Bio-Hermes: A Biomarker Study Initiated By The Global Alzheimer's Platform Foundation® To Compare Select Digital and Blood-Based Biomarkers With Clinical Diagnosis and Amyloid-β PET Images

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The Global Alzheimer's Platform Foundation® (GAP) is developing a program intended to validate blood-based biomarkers in a diverse population with Alzheimer's disease (AD).

Leverage Emerging Science	Emerging science suggests phospho-tau 217 (P-tau217) may have a role as a clinically relevant biomarker for diagnosing AD [1,2].
Improve Burden of Treatment	Blood-based biomarkers have the potential to substantially improve patient cost and burden in treating the disease.
Validate Blood-Based Biomarkers	GAP is developing a program intended to characterize the accuracy of multiple blood-based biomarkers in a diverse population and inform the role of these biomarkers in clinical care.

Current Limitations

- Diagnosis of AD in clinical trials primarily relies on cerebrospinal fluid (CSF) and brain imaging techniques (eg, Positron Emission Tomography or PET). These procedures are expensive, take time to analyze, and result in high-cost screen fails.
- The accuracy of plasma P-tau181 compared with plasma P-tau217 or P-tau231 in diagnosing AD has not been investigated in a single trial.
- Biomarkers have not been characterized in a diverse and unselected population.

Bio-Hermes Solutions

- GAP's biomarker trial (Bio-Hermes) will determine blood-based biomarker levels of amyloid-β (Aβ) 42/40, P-tau181/217/231, and neurofilament light (NfL) compared with centrally read and quantitated amyloid PET scans.
- GAP will explore if racial differences related to specificity and sensitivity of blood-based biomarkers exist by enrolling a minimum of 200 participants self-identifying as underrepresented minority populations.

Potential Impacts

- Patients are likely to prefer blood-based biomarker tests over CSF and PET diagnostic tests (lower cost and minimally invasive).
- A trial-ready and trial-willing cohort of potential therapeutic trial participants may lower screen fail rates and accelerate enrollment.

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Background

A time-consuming challenge in AD clinical trials is finding qualified participants. CSF sampling has been used to quantify tau and Aβ proteins in patients suspected to have AD. Numerous clinical trials have also employed PET scans to detect tau and Aβ proteins. These procedures are expensive, take time to analyze, and result in high-cost screen fails. Recent studies suggest P-tau217 may have a role as a clinically relevant biomarker for diagnosing AD [1,2]. However, more research is needed to directly compare blood-based biomarkers in a single trial and in a diverse and unselected population.

The Global Alzheimer's Platform Foundation® (GAP) is developing a program intended to compare leading AD biomarkers across a large population. Because African Americans and other underrepresented populations are at increased risk of developing AD [3] and race-associated differences in CSF tau markers may lead to misdiagnosis [4], GAP will also explore if racial differences related to specificity and sensitivity of blood-based biomarkers exist. Consistent with GAP's mission, broad access to deidentified data on patient characteristics, biological specimens, and biomarker data will enhance the field's ability to reduce the duration, cost, and variability of AD clinical trials as well as inform care of unselected patients in clinical practice.

Objectives

The objectives of the GAP Bio-Hermes Program are as follows:

- Develop a cost-effective and more accurate prescreening process using blood-based biomarkers to generate substantially large numbers of participants qualified and willing to participate in AD therapeutic clinical trials.
- Investigate if racial variability exists in the utilization of these blood-based biomarkers in identifying appropriate trial candidates.
- Provide well-characterized and enriched set of samples to inform the role of these biomarkers in clinical care.

References

1. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA*. Published online July 28, 2020. doi:10.1001/jama.2020.12134
2. Janelidze S, Stomrud E, Smith R, et al. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. *Nat Commun*. 2020;11(1):1683. Published 2020 Apr 3. doi:10.1038/s41467-020-15436-0
3. Steenland K, Goldstein FC, Levey A, Wharton W. A meta-analysis of Alzheimer's disease incidence and prevalence comparing African-Americans and caucasians. *J Alzheimers Dis*. 2015;50(1):71-6.
4. Howell JC, Watts KD, MW Parker, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther*. 2017;9(88):3-10. doi:10.1186/s13195-017-0315-1

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Methods

GAP will obtain a common set of cognitive tests, clinical diagnostic information, and selective blood-based biomarkers from each trial participant.

- A cognitive battery will be used to assess cognitive profiles relative to biomarker status and will consist of Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Rey Auditory Verbal Learning Test (RAVLT), Functional Activities Questionnaire (FAQ), and Digital Voice Analysis/AI-Natural Language Processing.
- Biospecimens will be collected to determine blood-based biomarker levels of Aβ 42/40, P-tau181/217/231, and NfL. Genetic status will be collected for apolipoprotein E (APOE), ABCA7, and ICM1.

The individual biomarker results will be compared with centrally read and quantitated amyloid PET scans, all encompassed within the biomarker clinical trial (Bio-Hermes). 1000 participants will be enrolled across 10 sites in GAP's network of leading clinical trial sites (GAP-Net). A minimum of 200 participants will be individuals self-identifying as underrepresented minority populations. The trial will endeavor to recruit participants that fall into 3 clinical diagnostic classifications: Cognitively Normal, Mild Cognitive Impairment, and Mild Alzheimer's Disease. The trial consists of 3 visits (screening/biospecimen collection, imaging, and Aβ PET disclosure) in a 90-day period.

The trial-ready cohort of participants developed during the Bio-Hermes trial will be available to GAP-Net sites participating in the program. Biological samples collected during the course of the trial will be deidentified and stored for future research.

Results

Enrollment in Bio-Hermes is expected to begin in late 2020 with a 1-year enrollment period.

The financial impact of utilizing blood biomarkers rather than PET imaging to select qualified participants for AD clinical trials will be evaluated.

Conclusions

GAP's Bio-Hermes Program may provide several benefits.

- Well-characterized samples and data that will facilitate the testing of blood-based and digital biomarkers as indicators of AD pathology, thereby enhancing screening of potential participants for AD clinical trials.
- The trial's commitment to enroll a substantial group (minimum of 200 of 1000) of historically underrepresented minority populations will further enrich the data provided by Bio-Hermes.
- A trial-ready and trial-willing cohort of potential therapeutic trial participants may lower screen fail rates and accelerate enrollment.

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