Genetic counselors at the forefront of helping researchers brace for the silver tsunami of CNS disorders

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The population is aging, triggering a "silver tsunami" of neurodegenerative diseases--especially Alzheimer's and Parkinson.[1,2,3] At the same time, precision medicine holds tremendous promise for many CNS disorders, including age-related neurodegenerative ones..

Researchers today better understand the heritability of neurological and psychiatric disease, although there is still so much more to learn. Through advances in genetics and genomics, they are making tremendous progress in identifying the genes and gene variants involved in neurodegeneration. As a result, genetic testing is making it easier to identify patients for clinical trials.

However, genetic testing in the context of clinical trials raises raise important ethical issues, including ones related to informed consent and disclosure of results. As is often the case with technology, the science may be outpacing our understanding of the broader implications. In fact, such concerns have spawned a relatively new field of study—neurogenethics.[4, 5]

In addition, myriad operational concerns exist for sponsors and sites; they range from finding patients to test and identifying which genes and mutations to test for, to designing appropriate protocols and managing the resulting data and results.

Genetic counselors can play a crucial role in helping sponsors address these operational and ethical issues, making trials more efficient, more patient-centered and, ultimately, more successful.

Before the test

Genetic counselors can provide pre-test genetic counseling for candidates who need to take a genetic test to determine eligibility for a clinical trial.

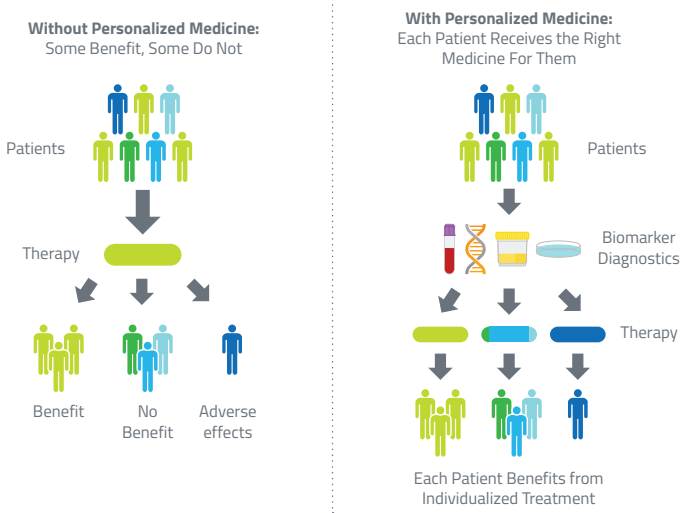
Not only does the pre-test counseling make patients aware of the possibility of unwelcome and unexpected results, it can also help determine if a different genetic test would be more appropriate—or if genetic testing is necessary at all. In addition, pre-test counseling allows counselors to address concerns related to genetic discrimination; alleviating those concerns can increase the pool of potential trial participants.

There's quite a bit to discuss.

Multi-gene panels: More data, more issues

Many neurodegenerative conditions, including Alzheimer's and Parkinson disease, involve variants in multiple genes; in other words, they are polygenic. Many are also multifactorial: They are determined by two or more genes, plus environmental factors. (Late-onset Alzheimer's is a good example of this.)

There's a third category: monogenic disorders. These are the result of a single non-working gene—examples include cystic fibrosis and sickle cell anemia. Although there are thousands of monogenic diseases for which a single gene test may be applicable, scientists now understand that most common conditions are multifactorial or polygenic.



The trend, then, is to move from single-gene testing to testing for a panel of genes. In some cases, researchers are opting for whole exome sequencing. Conceivably, researchers could screen 20,000+ genes and gather vast amounts of data across various neurologic conditions. From a scientific perspective more data is better, but it can place a tremendous burden on patients and families. One test could yield several life-altering results—including ones unrelated to the study.

For the patient, these incidental results can range from merely unwelcome to devastating. The test may identify a genetic mutation associated with a disease that is much more severe than the original clinical diagnosis. Or maybe it's just different, creating a new set of issues for the patient. For example, a mutation in the GBA1 gene can be associated with carrier status for the recessive condition Gaucher disease (meaning if both reproductive partners are carriers, a child could have the disease), and increased risk for Parkinson disease.

Genetic counselors can play a significant role here, helping patients understand the results and what they mean.

Guiding patient conversations after testing

When the genetic test is positive, patients face hard choices, especially when there is no effective treatment, such as with amyotrophic lateral sclerosis, Huntington disease and so many others. Consider Alzheimer's disease: Individuals with a variation in the APOE gene, called the e4 allele, have an increased risk for Alzheimer disease. Although this does not guarantee the person will develop Alzheimer disease, a positive test result could be devastating.[6, 7]

Research into Huntington disease illustrates the dilemma; many patients would simply prefer not to know the test results unless there is a treatment or clinical trial available.[8, 9, 10]

Genetic counselors can help individuals come to terms with the result and their choices They assess each person's needs and guide the conversation accordingly. Once the results are in hand, they can help patients better understand the implications of their results. It could involve explaining that presence of a particular mutation is not a death sentence and how non-genetic factors—such as nutrition—can influence one's predisposition to certain conditions, such as neurodegenerative disease. In that respect, the genetic counselor helps inform decisions beyond trial participation.[11, 12]

Answering questions is important, but often the mere presence of a counselor is enough to allay test-related stress and anxiety.[13, 14, 15] This, in turn, allows for more thoughtful, fact-based conversations about tests, trials and options.

The research is clear: Genetic counseling can be beneficial to patients and study partners by helping them understand the implications, and facilitating decision-making and informed consent.[16] Once a genetic risk is identified, patients then need to be counseled to know how to proceed.[17, 18, 19]

Research—and need—notwithstanding, genetic counseling has yet to be integrated into most clinical trial protocols.

So that raises the question: Who will do the counseling? Clinical investigators often lack the experience in speaking to patients about the results of genetic tests, and many fail to understand the disconnect between the scientific community's understanding of genetics and the general population's grasp of the topic. Healthcare professionals in the clinical setting may have a better grasp of what the patient needs to know, but they often lack the time or expertise to discuss findings in depth.

Genetic counselors have the expertise, tools and training to take on that task.

Patient-centered protocol design

So far, we've been talking mostly about patients, the candidates for trials.

That's because it's become increasingly important to put the patient first, especially in gene-based CNS trials. Clinical trial sponsors and CROs must balance the goals of the study with the motivation of the patient—and often, in these trials, the needs of the patient's family.

That starts long before the protocol is in place, and it requires thinking through the trial process and its repercussions.

For example, is a multigene panel test necessary? How important is it to test for a broad range of genes versus a small, targeted panel or a single gene? Sponsors and investigators often don't realize they can select which genes and variants to test for. They don't need to use an out-of-the-box panel. A panel can be customized for a sponsor, which allows them to incorporate all the relevant genetic markers and exclude the rest. Other times, a test should be broad enough to capture data that might help drive *future* trials regarding the sponsor's product pipeline. Because genetic counselors are intimately familiar with these diseases, they can help design and plan for the implementation of a genetic testing program.

Along those same lines, counselors often collect detailed medical and family histories during conversations with patients; insights learned from these interactions can help sponsors and CROs determine inclusion/exclusion criteria for their trials and identify potential barriers to participation.

Essential to the process is deciding how to obtain informed consent. That can be a challenge because, sometimes, risks are impossible to quantify. Moreover, each patient brings to the table values and cultural contexts.[20] Counselors also help control expectations: No one benefits if participants pin unrealistic hopes on a particular study.

The notion of *informed* consent becomes particularly problematic when there's potential cognitive decline and/or memory loss. Decisions about how investigators will obtain informed consent need to be made at the design level, not in the field.

Genetic counselors can help investigators anticipate questions as they are designing the protocol so they can be addressed, systematically, in advance—not in an ad hoc manner once recruiting has begun.

Among the issues to consider when incorporating genomic or genetic data into a clinical trial:

- How do you obtain patient consent for trials incorporating genetic/genomic data?
- How do you manage multiple consents?

- What do you explain during the consent process?
- How do you handle consent when diminished cognitive function is—or will be—an issue?
- How will you assess decisional impairment?
- How will you handle incidental genetic test results? What are the ethical and clinical considerations?
- What subsequent conversations and follow-up will you have with patients?
- How do you manage patient expectations of a clinical trial?
- How do you address patient misconceptions about genetic testing?
- Who will be responsible for each of the above?

Counselors connect

Biopharmaceutical companies are soliciting patient input at increasingly earlier stages of development. Having a genetic counselor on the team can amplify the patient's voice.

Genetic counselors at WCG's partner, InformedDNA, speak with thousands of patients each year and can provide patient experience data and insights that would otherwise be unavailable to sponsors. Because they use a telemedicine model and are licensed in all 50 states, they can provide access to genetic services to patients all over the country.

InformedDNA's nationwide network of genetic datasets allows for identification of potential candidates across various diseases, and—unlike genetic testing companies—they have the ability to reach out to those individuals and inform interested persons about available clinical trials. This unique database includes accurate diagnosis and germline mutation/variant data in a broad range of disease populations, including neurogenetics.

The beauty of such a registry is that it's a patient population that's ready and willing to learn more about their condition—a population that is already, to some degree, engaged. That matters, because the problem isn't just *finding* the candidates. Sponsors will need to engage them, address the options related to genetic testing and, finally, discuss participation in a clinical trial.

Think about the pool of patients who submitted to genetic testing but didn't qualify for a trial. Depending on how they were treated—how they were engaged—they could become more informed and eager volunteers for future trials. A genetic counselor who engenders trust can make all the difference. (For an example of how this worked for one biopharmaceutical company, see the sidebar on page 6.)

Genetic counseling may eventually become a standard part of programs supporting gene-based therapies. However, that day has yet to arrive, and many sponsors and CROs lack the deep scientific or operational expertise to appropriately integrate genetics into

their studies. They need the right expertise and infrastructure to deploy genetic-oriented trial solutions.

Until CROs and sponsors are able to develop that expertise themselves, they need outside experts to help them design protocols and appropriate genetic test panels, provide genetic counseling and test interpretation to potential participants. This ultimately improves the success of CNS clinical trials, allowing sponsors to bring urgently needed therapies to market faster.

WCG and Informed DNA have partnered to offer a genetics and clinical development solution to optimize the design of protocols and to ensure that all genetic information is appropriately applied to study design. To learn more, visit our Center for Genetics and Precision Medicine in Clinical Trials.

Alnylam's approach to genetic counselors: Guide researchers, counsel patients

One sponsor that has made use of genetic counselors is Alnylam Pharmaceuticals. It has discovered that incorporating genetic counselors makes a difference for patients and researchers.

Alnylam recently gained FDA approval for an RNAi therapeutic for patients with hereditary ATTR amyloidosis, a rare, progressive, adult-onset neurodegenerative disease.

Patients with this condition have a genetic mutation that prevents a type of protein from keeping its normal structure, Instead, the protein folds into an incorrect shape and accumulates in the heart, nerves and other organs.

This therapy represents a significant achievement: In the past, options were limited to symptom management, and patients would typically die within five years of diagnosis. Understandably, many affected patients did not undergo genetic testing to confirm the diagnosis.

Because this is a genetic disease, affected individuals' family members are frequently concerned about the risks for themselves and their children, but as with any neurodegenerative disease, decisions about undergoing presymptomatic testing are fraught with emotion.

Working with InformedDNA during the clinical trial phase, Alnylam was able to responsibly offer genetic testing to patients and families, confident they would receive the most appropriate education and counseling.

All of this helps drive recruitment and retention by ensuring patients are engaged, supported and educated. Moreover, by partnering with InformedDNA to provide pre- and post-test genetic counseling, Alnylam was able to both collect data related to program uptake and hear real-time feedback from the genetic counselors about potential barriers and struggles facing participants throughout the testing process that would otherwise have been unavailable to them. As a result, Alnylam is continuing engagement of genetic counselors in other clinical trials.

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