Genetic testing for Alzheimer’s disease risk [1]

Discovery [2]
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Testing for some risk genes, such as those that increase the chances of breast cancer, has become a standard part of medical care. Knowledge is power. Women can choose preventive surgery or periodic checkups to manage their risk.

But for Alzheimer’s disease, there are no preventive therapies so doctors do not recommend testing for risk genes. In this case, knowledge is not power. At least, not yet.

Experimental preventive therapies are now entering clinical trials, ushering in a new era of research. For instance, a new Alzheimer’s disease prevention trial [3]—which is slated to begin in late 2015 and jointly run by teams from Novartis and the Banner Alzheimer’s Institute in Phoenix, Arizona—is giving people a reason to consider genetic testing. It has also prompted researchers to think deeply about how Alzheimer’s risk testing should be done.

“Should prevention treatments become available for Alzheimer’s, more and more people will be getting genetic testing,” says Jessica Langbaum, principal scientist at Banner. “But in this in-between era of research, the question of testing takes careful consideration.”

The trial is focusing on late-onset disease, often called sporadic Alzheimer’s. People with an inherited risk of late-onset disease often have a gene variant called APOE4, which makes the amyloid plaques seen in many Alzheimer’s patients [4] more likely. Healthy individuals aged 60 to 75 who test positive for two copies of APOE4, one inherited from each parent, are eligible for the trial.

Registering for Research

In the US, the trial’s investigators plan to find some volunteers through the Alzheimer’s Prevention Registry [5], a website where people interested in participating in Alzheimer’s clinical trials sign up to receive email information about studies near them. The Registry, initiated by Banner and now jointly run by several institutions, has nearly 150,000 registrants and has so far been a valuable communication tool. For instance, a recent email alerting members about an online study generated 1,000 clicks in the first few hours.

“Our response rates are high,” says Langbaum. “We think we have a very motivated audience.”

Starting in November, Langbaum will expand the registry’s matchmaking capabilities to include genotyping for APOE4. This program, called GeneMatch, will allow registry members aged 55 to 75 to submit a sample of DNA for testing so they can be matched to studies,
Typically, patients receive genetic counseling before testing so they can make an informed decision about whether or not to proceed with testing. But here, DNA testing comes first because people with two copies of APOE4 are very rare, just 2 to 3 percent of the population.

“We might need to genotype eighty-thousand people to find the actual trial participants,” says Langbaum. “We flipped the model on its head to make it scalable.”

The flip puts testing first, but delays the delivery of information. Volunteers learn their gene status only if they respond to an invitation to join a trial. Invitations to the upcoming prevention trial will be sent to all registrants regardless of their APOE genotype, so as not to blindside people with an email that betrays their genetic risk. Some who are invited will learn that they have an increased risk of Alzheimer’s, but not enough of a risk to join the trial. These volunteers will be put back into the registry so they can be invited to join future trials.

### Making Informed Decisions

Those who receive an invitation and want to participate will visit the trial site nearest their home. This is the same place they will go to for medication and testing during the trial if they enroll. At the trial site, a genetic counselor will review the volunteer’s family history and potential risk. At this point, the volunteer chooses to opt in and hear their genotype results, or to opt out.

With over 60 trial sites, there aren’t enough genetic counselors specialized in Alzheimer’s disease to go around. So a centralized bank of counselors will counsel patients and deliver genotyping results over the phone or by video conference. “If we can show that remote counseling and disclosure is effective, then we can scale it to meet the need for counseling should prevention treatments become available,” says Langbaum.

People with two copies of the APOE4 gene can join the trial and receive one of two experimental treatments or placebo. Those with a different genotype cannot participate in the trial, but because of the way Novartis and Banner structured the process, they can be invited to participate in future trials.

“If people are giving of their DNA and registering because they want to be in research, they deserve to be able find the right opportunity,” says Langbaum.

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