TrialMatch to Speed Recruitment for AD Trials

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

An interactive telephone- and Web-based service now lets Alzheimer's patients, caregivers, and their physicians connect more easily with ongoing clinical trials.

The service—Alzheimer's Association TrialMatch—has the potential to greatly enrich the research into more effective treatment options and the ultimate goal of an Alzheimer's cure, William Thies, Ph.D., chief medical officer of the Alzheimer's Association, said at a press briefing. "Alzheimer's disease is clearly the No. 1 health challenge of the 21st century, and research is the only way to solve this problem," Dr. Thies said at the meeting in Honolulu. " TrialMatch provides a first-of-its-kind service in Alzheimer's by delivering a user-friendly and individualized guide to clinical trials."

Approximately 150 clinical studies for Alzheimer's and dementia are ongoing, but not enough patients volunteer for them, Dr. Reisa Sperling said in an interview. "At the rate we have people signing up now, it takes 12-18 months just to complete enrollment," said Dr. Sperling, director of clinical research at the memory disorders unit of Brigham and Women's Hospital, Boston.

Currently, there are 10 drugs in large-scale clinical trials and another 20 in preclinical studies. Even when patients do volunteer for trials, screening eliminates many candidates, she said. "For every patient we enroll, we typically need to screen three or four. TrialMatch will collect detailed information in a confidential way, online, and that will speed up the matching process considerably."

Interested parties can visit the TrialMatch Web site (www.alz.org/TrialMatch) and identify themselves as a patient, caregiver, physician, researcher, or health volunteer. The program then matches the user to trials for which they may qualify. At any time, users can also call a toll-free number (800-272-3900) to speak with a volunteer who will walk them through the process.

The studies included on TrialMatch include large, industry-sponsored drug trials, natural history and imaging studies, federally funded trials, and smaller, investigator-initiated studies. All of them are important, Dr. Sperling noted.

Alzheimer's disease threatens to overwhelm the national health care scene in the next 50 years, when there could be 1 million new cases diagnosed each year in the United States alone. "I'd like to take a page from the success some of my oncology colleagues have seen," Dr. Sperling said. "For example, as soon as 80% of children with certain pediatric tumors began enrolling in research, there were huge leaps forward in finding treatment. Finding answers is directly proportional to research."

Entering a clinical trial also is an important way for both physicians and patients to claim some power in a situation that can make them feel quite helpless, she added. "I hope this can change the landscape of thinking about what patients and doctors can do to be proactive about this disease. Instead of hiding from it, let's agree to fight it tooth and nail."

Dr. Eric Tangalos, codirector of education for the Mayo Clinic's Alzheimer's Disease Research Center in Rochester, Minn., agreed. "TrialMatch is a wonderful innovation," he said in an interview. "As a primary care physician, I want my patients and families to run toward a diagnosis rather than away from it. Moreover, people who volunteer for research studies tend to do better than people who do not volunteer. There is not only the direct benefit of being engaged but [also] a social and societal advantage that plays out positively for the volunteer." ■

Disclosures: *TrialMatch is funded by the Alzheimer's Association. Dr. Sperling and Dr. Tangalos had no relevant disclosures.*

TOMM40 Gene Varient May Enable Early AD Treatment

VITALS

Major Finding: Particular variants of the TOMM40 gene are associated with declines in regional gray matter volume and in verbal learning and memory that may presage Alzheimer's disease.

Data Source: Two prospective studies of healthy volunteers with TOMM40 genotyping, one involving MR imaging of 117 participants and another involving verbal learning and memory testing in 337 participants.

Disclosures: Both studies were funded by the National Institute on Aging. Neither investigator had any potential financial conflict.

BY MICHELE G. SULLIVAN

FROM THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE

People who have a newly discovered gene variant that increases the risk of Alzheimer's disease appear to experience subtle changes in both cognition and brain structure years before even the earliest signs of Alzheimer's appear.

The gene, TOMM40, was associated with small but measurable declines in verbal learning and memory, and with decreases in gray matter volume, particularly in the posterior cingulate and precuneus—both areas that are highly involved with memory retrieval.

"Brain changes in these regions are particularly interesting because they are also associated with a high amyloid burden in people with Alzheimer's," Sterling Johnson, Ph.D., said in an interview. "Many studies have shown that these areas are active when you are recalling the recent past. So seeing changes there fits very nicely with a major symptom of Alzheimer's: recent memory loss."

Dr. Johnson and Dr. Mark Sager, both of the University of Wisconsin, Madison, said the work may open an important door on the ability to risk-stratify patients for early treatment, potentially identifying them before they experience significant brain damage from the disease. "Right now we're spending billions of dollars on trying to find a disease-modifying therapy, but we don't really know who we would give that to," Dr. Johnson said. In the same way that those with high cholesterol benefit most from statins, patients with a demonstrated risk of Alzheimer's would be the best candidates for any drug therapy, he noted.

TOMM40 has variable lengths that are defined by how many thymidine bases are contained in a specific section of the gene. The very long form (30 or more thymidine bases) is associated with an earlier onset of Alzheimer's disease, whereas the very short length (20 or fewer) is associated with a later onset. Some people have a long form (20-30 bases) that confers intermediate risk for Alzheimer's disease.

In 2009, researchers at Duke University, Durham, N.C., first showed that among patients who developed Alzheimer's after 60 years of age and were homozygous or heterozygous for the apolipoprotein E e3 (APOE-3) allele, those with two copies of the long TOMM40 developed the disease an average of 7 years earlier than did those with shorter TOMM40 lengths (Pharmacogenomics J. 2009 Dec. 22 [doi:10.1038/tpj.2009.69]).

Dr. Johnson's study consisted of 117 healthy volunteers (mean age, 57 years) who were known to be homozygous for the APOE-3 allele. APOE-3 homozygotes are thought to have a neutral risk for Alzheimer's disease. He then tested the subjects to determine what variant of TOMM40 they had.

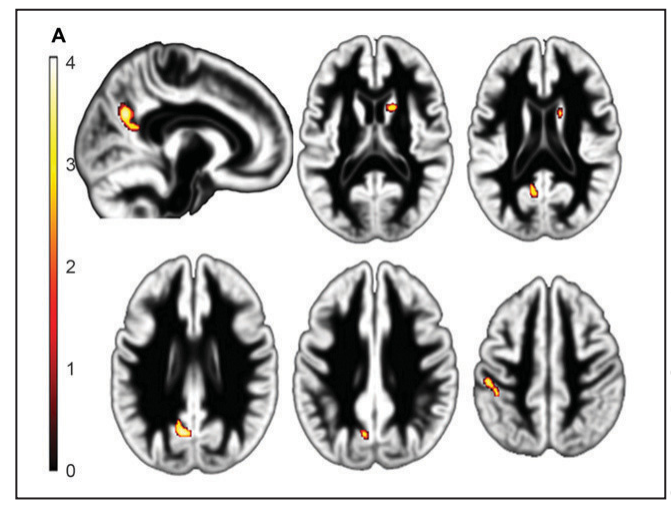
In Dr. Johnson's study group, 38 patients were homozygous for the very short length TOMM40; 44 had one short and one long or very long allele; and 35 were homozygous for the very long form of TOMM40. All of the volunteers underwent brain scanning with voxel-based morphometry to assess gray matter volume in different brain regions.

The subjects with two copies of the very long TOMM40 allele had significantly less gray matter in both the ventral posterior cingulate and the precuneus than did those with two short alleles. These are both regions that show early deterioration in late-onset Alzheimer's disease. "This is very important, because we are finding brain changes in people who are quite young," Dr. Johnson said. "The brain differences between the groups were very similar to, but less severe than, what is observed in full-blown Alzheimer's. It may be that the TOMM40 gene will be a useful measure of Alzheimer's risk in middle age, but additional research with longitudinal follow-up is necessary."

Dr. Sager examined the gene's potential effect on memory in a cohort of 337 adults (mean age, 54) who were genotyped for APOE and TOMM40. Of these, 128 were homozygous for the short form of TOMM40, indicating a lower risk. The long or very long forms were seen in 219 subjects. In the low-risk group, 57% had a family history of Alzheimer's, compared with 77% of the high-risk group—a significant difference.

All subjects took the Auditory-Verbal Learning Test, which involves five trials of learning two 15-word sets. The mean scores for both groups were within the normal range, but the mean was significantly lower in the group with longer forms of TOMM40.

He stressed that none of the subjects in either the brain volume study or the memory study had any observable memory difficulties in their everyday life.



COURTESY DR. STERLING JOHNSON

Patients with short TOMM40 had greater gray matter volume that did those with two very long versions.

"But these findings of gray matter loss and cognitive changes in these relatively young people are very important," and suggest that "we may have the ability to find people at risk of Alzheimer's very early on in the disease process, far in advance of any significant cognitive problems." ■