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The risk of knowing: Alzheimer's research volunteers

Volunteers for a cause

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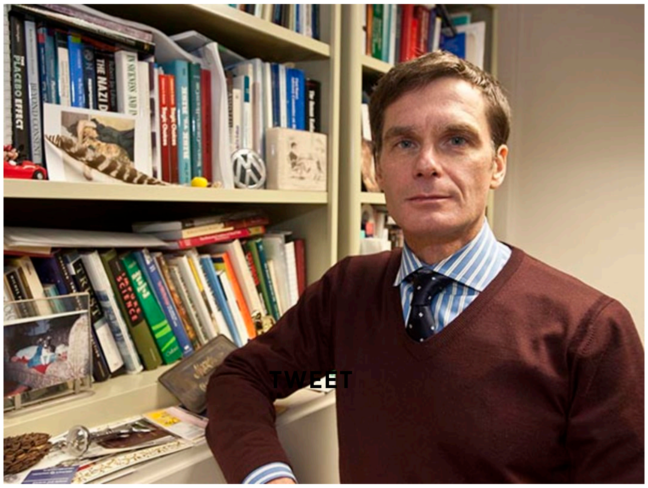

Penn ethicist Jason Karlawish is at the forefront of addressing who's at risk for developing Alzheimer's disease. (RON TARVER / Staff Photographer)

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by **Stacey Burling**, Inquirer Staff

Writer

Donald Jackson, 81, and his partner of more than 40 years, Myrna Roach, 74, are the kind of older people many of us would like to be one day.

Both still work and are energetic enough to travel extensively. They take medicine for high blood pressure and he has diabetes, but they feel healthy. They like to join clinical trials and know from one that their mental abilities have been stable for years.

Still, Roach has a strong family history of Alzheimer's disease. Jackson doesn't, but Alzheimer's is the disease he dreads above all others.

So, it was with a mixture of curiosity, anxiety, and altruism that the couple entered an unusual clinical trial at the University of Pennsylvania. Using a PET scan, their brains were examined for deposits of amyloid, one of the hallmark proteins found in the deadly dementia.

Then - even though there are currently no treatments that change the course of the disease and even though no one knows for sure how much amyloid deposits raise the risk of getting dementia - they were told the results so that researchers could measure how this powerful news affected them.

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Jason Karlawish, a Penn physician who is leading the psychological study, said people often join trials like this because they have seen what Alzheimer's does up close and want to help, even if they may not benefit. His pitch: "Do you want to be a partner with me to achieve the national goal of preventing Alzheimer's?"

On many levels, this is the stuff of science fiction: If you could know the future, would you want to? If you did, how would you change? Would other people treat you differently? Could society protect you from discrimination?

Karlawish's study is part of a larger clinical trial known as A4 (short for Anti-Amyloid Treatment in Asymptomatic Alzheimer's) that is testing the anti-amyloid drug solanezumab in people who are at risk for Alzheimer's disease but don't have symptoms yet. Frustrated that drugs like solanezumab haven't worked in patients who already are sick, doctors want to test in people with less damaged brains.

The trial is both an attempt to prevent Alzheimer's and to further define what it is.

Scientists now believe that the processes that lead to memory and thinking deficits in Alzheimer's start many years before symptoms are noticeable. Just as doctors try to prevent heart attacks by encouraging patients to exercise, lose weight, and take drugs, they hope to prevent Alzheimer's someday.

Robert Green, a medical geneticist at Boston's Brigham and Women's Hospital who studied how people responded to learning they had a mutation that raises the risk for

Alzheimer's, said we are entering an era when we could learn about all kinds of genetic time bombs that might - even will - make us sick in the future. He is now studying how people react to whole-genome results from direct-to-consumer companies.

"We are very close to a point where anyone who wants to learn genetic risk information will have the opportunity to do that," Green said.

Or, as Karlawish puts it, our ability to study risk factors for disease is transforming the "natural experience of aging" into the "monitored life at risk."

Green's earlier work found that some people were upset at first when they learned they had Alzheimer's risk mutations, but were fine a few months later. Some tried to lead a healthier life or bought long-term care insurance.

Margaret Lock, an anthropologist from McGill University in Montreal who still does research at 79, sees a big difference between telling people about genetic risk and a brain scan. She said participants in Green's study knew their true risk was a combination of genetic and environmental factors. They tended to focus on the environment.

She thinks knowing something is actually in your brain is a lot scarier. Given that researchers are still debating the role amyloid plays, she wouldn't tell patients about it. "Nobody in

Canada would tell somebody this," she said. "It's not necessary. You can do perfectly good work without disclosing."

Karlawish thinks disclosure has no place in a regular doctor's office until there's an effective treatment. But, he thinks it should be studied in clinical trials because someday people will have to know before they get medicines. That knowledge could affect how they respond to treatment.

In A4, only patients who want the information get it. Getting it, however, is a condition of being in the larger study and taking the drug. "My mission actually has been to make sure that those who want to know, know it, and those who don't want to know don't know it," Karlawish said.

We already have lots of information about risk. People who are obese and sedentary should know by now they're at risk for a host of deadly diseases. But Steven Arnold, director of the Penn Memory Center, thinks there's still something more sobering about learning you might lose your ability to think.

"The emotional impact of saying, 'You're at risk of losing your mind,' is worse than telling a diabetic, 'You're at risk of losing your leg,' " he said. "One is hitting you in your soul."

Not that long ago, Alzheimer's could only be definitively diagnosed by brain autopsy. Pathologists looked for clumps of amyloid and tangles of another protein called tau. Now, researchers are using PET scans and other biomarkers to find those proteins in the living. The tests are better for amyloid - the protein that has gotten the most attention from drug makers - than for tau.

This new information is revealing that dementia is more complex than it once seemed. Some patients diagnosed with Alzheimer's do not have the key proteins. It has always been known that some can have large amounts of amyloid in their brains without having symptoms. Would they get Alzheimer's if they lived long enough? Some experts think most would, but they don't know yet.

Tau is more closely linked to cognitive problems. A4 organizers are now discussing whether to test for it, Arnold said.

People over 80 often have a mix of problems, including Alzheimer's, stroke damage, and blood-vessel disease. Overall, our brains change for the worse as we age, making them less resilient.

What's important for researchers is that different drugs target different problems. Testing an anti-amyloid drug in people who have no amyloid is pointless and might make a good drug look less effective.

Patients in the A4 trial, though, are left wondering what their amyloid means. The short answer is that experts know it's a risk factor but can't say when symptoms are likely to develop. Arnold's best guess is that patients with deposits have a 60 to

80 percent chance of developing symptoms in the next five to 10 years. He tells them they might never get dementia. "It's really unsatisfying," he admits. It also leaves room for hope.

"The fact that they're in the study gives them a chance to improve the odds, and I think they appreciate that," he said.

Donald Jackson certainly does. In his younger days, the Philadelphia man said he had a nearly photographic memory. He still doesn't forget much and thinks his memory has been stable for 30 years. His fears of Alzheimer's stem mostly from watching Roach's mother die of it.

"It's the caregivers that take the brunt of the problem," he said.

Roach wasn't all that relieved to learn her brain is clear. "I'm probably going to get it anyway," she said. In fact, she could develop the deposits later.

Jackson seems remarkably calm about his bad news. He credits his equanimity to a tough childhood and years spent working on Air Force planes during missions.

"So it's there," he said. "What can you do about it? Nothing. That's the way I look at it."

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