![Alzheimer's Drug Discovery Foundation logo]

ADVANCING CUTTING-EDGE ALZHEIMER'S BIOMARKERS AND NOVEL DIAGNOSTIC TECHNOLOGIES

A PROGRESS REPORT FROM THE ALZHEIMER'S DRUG DISCOVERY FOUNDATION

DxA DIAGNOSTICS ACCELERATOR

SUPPORT DIAGNOSTIC RESEARCH FOR ALZHEIMER'S

CONTENTS

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THE DIAGNOSTICS ACCELERATOR ANSWERS A CRITICAL RESEARCH NEED

Imagine the day when a simple blood test can definitively diagnose Alzheimer's disease just as easily as it does high cholesterol, diabetes or an infection. Or the day when a simple scan can tell you about the presence of proteins associated with Alzheimer's disease in the eye or the health of the blood vessels in your brain. That is the bold vision of the Alzheimer's Drug Discovery Foundation's *Diagnostics Accelerator (DxA)*—to replace today's expensive and invasive PET imaging and spinal fluid taps with new gold standard methods for early, non-invasive and affordable diagnosis of Alzheimer's and related dementias. Since its 2018 launch, the DxA has made awards to researchers across the world who are working toward this goal.

The DxA strategically invests in promising research for Alzheimer's diagnosis using blood tests, eye scans, genetic tests and digital biomarkers.

SUPPORT AND COMMITMENT FROM PROMINENT PHILANTHROPISTS DRIVES THE DXA

Bill Gates and ADDF Co-Founder Leonard A. Lauder made foundational investments to create the *Diagnostics Accelerator*—a partnership to identify, support and bring to market simple, reliable, inexpensive and scalable diagnostic tests for Alzheimer's. Other prominent philanthropists quickly joined, including Jeff Bezos, MacKenzie Scott, the Dolby family, the Charles and Helen Schwab Foundation, The Association for Frontotemporal Degeneration and more.

Achieving the mission of the ADDF—rapid acceleration of drug development to prevent, treat and cure Alzheimer's—begins with the ability to accurately diagnose individuals as early in the disease as possible. That means finding biomarkers—measurable characteristics of the body that highly correlate with Alzheimer's disease. Biomarkers are essential in all medical specialties. For example, blood pressure and gene expression profiling are biomarkers that diagnose hypertension and different types of lymphoma, respectively.

The DxA strategically invests in promising research for Alzheimer's diagnosis using blood tests, eye scans, genetic tests (together called peripheral biomarkers) and digital biomarkers. Digital biomarkers connect our growing knowledge of early psychological and behavioral changes, including changes in the ability to complete routine daily activities that may signal Alzheimer's with rapidly evolving technology and data science. This allows researchers to capture and analyze larger amounts of data than ever before

DxA Proposal Review: Key Criteria

TECHNICAL AND REGULATORY	BUSINESS
■ Novelty of hypothesis	■ Ability to conduct/complete the research
■ Relevance of biological rationale and strength of supporting data	■ Experience of key team members and company leadership
■ Match between study design and hypothesis being tested	■ Investors, finanacial health, positioning relative to competitors
■ Research team experience	■ Company viability
■ Regulatory pathway (as applicable)	■ Timeline reasonability and commercialization plan

to find common patterns and develop diagnostic algorithms.

A review board composed of individuals with scientific, regulatory and business expertise diligently evaluates proposals for funding against specific criteria (see box above). The DxA review board provides feedback to applicants. For funded

applicants, support goes beyond funding, providing or connecting researchers to additional important expertise. For example, the DxA has engaged industry veterans with expertise in diagnostic method development to work directly with funded applicants, and experts in commercial strategy to ensure DxA funds can truly help funded investigators thrive.

NEW BIOMARKERS ARE ESSENTIAL TO PROGRESS AGAINST ALZHEIMER'S DISEASE

Biomarkers play a crucial role in all aspects of medicine — from research to disease diagnosis and treatment decisions. Overall, there are relatively few biomarkers for Alzheimer's disease. These include PET imaging tests that detect amyloid and tau in the brain, and spinal taps that test for the same proteins in the fluid that surrounds the brain and spinal cord. These biomarker tests are expensive and invasive, limiting their use in routine patient care, but they play an important role in clinical trials.

Amyvid™, an amyloid PET imaging test developed with early support from the ADDF, has been used in drug trials that target amyloid protein to ensure patients who have amyloid plaques in the brain are enrolled. Biogen's and Eisai's clinical trial of aducanumab and Eli Lilly's trial of donanemab are among the first to use this biomarker to successfully enroll the right patients into their trials.

Alzheimer's is a highly complex disease with multiple underlying causes, including misfolded

Validating biomarkers for many different causes of Alzheimer's will help clinicians provide personalized treatments.

proteins, inflammation, vascular dysfunction, genetic mutations and other malfunctions often connected to the biology of aging. Alzheimer's research has moved beyond drugs that target amyloid protein, necessitating development of a variety of biomarkers that can measure the impact of these contributors to the disease.

Validating biomarkers for many different causes of Alzheimer's will help clinicians provide personalized treatments—precisely targeting and treating the underlying causes unique to each patient, an approach already in use for patients with certain types of cancer.

> The ADDF's pioneering interest in biomarker research led to another breakthrough in 2020 when C2N Diagnostics launched the first ever commercially available biomarker blood test for Alzheimer's disease. PrecivityAD™, which measures amyloid levels in blood samples, is widely available to help physicians with early Alzheimer's detection and diagnosis. This test can correctly identify brain amyloid plaque status in 86% of patients. The ADDF provided $2.8 million in funding to C2N over the last decade.

BIOMARKERS CAN HELP ADVANCE NEW DRUGS AND GET THEM TO THE RIGHT PATIENTS

PRECISION
Trials
Ensuring the right patients are enrolled in the right trials

PRECISION
Outcomes
Showing that the drug being tested is working in its intended way

PRECISION
Treatments
Helping doctors find the right prescription for the individual patient once treatments are available

SHORT- AND LONG-TERM BENEFITS OF ALZHEIMER'S BIOMARKERS

- **Easily screen and diagnose** patients

- **Monitor and stage** disease progression

- **Measure response** to treatment

- **Improve the rigor and minimize cost** of clinical trials through targeted patient recruitment and assessment of outcomes

- **Guide precision treatment** individualized to each patient

FOSTERING BOLD IDEAS AND COLLABORATION

The *Diagnostics Accelerator* has made awards globally to dozens of world-class investigators and counting. The awards are made to both academic institutions and biotech companies and, so far, include research into blood, eye and digital biomarkers for early detection of Alzheimer's and related dementias.

The DxA employs a rigorous, strategic approach in its funding for peripheral and digital biomarker research, seeking out a range of research on inexpensive and minimally invasive biomarkers that reflect the pathological heterogeneity of Alzheimer's (see box on page 7). In other words, the DxA strategy recognizes that every potential drug target for this complex disease needs corresponding biomarkers. To that end, the DxA has funded research studying molecular and epigenetic markers, as well as neuroinflammation. When successful, these approaches will facilitate and streamline recruitment of appropriate participants in clinical trials and enable tracking of their disease progression and the effect of trial interventions.

Strategies that guide DxA awards align with the overall ADDF mission. We take a venture philanthropy approach in assessing applications because it is the best path to success for the ADDF, individual scientific investigators and, ultimately, people living with and at risk of Alzheimer's and their loved ones. Our venture philanthropy model seeks out high-risk/high-reward programs from academia and biotechnology companies worldwide, with any returns reinvested into the next great idea.

FOLLOWING A LONG-STANDING ADDF PHILOSOPHY — DXA INVESTS IN A DIVERSITY OF BIOMARKERS

Aging is the leading risk factor for Alzheimer's disease, which is why the ADDF has long focused on understanding and investing in research aimed at the many underlying mechanisms of aging. The answer to Alzheimer's likely lies in a combination treatment approach that addresses multiple pathways.

"Our work will enable better stratification of patients in clinical trials, and eventually, we hope, be useful in day-to-day clinical practice. That's why we're working now on ways to make testing as widely available in clinical labs as possible."

Thomas Montine, M.D., Ph.D.
Stanford University, Stanford, CA

Thomas Montine, M.D., Ph.D. at Stanford University and his team have identified three biomarkers associated with neuroinflammation in a cohort of Alzheimer's patients. They are currently evaluating these biomarkers in a larger cohort and more importantly, looking at ways to transfer the research method they use in their academic laboratory into a method that can be widely used in global clinical labs.

Judith Steen, Ph.D. at Boston Children's Hospital and her team are focused on tau protein. They recently showed for the first time that pathological tau—which causes tangles in the brain—is altered as we age and more so by disease. These studies may indicate that it will take different types of drugs to target tau effectively, and therefore different types of biomarkers to assess tau activity, and the effect of these drugs, as Alzheimer's disease progresses.

Kaj Blennow, M.D., Ph.D. at the University of Gothenburg and his team reported data in 2020 showing a new blood test they developed for a form of tau called p-tau181 may be the most sensitive tau test yet. It detected a steady rise in p-tau181 in blood that distinguished people with Alzheimer's from healthy individuals and those with other forms of dementia.

"In addition to adapting the International Shopping List Test to a mobile environment, we're also validating it for use among diverse populations. This will support earlier diagnosis, better access to clinical trials, and eventually better access to treatment for everyone."

Chris Edgar, Ph.D.
Cogstate Ltd, Australia

BIOMARKER TARGETS BY TEST TYPE*

BLOOD
Aβ40, Aβ42, tau species and fragments, NfL, exosome surface proteins, high molecular weight kininogen, aptamer-based approaches

EYE
beta amyloid, novel combinations of retinal biomarkers of neurodegeneration and vascular dysfunction

DIGITAL
expanding access to existing tests through mobile platforms, using technology to track and gather large data pools on early disease changes that can be analyzed and used to create diagnostic algorithms, new digital tools to measure apathy

GENETIC
cfRNA, microRNAs, mitochondrial DNA, RNA

*as of April 2021

Cecilia Lee, M.D. at the University of Washington and her team are evaluating multiple eye-related biomarkers using non-invasive technology and applying an algorithm to understand the contribution of each biomarker to early diagnosis of Alzheimer's disease or their ability to predict Alzheimer's development.

FOSTERING BOLD IDEAS AND COLLABORATION (cont'd)

LEVERAGING NEW TECHNOLOGIES AND BIG DATA TO DEVELOP DIGITAL BIOMARKERS

Traditional biomarkers are true to the two parts of the word— biological measurements that mark or indicate changes in health. Digital biomarkers are also objective and quantifiable, but they measure psychological and behavioral changes that relate to biological changes. DxA is investing in research that capitalizes on rapidly evolving digital technologies, data science and advances in artificial intelligence to develop digital biomarkers.

DxA digital investments focus on both novel approaches and adaptation of already validated assessments for digital use. For example, **Chris Edgar, Ph.D. of Cogstate Ltd** and his colleagues are adapting and validating the International Shopping List Test to be completed on either a smartphone or tablet at home. This will enable regular remote monitoring of individuals who may be unwilling or unable to travel to regular doctor appointments. They are also validating the test for use among diverse populations to support better access to clinical trials and eventually, better access to treatment for everyone.

Jennifer Myers, Ph.D. and her colleagues at Neurotrack Technologies, Inc. have developed a comprehensive digital platform that can be launched on smartphones, tablets or computers to assess cognitive health in aging populations. They are currently assessing its ability to distinguish between people with normal function, mild cognitive impairments and Alzheimer's disease.

Ramit Ravona-Springer, M.D. and her team at Sheba Medical Center are developing a virtual reality tool to objectively measure apathy, which affects many patients with dementia.

With newer technologies becoming more widely available every day, the DxA digital biomarker investments continue to expand. Other digital programs under active consideration include everything from abnormal brain rhythms during sleep using non-invasive earbuds, to overall sleep patterns,

> *"The Diagnostics Accelerator has been essential in helping us move toward our long-term goal of providing the Alzheimer's community with precise and easy-to-use diagnostic blood tests."*
>
> **Henrik Zetterberg, M.D., Ph.D.**
> *University of Gothenburg, Sweden*

physical activity levels and how people interact with their smartphones.

BOLSTERING ADDITIONAL INVESTMENTS THROUGH THOROUGH ASSESSMENT AND VETTING OF RESEARCH PROJECTS

As part of its due diligence process, DxA scientists perform a thorough assessment of each research program and its likelihood of succeeding in the near term (see box on page 3). This assessment can bolster important investment decisions from others.

At the 2020 *Clinical Trials on Alzheimer's Disease* conference, **Henrik Zetterberg, M.D., Ph.D., University of Gothenburg**, discussed the importance of the *Diagnostics Accelerator* support to his research into a blood test to detect beta amyloid protein fragments Aβ40 and Aβ42. Detection of these proteins in the blood is highly correlated with the presence and progression of Alzheimer's disease. This blood test is one of the most advanced in development. DxA scientific diligence and funding were catalytic for Dr. Zetterberg's commercial partners at Roche Diagnostics, unlocking additional internal funding to continue the development of this blood test.

Through a collaboration with Cogstate, global pharmaceutical company Eisai secured development

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and exclusive commercialization rights for the company's cognitive function tests.

DxA support can also help scientists advance their research and produce meaningful results that help them gain support from influential non-commercial partners. **DiamiR**, which is developing a diagnostic blood test to measure microRNAs associated with two integral components of Alzheimer's—neuron degeneration and inflammation—recently received a grant of $3.36 million from the National Institute on Aging to complete development of the test.

SUPPORTING SYNERGISTIC COLLABORATIONS TO ACCELERATE BIOMARKER RESEARCH

The DxA values meaningful collaborations between world-class researchers, clinical experts who provide direct patient care and have a deep understanding of the daily challenges of the disease, and diagnostics companies that understand regulatory pathways. These collaborations create synergies that can advance the field more quickly.

A research team led by **Eliav Shaked, M.Sc. of Retispec** in Toronto is testing the ability of an eye scanning technology called hyperspectral imaging to detect small changes in beta amyloid and other Alzheimer's biomarkers in the retina. Retispec is collaborating with the Toronto Memory Program, Canada's largest clinical trial site, and Sheba Medical

"The goals of our unique retinal scanner are to facilitate early diagnosis, improve the lives of patients and save the healthcare system money and resources. It will also make Alzheimer's clinical trials more efficient."

Eliav Shaked, M.Sc.
RetiSpec, Canada

Center in Israel to validate this novel test.

THE POWER OF DxA PARTNERSHIPS: PROVIDING ADDITIONAL SUPPORT FOR FUNDED INVESTIGATORS AND OTHERS

DxA partnerships demonstrate our commitment to opening new opportunities for our funded investigators and supporting the entire research enterprise to accelerate new discoveries.

In July of 2020, DxA announced a partnership with Eisai, Janssen, Roche and Shionogi to form one of the largest **biobank sharing programs** of blood and cerebrospinal fluid (CSF) specimens from Alzheimer's

patients who participated in earlier clinical trials. Clinical validation of biomarkers requires well characterized patient samples across multiple cohorts. This partnership makes these samples available to DxA-funded researchers.

DxA also announced a partnership with Sage Bionetworks in 2020 to establish an online repository for open data sharing among digital biomarker researchers who receive DxA awards. The **custom Digital Biomarker Development Platform** will store data from funded research and facilitate benchmarking, analysis and sharing of the results among the scientific community.

In November of 2020 DxA leadership published an online commentary calling for and laying out a plan for creating a comprehensive, harmonized, **open-access speech and language repository** to accelerate research into speech and language biomarkers. Technology is making it easier than ever to collect large amounts of speech and language data, but alone, researchers cannot take full advantage of the opportunities these digital technologies afford. A unified approach to collecting, analyzing and sharing data, the latter in **partnership with the Alzheimer's Disease Data Initiative**, will help create algorithms that can predict who will go on to develop Alzheimer's.

BUILDING ON SUCCESS, LOOKING TO THE FUTURE

The *Diagnostics Accelerator* has made important contributions to the search for diagnostic biomarkers for Alzheimer's disease and related dementias. It has done this through both direct support of world-class researchers and through key collaborations that provide additional support to funded investigators and the entire research community.

DXA IS CONTINUALLY ASSESSING AND FUNDING INNOVATIVE RESEARCH ALIGNED WITH ITS FUNDING PRIORITIES

To ensure that the DxA is continually funding innovative, leading-edge research, we accept proposals on a rolling basis. We encourage researchers working on blood and other peripheral markers, including saliva and urine, to apply.[1] We also encourage applications for research into digital biomarkers using a variety of platforms such as wearable devices, mobile/tablet apps, smart home systems, virtual and augmented reality platforms and desktop/web apps. The proposed platform should have the potential to be easily deployed at scale.

Researchers are encouraged to visit the *Diagnostics Accelerator* home page to learn more about our funding priorities and submission of proposals.

[1] *CSF and neuroimaging biomarkers will not be considered.*

PERIPHERAL BIOMARKER TARGETS

Proposed approaches are evaluated on biological plausibility linking the biomarker to disease pathophysiology. Examples of target areas include, but are not limited to:

- Vascular injury and blood-brain barrier integrity
- Neuroinflammation
- Neuroprotection and neurodegeneration

- Biomarkers of interest for frontotemporal degeneration
- Protein misfolding
- Synaptic integrity and/or activity
- Mitochondria and metabolic function

DIGITAL BIOMARKER SYMPTOM DOMAINS

Proposed approaches are evaluated based on the existing evidence around the biologic link of the symptom domain to disease and how measuring it will improve current patient screening or monitoring methods. Symptom domains of interest include, but are not limited to:

- Cognition
- Activities of daily living
- Motor function
- Sensory acuity

- Affect
- Sleep patterns and characteristics
- Pain assessment
- Autonomic nervous function

WORLD-CLASS INVESTIGATORS

BIOMARKERS

EYE

BLOOD

DIGITAL

1. LEYLA ANDERSON, NEUROVISION IMAGING & BLAINE ROBERTS, EMORY UNIVERSITY

Measuring levels of proteins and metabolites in patient samples from one of the largest ever studies of Alzheimer's disease

2. RHODA AU, BOSTON UNIVERSITY

Digital profiles to identify changes in cognition, walking, balance, mood and depression that could signal early stage Alzheimer's

3. MARTA BARRACHINA, ADMIT THERAPEUTICS

Measuring intracellular dysfunction by examining mitochondrial DNA

4. KAJ BLENNOW, UNIVERSITY OF GOTHENBURG

Measuring brain-specific tau

5. YUVAL DOR, HEBREW UNIVERSITY

Measuring a form of DNA that is only released when brain cells die

6. CHRIS EDGAR, COGSTATE LTD

Validating a mobile app to extend access to the International Shopping List Test among diverse populations

7. FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH

Assessment of 6 top performing blood tests to measure amyloid in plasma

8. LAURA IBANEZ, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Measuring levels of 25 cell-free RNA molecules

9. RUSSELL LEBOVITZ, AMPRION, INC.

Validating a technology to detect soluble protein aggregates

10. TOM MACGILLIVRAY, UNIVERSITY OF EDINBURGH

Eye scan analyzing a novel combination of retinal biomarkers that signal brain neurodegeneration

11. THOMAS MONTINE, STANFORD UNIVERSITY

Blood test to measure three biomarkers associated with Alzheimer's disease and neuroinflammation

12. SALIHA MOUSSAOUI, AMONETA DIAGNOSTICS

Measuring two species of RNA that may signal mild cognitive impairment due to early Alzheimer's

13. AMBER MURRAY, BIOLOGICAL DYNAMICS

Using a new system to capture and analyze proteins related to Alzheimer's on the surface of exosomes

List of investigators as of April 30, 2021.

14. JENNIFER MYERS, NEUROTRACK

Using remote devices to allow for almost continuous tracking of eye, voice and touch changes

15. RODNEY PEARLMAN, BLUEFIELD PROJECT TO CURE FTD

Measuring NfL levels in people who carry an inherited form of frontotemporal degeneration

16. GREGORY PENNER, NEONEURO S.A.S.

Using small synthetic DNA sequences called aptamers to measure amyloid levels

17. RAMIT RAVONA-SPRINGER, SHEBA MEDICAL CENTER

Virtual reality tool to objectively measure apathy, which often affects patients with Alzheimer's

18. ELIAV SHAKED, RETISPEC

Hyperspectral imaging to detect beta amyloid and other Alzheimer's biomarkers in the retina

19. JUDITH STEEN, BOSTON CHILDREN'S HOSPITAL

Measuring tau and TDP-43

20. BRUNO STEINKRAUS, HUMMINGBIRD DIAGNOSTICS

Measuring combinatorial signatures of microRNAs

21. SIDNEY STRICKLAND AND ERIN NORRIS, ROCKEFELLER UNIVERSITY

Measuring high molecular weight kininogen, which is associated with brain blood vessel impairment

22. SAMUIL UMANKSY, DIAMIR BIOSCIENCES

Measuring brain- and inflammation-associated microRNAs

23. PETER VAN WIJNGAARDEN, CENTRE FOR EYE RESEARCH AUSTRALIA

Eye scan with a special camera designed to detect amyloid in the retina

24. GUOLIANG XING, CHINESE UNIVERSITY OF HONG KONG

Using remote devices to collect data on activities of daily living

25. HENRIK ZETTERBERG, UNIVERSITY OF GOTHENBURG

Measuring beta amyloid protein fragments $A\beta_{40}$ and $A\beta_{42}$

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