.

The "timing hypothesis" posits that the neuroprotective action of estrogen therapying the brain is maximized when initiated around menopause onset. This hypothesis is grounded in the "healthy cell bias hypothesis", where estrogen exerts beneficial effects on healthy neurons but may worsen established neuropathology if introduced too late or when damage or amyloidosis are already present[16]. Thus, the timing of treatment initiation and the neurological health of the patient at treatment onset are both important factors to consider[12,13,16].

Thrust 1B aims to use biological markers to determine the critical "window of opportunity" during which neuroendocrine interventions are most effective at reducing Alzheimer's risk in women. Priority will be given to longitudinal designs and large-scale, cross-sectional studies of asymptomatic women with and without risk factors for Alzheimer's, such as family history and/or APOE-4 genotype. Brain neuroendocrine markers are the primary focus, followed by clinical and peripheral measures (see above).

- Generate **age-specific curves** of the brain's neuroendocrine sensitivity, identifying when hormone receptors upregulate, downregulate, or lose function entirely across the menopausal transition, **at P<0.05**.
- These curves need to provide actionable data into when hormonal interventions might yield maximum benefit.

1C. Demonstrate a ≥22% reduction in Alzheimer's risk with a specific focus on hormone therapy, while ensuring that treatment does not increase the risk of reproductive cancers like breast cancer.

Evaluate the efficacy of hormone therapy against Alzheimer's pathology biomarkers, chiefly Aβ deposition, in clinically normal women. Anti-amyloid therapy trials of FDA-approved drugs Aducanumab and Lecanemab have demonstrated that reductions of 16-22% in Aβ burden in Aβ-

positive regions, measured as PET standardized uptake value ratios (SUVRs), correspond to meaningful Aβ clearance in patients with Alzheimer's or Mild Cognitive Impairment (MCI)[38,39]. On the other hand, in the A4 study of individuals with preclinical Alzheimer's, ages 65-85, the Solanezumab group exhibited a smaller Aβ increase compared to placebo, with a mean difference of ~2.4% SUVR, which did not reach significance[40].

We are interested in studies that adapt successful thresholds to hormonal interventions. A ≥22% SUVR difference aligns with the upper range of Aβ burden reductions observed in FDA-approved anti-amyloid therapy trials, making it a meaningful and realistic benchmark. Achieving this threshold in asymptomatic, at-risk women would serve as proof of concept that hormonal therapies can reduce Alzheimer's pathology before cognitive decline manifests.

We are particularly interested in the impact of existing hormone therapies, such as menopause hormone therapy, oral contraceptives, and endocrine therapies for reproductive cancers, on Alzheimer's pathology biomarkers. We will also entertain novel non-hormonal therapies, such as neurokinin 3 receptor antagonists, for which either compelling data or strong scientific evidence of efficacy exist. Testing of hormone therapies in combination with the neuroendocrine measures included in 1A is desirable, as is stratification by genetic risk factors for Alzheimer's, such as family history or Apolipoprotein E (APOE) epsilon 4 allele. Importantly, studies must also assess the impact of hormone therapy on the risk of reproductive cancers (breast, ovaries, endometrium) to ensure overall safety and feasibility.

Additionally, having visibility into the health status of the brain before intervention is important to tailor treatments effectively, identify individuals most likely to benefit, and avoid potential harm in those with advanced or irreversible pathology.

- Demonstrate **reductions in Aβ burden of ≥22%** (i) pre- vs. post-intervention, and/or (ii) between treated and untreated groups. Methods may include, but are not limited to, PET imaging, CSF and blood-based biomarkers. ***Studies must be sufficiently powered (≥80%) to detect group differences of 22% or greater at a significance level of α=0.05, given the sample size.***
- Perform mediation analyses showing direct and indirect pathways linking hormone therapy to reductions in Alzheimer's pathology within the identified window of opportunity.
- Leverage biomarkers, imaging techniques, and clinical assessments to evaluate brain health before vs. after hormone-based interventions, aligning treatment with individual risk profiles and therapeutic windows. To optimize therapeutic outcomes, studies should ***identify neuropathological predictors of positive versus negative effects of hormone therapy on Alzheimer's risk, at P<0.05***. These should include, but not be limited to: (i) clinical and AD biomarker measures of Alzheimer's risk and (ii) brain health status evaluated using clinically relevant techniques such as MRI (T1- and T2-weighted imaging, FLAIR).

Thrust Area 2. Develop high-affinity *in vivo* brain imaging probes for neuroendocrine function in clinical populations and their potential therapeutic application.

Thrust 2 focuses on developing high-affinity neuroendocrine imaging tests. These imaging tools are key to enabling precise quantification of neurohormonal receptor density and/or function in the brain. In addition, we are interested in the potential for these probes to have therapeutic application.

2A. Develop neuroendocrine imaging probes with high specificity and affinity to assess *in vivo* brain hormone receptor activity in clinical populations.

Imaging hormone neuroreceptor density is a missing link to firmly establishing neuroendocrine aging's role in Alzheimer's risk. Currently, PET is the only imaging technique that allows imaging of *in vivo* neuroreceptor activity. Established PET tracers can serve as benchmarks for developing high-affinity brain hormone imaging probes. Key parameters for clinical use include binding affinity (e.g., specific binding to target receptors), binding potential (BPnd, e.g. signal-to-noise ratio), and effective dose equivalent (ED, e.g. amount of radioactivity to the patient).

In Alzheimer's research, [18F] Flutemetamol, [18F]Florbetapir and [18F]Florbetaben are FDA-approved ligands for Aβ imaging. While their signal-to-noise ratios are modest (~2:1), the combination of high binding affinity and low ED (~2-5 mSv) has enabled their widespread diagnostic use. The most utilized neuroreceptor tracers, [11C]Raclopride and [18F]Fallypride, both dopamine D2/D3 receptor ligands, have moderate to high binding affinity (Kd 3-10 nM), and a high BPnd (>4:1), ensuring reliable signal detection for receptor quantification. These tracers collectively set standards for specificity, safety, and clinical utility, providing a roadmap for the development of high-affinity neuroendocrine imaging probes.

Currently, 18F-Fluoroestradiol (FES) is the only commercially available estrogen receptor (ER) ligand. It is primarily used in oncology, demonstrating favorable pharmacokinetics, including high binding affinity (Kd ~0.5 nM) and low ED (<5 mSv). In terms of brain studies, while the 18F-FES signal in the pituitary gland is high and specific[41,42], its low signal-to-noise ratio in other brain regions highlights the need for improved tracer designs.

We are particularly interested in PET neuroreceptor ligands targeting estrogen receptors (ERs) and secondarily, progesterone receptors (PR). Tracers that measure estrogen and progesterone synthesis or activity may be of interest. Development of non-invasive imaging modalities is also a strong focus. While preclinical studies are intrinsic steps in tracer development, our preference is for work that is directly on the development of imaging probes designed for ***human brain imaging***.

Key parameters to consider include[43], but are not limited to:

- Receptor occupancy (>80%), to ensure sufficient engagement for both diagnostic imaging and therapeutic efficacy.
- Small molecular weight (MW < 500 Daltons) and balanced lipophilicity (2 < LogP < 4) to ensure adequate permeability across the blood-brain barrier.
- Compounds with favorable pharmacokinetic properties, such as optimal binding affinity (Kd<6 nM, reflecting robust and specific receptor targeting).

- Binding potential (Bmax/Kd) or target-to-background ratios ≥3:1, ensuring a strong signal for accurate quantification.
- Low ED (<5 mSv) to ensure patient safety and compliance with regulatory standards.

2B. Provide proof-of-concept evidence that the neuroendocrine imaging probes developed in Aim 2A have therapeutic potential.

Demonstrate that the imaging probes developed for neuroendocrine receptor imaging can also function as therapies by guiding precision dosing while minimizing side effects. This dual-use approach leverages the diagnostic and therapeutic potential of the same molecular scaffold and is the backbone of the field of *theranostics*.

Imaging probes offer unparalleled precision in targeting and quantifying neuroendocrine receptor activity *in vivo*. By using PET imaging, these probes can map receptor distributions, determine receptor saturation thresholds, and identify dose-response relationships in real time. Once optimal dosing is established, the radioactive isotope can ideally be removed, and the molecule repurposed at physiologic concentrations as a therapeutic agent. This strategy minimizes off-target effects and maximizes receptor-specific therapeutic efficacy.

While this dual application has not been used for the brain, it is in use for some tumors. For example, the somatostatin analogue Lutetium-177 DOTATATE (Lu-177 DOTATATE) is used in peptide receptor radionuclide therapy (PRRT) to treat neuroendocrine tumors by delivering targeted radiation to cancer cells expressing somatostatin receptors. When labeled with Gallium-68, Ga-68 DOTATATE serves as a PET ligand to image somatostatin receptor-positive tumors, aiding in diagnosis and treatment planning.

This dual-use strategy maximizes the value of neuroendocrine imaging probes by integrating diagnostic and therapeutic functions for brain health. By directly linking receptor engagement to therapeutic efficacy, such probes could accelerate the development of precision medicines for Alzheimer's prevention and neuroprotection in at-risk women.

- Use PET imaging to determine receptor occupancy at various doses of the imaging probe and map dose-response curves to identify the **minimal dose required for receptor saturation (>80% occupancy) while avoiding saturation-induced side effects.**
- After establishing dosing parameters, provide proof-of-concept evidence that the ligand can transition from an imaging probe to a therapeutic agent by removing the radioactive isotope and scaling the dose to physiologic or therapeutic concentrations. Preclinical validation would ideally include testing for dose-response effects, including reduction of side effects, and establishment of safety margins. Proof-of-concept animal studies testing the efficacy of the ligands in altering Alzheimer's biomarkers or cognition are welcome.

Thrust Area 3. Development of predictive models that halve Alzheimer's risk in women and their deployment as risk assessment tools for clinical use.

Biomarker screening accuracy and outreach (percentage of the at-risk population reached) must combine to identify at least 330 million women globally who are both at risk and reachable for treatment. Additionally, the impact of preventative efforts depends on treatment efficacy and frequency.

Because of the combined effect, preference will be given to screening techniques with outreach that are cost-effective and scalable, and to effective interventions that require minimal infrastructure, are easy to administer, and can be widely accessible across diverse populations. These tools should be designed to provide accurate and scalable methods to identify and monitor at-risk individuals, enabling early intervention and more precise targeting of preventative treatments to reduce Alzheimer's risk globally.

3A. Demonstrate a ≥50% reduction in population-attributable risk (PAR) in female Alzheimer's cases by modeling neuroendocrine risks and therapies.

About 45% of Alzheimer's risk is linked to 14 modifiable factors, including diabetes, hearing loss, hypertension, physical inactivity, smoking, and midlife depression[4,5]. Targeting these modifiable risks could substantially alleviate the global burden of the disease. However, current population-attributable risk (PAR) estimates fail to consider variations in risk profiles between men and women. Female-specific factors, such as neuroendocrine influences (e.g., age at menopause and hormone therapy use), remain unaccounted for in these models. We also emphasize the need for taking diversity into account. Hispanic and Black women are at a higher risk of developing dementia and may experience more severe menopausal symptoms compared to White women. Incorporating diverse populations will ensure that findings are applicable across different groups and help address health disparities.

- Develop female-specific PAR models that **identify ≥50% of the preventable fraction of Alzheimer's cases in women**. For instance, incorporating neuroendocrine biomarkers, reproductive history, and hormone receptor data could significantly enhance the predictive power of these models. Approaches may include, but are not limited to, analysis of biobanks, health insurance databases, and both national and global health repositories. Integration of meta-analytic data is also welcome. Computational methods such as predictive modeling and machine learning algorithms are preferred.
- Resulting models should have **predictive value sufficient to inform clinical decisions, with the goal of reducing Alzheimer's lifetime risk by 50% or greater in women**, e.g. aiming to decrease risk from an estimated 1 in 5 to 1 in 10.

3B. Integrate findings across thrusts into a practical tool for assessing Alzheimer's risk in women.

This approach aims to develop a clinical framework for predicting an individual's baseline risk using accessible and cost-effective measures to maximize outreach. Established clinical tools for cardiovascular disease (CVD) and breast cancer serve as benchmarks for informing the development of Alzheimer's risk models. These tools exemplify how integrating diverse clinical,

biomarker, and lifestyle data can create actionable risk assessments to guide prevention and treatment strategies. Examples include the Framingham Risk Score calculator, which estimates 10-year CVD disease risk, or the Gail Model, which estimates 5-year and lifetime invasive cancer risk. These tools integrate diverse data into accessible, scalable models that inform personalized preventive care.

Effective tools demonstrate high sensitivity (correctly identifying those at risk) and specificity (avoiding false positives), ensuring clinical utility and actionable outcomes, with **overall accuracy >80%**. By adopting these principles, Alzheimer's risk tools can emulate the success of CVD and breast cancer models in empowering precision prevention for women.

- Develop predictive models and causal measures of Alzheimer's risk reduction in women, integrating neuroendocrine biomarkers with genetic, medical, and lifestyle indicators. Models must combine neuroendocrine biomarkers (e.g., hormone levels, receptor density, number of hot flashes, overall menopause symptom severity) with genetic (e.g., family history, APOE genotype), medical (e.g., comorbidities, menopause history), and lifestyle factors (e.g., physical activity, diet), and leverage results from Thrusts 1A-C and 3A. We are especially interested in models that identify surrogate markers or predictors that are validated based on gold-standard brain measures, but that can approximate neuroendocrine biomarkers without relying on the brain measures. For example, algorithms that use a combination of blood-based hormone levels, reproductive history, and genetic data to estimate Alzheimer's risk.
- Integrate findings into a comprehensive, practical tool for assessing Alzheimer's risk in women. Tools should **provide >80% accuracy for predicting baseline Alzheimer's disease risk** in women, similar to existing cardiovascular and breast cancer models.

Identification of the best combination of clinical and biomarker indicators to predict Alzheimer's risk, would support implementation in clinical settings, focusing on non-invasive and cost-effective measures. They should be intuitive, transparent, and based on evidence-backed parameters to promote widespread adoption in clinical settings.

Program Director.

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