Presymptomatic ALS genetic counseling and testing

Experience and recommendations

Michael Benatar, MD, PhD
Christine Stanislaw, MS, CGC
Eliana Reyes, BA
Sumaira Hussain, BS
Anne Cooley, BS, MPH
Maria Catalina Fernandez, MD
Danielle D. Dauphin, BA
Sara-Claude Michon, PhD
Peter M. Andersen, MD, PhD
Joanne Wuu, ScM

Correspondence to Dr. Benatar: mbenatar@miami.edu

ABSTRACT

Remarkable advances in our understanding of the genetic contributions to amyotrophic lateral sclerosis (ALS) have sparked discussion and debate about whether clinical genetic testing should routinely be offered to patients with ALS. A related, but distinct, question is whether presymptomatic genetic testing should be offered to family members who may be at risk for developing ALS. Existing guidelines for presymptomatic counseling and testing are mostly based on small number of individuals, clinical judgment, and experience from other neurodegenerative disorders. Over the course of the last 8 years, we have provided testing and 317 genetic counseling sessions (including predecision, pretest, posttest, and ad hoc counseling) to 161 first-degree family members participating in the Pre-Symptomatic Familial ALS Study (Pre-fALS), as well as testing and 75 posttest counseling sessions to 63 individuals with familial ALS. Based on this experience, and the real-world challenges we have had to overcome in the process, we recommend an updated set of guidelines for providing presymptomatic genetic counseling and testing to people at high genetic risk for developing ALS. These recommendations are especially timely and relevant given the growing interest in studying presymptomatic ALS. ***Neurology*® 2016;86:2295–2302**

GLOSSARY

ALS = amyotrophic lateral sclerosis; **CLIA** = Clinical Laboratory Improvement Amendments; **fALS** = familial amyotrophic lateral sclerosis; **FTD** = frontotemporal dementia; **HD** = Huntington disease; **Pre-fALS** = Pre-Symptomatic Familial ALS Study; **psGT** = presymptomatic genetic testing; **sALS** = sporadic amyotrophic lateral sclerosis; ***SOD1*** = superoxide dismutase-1.

Published guidelines for presymptomatic genetic testing (psGT) in amyotrophic lateral sclerosis (ALS)[1–3] have been based in part on experience in Huntington disease (HD)[4,5] and other late-onset neurodegenerative diseases such as Alzheimer disease,[6,7] and in part on experience in a small number of first-degree relatives of patients with superoxide dismutase-1 (*SOD1*) familial ALS.[8] As the spectrum of identified genetic causes of ALS expands and the landscape of ALS genetics becomes ever more complex,[9,10] there is an increasing need to revisit the proposed guidelines. In this article, we highlight clinically relevant aspects of the genetic complexity of ALS and, drawing on the extensive experience acquired through the ongoing Pre-Symptomatic Familial ALS Study (Pre-fALS), present an approach to psGT that we have developed and refined over the last 8 years. While our experience derives from, and is most relevant to, psGT in the research arena, it may also inform the more controversial endeavor of psGT in a clinical setting.

BACKGROUND AND RATIONALE **"Familial," "sporadic," and "genetic" ALS.** Traditionally, a distinction has been drawn between familial ALS (fALS) and sporadic ALS (sALS) based on the presence or absence of a family history of ALS, with a genetic etiology presupposed for fALS, but not for those without a family history. This distinction, however, is artificial and the inference about genetic etiology incorrect, as all the genes known to cause fALS have also been identified in patients with (seemingly) sALS.[9] Some have proposed as an alternative the term hereditary ALS.[11] While there are many reasons why ALS with a known genetic cause may not reveal a family history (e.g., recessive inheritance, compound heterozygosity, de novo mutations, illegitimacy, misdiagnosis, small sibship size, reduced penetrance, lack of family information),[12] the presence of a family history

From the Department of Neurology (M.B., E.R., S.H., A.C., M.C.F., D.D.D., S.-C.M., J.W.), University of Miami, FL; Winship Cancer Institute and Department of Human Genetics (C.S.), Emory University, Atlanta, GA; and Department of Pharmacology and Clinical Neuroscience (P.M. A.), Umeå University, Sweden.

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of ALS (or a combination of ALS and frontotemporal dementia [FTD]) is an excellent yardstick of the likelihood that the disease has a significant genetic contribution.

Complexity of ALS genetics. Understanding of the genetic contribution to ALS has evolved rapidly in recent years. Since the initial discovery over 20 years ago that mutations in the *SOD1* gene are responsible for 12%–23% of fALS cases,[13] a further 31 genes have been implicated in the etiology of both sporadic and familial forms of the disease.[14] Notwithstanding this remarkable growth, the genetics of ALS remains complex (table).

Most genes associated with ALS display allelic heterogeneity; that is, different mutations within each gene may cause the same clinical phenotype. For example, 188 coding mutations in *SOD1* have been described (http://alsod.iop.kcl.ac.uk). Collectively, the identified genetic risk factors are responsible for ~50%–70% of fALS cases, with significant differences between seemingly similar populations.[9,15] Unlike HD, therefore, in which an expanded CAG trinucleotide repeat underlies almost all cases of HD, ALS may result from many different specific mutations in a multitude of genes, and in 30%–40% of patients with fALS (and ~90% of patients with seeming sALS), the predisposing genetic cause (if any) of disease remains enigmatic despite much research.

Moreover, many of the genes that may cause ALS are pleiotropic, meaning that the same genetic mutations may produce vastly different clinical phenotypes.[9] The GGGGCC hexanucleotide repeat expansion in *C9ORF72*, for example, may cause ALS, FTD, or ALS-FTD. Similarly, mutations in *VCP* may cause ALS,[16] multisystem proteinopathy,[17] or even hereditary spastic paraplegia.[18] The determinants, genetic[19] or otherwise, of this pleiotropy are largely unknown. Also unknown are the factors responsible for the widely varying age at disease onset, even among family members who share the same primary genetic cause of disease. These unknowns stand in contrast to our more nuanced understanding of the genotype–phenotype relationship in HD; for example, where the age at which clinical manifestations of disease are expected to appear can be predicted with reasonable accuracy based on CAG repeat expansion length.[20]

While our knowledge of the penetrance of the various mutations that may cause ALS is limited, existing data suggest that penetrance is variable and more often incomplete than complete.[9,21] In *SOD1*, for example, penetrance is high for some mutations (e.g., A4V, H46R) but low for others (e.g., D76Y, D90A, I113T). Importantly, penetrance can only clearly be defined by studying both those who manifest disease and family members who might harbor the relevant genetic mutation but who are not (yet) clinically affected. Related issues include occasional reports of affected family members who are discordant for the results of genetic testing[22,23] and emerging evidence for oligogenic inheritance; i.e., the presence of multiple mutations in ALS susceptibility genes within the same individual.[24,25] While probably rare, these 2 issues significantly complicate the communication of risk to unaffected family members, especially when genetic testing is performed only for mutations identified in other family members.

The genetic landscape of ALS is therefore complex and most importantly, incompletely understood. Clearly articulating both the complexity and uncertainty of ALS genetics to people contemplating or undergoing genetic testing represents a major challenge to presymptomatic genetic counseling in the population potentially at risk for ALS. The rapid pace of scientific progress, and the ever-changing landscape of ALS genetics, further heighten this challenge.

Rationale for presymptomatic genetic testing. Given the aforementioned complexities of ALS genetics, one might argue against psGT. However, the study of at-risk individuals is critical to the development of therapeutics to retard progression and preventive interventions to delay or inhibit onset.

Beyond the scientific knowledge gained by studying a presymptomatic population, genetic testing may in fact directly benefit those undergoing testing. In our experience, many of the individuals seeking testing are of the mindset that knowledge is power. They want to be proactive about their own health and that of their family. While there is no therapeutic or preventive intervention currently available, at-risk individuals may make life decisions or long-term lifestyle choices, such as buying a 1-story home rather than a 2-story home (as reported by one of our participants), based on their gene mutation carrier status. Individuals are also interested in obtaining information about their own risk status to share with their children.[26] Younger individuals may elect not to have biological children, or they may pursue preimplantation genetic testing to avoid passing the mutation to

Table Complexity of amyotrophic lateral sclerosis genetics

1. Genetic diversity
2. Allelic heterogeneity
3. Genetic pleiotropy
4. Variable penetrance
5. Genetic discordance
6. Oligogenic etiology

the next generation. Additionally, many individuals seeking psGT have expressed the sentiment that they have reached a point in their lives where the anxiety of living with the unknown is worse than knowing whether or not they are at genetic risk.[27] Finally, the opportunity to help advance ALS research can be empowering for individuals who have seen family members succumb to the disease, a sentiment shared by many of our participants.

PRESYMPTOMATIC GENETIC TESTING IN THE Pre-fALS STUDY Pre-fALS is a longitudinal natural history and biomarker study of individuals who are at genetic risk for developing ALS but who, at the time of enrollment, demonstrate no clinical evidence of disease.[28] The study population comprises presymptomatic individuals (English-speaking, recruited from across North America) who are carriers of any ALS-associated gene mutation (e.g., in *SOD1*, *C9orf72*, *TARDBP*, *FUS*, *VCP*, …), the only population known to be at risk for ALS and in whom a study of presymptomatic disease may be considered. The rationale for Pre-fALS and the logistics of studying a population at genetic risk for ALS have been described.[28]

To appraise study participants' psychosocial readiness to undergo psGT, we have used components of the Mini International Neuropsychiatric Interview, a short structured interview, to screen for anxiety and depression, alcohol and substance abuse, and suicidality.[29] During predecision counseling (to help individuals decide whether or not to undergo psGT and whether to learn the results) and during pretest counseling, we also evaluate sources of social support.

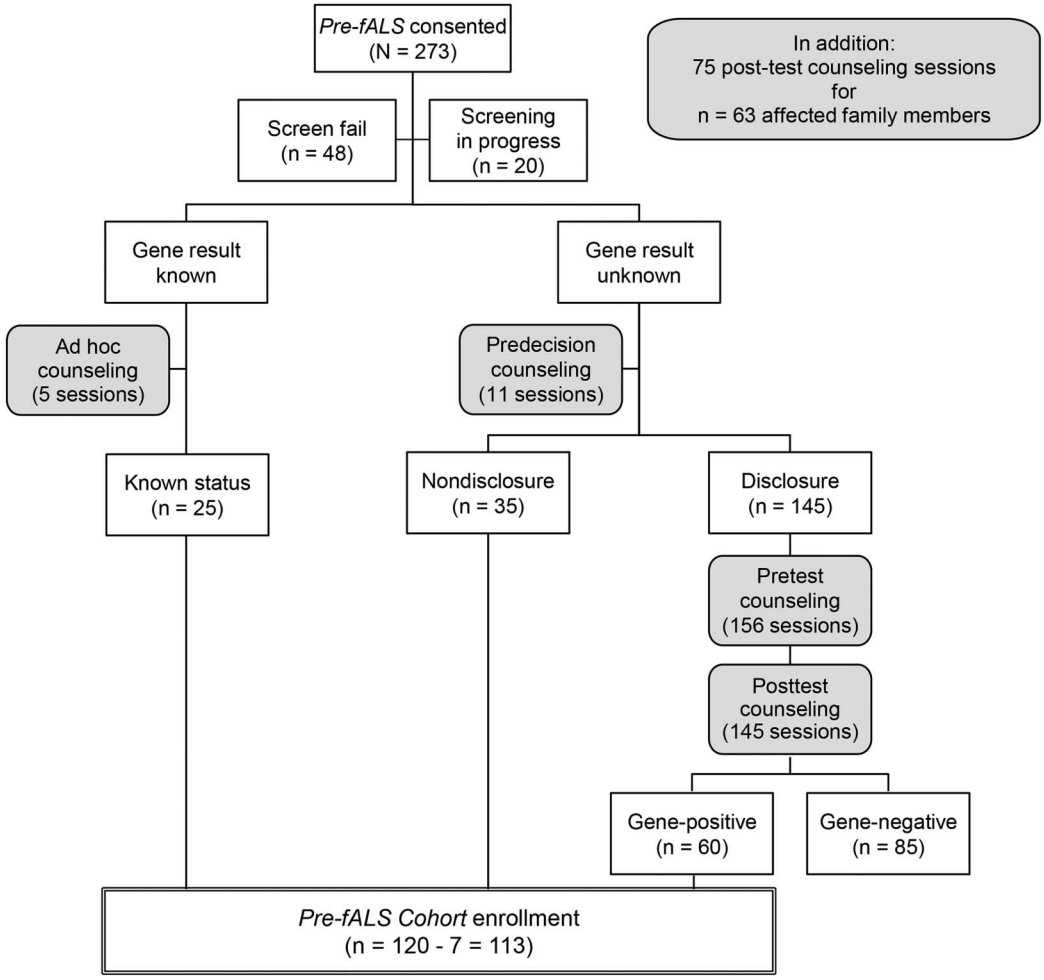
During the pilot phase of Pre-fALS (2007–2010), the first 40 participants in the disclosure group were randomized to receive pretest and posttest genetic counseling either in-person or via telephone. A semi-structured qualitative assessment of a random sample of 20 of these participants informed the decision to continue Pre-fALS using telephone counseling for both pretest and posttest sessions and to offer those contemplating genetic testing a predecision counseling session to help decide whether to learn the results of genetic testing.[27]

Currently in Pre-fALS, we only test for mutations already documented in affected family members. That we do not test for all known genetic variants implicated in ALS is clearly communicated during the informed consent process and counseling sessions. As of February 2016, 273 individuals have provided consent to participate in Pre-fALS. Among the 205 in the known status, nondisclosure, and disclosure groups, we have provided a total of 317 presymptomatic counseling sessions, including ad hoc, predecision, pretest, and posttest counseling (figure). In addition, we have provided counseling to 63 ALS-affected individuals for whom we have performed genetic testing in order to genotype the family, which is a prerequisite for family members' Pre-fALS eligibility.

PRINCIPLES AND PRACTICE OF ALS PRESYMPTOMATIC GENETIC TESTING

1. Voluntary and informed consent
   - 1.1. The decision to undergo psGT should be voluntary, with informed consent obtained and documented.
     - a) In the absence of an effective preventive therapy, individuals electing to undergo psGT should be ≥18 years old.
     - b) During the consent process, individuals should be informed of alternatives to testing and learning results; e.g., not to take the test at all, to undergo testing but not to learn the results, or simply to provide a DNA sample for future research.
     - c) The individual's rationale for pursuing genetic testing should be explored (to establish that the decision is truly voluntary and that there is no coercion; e.g., by family members or researchers).
2. Psychosocial readiness
   - 2.1. Individuals should be evaluated for psychosocial readiness to undergo psGT. In the presence of active psychiatric conditions, current substance abuse, or risk factors for suicide, or in the absence of a social support system, psGT should be delayed/deferred until these matters have been resolved or adequately treated.
   - 2.2. Effective communication among study coordinators, genetic counselors, and neurologists helps minimize the chance of missing an important psychosocial red flag.
3. Genetic counseling and testing logistics
   - 3.1. Testing and counseling should be done within the context of specialized units.
   - 3.2. The limited availability of such specialized units with genetic counselors experienced in ALS genetics underscores the need to consider nontraditional approaches to presymptomatic genetic counseling (e.g., via telephone).
   - 3.3. Counseling may be performed without face-to-face interaction, but the intent to do so should be explicitly discussed with the individual during the informed consent process.
   - 3.4. Multiple (at least 2) counseling sessions should be performed.
     - a) These may include predecision counseling as well as pretest and posttest counseling.

Figure Presymptomatic genetic counseling in the Pre-Symptomatic Familial ALS Study (Pre-fALS)



As of February 2016, 273 individuals provided consent to participate in Pre-fALS. A total of 48 failed early screening procedures and were excluded; 20 are still in the early stage of screening. Among the 25 known status participants, 5 requested and received ad hoc genetic counseling (due to the absence or inadequacy of prior genetic counseling). A total of 11 participants requested and received predecision counseling to aid their decision of whether to learn genetic test results; over half of them ultimately chose to enroll in the nondisclosure arm of the study. A total of 145 disclosure participants have completed pretest counseling (with 11 participants receiving a second pretest counseling session because of a prolonged delay following the initial pretest counseling session), and all of them have also completed posttest counseling. In total, we have provided 317 counseling sessions to 161 presymptomatic participants, and 113 participants have been enrolled in the Pre-fALS Cohort (with 7 eligible participants excluded due to difficulty scheduling study visits). In addition, we have provided 75 posttest counseling sessions to 63 affected individuals for whom we have performed genetic testing in order to genotype the family, which is a prerequisite for their family members' eligibility for Pre-fALS. A total of 12 of them received an additional counseling session after results of a more recently discovered gene mutation became available.

b) Test participants may request additional counseling sessions as needed.

3.5. Test participants should receive a written summary of the verbal communication after each counseling session.

3.6. Test participants may decide at any time not to receive the results or not to proceed with testing.

3.7. Testing should be performed in a laboratory with the requisite expertise.

a) A Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory should be used when psGT is being performed in the clinical arena.

b) Testing may be performed in an experienced research laboratory for research studies, provided that the type of laboratory being used is disclosed and discussed during the informed consent and counseling sessions.

3.8. Results should be delivered as soon as reasonably possible after completion of the test, although individuals should have the option to opt out or delay receiving results in the

event that personal circumstances or desire to learn results changes.

3.9. Individuals who undergo psGT (regardless of the test result) should receive some long-term follow-up to help detect and minimize any potential adverse effect of learning the results.

3.10. Results should not be communicated to others (e.g., family members, primary care physician) without the explicit written consent of the individual who has undergone testing.

a) Who (in addition to, or instead of, the test participant) can have access to the test results should be determined and documented during the informed consent process.

b) Extra caution must be exercised to avoid inadvertent disclosure of results through, for example, study design in which only positive results are released to the participant, imprudent or accidental reference to one family member when interacting with another, or scientific publication without sufficient masking.

3.11. The individual should be informed of how test results will be stored and whether they will form part of the official medial record.

a) Given the current structure of the US health care system and that of most Western European countries, research test results should be kept separate from the medical record and caution must be exercised to avoid inadvertent communication of the result to a health care provider.

4. Predecision counseling

4.1. Explore motivations for testing, including perceived benefits and personal lifecycle timing. Does the individual want the results to make decisions about moving forward with a relationship or having children? Does he or she have young children or adult children or grandchildren? How does he or she feel about sharing the test results with family members?

4.2. Explore basis for the participant's difficulty in choosing between learning or not learning results.

4.3. Explain that choosing not to be tested or learn the results of testing does not mean that an individual cannot change his or her mind in the future.

4.4. Address issues that will be explored in more detail in the pretest counseling session (e.g., potential psychological effects of testing, availability of an appropriate support system, and concerns about medical, life, disability, and long-term care insurance).

4.5. As appropriate, allow for some minimal interval (we suggest at least 1 week) between counseling and the decision to undergo testing to allow sufficient time for individuals to assimilate information and to make an informed decision, without undue pressure, about whether or not to proceed.

5. Pretest counseling

5.1. Individuals should have the option to have a support person present.

5.2. If the individual has not undergone predecision counseling, it is essential to utilize the pretest counseling session to cover relevant issues that would have been addressed at the predecision stage.

5.3. Discussion should include the following:

a) Disease-specific information (e.g., early signs/manifestations of disease)

b) Gene-specific information (i.e., issues discussed in detail above)

c) Limitations of available genetic testing (e.g., limits of current knowledge of ALS genetics, pros and cons of testing in a research vs CLIA laboratory)

d) Potential psychosocial effects of genetic test results include:

- For the individual undergoing testing: Family history and the individual's personal experience with the disease should be solicited. Inquiring whether the individual was a direct caregiver, whether the affected family member died while very young, and whether the individual has lived apart from the family and might not have experienced the direct effect of disease are all factors relevant to appraising whether the individual has critically considered the potential personal effect of genetic testing.
- For family members and relationships (e.g., parent, spouse/partner, child): This is especially important if testing would provide information about another person who has not requested testing. The issue will arise, for example, when only one of two identical twins undergoes testing or when the test result may identify a family member as an obligate carrier.
- Potential for survivor guilt.

e) Potential legal implications of genetic testing. While these vary by country, in the United States, current antidiscrimination legislation (www.genome.gov/10002077) includes the following:

- Genetic Information Nondiscrimination Act (GINA) HR 493 (2008): Prohibits health insurers from using family

medical history in decisions regarding eligibility, coverage, underwriting, or premium-setting. Prohibits employers with over 50 employees from requesting or using genetic information in decisions regarding hiring, firing, promotions, salary, and assignments.
- The Affordable Care Act (2010): Prohibits insurers from refusing coverage due to preexisting conditions.
- Executive Order 13145 (2000): Prohibits federal employers from requesting, requiring, or using genetic information in employment decisions.

Limitations of current US legislation include the following:
- No federal legislation regulates the use of genetic information in underwriting for the life, disability, and long-term care insurance industries.
- The Genetic Information Nondiscrimination Act does not apply to individuals receiving care through Federal Employee Health Benefits programs, the Veterans Health Administration, the US Military (Tricare), or the Indian Health Service, although some of these organizations have internal policies related to the use of genetic information.

f) Information about other sources of support (e.g., relevant lay organizations)
g) Specific plans for disclosure of test results, including when and how this will be done
h) Current lack of prevention and treatment options

5.4. Family and social support and circumstances that may affect psychosocial readiness to receive results (e.g., recent death of family member with ALS, job loss, other health issues). This should also be reexplored at the start of the posttest counseling session.

6. Posttest counseling
6.1. The individual should be encouraged to have a friend or family member present at the time of result disclosure, which should be done at a prearranged time and location.
6.2. Immediately prior to disclosure, confirm that the individual is ready to receive results. Offer the individual the opportunity to elect not to receive results or to postpone disclosure to a later date.
6.3. Discuss implications for the individual.
a) Clinical: Underscore the inability to predict the "when and how" symptoms of ALS may present for individuals at genetic risk.
b) Psychological: Discuss the potential for significant psychological effect even in the context of the individual not being a gene mutation carrier.

6.4. Discuss implications for the family, including the potential changes in knowledge of risks and testing options for children, siblings, and extended family members once this individual learns his or her test results.
6.5. Identify resources: For example, foundations (although these are often more focused on people with ALS than the community of people at genetic risk) and other nonprofit organizations. In the research context, the research program itself will serve as a resource.

RECOMMENDATIONS FOR RESEARCH Providing psGT for people possibly at risk for ALS is a difficult undertaking requiring close collaboration among an experienced neurologist, genetic counselor, geneticist, and research team that is sensitive to the complexity of the relevant issues and process. With appropriate care and consideration, however, psGT with delivery of results can be done safely and effectively in the research arena. Over the course of the last 8 years, in the midst of tremendous progress in unraveling the genetic basis for ALS, we have provided genetic counseling to 161 unaffected Pre-fALS participants with a variety of genetic mutations, overcoming a host of challenges along the way. This experience has enabled us to validate some prior recommendations for genetic counseling and testing in this population, to refine others, and to identify areas that would benefit from further research. Notable examples of the latter include the following:

1. In addition to evaluating individuals' psychosocial readiness to undergo psGT, long-term follow-up should be in place to help detect and minimize any potential adverse effect of learning the results (positive or negative). The best approach to screening for and identifying potential long-term adverse consequences of psGT with provision of results is an area that would benefit from further examination.
2. In addition to providing counseling by phone for those who live far away,[27] there is value in exploring the utility of secure video conferencing to provide counseling.
3. Little is known about attitudes to psGT in non-English-speaking populations and how cultural differences may shape attitudes.
4. Special attention must be dedicated to communicating the limitations of currently available genetic testing and knowledge—what we know, what we do not know, and the implications of positive or

negative test results in this context—for the individual being counseled and his or her family members. This issue is especially acute in light of emerging reports about genetic discordance and the oligogenic contribution to ALS; for example, raising the question of whether psGT should be informed by testing for all known ALS genes in affected family members.

5. The laboratory performing the actual DNA analysis should either be certified to do so or should have documented extensive experience performing the actual DNA test in question. This issue is especially important in light of a recent blinded study testing for the GGGGCC-repeat expansion mutation in *C9orf72*, which revealed that only 5 of 14 well-known laboratories correctly identified the genotype in all 78 tested DNA samples.[30]

While the foregoing discussion focuses primarily on psGT in the research arena, there is a growing interest from the community of family members at potential genetic risk for ALS to undergo psGT in the clinical arena. Our recommendation is that this should be undertaken only after careful consideration and discussion of the potential pitfalls of doing so with the individual requesting testing. If an informed decision is made to proceed, the principles outlined in this article to guide best practice in the research arena may be applied to guide clinical testing.

AUTHOR CONTRIBUTIONS

M. Benatar: study concept and design, study execution, genetic counseling, participant evaluation, manuscript writing, and critical revision. C. Stanislaw: genetic counseling, manuscript writing, and critical revision. E. Reyes: participant recruitment and evaluation. S. Hussain: participant recruitment and evaluation. A. Cooley: participant recruitment and evaluation. M.C. Fernandez: participant recruitment and evaluation. D.D. Dauphine: participant recruitment and evaluation. S.C. Michon: participant recruitment and evaluation. P.M. Andersen: genetic testing, critical review and editing of manuscript. J. Wuu: study concept and design, study execution, data management, manuscript writing, and critical revision.

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