NeuroQuest

**Developing biomarkers for early diagnosis
of Alzheimer's Disease**

NOVEMBER 2015

our mission: developing a screening test

NeuroQuest is developing a simple blood screening test for populations aged 60 and older. The test will serve as a surrogate to PET scans indicating formation of brain amyloid plaques in the pre-clinical stage of Alzheimer's.

challenge: identifying a screening tool for the general population

Alzheimer's

2015

Alzheimer's

2015   2020   2025
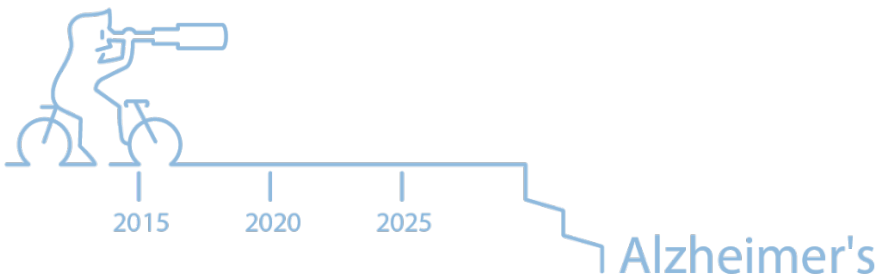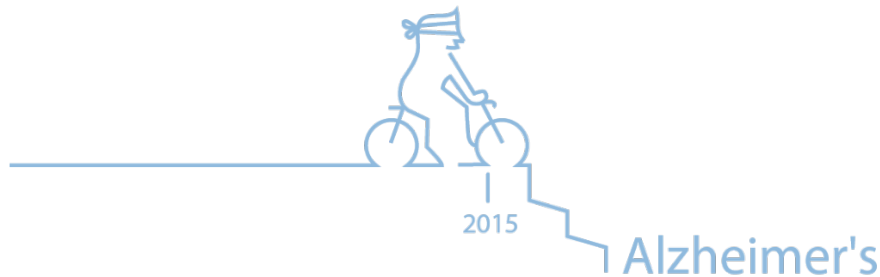
At NeuroQuest, we believe you need to know where you are starting from to find the end to a disease like Alzheimer's.

Our mission: Develop a viable screening tool for the general population that is accurate, affordable, and accessible – a test that gives patients and their families time to fight, and plan for the future.
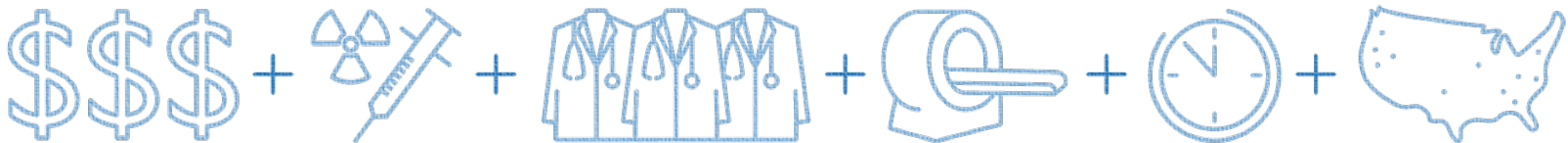
PET scans – inaccessible technology

Drawback of current technologies

Reliable and relatively inexpensive disease-predictive markers are urgently needed before there is a loss of brain function.

PET imaging for beta-amyloid plaques, represent the "gold standard" for confirmatory diagnosis of beta-amyloid in the brain years before clinical signs of Alzheimer's.

While PET imaging techniques do make it easier for neurologists to spot a person affected by early-stage Alzheimer's, PET scans alone have their drawbacks:

- They require highly specialized and trained manpower.
- Turnover time is long.
- Availability is limited.
- Testing involves risk of injecting radiolabeled substance.

our product – blood test kit

Our Unique Selling Proposition

NeuroQuest offers a unique screening test with high specificity to the expensive confirmatory PET imaging test.

The test is based on the following:

- Measures peripheral changes in myeloid cell populations
- Inexpensive and simple
- Readily available
- Quick turnover

To date, no objective, accurate, cost-effective and practical tool for early diagnosing Alzheimer's exists. The unmet need and the size of the market are fueling research and investment in companies searching for a way to diagnose neurodegenerative diseases in general and Alzheimer's in particular.

The primary tests used to diagnose Alzheimer's are blood tests (used to exclude other potential diseases, not to diagnose Alzheimer's), psychological examination, MRI and PET scans, and CSF tests – which all have limited use due to their costs, limitations, and drawbacks.

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the scope of Alzheimer's Disease

Worldwide, nearly 44 million people have Alzheimer's or a related dementia.

In the United States, 5.3 million people are living with Alzheimer's. Unless a cure is found, that number will rise to 16 million by 2050.
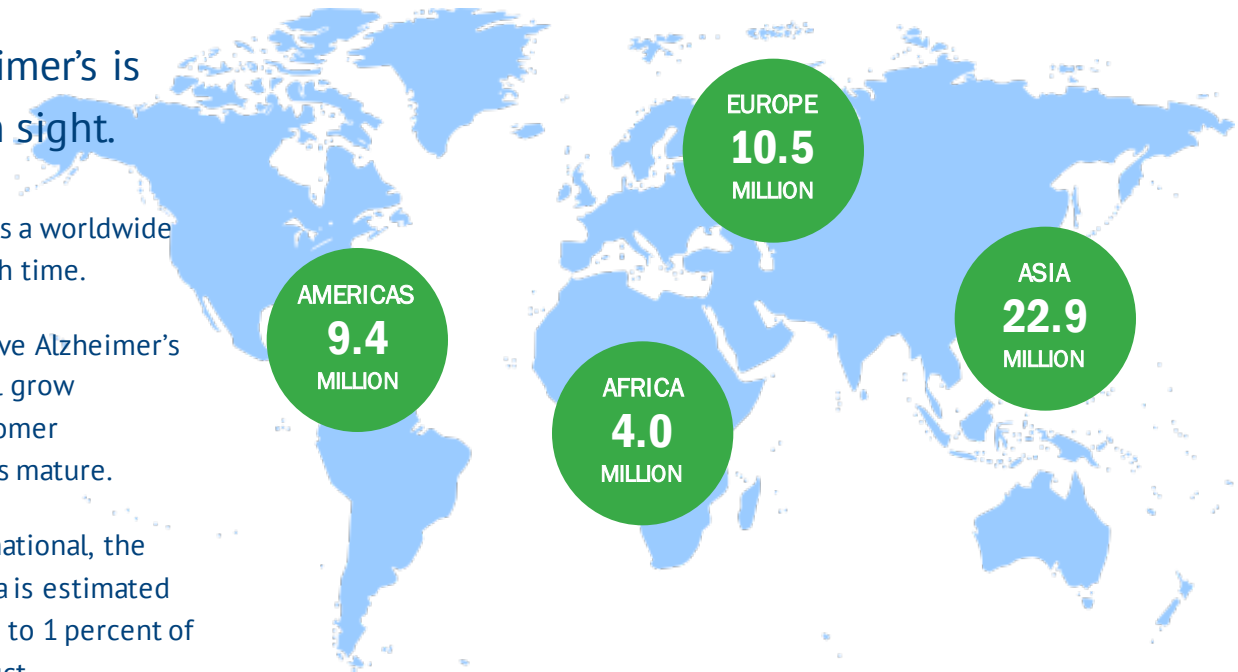
Alzheimer's – spiraling out of control

The global impact of Alzheimer's is staggering – with no end in sight.

The facts are self-evident: Alzheimer's is a worldwide problem that is only growing larger with time.

Worldwide, nearly 47 million people have Alzheimer's or a related dementia. That number will grow exponentially as the American baby boomer generation and other worldwide cohorts mature.

According to Alzheimer's Disease International, the global cost of Alzheimer's and dementia is estimated to be at $818 billion. That is equivalent to 1 percent of the entire world's gross domestic product.

EUROPE
10.5
MILLION

ASIA
22.9
MILLION

AMERICAS
9.4
MILLION

AFRICA
4.0
MILLION

the human and financial impact

The costs of Alzheimer's are real, impactful and growing.

- One in eight Americans will develop Alzheimer's

- The cost of caring for Alzheimer's patients in the United States is estimated to be $226 billion in 2015.

- In 2014, caregivers of people with Alzheimer's and other dementias provided an estimated 17.9 billion hours of informal (unpaid) assistance, valued at $217.7 billion.

- Medicare and Medicaid will pay $154 billion in 2015 for people with Alzheimer's and other dementias.

- By 2050, these costs could rise as high as $1.1 trillion in the United States alone.

1 in 8

Americans over age 65 have Alzheimer's disease.

Nearly half of all Americans over age 85 have Alzheimer's or another form of dementia.

defining a starting point to end Alzheimer's

Many organizations are trying to end Alzheimer's. We can only hope they will find success. We believe, however, to find the end, you have to know where you're starting from. Finding that starting point is our goal.

the three stages of Alzheimer's

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association proposed revised criteria and guidelines for diagnosing Alzheimer's.

Those criteria incorporate biomarkers for early diagnosis and established a newly defined stage of AD referred to as pre-clinical AD. Today, the three recognized stages of Alzheimer's disease are:

- **Pre-clinical** – Individuals who do not yet have outward symptoms of Alzheimer's but do have some of the early brain changes of Alzheimer's (as detected by brain imaging and other biomarker tests).

- **Mild cognitive impairment (MCI)** – Those who have very mild symptoms but can still perform everyday tasks.

- **Dementia** – Those whose symptoms are more pronounced and interfere with carrying out everyday tasks.
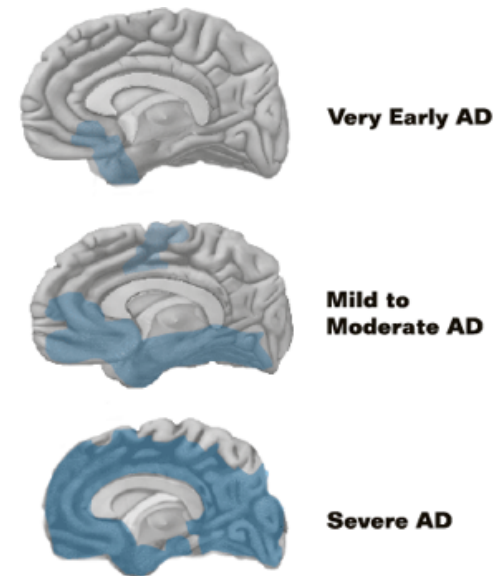
As Alzheimer's disease progresses, neurofibrillary tangles spread throughout the brain (as shown in blue). Plaques also spread throughout the brain, starting in the neocortex. By the final stage, damage is widespread and brain tissue has shrunk significantly.

section 02

challenge: identifying pre-clinical Alzheimer's

Currently, the primary tests used to diagnose Alzheimer's have limited use due to their costs, limitations, and reliability.

In the pre-clinical stage, individuals have measurable changes in the brain, cerebrospinal fluid and/or blood (biomarkers) that indicate the earliest signs of disease, but they have not yet developed noticeable symptoms such as memory loss.

This pre-clinical stage reflects current thinking that Alzheimer's-related brain changes may begin 20 years or more before symptoms occur.
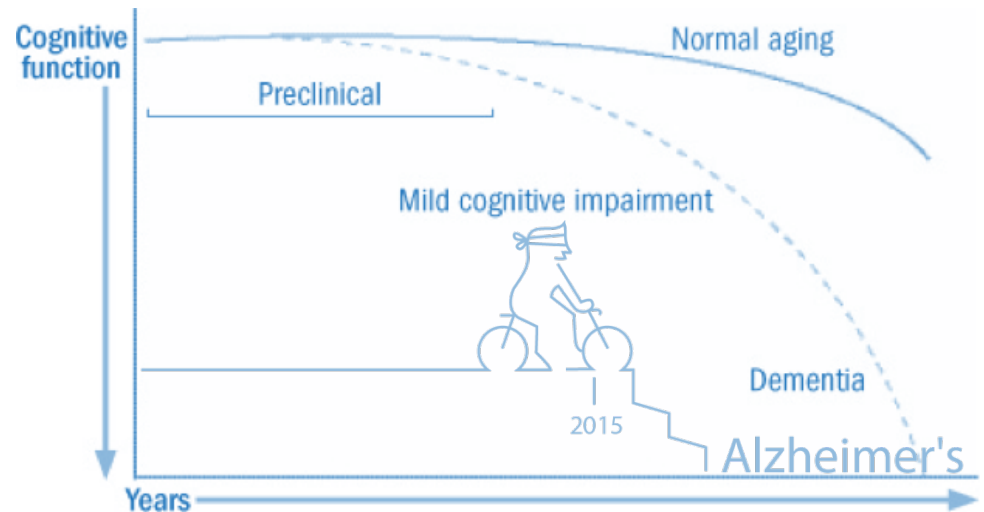
section 02

challenge: identifying a screening tool for the general population

The revised definition of Alzheimer's is: **Dementia with beta-amyloid plaques in the brain.**

Based on that definition, PET imaging for beta-amyloid plaques, represent the gold standard for confirmatory diagnosis of beta-amyloid. However, due to their high cost and limited availability, they are a poor screening tool for the general population at risk for Alzheimer's.

Early detection by a simple and affordable blood test will be an essential tool for early intervention by dramatically reducing the cost of subjective cognitive tests and batteries of non-specific diagnostics, bridging the gap to access and reimbursement for PET imaging, allowing patients earlier access to therapies under development, and providing pharma companies with early stage patients with whom new therapies show the most promise.

section 02

solution: identifying pre-clinical Alzheimer's with biomarkers

Biomarker tests will be essential to identify which individuals are in these early stages and should receive disease-modifying treatment.

Many researchers believe that future treatments to slow or stop the progression of Alzheimer's disease and preserve brain function will be most effective when administered during the pre-clinical and MCI stages of the disease.

NeuroQuest's diagnostic, blood-based biomarker test is designed to be a highly translatable, relatively high-throughput and cost-effective surrogate blood test for PET-amyloid status diagnosis.

To be effective, any biomarker must not only detect a fundamental biological process in the disease, but be validated in an adequately powered study with neuropathologically confirmed cases. The ideal biomarker should have sensitivity greater than 80 percent for detecting disease and specificity also greater than 80 percent. Biomarker categories identified by the 2011 criteria and guidelines:

- Biomarkers showing the level of beta-amyloid accumulation in the brain

- Biomarkers showing that neurons in the brain are injured or actually degenerating.

the value proposition – what's in it for everyone?

Pharmaceutical companies

- Facilitates new drug development, clinical trials
- Reduces drug development costs and time
- Increases drug revenues with earlier, better diagnosis

Healthcare providers

- Reduces cost and impact of inappropriate, ineffective drug use
- Saves costs of repeated, multiple tests
- Helps improve patient care and reduces ongoing care costs

Clinicians

- Provides easy to administer, accurate diagnostic tool
- Helps improve patient care and strengthens the diagnostic arsenal
- Offers additional test revenue opportunity

Patients and their families

- Reduces cost, time and impact of tests and delayed diagnosis
- Enables financial and care planning
- Facilitates appropriate use and monitoring of medication

> **"The scientific community and the FDA believe it is critical to identify and study patients with very early Alzheimer's disease before there is too much irreversible injury to the brain. It is in this population that most researchers believe new drugs have the best chance of providing meaningful benefit to patients."**
>
> *- Russell Katz, MD, Director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research*

section 02

the science behind NeuroQuest

Renowned researchers backed by substantive, peer-reviewed literature and licensed intellectual property combine to form the foundation of NeuroQuest's blood-based diagnostic test for Alzheimer's.

the three keys to our science

Intellectual property

Our technology uses immune cells from peripheral blood as biomarkers to screen for pre-clinical signs of Alzheimer's. NeuroQuest licensed the intellectual property covering this technology from Yeda (the Weizmann Institute Technology Transfer Arm), and holds exclusive global rights for its development and commercialization.

Award-winning research

NeuroQuest has developed a unique blood-based diagnostic test for Alzheimer's based on the specific response of the immune system. This test is based on the research work of Prof. Michal Schwartz, Chair of Neuroimmunology at the Weizmann Institute and head of NeuroQuest's Scientific Advisory Board. Her research group has pioneered work in the field of neuroimmunology for more than a decade.

Clinical trial data

A recent exploratory study with the Australian Imaging, Biomarker, and Lifestyle Flagship Study of Aging (AIBL) demonstrated the ASSAY has more than 90 percent sensitivity and 80 percent specificity in diagnosis of beta-amyloid positive. This surpasses the minimum 80 percent sensitivity and specificity criteria for ideal biomarkers as defined by the U.S. Alzheimer's Association.

our science – the deep dive

Immunosuppressive cell populations in Alzheimer's are key players in the inability of the body to mount a systemic immune response needed for mitigation of disease pathology

The Schwartz group suggested that recruitment of inflammation-resolving immune cells to the diseased brain is needed for arresting neuroinflammation, and is dependent on the activity of the choroid plexus (CP), which may dysfunction under brain pathologies.

The Schwartz group's research showed that in brain aging the CP displays an IFN type I (IFN-I) response signature, including a dramatic rise of IFN-β expression. Collaborating with the group of Tony Wyss-Coray (Stanford University, California). They also showed that by rejuvenating the blood composition of aged mice, CP activity is amendable for restoration and the effect was associated to partial restoration of cognitive function.

Current research shows, CP gateway activity for allowing immune cells to traffic the CNS is suppressed along disease progression. The findings show that circulating immune cell populations, with immunosuppressive functions, dramatically affect CP function.

Specifically, systemic Foxp3+CD4+ Treg-mediated immunosuppression as a negative player in AD pathology, acting at least in part by interfering with IFN-γ-dependent activation of the CP, which is needed for orchestrating recruitment of inflammation-resolving leukocytes to the CNS.

Using genetic conditional ablation of Foxp3+ Treg cells in AD-Tg mice, and various pharmacological approaches to target these cells, Schwartz' findings show that activation of the CP for supporting leukocyte trafficking to the CNS is followed by accumulation of immunoregulatory cells at cerebral sites of Aβ pathology, plaque clearance, and mitigation of cognitive decline.

These findings point to immunosuppressive cell populations in Alzheimer's as key players in the inability to mount a systemic immune response needed for mitigation of disease pathology.

section 03

our science – a look inside the brain
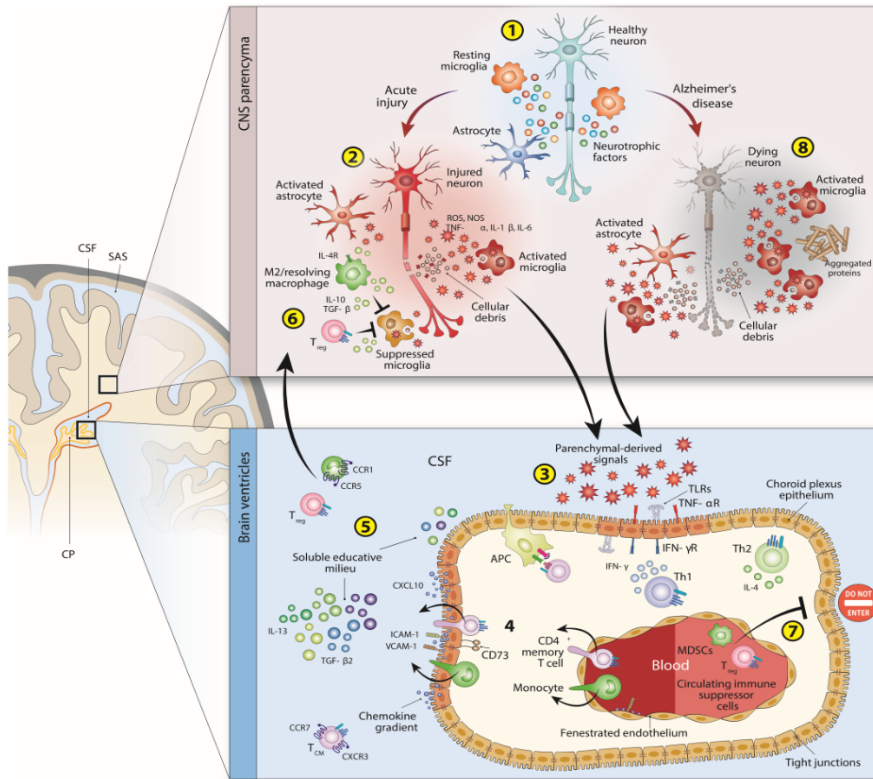
In chronic neurodegenerative diseases in general, and Alzheimer's in particular, circulating immune suppressor cells (such as Tregs and myeloid-derived suppressor cells) maintain peripheral immune suppression and inhibit immune cell trafficking to the central nervous system.

current clinical data

Clinical studies performed in collaboration with the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Aging (AIBL) have substantiated our approach.

AIBL pilot study: results

Two NeuroQuest biomarker models surpassed the 80 percent threshold for sensitivity and specificity as defined by the U.S. Alzheimer's Association

The trial included 69 subjects including 49 healthy controls, 15 MCI and 5 Alzheimer's subjects. It was designed to evaluate the correlation between blood immune cell characteristics (associated with Prof. Schwartz' theory) and Alzheimer's diagnosis, and to assess the degree to which NeuroQuest biomarkers could accurately identify subjects who show presence or absence of amyloid in their brain. Our results were validated by PET imaging.

Model 1

91%

80%

Sensitivity

Specificity

88%

94%

Model 2

section 04
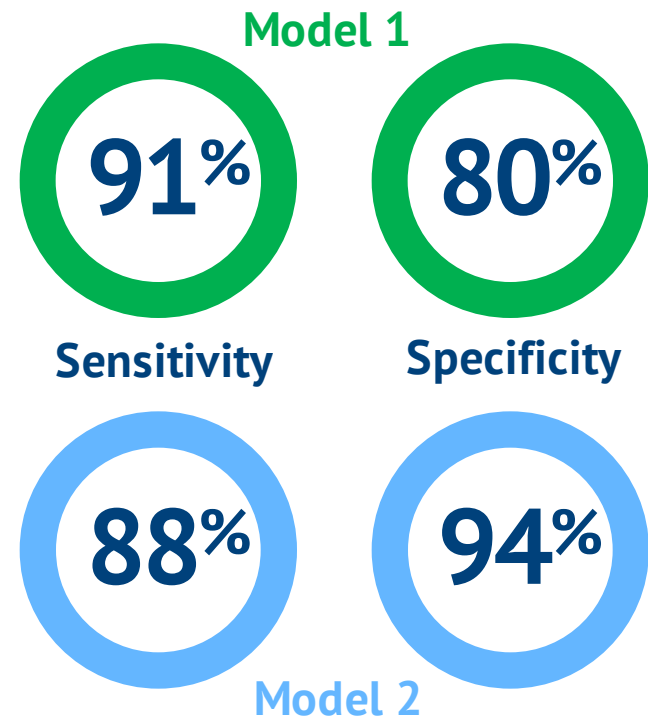
AIBL pilot study: conclusions

Results substantiate Prof. Schwartz' theory of "protective autoimmunity"

The blood-based immune biomarkers in Alzheimer's disease developed by NeuroQuest show specific immune cell clusters which can distinguish between amyloid negative versus positive subjects with high level of sensitivity and specificity.

The NeuroQuest diagnostic blood test can serve as a screening test with high specificity to expensive, confirmatory PET imaging. The test is highly translatable; relatively high-throughput and a cost-effective surrogate for PET-amyloid diagnosis.

Model 1

91%

80%

Sensitivity

Specificity

88%

94%

Model 2

section 04
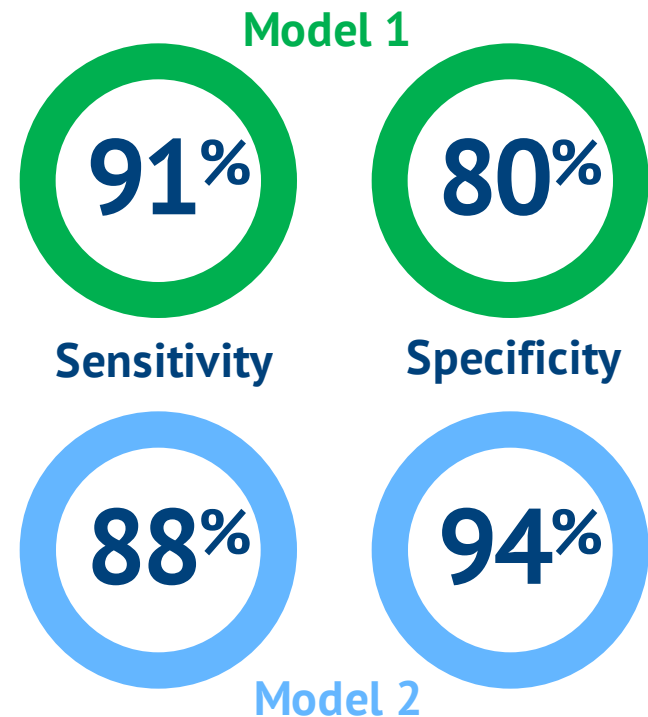
our business model

By 2019, short-run revenues will primarily come from commercialization of laboratory developed tests and co-development agreements with strategic partners. Medium- to long-term revenue can be expected from direct kit sales and royalties.

three-tiered approach to revenue

Commercialization of lab tests through CLIA

The company intends to commercialize its tests in the U.S. market through classification as laboratory developed tests (LDTs) approved through a laboratory certified under The Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Strategic research collaborations

We will focus on entering into research and development agreements with pharmaceutical companies to enable development of companion diagnostics as "research only" diagnostic tests to:

- Help define appropriate therapy regimens.
- Pre-select individuals for inclusion in clinical trials.

Direct kit sales and royalties from partnering

In later stages, NeuroQuest intends to sell complete test kits to expand its activity to non-CLIA labs. Additional revenues will be generated from development agreements with imaging companies who have expressed a need for blood-based tests as a tool to select patients for costly PET imaging.

section 05

the competitive landscape

To date, no objective, accurate, cost-effective and practical tool for early diagnosing Alzheimer's exists. The unmet need and size of the market are fueling research and investment.

diagnostic tests lacking competitive advantage

Tests being used to help diagnose Alzheimer's all have limited utility due to cost, limitations, and/or reliability.

Cerebrospinal Fluid (CSF). CSF samples and protein assays are currently one of the best tools in the diagnosis of Alzheimer's. However, obtaining a CSF sample involves an invasive procedure (a lumbar puncture) which most patients find mentally troubling and physically painful.

Magneto encephalography (MEG). These huge and costly instruments are scarcely available in the United States and Japan, let alone globally. They are great research tools but they will likely never become commonplace in clinical practice in their present form.

Magnetic Resonance Imaging (MRI). This relatively commonplace technology measures the anatomy of the brain and is useful to insure there is no gross brain tumor or evidence of other injury. It cannot, however, diagnose Alzheimer's, merely rule out other causes.

Electroencephalogram (EEG). EEG attempts to "make movies" of the brain to capture dynamics, as opposed to static snapshots. But, the vast majority of peer reviewed EEG literature is constrained by the brain being in a "resting state" for up to 20 minutes. Unfortunately, the brain can't rest for 20 minutes, let alone even 1 minute, as it wanders off and thinks about other activities. Given this, we believe attempts to use EEG diagnostically will continue to fall short.

PET diagnostics as complementing vs. competing technology

Positron Emission Tomography (PET). These large multi-million dollar cameras record radioactive tracers injected into the blood stream to image brain energy consumption, allowing the visualization of plaques in live patients. While considered the "gold-standard" in Alzheimer's diagnostic testing, PET imagery is not a viable mainstream tool given its cost and accessibility.

Due to the high cost of PET scans for beta-amyloid, their commercial success will depend on good biomarkers. **This is why PET imaging and some MRI diagnostics are seen as a complement to biomarkers rather than competitive technologies.**
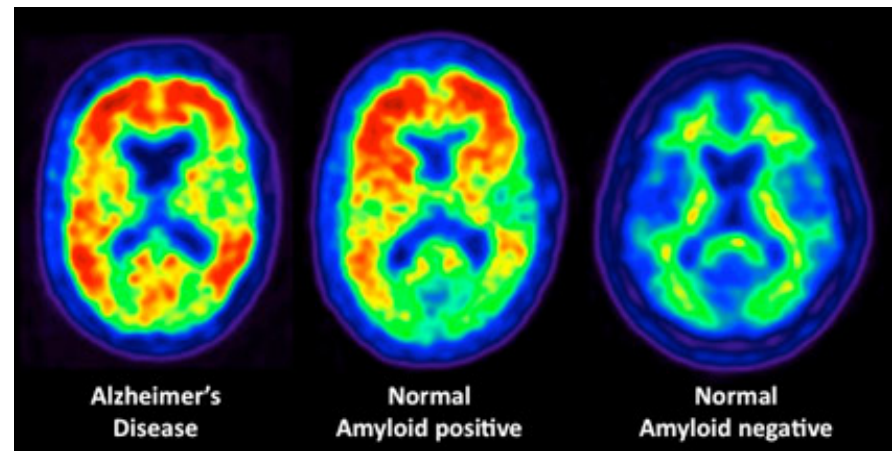
PET imaging for beta-amyloid plaques, represents the best technology for confirmatory diagnosis of beta-amyloid and by definition, Alzheimer's.

the challenge of blood-based diagnostic tests for Alzheimer's

Blood is the ultimate biological specimen; but the brain is ultimately protected from its intrusion.

The Alzheimer's research community would love to find blood-based biomarkers and thus diagnostics of the brain. However, the blood-brain barrier provides a protective barrier from internal insult within a host.

To date, no one has compellingly shown that a peripheral measure in the blood is truly diagnostic of what is going on within the privileged compartment of the brain and the central nervous system. This makes discovery of blood-based biomarkers for Alzheimer's difficult at best.

The necessary verification and validation of any of those markers by several groups has not yet occurred and additional research will be required to demonstrate that the peripheral measure in the blood is meaningfully reflective of the brain and CNS.

A number of tests to diagnose Alzheimer's are in development. None offer definitive results; many use algorithms to examine proteins or biomarkers and determine which do, or do not, point to the disease. As these are top down approaches, many have ended unsuccessfully upon testing of their algorithms on larger independent samples.

section 06

others are researching a blood-based diagnostic test

We regularly monitor the business landscape for potentially competitive technologies.

At painfully regular intervals, we see news headlines about a new diagnostic test for Alzheimer's that is cost-effective, easy to administer and non-invasive. Unfortunately for the Alzheimer's community there is often little substance, study or science behind these stories, only disappointment.

Currently, NeuroQuest is one of only a handful of companies who are making progress with the development of a blood-based diagnostic test – and the <u>only</u> one using the protective autoimmunity approach.

11 Are researching a diagnostic blood test

3 Are actively conducting clinical research

1 Using protective autoimmunity approach as a diagnostic tool

section 06

meet the NeuroQuest team

Founded under the framework of the Israel Chief Scientist's technology incubators program and Trendlines Medical - Misgav Venture Accelerator, NeuroQuest has assembled a team with extensive experience in management, R&D, clinical trials, and business development.

covered: from research to management

Dan Touitou

Chief Executive Officer

- Former CEO of Juvenis Ltd. Israel
- Former founder and CEO of Novel Therapeutic Technologies (NTT)
- Executive MBA with honors from Derby University, England and Bsc. Pharmacy with honors from the Hebrew University

Dr. Etai Gilboa

Business Development and Strategic Alliances

- Investor Affairs Manager, Trendlines Group
- Manager, Israel Medical Device Opportunity
- Business Development Director, The Haifa Life Science Park
- Doctorate, Political Science/Public Management

Prof. Michal Schwartz

Inventor, Head of the Advisory Board

- Professor of Neuro-immunology, Weizmann Institute of Science
- Visiting professor at Cedars Sinai Medical Center in California
- Founder, Proneuron
- Ph.D. in Chemical Immunology, B.Sc. In Chemistry, Weizmann Institute

Dr. Jacobo Mintzer

VP of Clinical Affairs

- Director, Roper St. Francis Clinical Biotechnology Research Institute
- MD, Professor, College of Health Professions, Medical University of South Carolina (MUSC), Charleston
- Professor, Neuroscience and Psychiatry, MUSC, Charleston

section 07

key partnerships to accelerate success

Business Partnerships

NeuroQuest has established its U.S. subsidiary and clinical development center at the Roper St. Francis Clinical Biotechnology Research Institute with the assistance and financial support of the South Carolina Research Authority (SCRA).

NeuroQuest licensed from Yeda (the Weizmann Institute Technology Transfer Arm) the intellectual property covering this technology and holds an exclusive global license for its development and commercialization.

Clinical Partnerships

SELAH is a S.C.-based commercial stage, clinical diagnostic company who will manage the commercialization, reimbursement strategy and regulation during the laboratory developed test (LDT) launch phase.

NeuroQuest received strong independent endorsement of its platform with the collaboration of the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Aging (AIBL), one of the largest studies of its kind in Australia and one of the largest in the world.

מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

SCRA

ROPER
St FRANCIS
HEALTHCARE

aibl
The Australian Imaging, Biomarkers and Lifestyle
Flagship Study of Ageing

Selah
GENOMICS
THE POWER OF PRECISION
GENOMICS FOR PERSONALIZED MEDICINE

section 07

financial projections

NeuroQuest estimates its test to be a game-changer with annual sales approaching $225 million by 2023, and multi-billion potential once the kit is available worldwide.

Five-year revenues projections

(ooo)	2019	2020	2021	2022	2023
U.S. Revenues	$875	$2,678	$11,705	$39,795	$60,887
European Revenues	$1,045	$3,197	$13,975	$47,516	$127,223
Asia-Pacific Revenues	0	$1,071	$4,682	$3,247	$8,695
Rest Of World Revenues	0	$5,510	$11,616	$19,032	$28,049
Net Sales	$1,920	$12,456	$41,977	$109,591	$224,853
Total Operating Expenses	$825	$4,982	$15,112	$33,973,000	$69,704
Net Profit (after taxes)	**$605**	**$3,408**	**$12,089**	**$35,507,000**	**$69,614**

Revenues are projected over a five-year period commencing at 2019 with commercialization of the laboratory developed test (LDT) with long-term revenues expected from kit sales. The LDT initial target price is estimated at $300-$350. Kit price is estimated at $150.

section 08

outlays and expenses

NeuroQuest plans to conduct three clinical trials within the next 3 years. We will monitor our cash flow diligently, and develop contingency plans well in advance in accordance to the expected expenses and forecasted funding.

projected cash flow 2016-2018

Category	2016	2017	2018	Total 3 Years
Opening Balance	$200,000	$693,187	$1,776,736	
Collections				
Shareholders	$1,500,000	$3,500,000	$0	**$5,000,000**
Research Grants	$315,000	$1,010,000	$1,875,000	**$3,200,000**
Incoming Cash	$1,815,000	$4,510,000	$1,875,000	**$8,200,000**
R&D[1]	$874,638	$2,857,718	$2,586,960	**$6,319,316**
Sales & Marketing[2]	$99,000	$214,000	$376,550	**$689,550**
G&A[3]	$348,174	$354,733	$401,674	**$1,104,582**
Total Expenditures	**$1,321,813**	**$3,426,451**	**$3,365,184**	**$8,113,448**
Ending Balance	**$693,187**	**$1,776,736**	**$286,552**	

[1] NeuroQuest plans to conduct three clinical trials within the next 3 years.

[2] CLIA Lab will manage commercialization, reimbursement strategy and regulation of the ASSAY during the LDT launch phase.

[3] The majority of the G&A expenses relate to fixed operating costs.

the way ahead

The results of the initial AIBL pilot study will be followed by three validation studies to pave the way for commercialization of the laboratory developed test.

planned validation study milestones

Study location	Scope	Start date	End date
AIBL, Australia	200 subjects	April 2016	March 2017
United States	400 subjects	January 2016	March 2017
Europe	400 subjects	March 2017	September 2018

Clinical validation study objectives:

- Validate the test across a range of patients and confirm the diagnostic accuracy (or clinical validity).
- Provide the required clinical proof to commercialize the test as an LDT in a CLIA laboratory.
- Achieve buy-in from key opinion leaders in the Alzheimer's disease research community necessary to establish our diagnostic blood test as a clinically useful tool to assist the early diagnosis Alzheimer's.
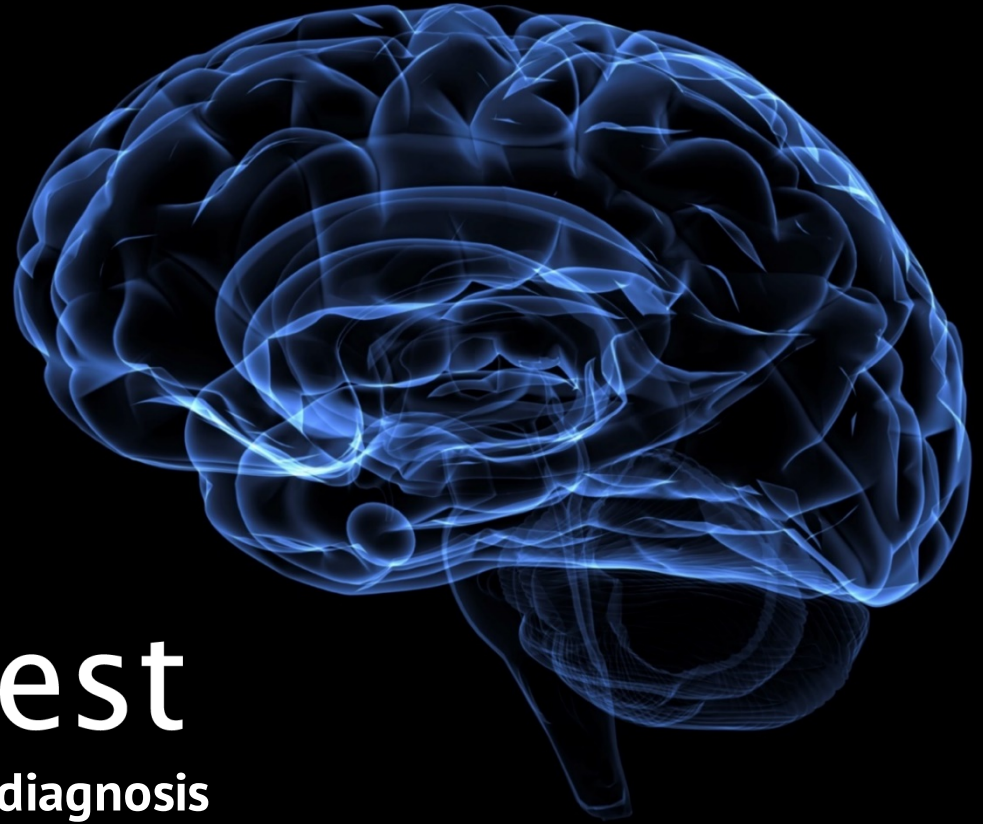
NeuroQuest

Developing biomarkers for early diagnosis of Alzheimer's Disease

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