Genetic testing for Alzheimer's disease 'not appropriate'

[PALO ALTO, CALIFORNIA] Despite advances in the understanding of the genetic basis of Alzheimer's disease, genetic testing for the disease is not appropriate for most people—even for diagnostic purposes. That is the conclusion of a group of scholars, physicians, lawyers and patient advocates brought together by Stanford University's Program in Genomics, Ethics and Society.

In a draft report released last Saturday (25 October), the group points out that the value of the additional information that genetic testing provides must be balanced against the financial and psychological cost. Predictive tests should be considered in the context not only of their sensitivity and specificity, but also in relation to prospects for treatment and the non-medical risks and benefits of the test.

Only those with a clear family history of Alzheimer's disease, especially with onset before the age of 60, might be possible candidates for testing for highly penetrant mutations, such as *APP*, *PS1* or *PS2*, the group says. Most individuals are unlikely to have these genes, which are estimated to cause less than 2 per cent of Alzheimer's cases.

More common is a susceptibility gene, APOE, of which one allele, E4, appears to be linked to about a 14-fold increase in risk for late-onset Alzheimer's among certain ethnic groups. About 50 per cent of all Alzheimer's cases may be attributable to E4, says Neil Risch, a professor of genetics at Stanford and co-author of a recent metanalysis. As a result, a test for APOE has much wider applicability and greater commercial potential than the other mutations.

But there is general agreement that APOE offers little predictive value — partly because there are so many causes of Alzheimer's, and not much is known about how the gene acts. Nor, according to the Stanford group, is a diagnosis confirmed by the APOE allele of clear value, especially in the light of its lack of usefulness for treatment, and its wideranging implications for family members who must act as surrogates for the person with dementia.

The group also pointed to the significant financial cost, which can be as high as \$1,500 to \$2,000, and to the potential psychological and social harm to early-stage affected individuals and relatives, who would inevitably learn of the probable nature of their own genotype.

A diagnostic test for APOE was first offered in 1993, but was withdrawn three months later after criticism. Now Athena Diagnostics offers tests for both APOE and PSI, but only for diagnostic purposes after a doctor has signed a statement that the gene donor is clinically demented. Sally Lehrman

NIH pilots faster feedback for grant resubmissions

[WASHINGTON] J. Brice Weinberg, a professor of medicine at the Veterans Affairs & Duke University Medical Centers in Durham, North Carolina, had that sinking feeling early last March when he received an e-mail informing him that he had failed to obtain funding for a major malaria study.

But his disappointment turned to hope when he read a paragraph at the end of the rejection from the US National Institutes of Health (NIH). This said his application could be quickly reconsidered if he answered a list of questions in an 'abbreviated amended' application.

By the end of April, NIH's Tropical Medicine and Parasitology (TMP) study section had Weinberg's seven-page response. And by September he had received the first instalment of a \$2-million, five-year grant for an international, multi-centre study of the function of nitric oxide in severe malaria.

The speedy reapplication gave him and his co-researchers "a terrific boost", says Weinberg. Not only were they saved the effort of rewriting the application for standard resubmission, but they saw their money at least four months earlier than would have been the case if they had been successful on a conventional second try.

The speedy reprocessing is just one part of an experiment that could eventually be introduced widely across NIH in which peer reviewers in the TMP study section are trying to reduce the time from the receipt of applications to when scientists see money—or learn why they are not getting any.

It's a "total package" that is trying to use new technology to improve the review process, says Elvera Ehrenfeld, who heads NIH's Center for Scientific Review — formerly the Division of Research Grants. For example, the trial programme also aims to return assessments electronically to near-miss applicants within days of a study section meeting, rather than the typical six to eight weeks.

"Not only do those who get funded see a benefit, but those who don't get funded but are on the borderline, also benefit," says John McGowan, the pilot programme's overseer. McGowan is deputy director of the National Institute of Allergy and Infectious Diseases (NIAID), which funds almost all TMP grants.

Moriya Tsuji, an assistant professor of parasitology at New York University School of Medicine, says that receiving reviewers' criticisms in mid-July 1996 rather than mid-August enabled him to alter preliminary experiments and make critical revisions to his application in time for a 1 November resubmission deadline.

"If I had started in the middle of August, I

wouldn't have finished [by the deadline]," says Tsuji, who on his resubmission received a \$650,000 grant to study the use of adenovirus as a vector for malaria vaccine.

The pilot programme also uses electronics to help reviewers. Study section members log on to a secured Internet website one week before they meet, and upload their assessments of applications. The chance to digest the written opinions of their co-reviewers before the meeting means that applicants get more considered, better reviews, says Diane Wallace Taylor, a professor of biology at Georgetown University, who until recently was a TMP reviewer.

But most important in speeding the process is that the study sections' critiques and scores are sent electronically within days directly to the NIAID Advisory Council, which must approve all grants. Top-scoring grants can therefore be immediately cleared by council delegates, shaving two to four months off the approval process.

The pilot programme — which ends next February — has raised some concerns. Franklyn Prendergast, director of the Mayo Cancer Center in Rochester, Minnesota, worries that the speedy amendment process could swamp both reviewers' time and institute budgets. And Tony Mazzaschi, a research policy analyst at the Association of American Medical Colleges, says: "The real challenge is going to be to do it in a much larger set of study sections."

But parts of the programme are spreading. The NIAID has since 1995 been using electronic approval by council for almost all institute-funded grants that fall within funding range. And the National Institute of Dental Research, the National Institute of General Medical Sciences and the National Institute of Deafness and Other Communication Disorders have all launched or are launching systems using electronic initial peer review.

MeredithWadman

