To Reveal or Not to Reveal? New Data on the Question

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As the Alzheimer's disease (AD) field moves closer to using genetic and biomarker data to identify people at risk, researchers are urgently trying to tackle whether and how to disclose that information to people in both routine clinical care and research settings. This past February, Alzforum published a detailed account of the issues involved and ongoing studies aimed at these goals (see ARF related news story). In Vancouver at the Alzheimer's Association International Conference 2012, three of the featured researchers updated attendees on their projects at a plenary session dedicated to the topic.

"This move from research to clinical application is starting to occur with different biomarkers," said **Scott Roberts**, University of Michigan, Ann Arbor. Chairing the session, Roberts spoke of the need to use biomarkers responsibly in research. The coming shift from research to clinic "raises the stakes in terms of trying to think about how we communicate this information to providers and patients," he told the audience.

First up was **Robert Green**, Brigham and Women's Hospital, Boston, who for a decade has been conducting research examining whether it is psychologically harmful to divulge ApoE4 carrier status, which is associated with a higher risk of AD, to cognitively normal people (see ARF related news story and ARF Live Discussion). For the most part, the answer has been, no. "We have been able to chip away at this notion that genetic information is inherently harmful," he told the audience.

But what if a person already has mild cognitive impairment (MCI)? Having both an ApoE4 allele and MCI means a person has about a 50 percent chance of developing AD within three years (see ARF related news story), a rather more imminent prospect than the comparatively abstract concept of lifetime risk. That is why Green and colleagues are now conducting REVEAL IV. In this study they assess the risk of telling patients with MCI, ages 55-90, and their study partners whether the patient carries ApoE4. So far, the research team has preliminarily assessed only a small group of 30 patients—half of whom got their results and the other half who didn't—to be sure the study is safe. The researchers assessed anxiety, change in health behavior, and insurance/lifestyle changes by phone one to three days after disclosure, then again at six weeks

and six months. “So far we have not demonstrated robust anxiety, depression, or distress among either the subjects or their partners when they receive E4 information,” Green said. “We can start to assuage the concerns of people who felt that this was a bad idea.”

But ApoE4 status, even if you have MCI, still only imparts genetic odds. What if people already have plaque buildup in their brains? Patients are likely to consider that a more definite sign that they are on the road to Alzheimer’s. With the recent FDA approval of Amyvid (see ARF related news story) as the first of an expected handful of F18-labeled amyloid detectors for positron emission tomography (PET), many clinicians are gearing up for potential public demand of the test (see ARF related news story). “The increasing popularity and pending commercial availability of amyloid imaging tools are raising a number of questions about disclosing amyloid imaging results under various clinical scenarios,” **Jennifer Lingler**, University of Pittsburgh, Pennsylvania, told the audience. One question is whether knowing that one is likely developing Alzheimer’s heightens anxiety in people who already know something is wrong with their minds.

Since the PET tracer aims to help rule out AD as a cause in people with cognitive deficits, some of the first to get the test will likely be people with MCI. For that reason, Lingler’s trial involves disclosing a mock plaque status to MCI patients and their caregivers. (Patients know it is a mock trial.) For now, Lingler wants to know if information is presented in a comprehensible way. A panel of experts developed standard scripts to deliver in a disclosure session, and Lingler tried them out in 10 pairs of patients and family members. Four pairs each heard "positive" and "negative" scripts, while two received the inconclusive script.

Participants later rated how strongly they agreed or disagreed with statements such as: The session was “easy to follow,” “included the right level of detail,” etc. The feedback was generally positive, Lingler said. “Folks found the session easy to follow and the information clearly presented,” she said. The team is taking into account all feedback and additional questions participants asked, and will use them to make modifications to future scripts. They will also build in some flexibility with regard to length of the session and level of detail, depending on the participant’s preferences. Lingler’s next trial will assess outcomes of MCI patients who receive real imaging results.

Perhaps an even more contentious issue is whether doctors or researchers should reveal plaque status to cognitively normal people. While amyloid deposition in people with MCI appears highly predictive of progression to AD dementia, the research on whether cognitively normal people with plaque progress to AD is at an earlier stage. **Jason Karlawish**, University of Pennsylvania, Philadelphia, is part of a team tackling that question within the A4 trial (see ARF related news story), in which participants will learn their plaque status by virtue of taking part in the study, he explained. “We have great concern that it may cause despair,” said Karlawish. Within the A4 trial, he and colleagues will deliver scripts developed by amyloid imaging and

genetic counseling experts to prospective A4 participants as part of counseling both before and after the amyloid test. The scripts explain what amyloid imaging is and what it means to have a positive or negative result. The researchers will check whether participants understand their amyloid status and risk. They will monitor participants' mood throughout the study and note any changes in lifestyle, behavior, or perceived quality of life after disclosure. These results will inform future protocols that the research group will help develop, Karlawish said.

A parallel effort to issue consensus guidelines for diagnostic disclosure of biomarker status in people with MCI is afoot in Europe as part of the European Alzheimer's Disease Consortium (EADC) (see ARF related news story). The guidelines themselves are not quite baked yet, according to **Pieter Jelle Visser**, University of Maastricht, the Netherlands. In the meantime, however, leaders of the initiative are outlining their thinking in a freely available editorial in a special prevention issue of the journal Biomarkers in Medicine. The authors, including Visser, advocate for shared decision-making, which entails a joint decision between both patient and provider to get biomarker results. The process will likely include thorough pre-test counseling in which the provider explains the current uncertainties in biomarker statistics, possible test outcomes and their meaning, and risks involved with getting tested.—Gwyneth Zakaib.

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