

# Recommendations for Genetic Testing of Inherited Eye Diseases

## Report of the American Academy of Ophthalmology Task Force on Genetic Testing

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Genetic testing can make a very positive impact on individuals and families affected with inherited eye disease in a number of ways. When properly performed, interpreted, and acted on, genetic tests can improve the accuracy of diagnoses and prognoses, can improve the accuracy of genetic counseling, can reduce the risk of disease occurrence or recurrence in families at risk, and can facilitate the development and delivery of mechanism-specific care. However, like all medical interventions, genetic testing has some specific risks that vary from patient to patient. For example, the results of a genetic test can affect a patient's plans to have children, can create a sense of anxiety or guilt, and can even perturb a patient's relationships with other family members. For these reasons, skilled counseling should be provided to all individuals who undergo genetic testing to maximize the benefits and minimize the risks associated with each test.

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### The Role of the Ophthalmologist in Genetic Testing

Ophthalmologists should be aware that sensitive and specific genetic tests now exist for dozens of inherited eye diseases. Whenever the clinical findings suggest the presence of an inherited eye disease, the treating ophthalmologist should either discuss the potential value of genetic testing with their patient and order the appropriate tests (if any) herself or himself or should offer a referral to another physician or counselor with expertise in the selection and interpretation of genetic tests. The ophthalmologist should strive to make the most detailed and specific clinical diagnosis possible to aid in the proper ordering and interpretation of the test. Ophthalmologists who order genetic tests either should provide genetic counseling to their patients themselves, if qualified to do so, or should ensure that counseling is provided by a trained individual such as a board-certified medical geneticist or genetic counselor. Treating ophthalmologists also should ensure that their patients receive a written copy of their genetic test results.

There are a number of web-accessible resources available to help ophthalmologists choose appropriate genetic tests and to locate knowledgeable genetics professionals to assist them with specific patients. For example, the National Institutes of Health Genetic Testing Registry ([www.ncbi.nlm.nih.gov/gtr/](http://www.ncbi.nlm.nih.gov/gtr/)) is a new web-based clinical tool that includes a database of Clinical Laboratories Improvement Amendments–approved genetic tests and context-specific

links to key resources such as GeneReviews, professional practice guidelines, PubMed reviews, and Online Mendelian Inheritance in Man(r) (OMIMr) records. There is also an assortment of clinical referral resources including links to the American College of Medical Genetics (<http://www.acmg.net>), the American Board of Genetic Counseling (<http://www.abgc.net>), and the National Society of Genetic Counselors (<http://www.nsgc.org>). The websites of the latter organizations provide listings of genetics professionals by zip code.

### The Definition of Genetic Testing

In the broadest sense, any clinical or laboratory investigation that provides information about the likelihood that an individual is affected with a heritable disease can be considered a genetic test and carries with it many of the attendant benefits and risks. For example, the ophthalmoscopic identification of multiple retinal angiomas in the child of an individual with von Hippel-Lindau disease will have the same medical, psychological, and insurability ramifications as a DNA-based test that identifies the causative mutation in this individual. Neither test is infallible, because ophthalmologists can make errors in clinical observation, and laboratory technicians can make errors in the physical manipulation of a sample. However, with proper care and training, such errors can be very rare in both cases. The primary differences between modern DNA-based testing and other

diagnostic methods are that DNA based methods (1) can establish the predisposition to a genetic disease decades before the disease will be detectable by even the most sensitive clinical tools (i.e., presymptomatic testing) and (2) can evaluate numerous molecular hypotheses concurrently. The clinical value of a genetic test is maximized when its results and implications are explained thoroughly and are discussed with the patient by a knowledgeable physician or trained counselor. Thus, for the purposes of this document, a genetic test is defined as the sum of 5 parts: (1) the clinical determination that a genetic eye disease is likely to be present, (2) the molecular investigation of genomic DNA samples from 1 or more individuals, (3) the analysis of the resulting molecular data in the context of relevant published literature and public databases using appropriate statistical methods, (4) the interpretation of the data in the context of the clinical findings, and (5) the counseling of the patient about the interpreted findings and their implications. It is important to consider the cost of all 5 components as one seeks to maximize the benefit per health care dollar of these powerful genetic technologies.

### Presymptomatic Testing

Presymptomatic testing has 3 significant potential advantages. It can allow (1) a physician to administer a preventive therapy before clinically detectable damage to tissues has occurred, (2) a physician to increase surveillance for treatable manifestations of the disease, and (3) at-risk individuals to make informed reproductive and career decisions at a time in their lives when a disease is not yet clinically detectable. However, the first 2 of these advantages depend on the availability of some type of effective therapeutic intervention for at least some of the manifestations of the disease, and the third is typically important only to adults.

### Parallel or Bundled Testing

The parallel testing of numerous genetic loci, such as occurs with whole exome sequencing, has the theoretical advantages of reducing the cost per locus of testing, reducing the dependence on an accurate and specific clinical diagnosis, and facilitating the discovery of new disease-causing genes. For example, one can now assess more than 90% of the coding sequences in the human genome (nearly 20 000 genes and more than 50 million nucleotides) at a cost that is comparable with more conventional tests that specifically assess only a few genes. Thus, one in principle could discover the 2 variations responsible for a patient's autosomal recessive condition with little more pretest diagnostic information than retinal degeneration. However, there are 4 factors that currently limit the usefulness of unfocused, massively parallel testing in the routine practice of medicine: (1) the vast amount of incompletely characterized sequence variation in the genome, (2) the cost of meaningful analysis of such variations in individual patients, especially in the context of public databases and other published

medical literature, (3) the inability to determine the parental origin of potentially recessive alleles without also testing family members, and (4) the financial and psychological cost of counseling a patient concerning the clinical ramifications of any and all potentially disease-causing variations observed in their genome. For example, the detection of 2 amino acid-altering variants in a gene known to cause autosomal recessive Stargardt disease would be much less likely to be relevant to a patient with the clinical findings of retinitis pigmentosa and hearing loss than the observation of a single coding sequence mutation in a gene known to cause Usher syndrome. The opposite would be true for a patient with normal hearing and early-onset macular disease.

A major issue with extensively parallel genetic testing (e.g., hundreds or thousands of genes) is the collateral discovery of numerous clinically relevant findings that are unrelated to a patient's presenting symptoms. For example, 1 in 25 white individuals is a carrier for cystic fibrosis. There is a significant financial and emotional cost associated with counseling a patient with an eye disease about the possibility or reality of discovering a mutation known to cause cystic fibrosis, breast cancer, colon cancer, or a neurodegenerative disease. The chance of making such a discovery, and thereby incurring the responsibility for appropriate counseling and referral to other health care specialists, is proportional to the amount of the genome one assesses in each genetic test.

Despite the foregoing, there are some situations in which limited parallel testing is the most effective strategy. When a clinical disease is caused by multiple different genes (e.g., nonsyndromic retinitis pigmentosa, Usher syndrome, Leber congenital amaurosis, and Bardet Biedl syndrome), it often is best to order a single test that has been designed specifically to evaluate efficiently all of the genes known to cause the patient's clinical findings.

### Monogenic versus Complex Disease

Some inherited diseases are caused by mutations in a single gene, and the detection of the responsible mutations can predict the development of the disease with relatively high accuracy. Such monogenic disorders tend to be fairly rare in the population (e.g., Best disease and the *TGFBI*-related corneal dystrophies) and tend to be transmitted in one of the recognizable inheritance patterns: autosomal dominant, autosomal recessive, X-linked, or mitochondrial. Other heritable disorders are caused by the interaction of variants in multiple genes with each other and the environment. Complex disorders (e.g., age-related macular degeneration and glaucoma) tend to be more common in the population than monogenic diseases, and the presence of any one of the disease-associated variants is not highly predictive of the development of disease. In many cases, standard clinical diagnostic methods like biomicroscopy, ophthalmoscopy, tonography, and perimetry will be more accurate for assessing a patient's risk of vision loss from a complex disease than the assessment of a small number of genetic loci. Genetic testing for complex diseases will become relevant to the routine practice of medicine as soon as clinical trials

can demonstrate that patients with specific genotypes benefit from specific types of therapy or surveillance. Until such benefit can be demonstrated, the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted.

### Clinically Relevant Turnaround Time

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In general, the speed with which a genetic test is performed, interpreted, and reported is directly proportional to its cost. This is especially true for relatively rare conditions for which batched processing can be used to reduce the cost when a short turnaround time (e.g., 2 weeks) is not clinically necessary. Most inherited eye diseases are slowly progressive and patients are rarely examined by their physicians more than once per year. Thus, in some cases, it is reasonable to take advantage of the cost reduction afforded by a longer turnaround time (e.g., 6 months), whereas in others, the additional cost associated with an expedited test is worthwhile because it may allow more rapid access to effective therapy or to information that is needed urgently for family planning or career decisions. Thus, we support the concept of the clinically relevant turnaround time, in which laboratories can perform tests at different speeds according to the specific clinical situation, resulting in maximum clinical benefit at the lowest possible cost.

### Specific Recommendations

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1. Offer genetic testing to patients with clinical findings suggestive of a Mendelian disorder whose causative gene(s) have been identified. If unfamiliar with such testing, refer the patient to a physician or counselor who is. In all cases, ensure that the patient receives counseling from a physician with expertise in inherited disease or a certified genetic counselor.
2. Use Clinical Laboratories Improvement Amendments–approved laboratories for all clinical testing. When possible, use laboratories that include in their reports

estimates of the pathogenicity of observed genetic variants that are based on a review of the medical literature and databases of disease-causing and non–disease-causing variants.

3. Provide a copy of each genetic test report to the patient so that she or he will be able independently to seek mechanism-specific information, such as the availability of gene-specific clinical trials, should the patient wish to do so.
4. Avoid direct-to-consumer genetic testing and discourage patients from obtaining such tests themselves. Encourage the involvement of a trained physician, genetic counselor, or both for all genetic tests so that appropriate interpretation and counseling can be provided.
5. Avoid unnecessary parallel testing—order the most specific test(s) available given the patient’s clinical findings. Restrict massively parallel strategies like whole-exome sequencing and whole-genome sequencing to research studies conducted at tertiary care facilities.
6. Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies.
7. Avoid testing asymptomatic minors for untreatable disorders except in extraordinary circumstances. For the few cases in which such testing is believed to be warranted, the following steps should be taken before the test is performed: (1) the parents and child should undergo formal genetic counseling, (2) the certified counselor or physician performing the counseling should state his or her opinion in writing that the test is in the family’s best interest, and (3) all parents with custodial responsibility for the child should agree in writing with the decision to perform the test.

### Footnotes and Financial Disclosures

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