

## PRODUCT DEVELOPMENT

# DIAGNOSING AD TRIALS

BY ERIN MCCALLISTER, SENIOR EDITOR

A battery of expensive late-stage failures has made it obvious to Alzheimer's disease companies that more and better diagnostics will be essential to get new disease-modifying therapies to patients. But so far, the approaches being tested are too limited in number and too small in scope to provide the necessary tools.

After the first wave of molecules targeting [beta amyloid](#) failed in the clinic, companies began designing studies to enroll patients they believed were more likely to respond based on a confirmed diagnosis of AD and staging methods that suggested their disease had not yet passed the point of no return.

Strategies included enrolling patients believed to have earlier stage disease based on clinical diagnoses involving physicians' assessments of cognition, confirming plaque deposition with PET imaging agents, and enrolling or stratifying patients based on the [apolipoprotein E \(APOE\) epsilon 4 \(APOE4\)](#) risk marker.

Even so, the tally of failures has only continued to grow. Three programs testing agents with three different mechanisms in early stage and/or high-risk populations have failed since September.

Part of the problem is that none of the diagnostic approaches are very sensitive.

The only validated and approved class of diagnostic tools — amyloid PET imaging agents — aren't sufficient to definitively diagnose AD. Amyloid imaging cannot be used to stage AD because after plaques develop, some patients take years to show cognitive worsening, while others may develop full-blown AD within months.

In addition, Phase III trials of agents targeting amyloid that have used PET imaging to measure reductions in plaque burden have not established a correlation between plaques and clinical outcomes such as cognition and memory.

Without better tests, there is no good way to balance treatment and placebo arms to control for differences in risk of progression or to ensure that a trial doesn't enroll

too many patients who progress slowly and could not see a benefit during the time frame of a trial.

"If we don't have access to good diagnostics, we are handicapped in running state-of-the-art clinical trials," said Andrea Pfeifer, CEO of [AC Immune S.A.](#)

AD companies with therapeutic candidates in the clinic agree that a more diverse set of diagnostics are necessary to identify patients before amyloid plaques or tau tangles appear, and to measure disturbances in other causative pathways in AD that could be used to select patients for clinical trials based on the therapeutics' mechanism of action.

They also need tests for disease staging or risk stratification, and surrogate markers that are correlated with or predictive of treatment response.

Companies are also mining academic and collaborative longitudinal studies for biomarkers that could be used as diagnostics or surrogate markers.

But the majority of these studies are probably too small to produce robust surrogate markers. Some of the therapeutic company executives believe the work could be accelerated if companies would share data and biological samples from past and ongoing trials.

### BEYOND AMYLOID

Among at least 14 AD diagnostics in development, five assess tau, a marker associated with more advanced stages of AD, five target beta amyloid, and one targets both (see "AD Diagnostics Pipeline").

The tau tests could be used for disease staging, while most of the beta amyloid tests are intended to diagnose AD.

[ProMIS Neurosciences Inc.](#) is developing a test to measure levels of five beta amyloid epitopes that could be used to identify which patients are best suited for therapies that target specific amyloid epitopes.

But there are at least four disease mechanisms implicated in AD besides aggregation of beta amyloid and tau —



SOURCE: THINKSTOCK

neuroinflammation, vascular pathology, loss of protein homeostasis and mitochondrial dysfunction.

“Alzheimer’s disease has been far too monocular with regards to therapeutic development and with diagnostics,” said Charles Stacey, president and CEO of [Accera Inc.](#) “There are other pathways where things are happening that are critical to the disease.”

“Too much of the funding and focus so far has been on amyloid, but we need to move on from this and explore other areas if there is any hope,” added David Grainger, co-founder and partner at [Medicxi](#), which has three portfolio companies evaluating AD therapeutics that address APOE biology.

Stacey said the lack of biomarkers for therapies with targets outside of the amyloid and tau aggregation pathways can make it difficult to ensure trials are enrolling the appropriate patients. That wasn’t the reason Accera said its [AC-1204](#) missed the primary endpoint in the Phase III NOURISH AD trial last week; the company chalked the miss up to insufficient bioavailability.

Nonetheless, Accera is looking for biomarkers in its trials that could be used to screen or stratify patients. AC-1204 is a powder formulation of caprylic triglyceride, a semisynthetic medium-chain triglyceride (MCT) that induces a mild state of ketosis. The compound is intended to improve metabolism in the brain to restore mitochondrial function in AD.

“We are looking for biomarkers that are more associated with metabolism,” Stacey said, including labeled oxygen and ketone bodies among others.

Few diagnostics companies have stepped up to fill the void, in part because difficulty getting diagnostics reimbursed has led many venture investors to walk away from the space (see “Money Troubles”).

One exception is [Cytox Ltd.](#), which has completed pilot studies of its [mTOR Research Assay](#) to diagnose AD.

The assay screens for 130,000 SNPs, including about 30,000 associated with mTOR signaling in AD. Cytox has found that differentially expressed mTOR pathway genes may regulate key cellular functions linked to AD.

The remaining SNPs are correlated with amyloid deposition and other pathways implicated in AD in genome-wide association studies.

Cytox uses an algorithm to determine an individual’s likelihood of having AD based on the SNP screen.

According to CEO Richard Pither, “The real value of this test in the long term would be to use it in a Phase II trial for a therapeutic targeting amyloid or another pathway in AD, and once you’ve got that data, look at the responders and non-responders to see if we can find signals in our assay and use that to enrich the Phase III trial.”

“We are talking to companies who are working off the amyloid path who are looking to test their drugs in patients who are symptomatic or asymptomatic to maybe help them find subjects that could respond to their therapies,” said Pither.

For instance, he said, the test could be used to screen blood from responders and non-responders in the experimental arms of a trial of an agent that targets neuroinflammation, and the results could be analyzed to see how the SNP signatures differ.

Cytox has raised about £6 million (\$7.4 million) from Spark Northwest Fund for Biomedical, Wren Capital, Rainbow Seed Fund, Seneca Partners and private investors.

Some therapeutics companies working outside of beta amyloid are looking for new biomarkers in specimens obtained from clinical trials that might eventually be turned into companion diagnostics.

[Probiodrug AG](#) is evaluating the effects of its [PQ912](#) on a range of biomarkers in its Phase IIa SAPHIR study in early AD. PQ912 is a [glutaminyl cyclase](#) inhibitor that acts upstream of beta amyloid to reduce the production of neurotoxic pyroglutamate beta amyloid.

Included among the exploratory endpoints in SAPHIR are changes in guanylyl cyclase activity, pyroglutamate beta amyloid, other beta amyloid oligomers, inflammatory biomarkers and [neurogranin](#), which is elevated in AD and is associated with synaptic loss.

“This will help us to understand how these biomarkers relate to our candidate and how that relates to our current understanding of the disease pathology,” said Inge Lues, chief development officer.

SAPHIR is expected to read out next quarter.



## AD DIAGNOSTICS PIPELINE

At least 14 diagnostic tools are in development for Alzheimer's disease. Almost half are intended to diagnose AD and could be used to improve clinical trials of therapeutics by excluding patients with dementia or cognitive impairment from other causes. All but one target beta amyloid (shown in blue). **Cytox Ltd.** and **Thermo Fisher Scientific Inc.** (NYSE:TMO) are developing the MTOR Research Assay, which screens more than 130,000 SNPs, including about 30,000 associated with mTOR signaling in AD.

Eight tests are being developed for disease staging and could be used in drug trials to stratify patients at high risk of disease progression. Among these, one targets beta amyloid and tau, while five target tau exclusively (shown in green). The most advanced

of the tests with a novel target (shown in gold) is **Zinfandel Pharmaceuticals Inc.**'s algorithm that predicts risk based on the presence of apolipoprotein E (APOE) and translocase of outer mitochondrial membrane 40 homolog (TOMM40; TOM40) in the blood, along with age.

At least one company is developing a companion diagnostic: **ProMIS Neurosciences Inc.** (TSX:PMN) is developing a test to measure the amount of different beta amyloid epitopes in CSF. The company will then design anti-beta amyloid candidates that target the most prevalent epitopes. *Sources: BCIQ; Company websites, BioCentury reporting*

COMPANY	PRODUCT	PRECLINICAL	PILOT/PHASE I	PIVOTAL/PHASE III
<b>AD DIAGNOSIS</b>				
ARACLON	Abtest blood test			
ASTRAZENECA / NAVIDEA	NAV4694 $\beta$ -amyloid tracer			
NEUROVISION IMAGING	Retinal imaging test			
CYTOX / THERMO FISHER	MTOR Research Assay			
COGNOPTIX	SAPPHIRE II eye test			
<b>DISEASE STAGING/RISK STRATIFICATION</b>				
SIEMENS / ELI LILLY	Flortaucipir F 18 tau tracer			
ZINFANDEL / TAKEDA	Risk stratification algorithm			
AC IMMUNE / PIRAMAL	Tau-PET tracer			
APRINOIA	APN-1607 tau tracer			
MERCK / CERVEAU	MK-6240 tau tracer for neurofibrillary tangles (NFTs)			
AC IMMUNE	Blood and CSF tests for tau, $\beta$ -amyloid			
AC IMMUNE / BIOGEN	$\alpha$ -synuclein-PET tracer			
APRINOIA	APN-1701 tau tracer			
<b>COMPANION DIAGNOSTIC</b>				
PROMIS	Amorfix A4 aggregated $\beta$ -amyloid assay			

Genentech Inc. and partner AC Immune are testing whether a tau imaging agent could serve as a companion diagnostic for their anti-tau mAb in Phase I. The Roche unit and AC Immune also have anti-beta amyloid mAb crenezumab in Phase III.

Genentech also has RO7105705 in Phase I. Its target is not disclosed.

In addition, Genentech is looking at potential markers for other pathologies that may coexist with amyloid and tau in AD patients, such as TAR DNA binding protein 43 (TDP-43; TARDBP).

“TDP-43 pathology and other signals have been found in autopsy samples, and these can help us to understand the heterogeneity of patients and will help us to inform in the future which therapeutics to target and what outcomes to look at,” said Lee Honigberg, senior scientist and associate director of OMNI Biomarker Development at Genentech.

## IN FOR THE LONG HAUL

Several therapeutics companies are hoping to meet another diagnostic need — the ability to stage disease and stratify trials by risk of progression — by mining data from longitudinal studies.

“Amyloidosis is separated by time and mechanism from that which causes neurodegeneration in AD. So we need better biomarkers for this neurodegeneration that occurs with AD,” said David Knopman, a clinical neurologist at Mayo Clinic.

At least six longitudinal studies are under way (see “Going Long in AD”).

AstraZeneca plc is the industry partner for the Deep and Frequent Phenotyping study in 250 volunteers over age 55 with and without APOE4. The study is assessing traditional imaging markers, CSF markers, changes in gait, MRI and cognition. The measurements are being taken every two months, and the study is expected to report data in 2018.

“This will hopefully give us more of an idea about the early prodromal state and how it progresses from mild to moderate, with some potential diagnostic markers that could be used to define the patient population that will progress more or less quickly,” said Iain Chessell, head of AZ’s neuroscience innovative medicines and early development group.

The pharma has two AD programs in the clinic — AZD3293, a beta-site APP-cleaving enzyme (BACE) inhibitor in Phase III trials for early and mild AD; and MEDI1814, a mAb against beta amyloid 42 that has completed Phase I testing to treat mild to moderate AD. Both are partnered with Eli Lilly and Co.

Biogen Inc. has been mining the Alzheimer’s Disease Neuroimaging Initiative (ADNI) study for biomarkers for staging and risk stratification. ADNI is monitoring imaging, blood and CSF markers, and cognitive function in individuals over age 55 with no signs of cognitive impairment, as well as those with mild memory problems or a diagnosis of mild dementia due to AD.

“If the solution to seeing a therapeutic effect is to treat earlier, we have to develop a road map of biomarkers that help us understand the evolution of Alzheimer’s disease,” said Meena Subramanyam, VP of translational sciences at Biogen.

Biogen has yet to test any of the fluid biomarkers it has identified from ADNI in clinical trials. “We are very much in the exploratory research phase and ensuring that we’re using the right reagents and assays with the right sensitivity first,” she said.

Biogen’s most advanced AD programs are in Phase III, including the anti-beta amyloid mAb aducanumab, and the BACE inhibitor elenbecestat, which is partnered with Eisai Co. Ltd. However, the company also is looking for biomarkers in other pathways.

“We are looking at inflammation, and other neuronal markers so we are not just limited to amyloid beta or CSF beta,” Subramanyam told BioCentury.

## SURROGATE QUEST

Several companies also hope the longitudinal studies will yield markers that could be used as surrogate endpoints of efficacy.

Honigberg said Genentech has used data from ADNI to help identify potential surrogate markers.

“We need large cohorts where you’ve done consistent measurements, whether it’s in the cerebral spinal fluid, blood or imaging, to understand the range and what the correlations are,” he said.

## MONEY TROUBLES

In general, few life sciences VCs want to fund diagnostics companies because product sales are often constrained by unfavorable reimbursement decisions, making it difficult to realize returns on R&D investment.

“It is not an attractive model to invest in because all of the money follows the therapeutics as opposed to the diagnostic,” said David Grainger, co-founder and partner at Medicxi.

In Alzheimer’s disease, he added, the situation is only made worse due to the lack of available therapies. “There’s not a lot of point in having a diagnostic for AD unless you have some treatment you could give to people,” he told BioCentury. Medicxi has three AD therapeutics companies in its portfolio.

BioCentury’s BCIQ database contains only three stand-alone diagnostics companies that have disclosed financings from VCs and have AD tests in the clinic.

AC Immune S.A.’s hybrid model helped it raise a significant amount of capital. The biotech has a pipeline of therapeutics and diagnostics for AD.

Between its founding in 2003 and its IPO last September, the biotech raised \$120 million in VC money. The IPO brought in \$66 million.

“I do believe that this duality of diagnostics and therapy made a substantial impact on our IPO,” said CEO Andrea Pfeifer.

She also thinks stand-alone AD diagnostics companies are worthy investments: “I think value can be added if you have a good diagnostic in AD but no drugs to treat with. We will need both, but the treatment without the diagnostic is not working.”

— ERIN MCCALLISTER

The company is investigating whether changes in fibrillar amyloid could correlate with improved cognition and provide a better readout on the likelihood of Phase III success.

“We know that change in amyloid PET doesn’t necessarily correlate with improved cognition, and that’s the one that’s been explored the most,” Honigberg said. But he noted that finding a good surrogate is a chicken and egg-type problem.

“To truly know that something in Phase II is informative in Phase III, you have to work your way back. So you need a successful Phase III first,” he said. “It doesn’t just have to be a biomarker, it could be a combination of a really sensitive memory test and a biomarker.”

Accera’s Stacey agreed new cognition and memory tests may be needed.

“Even on the clinical endpoints of ADAS-Cog and [CDR] sum of boxes, it could be that there are other more sensitive cognitive batteries that we could be using,” he said. “If we can develop them, it will be more helpful in making sure our trials are more successful.”

**Merck & Co. Inc.** thinks tau could be a good surrogate marker to demonstrate POC before going into larger Phase III studies.

“The initial data we’ve seen show that there is a relationship with the amount of tau you see by PET and cognitive decline,” said Jeffrey Evelhoch, VP of translational biomarkers.

Merck had relied on reductions in CSF beta amyloid in the Phase II portion of the Phase II/III EPOCH study of its BACE inhibitor verubecestat to provide evidence of a biologic effect since there were no

## GOING LONG IN AD

Companies are mining at least six ongoing longitudinal studies in Alzheimer’s disease to identify biomarkers that could aid in diagnosis and prognosis. Some of these studies have been running for over 20 years, with data available upon request to companies. The Deep and Frequent Phenotyping study that began last year is expected to report its first set of data in 2018. The European Prevention of Alzheimer’s Dementia project includes a biomarker identification phase, and a subsequent adaptive study of experimental agents. Data collected annually for all studies below, except the Deep and Frequent Phenotyping study, which is repeating all tests every two months; *Sources: Study websites; ClinicalTrials.gov*

Study name	Start date	Purpose	Population	Data collected	Managing institution	Industry collaborators
Deep and Frequent Phenotyping	2016	Identify biomarkers for patient stratification in clinical trials and markers that could be used as surrogate endpoints	250 subjects over age 55 already participating in Dementias Platform UK, including people at risk of developing AD and those not at risk	PET beta amyloid and tau imaging; structural MRI; cognitive assessment; CSF; changes in gait; experimental peripheral and electrophysiology biomarkers	University of Oxford	<b>AstraZeneca plc</b> (LSE:AZN; NYSE:AZN)
European Prevention of Alzheimer’s Dementia (EPAD) cohort study	2015	Construct a risk stratification algorithm to predict individuals most likely to develop AD who can then be enrolled in an adaptive trial of experimental therapies	6,000 subjects over age 50 at high risk of developing AD	PET imaging; cognitive assessments; serum, CSF, urine and saliva screening for beta amyloid, tau, other biomarkers	University of Edinburgh	15 biopharmas
Alzheimer’s Disease Neuroimaging Initiative (ADNI)	2004	Define biomarkers for use in clinical trials and to determine the best way to measure the treatment effects of AD therapeutics; identify biomarkers to detect predementia AD	2,000 subjects age 55-90, including those with no memory impairment, mild cognitive impairment, and mild Alzheimer’s dementia	FDG-PET; PET beta amyloid and tau imaging; structural MRI; cognitive assessments; CSF measures of beta amyloid and tau	University of California San Francisco (UCSF)	17 biopharmas
Biomarkers of Cognitive Decline Among Normal Individuals: the BIOCARD cohort	1995	Identify biomarkers associated with progression from normal cognitive status to cognitive impairment or dementia	265 middle-aged patients screened annually over 1995-2005 and again from 2009 onward; three-quarters had a close family member with AD	PET beta amyloid and tau imaging; MRI; cognitive testing; CSF and blood specimens	Johns Hopkins University	<b>Eli Lilly and Co.</b> (NYSE:LLY)
Religious Orders Study	1993	Discover what changes in the brain are responsible for memory and movement problems; examine transition from normal functioning of the aging brain to mild cognitive impairment	1,168 nuns, priests and brothers with a mean age of 75.7 years	MRI; cognitive and motor testing; plasma, serum and urine analysis; postmortem tissue analyses and imaging	Rush University Medical Center	None
The Nun Study	1986	Assess what factors in early, mid- and late life increase the risk of AD and other brain diseases	678 nuns age 75 and up	Functional and cognitive assessment; blood samples; postmortem tissue analyses; archived medical history	University of Kentucky, University of Minnesota, School Sisters of Notre Dame	None



**“IF WE DON’T HAVE ACCESS TO GOOD DIAGNOSTICS, WE ARE HANDICAPPED IN RUNNING STATE-OF-THE-ART CLINICAL TRIALS.”**

**ANDREA PFEIFER, AC IMMUNE**

surrogates for clinical benefit. In February, Merck stopped the study for futility.

Evelhoch said CSF beta amyloid turned out not to be sensitive enough to serve as a surrogate for changes in cognition. “There is too much noise between the marker and the clinical measures,” he said.

Merck is hopeful that the tau tracer [MK-6240](#) is more sensitive. In January, the pharma licensed the program to [Cerveau Technologies Inc.](#), which will work with other AD therapeutics companies to test the tracer in future validation studies.

If it correlates with changes in cognition, it could be used as a surrogate marker in future Phase II studies to potentially avoid expensive Phase III blowups.

#### SHARE AND SHARE ALIKE

Some of the executives who spoke to BioCentury think much larger data sets will be necessary to identify prognostic markers, and said data sharing is the best or only approach to accumulating enough.

“There are certain areas where you have to work together to change the field. I would say diagnostics is part of that. We need to get as much information from as many collaborators as possible to find the best surrogate marker, get approval of that marker, and that surrogate could really change the whole field,” Pfeifer told BioCentury.

According to George Vradenburg, chairman of the patient advocacy group [UsAgainstAlzheimer’s](#), ADNI proved too small to yield statistically significant correlations between biomarkers and cognitive decline in the DREAM project.

DREAM was a 2014 collaboration between the Global CEO Initiative on Alzheimer’s Disease and [Sage BioNetworks](#). [UsAgainstAlzheimer’s](#) is one of the organizers of the CEO initiative.

At the time, ADNI had data from only 767 subjects.

“It was inconclusive because you didn’t have a big enough sample size,” Vradenburg told BioCentury.

He believes the data sets need to be orders of magnitude larger, akin to the NIH-funded Health and Retirement Study that is following about 20,000 individuals.

There is a large repository for shared data from AD trials, which was created under the [Critical Path Institute’s](#) Coalition Against Major Diseases initiative.

Companies have contributed data from over 10,000 patients enrolled in the placebo arms of clinical trials to treat AD. However, it does not include information on biomarkers, or tissue and serum samples. It is limited to cognitive measurements, APOE4 genotype status and concomitant medications.

“We can definitely do more,” said Stacey. “It is critical that we make sure we take any lesson we can from these studies.”

“We have pharma companies that are sitting on failed therapeutic assets, but they know that there was a spectrum of responders in that study, so the question is can you pull out the genetic subsets of responders and non-responders with a tool like ours to maybe better plan the next study,” added Cytos’s Pither.

Lilly has shared data from many of its studies of the anti-beta amyloid mAb [solanezumab](#) and its gamma secretase inhibitor [semagacestat](#) with the Alzheimer’s Disease Cooperative Study Group’s Data Analysis and Publication Committee. The committee assumes the responsibility for further analysis and publication of the results.

Genentech has said it will share data and tissue samples obtained from an ongoing Phase II trial of [crenezumab](#) in 300 asymptomatic Columbian individuals who harbor the [PSEN1 E280A](#) autosomal dominant mutation.

The primary endpoint is change in Alzheimer’s prevention initiative (API) composite cognitive test total score, but the study will also measure biomarkers as secondary endpoints, including cerebral fibrillar amyloid levels and regional cerebral metabolic rate of glucose. Data from the five-year study are expected in 2020.

“There will be a way for people to apply for data sharing, so I think that we’re on the right path to sharing,” said Honigberg.

Many companies and academics involved in data sharing collaborations in a variety of indications have told BioCentury the ability to pool and analyze data collected across studies will require standardization of biomarker assays and data. This will be true in AD, as well. For example, changes in beta amyloid plaque formation can be measured differently

across studies depending on the protocols used by the laboratories conducting the assessments.

Ryan Watts, CEO of [Denali Therapeutics Inc.](#), thinks data sharing could help companies understand what type of effect size would be needed to see a change in cognitive decline, but he is skeptical it could provide much more benefit. Denali has a [RIP1 inhibitor](#) in preclinical development for AD.


## “ALZHEIMER’S DISEASE HAS BEEN FAR TOO MONOCULAR WITH REGARDS TO THERAPEUTIC DEVELOPMENT AND WITH DIAGNOSTICS.”

CHARLES STACEY, ACCERA

“Unless we have an incredible longitudinal data set where you had medical reports, cognitive endpoints and access to blood samples, CSF samples and the genetics, it will be challenging,” he said.

He did say Genentech’s Columbian study could be one place to start. “It is a well-defined genetic population with age-matched controls” who do not have the PSEN1 mutations, he said.

Timothy Harris, venture partner at [SV Life Sciences](#), thinks studies like the crenezumab trial in genetically predisposed subgroups of individuals are the best place to start searching for surrogates.

“Those are the populations where you know that because of the mutations, they will get the disease. So you start early on to understand what their brain looks like when they’re younger and then can watch and see what changes as the disease develops,” he told BioCentury. Harris was previously SVP for precision medicine at Biogen and is currently a partner at the [Dementia Discovery Fund](#). 

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### COMPANIES AND INSTITUTIONS MENTIONED

**AC Immune S.A.** (NASDAQ:ACIU), Lausanne, Switzerland  
**Accera Inc.**, Boulder, Colo.  
**Alzheimer’s Disease Cooperative Study Group**, La Jolla, Calif.  
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Biogen Inc.** (NASDAQ:BIIB), Cambridge, Mass.  
**Cerveau Technologies Inc.**, Boston, Mass.  
**Critical Path Institute**, Tucson, Ariz.  
**Cytox Ltd.**, Birmingham, U.K.  
**Denali Therapeutics Inc.**, South San Francisco, Calif.  
**Eisai Co. Ltd.** (Tokyo:4523), Tokyo, Japan  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**Genentech Inc.**, South San Francisco, Calif.  
**Mayo Clinic**, Rochester, Minn.  
**Merck & Co. Inc.** (NYSE:MRK), Kenilworth, N.J.  
**National Institutes for Health**, Bethesda, Md.  
**Probiodrug AG** (Euronext:PBD), Halle/Saale, Germany  
**ProMIS Neurosciences Inc.** (TSX:PMN), Toronto, Ontario  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Sage Bionetworks**, Seattle, Wash.  
**UsAgainstAlzheimer’s**, Chevy Chase, Md.

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