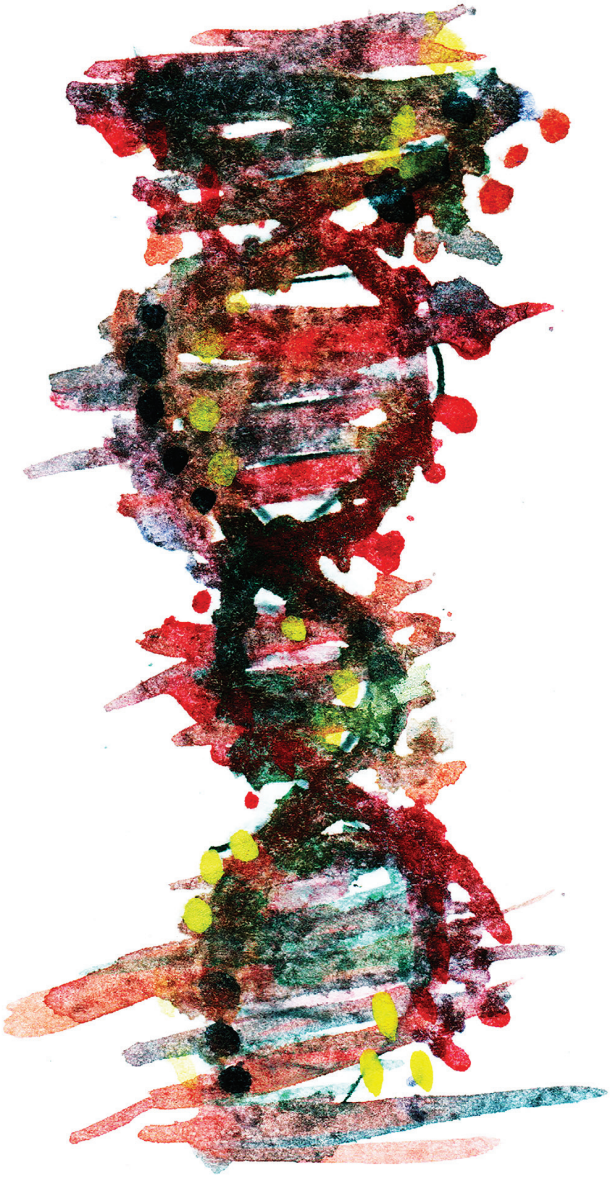
GENETIC TESTING IN THE RETINA PRACTICE

What's changing and why it matters.

By Timothy S. Lee, MD; Eric W. Lai, MD; and Sidney A. Schechet, MD



Retina specialists play a critical role in the early detection of inherited retinal diseases (IRDs). While individually rare, they collectively affect approximately 1 in 1,000 people worldwide.[1,2] The latest diagnostic yield of genetic testing in suspected IRD cases ranges from 65% to 70%, with 51% of cases initially misdiagnosed. On average, it takes 15 years for these patients to receive a correct diagnosis,[3] although ophthalmologists can identify IRDs more efficiently than general medical genetics clinics by approximately 16 months.[4] Thus, a detailed eye examination can raise clinical suspicion and help guide the decision to pursue genetic testing (Figure).[5-7]

ADVANCES IN GENETIC TESTING

Genetic testing for IRDs primarily relies on next-generation sequencing (NGS), using targeted panels of known IRD-associated genes to provide a relatively fast and accurate diagnosis. If NGS does not identify a causative mutation, particularly in those without a clear clinical diagnosis, broader approaches such as whole-exome sequencing (WES) or whole-genome sequencing (WGS) can be considered.[8,9]

WES enables comparison with all exons, including genes not found in a targeted gene panel sequencing,[10] while WGS tests the entire genome and has a wider scope than WES. When comparing the type of sequencing, NGS can be used to detect smaller genetic variants and has higher throughput; NGS has a poorer ability to detect larger genetic variants, including structural variants. In comparison, long-read sequencing, which involves reading several kilobases, has a better ability to detect larger, complex genetic variants, including structural variants and insertion-deletion errors, but can be more expensive and have a lower throughput.

There are several ways to obtain specimens for genetic testing. The least invasive and most cost-effective methods are through saliva and buccal swabs, which can be self-collected by patients at home, that are mailed directly to the testing company for processing. Sometimes, whole blood is

TABLE. AVAILABLE INHERITED RETINAL DISEASE PANELS

Company	Number of Genes Tested	Specimen Collection	Cost	Time to Results
My Retina Tracker	110; does not include mitochondrial genes	Whole blood specimen	Free through Foundation Fighting Blindness	Approximately 21 to 28 days
Invitae	330; does not include mitochondrial genes	Whole blood (preferred) or saliva specimen	Insurance, sponsorship through Invitae Unlock, or out-of-pocket	Approximately 10 to 21 days
Blueprint Genetics	351; includes mitochondrial genes	Whole blood or saliva specimen	Insurance or out-of-pocket	Approximately 28 days

the preferred specimen for genetic testing, as it has a higher DNA yield and can provide more information. However, blood samples must be taken in an outpatient laboratory and are more expensive. All the genetic testing companies collect saliva and whole blood samples (Table).

Despite these advances, genetic testing can yield inconclusive results. A common challenge is the identification of variants of uncertain significance (VUS)—genetic changes for which the effect on disease risk is unclear (see, "VUS: A Guide for Retina Specialists"). In one laboratory's experience, approximately 17% of unsolved IRD cases included at least one VUS.[11] These variants can potentially be reclassified through further investigations such as functional studies and segregation analyses. Classification categories include "benign," "likely benign," "uncertain significance," "likely pathogenic," and "pathogenic." However, even with reclassification, ambiguity can persist, necessitating careful clinical judgment when making management decisions.

To help improve access to genetic testing, several companies offer in-clinic or at-home testing kits, along with genetic testing analysis and, in some cases, genetic counseling.

Still, genetic testing for IRDs and other conditions has potential drawbacks. Patients can have significant psychological and familial distress that can lead to grief, anxiety, and uncertainty about their diagnosis. If genetic diseases are identified, insurance companies may impose higher premiums or even denials. Privacy and data security issues are also of concern, especially with the storage and use of this information for research and other databases. Furthermore, genetic testing may be inconclusive. Even when a pathogenic variant is identified, there may not be effective treatments available, limiting the effect on clinical management.

KEY TAKEAWAYS

- The latest diagnostic yield of genetic testing in suspected inherited retinal disease (IRD) cases ranges from 65% to 70%; 51% are initially misdiagnosed.
- To help improve access to genetic testing, several companies offer in-clinic or at-home testing kits, along with genetic testing analysis and, in some cases, genetic counseling.
- Genetic testing and referral to an IRD specialist can facilitate accurate diagnoses, provide insight into overall prognosis, guide family planning, and enable more personalized treatment strategies.

GENETIC TESTING OPTIONS

My Retina Tracker is a national IRD registry provided by the Foundation Fighting Blindness.[12] The genetic testing is provided by Prevention Genetics with an all-inclusive testing kit to be used in clinic or at home. The targeted gene panel consists of 110 genes and does not contain mitochondrial genes. Although a smaller gene panel than other testing options, this registry is typically free for eligible patients and useful for common IRD presentations. The turnaround time for results is estimated to be about 3 to 4 weeks. A third-party service called InformedDNA also provides optional genetic counseling for the patient.

Invitae offers an IRD panel that consists of 330 genes associated with various IRDs, including retinitis pigmentosa (RP), cone-rod dystrophy, Leber congenital amaurosis, and more.[13] However, this larger testing panel does not include mitochondrial genes. The Invitae panel can be subsidized through insurance if testing is indicated. Of note, Invitae also offers the Invitae Unlock sponsored program that allows patients to undergo testing for free if they meet the program eligibility criteria, with free counseling available as well. The turnaround time for this gene panel ranges between 10 and 21 days, with an average of 14 days.

Formerly the provider of the genetic panel for My Retina Tracker, Blueprint Genetics offers its own retinal dystrophy panel that consists of 351 genes, which *does* include those of mitochondrial origin.[14] Although it may carry a higher fiscal burden, the Blueprint Genetics panel can be subsidized through insurance if testing is indicated. The turnaround time for this testing panel is approximately 4 weeks.

Johnson & Johnson recently announced its own IRD registry, the EYERD Registry.[15] The company is recruiting patients, intending to use the registry as a database for

Rare and Inherited Retinal Disease

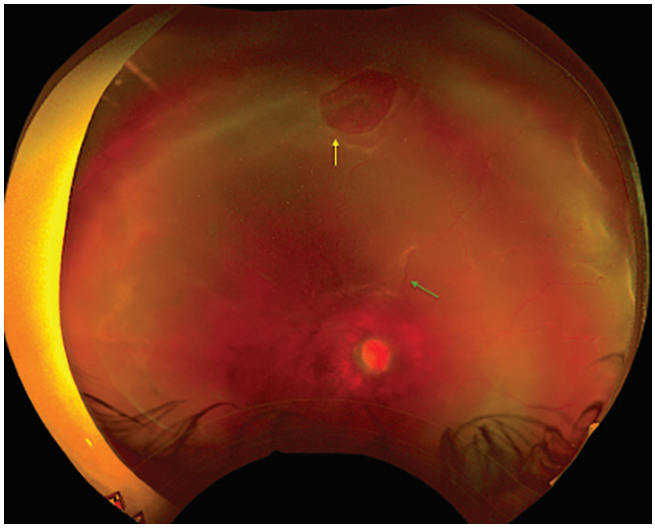


Figure. This patient with high myopia presented with a retinal break (yellow arrow), vitreous veils (green arrow), and a rhegmatogenous RD. Genetic testing revealing a diagnosis of Stickler syndrome type IV.

research on treatment options and to emphasize earlier diagnosis of IRDs, with an emphasis on X-linked RP and achromatopsia. In some instances, genetic testing may be available at an academic institution's genetics clinic.

If genetic variants are identified, phase testing can provide risk-stratification of these variants. Phase testing involves determining whether genetic variants within the same gene are located on the same or opposite chromosome, in cis or in trans, respectively. Phase testing is especially important in patients with identified recessive genetic conditions or for determining compound heterozygosity. The information gathered from phase testing can be used to counsel patients and allow for further management decisions.

CASE OVERVIEW

A 32-year-old man with a history of high myopia (-15 D OU) was referred to the retina clinic for suspicion of a retinal detachment (RD) after sustaining a traumatic head injury. The patient had a BCVA of 20/70 OD and 20/40 OS. On examination, the patient had macular subretinal fluid and a chronic, macula-off RD, along with multiple retinal breaks in the right eye (Figure). Both eyes had a posterior staphyloma. The patient had no apparent systemic syndromic features and no relevant positive family history. Due to the patient's severe myopia, chronic and severe RDs, and bilateral vitreous syneresis/veils, there was suspicion that he may have an underlying genetic disorder.

After RD repair, the patient underwent Invitae panel testing and was found to have a homozygous mutation in the *COL9A1* gene, confirming an autosomal recessive inheritance pattern and supporting the diagnosis of Stickler syndrome type IV. Based on these genetic findings, together with the clinical features, the diagnosis was ultimately established. In comparison to the autosomal dominant (AD) variant, autosomal recessive (AR) Stickler syndrome is much rarer. The proportion of *COL2A1* AD variants causing Stickler syndrome is about 80%, with *COL9A1* AR variants responsible for less than 1% of Stickler syndrome cases.[16]

AD Stickler syndrome has the typical findings of high myopia, vitreoretinal degeneration, and syndromic features including midface hypoplasia and cleft palates; AR Stickler presents with similar ocular findings but with heterogeneous expression of syndromic features. Even without a reported family history, genetic diseases can still occur de novo, and testing within the family should be pursued. Therefore, the patient was encouraged to have his family members undergo testing and ophthalmologic examinations, and he was referred to genetics for further evaluation and counseling.

IRDS IN CLINICAL PRACTICE

The evolving landscape of IRD diagnosis and management underscores the critical role of genetic testing as a diagnostic tool when clinical suspicion is high. Approximately half of the patients referred with clinical suspicion of an IRD receive a different diagnosis at the end of testing, with the potential of a delayed diagnosis of about 15 years.

Referral to an IRD specialist should be highly considered for patients with a strong family history of vision loss or known IRDs, any progressive, rapid vision loss unexplained on examination, any notable systemic/external findings that suggest an IRD, unusual examination findings, and when considering any IRD testing. Once testing is performed, the IRD specialist can analyze and interpret genetic tests along with the patient's history and examination findings to pursue a diagnosis and potential management.

Furthermore, counseling and education are important aspects of IRD care. Physicians should fully discuss the purpose and possible outcomes of testing. The effects of genetic testing go beyond the medical scope and can affect many aspects of the patient's life. It is especially important to counsel patients about these effects and suggest they pursue resources that are available to them if necessary.

Timely genetic testing is crucial when there is clinical suspicion of an inherited or syndromic retinal disorder. Available testing panels can facilitate accurate genetic diagnoses, providing insight into overall prognosis, guiding family planning, and enabling more personalized treatment strategies, including potential clinical trial opportunities. ■

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VUS: A GUIDE FOR RETINA SPECIALISTS

By Vinit B. Mahajan, MD, PhD

A variant of unknown significance (VUS) is a statistically rare genetic change found in a patient's DNA. However, rare does not equate to disease-causing; in fact, most VUS are benign variants that haven't been studied enough to know for certain.

INTERPRETING GENETIC TEST RESULTS

Genetic testing results typically come with a classification. If a variant is labeled pathogenic, there is strong evidence that this variant causes disease, which is useful information for diagnosis and counseling. When results show likely pathogenic, there is probable disease association but some uncertainty; with the appropriate caveats, this finding can be used for diagnosis and counseling. When the results list a VUS, there is insufficient evidence to classify the variant either way—this should not be used for clinical decisions. Variants classified as likely benign or benign are probably or definitely not disease-causing and can generally be ignored.

WHY ARE VUS COMMON IN RETINAL GENES?

Some genes are particularly prone to generating VUS reports, such as *ABCA4* (associated with Stargardt disease), *USH2A* (Usher syndrome and retinitis pigmentosa), and other Stargardt-associated genes. These genes are large, providing more locations where rare variants can occur. In addition, there is high natural variation in these genes across the normal population, and limited functional studies exist on most variants that have been identified. Finally, many variants have never been seen before in medical literature or databases, making it impossible to know their significance.

WHAT NOT TO DO WITH A VUS

Clinicians should never tell patients they have the gene for a particular disease based on a gene classified as VUS, as a VUS cannot be used for a definitive diagnosis. A VUS alone should never dictate treatment decisions. In addition, clinicians should not assume that a VUS will eventually be reclassified as pathogenic because many remain uncertain indefinitely, and some are eventually reclassified as benign.

WHEN CAN A VUS BE CLARIFIED?

A VUS may be resolved and reclassified, often when there is a strong multi-generational pedigree showing clear segregation of the variant with disease. Having multiple affected family members available for testing can be extremely helpful.

Additionally, functional studies that demonstrate biological effect of the variant can provide clarification. However, these approaches require genetics expertise to properly execute and interpret.

KEY TAKEAWAY FOR BEST PRACTICE

When genetic testing reveals a VUS, clinicians should explain to the patient and their family that unknown significance truly means we don't know if this variant is related to their condition, and refer them to a genetic counselor or geneticist for expert interpretation. Clinical findings, imaging results, and family history should dictate the diagnosis. ■

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