New Diagnostic Guidelines and DTC Testing for Alzheimer's Disease

by Dan Vorhaus

Last month, the National Institute on Aging and the Alzheimer’s Association issued new diagnostic guidelines that divide Alzheimer's disease into three distinct stages, reflecting recent evidence that the disease begins to affect the brain years before symptoms become evident. The expanded definition of Alzheimer's includes two new phases of the disease:

1) presymptomatic and 2) mildly symptomatic but pre-dementia, along with (3) dementia caused by Alzheimer’s. This reflects current thinking that Alzheimer’s begins creating distinct and measurable changes in the brains of affected people, perhaps decades, before memory and thinking symptoms are noticeable.

At least for the moment, the new guidelines are intended to be used only with patients enrolled in clinical trials, making them more of a work in progress and not a standardized method of determining disease onset in Alzheimer's patients.

**Federal Alzheimer's Activity.** The revisions to the diagnostic guidelines - the first in nearly three decades - indicate how far scientists have come in understanding the disease and are reflected in new legislation introduced in both the Senate (S.728) and the House (H.R.1386) that would expand Medicare coverage of Alzheimer’s to cover “comprehensive Alzheimer’s disease diagnosis and services,” including for individuals who fall under stage (1) or (2) of the new guidelines.

More significantly, the new guidelines and proposed legislation follow closely on the heels of the passage, earlier this year, of the National Alzheimer's Project Act (NAPA). NAPA (pdf) charges the Secretary of Health and Human Services with developing “an integrated national plan to overcome Alzheimer’s,” including by accelerating the development of treatments, improving patient diagnosis and care and coordinating efforts across all Federal agencies. Although NAPA did not include any Federal appropriations, its supporters believe it represents a significant commitment to fighting the disease and will lead to an increase in funding, as well as in awareness.

**DTC APOE Testing.** As Alzheimer’s researchers continue to refine how to define and diagnose the disease – and, of course, seek treatments as well – and the Federal government attempts to coordinate and strengthen its attack on the disease, a few companies are offering consumers the ability to take diagnostic testing for Alzheimer's disease into their own hands.

Recently, direct-to-consumer (DTC) genetic testing company 23andMe introduced an optional Alzheimer’s health report for its customers (of European ancestry). 23andMe customers who have been genotyped on the company’s latest platform – or who are willing to upgrade – can choose to learn which variants of the apolipoprotein E (APOE) gene they carry. The APOE gene, which comes in at least three different versions or alleles (?2, ?3 and ?4), has been shown to affect an individual's risk of developing late-onset Alzheimer’s, although the full physiological and genetic complexity of the disease is likely far from understood.

While 23andMe’s customers must separately choose to learn their APOE status, and are presented with a detailed report (pdf) outlining the gene’s predictive limitations in the face of other important factors, at least one prominent Alzheimer’s researcher has already criticized 23andMe for providing APOE results DTC. Allen Roses, a researcher at Duke University who helped to identify the link between APOE and late-onset Alzheimer’s disease, “believes that 23andMe should not report APOE status through DTC channels,” according to Pharmacogenomics Reporter. (In addition to 23andMe, other DTC genetic testing services, including the Decode Genetics service deCODEme, also offer customers the opportunity to examine their APOE status.)

At the center of the debate is whether individuals will benefit or be harmed, on balance, from learning whether they are at increased risk of developing a genetically influenced – but not determined – condition such as Alzheimer’s Disease for which there is no known cure.

This is exactly the issue that researchers at Boston University have sought to examine through the REVEAL (RISK Evaluation and Education for Alzheimer’s Disease) Study, while the REVEAL study is ongoing, proponents of DTC genetic testing in general, and of APOE testing in particular, point to preliminary findings which indicated that reporting APOE status to individuals “did not result in significant short-term psychological risks.” (pdf) Study researchers also recently published additional findings, concluding that one year after the initial disclosure of APOE status “test recipients still consider the pros to strongly outweigh the cons.”

Opponents of DTC testing, on the other hand, note that (1) the preliminary REVEAL findings measure only short-term outcomes, (2) individuals who tested negative for the APOE genotype associated with higher risk did experience reduced test-related distress, and (3) the initial REVEAL data involved subjects with significant exposure to Alzheimer’s disease who received direct access to genetic counseling, neither of which may apply to many DTC customers. (For more, see the final section of this Pharmacogenomics Reporter piece.)

**A Matter of Utility.** Then there is the issue of "clinical utility." While there is no universally accepted definition of "clinical utility," it is generally used to refer to the usefulness of a test or other procedure to alter (hopefully for the better) medical care. For example, the Centers for Disease Control and Prevention (CDC), in describing its ACCE model process for evaluating genetic tests, defines clinical utility as "how likely the test is to significantly improve patient outcomes.”

At least for the moment, there is no established cure or prevention strategy for Alzheimer's disease, meaning that a genetic test designed to indicated predisposition to the disease fails to satisfy many traditional definitions of "clinical utility." This lack of clinical utility, particularly for pre-symptomatic individuals, is frequently cited as a reason why such information should not be returned. For example, Muin Khoury, director of the CDC's Office of Public Health Genomics, told Pharmacogenomics Reporter he believes tests that lack a sufficient level of demonstrated clinical utility, including, presumably, APOE testing, "should be offered in a medical setting, with counseling," and should not be made available DTC. Similarly, last fall the European Society of Human Genetics issued genetic testing guidelines (pdf) in which it opposed “the
premature DTC commercialization of various genetic tests,” including tests for which clinical utility is unproven.

Proponents of DTC genetic testing, including 23andMe, have adopted a very different perspective, arguing that APOE information – as with other genetic information – should be available to any individual who desires it. The “utility” noted by DTC proponents is slightly different, with a focus on “personal” as opposed to “clinical” utility. Even if it is unable to alter a course of treatment or improve a patient’s likely outcome, genetic information may still possess significant personal utility for some individuals.

For example, to return to APOE testing, the REVEAL study has demonstrated that even though there are no proven effective treatments for Alzheimer’s Disease, providing participants with genetic information regarding their genetic risk of Alzheimer’s has been found “to be useful by allowing [individuals] to prepare their families and arrange personal affairs including long-term care.” (The quoted language is supplied by Khoury et al. and is the byproduct of a 2009 joint NIH/CDC workshop investigating, among other topics, the utility of personal genomic tests. A summary is also available here.)

What’s Next? For patients and family suffering through Alzheimer’s at any stage of the disease, the hope is that increased Federal funding and continued scientific awareness will continue to improve the ability to diagnose the disease early and accurately but, soon, begin to supply effective treatments or even preventative measures.

As for DTC genetic testing for Alzheimer’s disease, 23andMe now offers what is likely the most widely available and least expensive DTC test (although there are other avenues for consumer-ordered APOE genetic testing, including DTC competitor deCODEme) and has pushed the door wide open for individuals to directly assess (a portion of) their genetic risk for Alzheimer’s disease. At least so far, despite objections from scientists and policymakers like Roses, Khoury and others, regulators have not expressed any public concern with 23andMe’s decision to offer APOE testing and Alzheimer’s risk analysis as part of its service.

Looking ahead, however, there are at least two potential barriers to the continued availability of DTC APOE genetic testing. With the FDA continuing to evaluate the appropriate regulatory approach to DTC genetic testing (the latest opportunity for public comment closed earlier this month), there is no guarantee that DTC genetic testing services such as the one offered by 23andMe will remain available indefinitely in its current form.

And more specifically to DTC APOE genetic testing, Turna Ray of Pharmacogenomics Reporter recently noted that Duke University is considering whether DTC companies, including 23andMe, are infringing APOE patents developed by Duke and exclusively licensed to Athena Diagnostics. As discussed in Ray’s article, a variety of factors, including the uncertain status of Duke’s APOE patents (which claim an association between APOE variants and Alzheimer’s risk) in light of the ongoing Myriad gene patent litigation, suggest that both Duke and Athena may elect to be cautious in considering whether to challenge 23andMe’s DTC APOE testing.

For the moment, anyway, new and recent customers of 23andMe (those genotyped on the company’s current v3 platform) have the option to explore their APOE status if they so choose. Earlier customers (those genotyped on the v2 platform) are left with a choice: upgrade to 23andMe’s latest offering, wait until a later date for APOE genotyping or, as my colleagues at Genomes Unzipped will discuss soon, make an educated guess on the basis of their v2 results.