

# Molecular Diagnosis and Genetic Counseling in Ophthalmology

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**T**he science of genetics is impacting medicine at a rapid pace. Through efforts such as the Human Genome Project and the HapMap Project, our knowledge of the human genetic landscape is rapidly evolving.<sup>1,2</sup> The number of genes known to cause mendelian genetic disease in ophthalmology has greatly increased over the past decade (**Figure 1**).<sup>3</sup> With the identification of mutations in complement factor H as a major risk factor for age-related macular degeneration, vision science is also at the forefront of tackling the problems of more common, complex diseases.<sup>4-6</sup>

The tools of genetic diagnosis, however, are not just for the laboratory scientist; they have the potential to revolutionize the way ophthalmology is clinically practiced. Consider a family who has just had a child affected by what appears clinically to be Leber congenital amaurosis. Molecular diagnosis may offer this family a confirmation of the diagnosis, a definition of the recurrence risk, the possibility of future prenatal diagnosis, and even potential treatment trials.

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However, like any other tool in medicine, genetic tests have to be ordered and interpreted correctly and responsibly to avoid doing harm. This requires a thorough knowledge of the capabilities and the limitations of genetic testing, as well as a compassionate understanding of the counseling principles that go hand in hand with genetic testing. We will begin by reviewing select laboratory tests and their relevance to clinical practice. Before a tube of blood is drawn or a sample taken, however, patients must be counseled as to the indications, ramifications, and alternatives to genetic testing. We will therefore proceed with a discussion of the role of ge-

netic counseling in ophthalmology and end with suggestions on how to integrate molecular medicine into your practice.

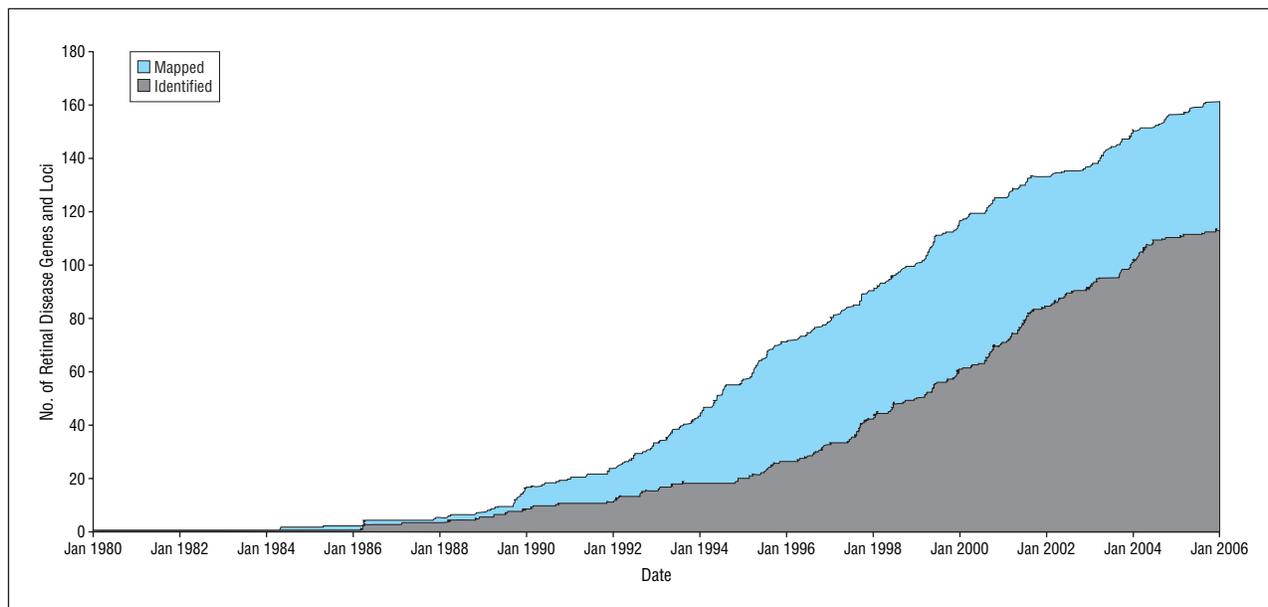
## GENETIC TESTING IN OPHTHALMOLOGY

### Cytogenetics

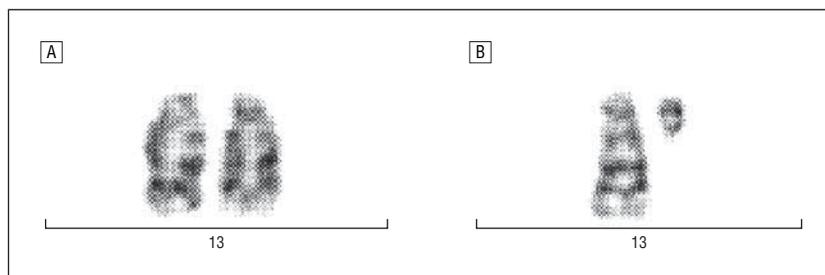
Humans have 22 pairs of homologous autosomes and 2 sex chromosomes (XX in females, XY in males) for a total normal chromosome number of 46. During the process of meiosis, these chromosomes pair, recombine, and segregate such that each gamete normally receives 1 homologue of each autosome and 1 sex chromosome. The process of fertilization restores the amount of genetic material to the normal state.

During mitosis, chromosomes can be visualized microscopically after staining with an agent such as Giemsa (G-banding). Each chromosome has a characteristic banding pattern, consisting of alternating light and dark bands. The resolution of this cytogenetic technique, known as karyotyping, ranges from approximately 450 to 850 bands, depending on the exact phase of mitosis examined. Even at its highest resolution, however, karyotyping only provides a broad overview of the genetic landscape; each chromosomal band represents large segments (megabases) of DNA and multiple genes.

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**Figure 1.** The number of cloned genes and genetic loci associated with inherited retinal disease as a function of time. Data and figure courtesy of Stephen P. Daiger, PhD, the University of Texas Health Science Center (<http://www.sph.uth.tmc.edu/retnet/sum-dis.htm#D-graph>).



**Figure 2.** Example of somatic mosaicism for a cytogenetic abnormality in a 4-month-old boy seen at the ophthalmology clinic for evaluation of bilateral uveal colobomata. He had a history of failure to thrive, agenesis of the corpus callosum, conductive hearing loss, dysmorphic facial and skeletal features, small kidneys, and hypospadias. Although a karyotype of peripheral blood lymphocytes was normal (A), a repeat study on a skin biopsy specimen revealed almost complete absence of 1 homologue of chromosome 13 (B). Because this abnormality would be predicted to delete the retinoblastoma gene locus on 13q14, the patient began surveillance for the presence of ocular tumor. Karyotype images courtesy of Children's Hospital of Oakland.

Occasionally, the nature of the genetic material in a gamete (sperm or egg) is not normal and the fetus/child who inherits this genetic material may, therefore, have disease. Abnormalities range from aneuploidy (a chromosome number not a multiple of 23) to more subtle abnormalities, such as partial deletion or duplication of chromosomes, insertions, and translocations. Occasionally, individuals have chromosomal abnormalities in some, but not all, of their cells (mosaicism, **Figure 2**).

A more detailed view of chromosomal structure can be obtained by probing for specific genomic DNA sequences with fluorescently tagged probes (fluorescent in-situ hybridization). Fluorescent in-situ hybridization enables for the detec-

tion of smaller abnormalities that cannot be detected using traditional karyotyping. For example, in their recent review of chromosomal abnormalities in patients with aniridia, Crolla and van Heyningen<sup>7</sup> found that 13 of 30 patients studied had chromosomal abnormalities on the short arm of chromosome 11 (11p13) that were only detectable by fluorescent in-situ hybridization. Because 3 of these cases involved the *WT1* tumor suppressor gene, this test had tremendous clinical impact on clinical tumor surveillance (**Figure 3**).

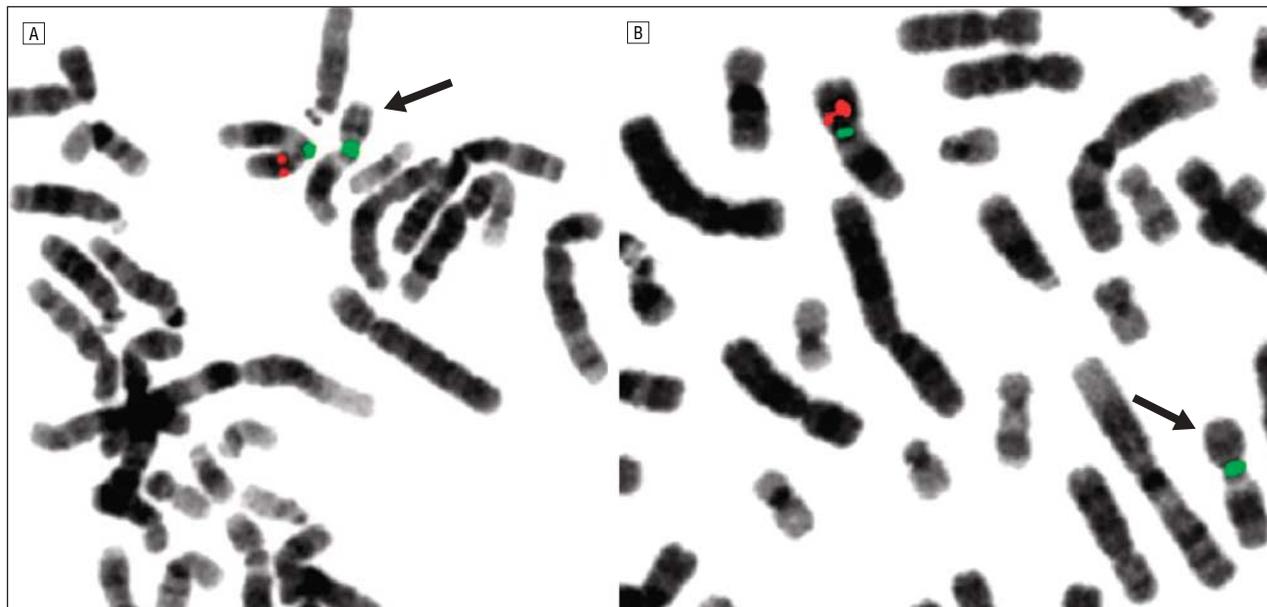
Newer technologies are allowing the interrogation of smaller and smaller pieces of the human genome, blurring the traditional boundaries between cytogenetics

and molecular biology.<sup>8</sup> Methods such as comparative genomic hybridization are useful for detecting small deletions and/or duplications in chromosomes. Because tumor progression is often accompanied by such chromosomal abnormalities, comparative genomic hybridization arrays may potentially be helpful in assessing prognosis and treatment in ocular oncology.<sup>9,10</sup> These "array-based" techniques are generally not as useful in detecting complex genomic rearrangements (eg, inversions).

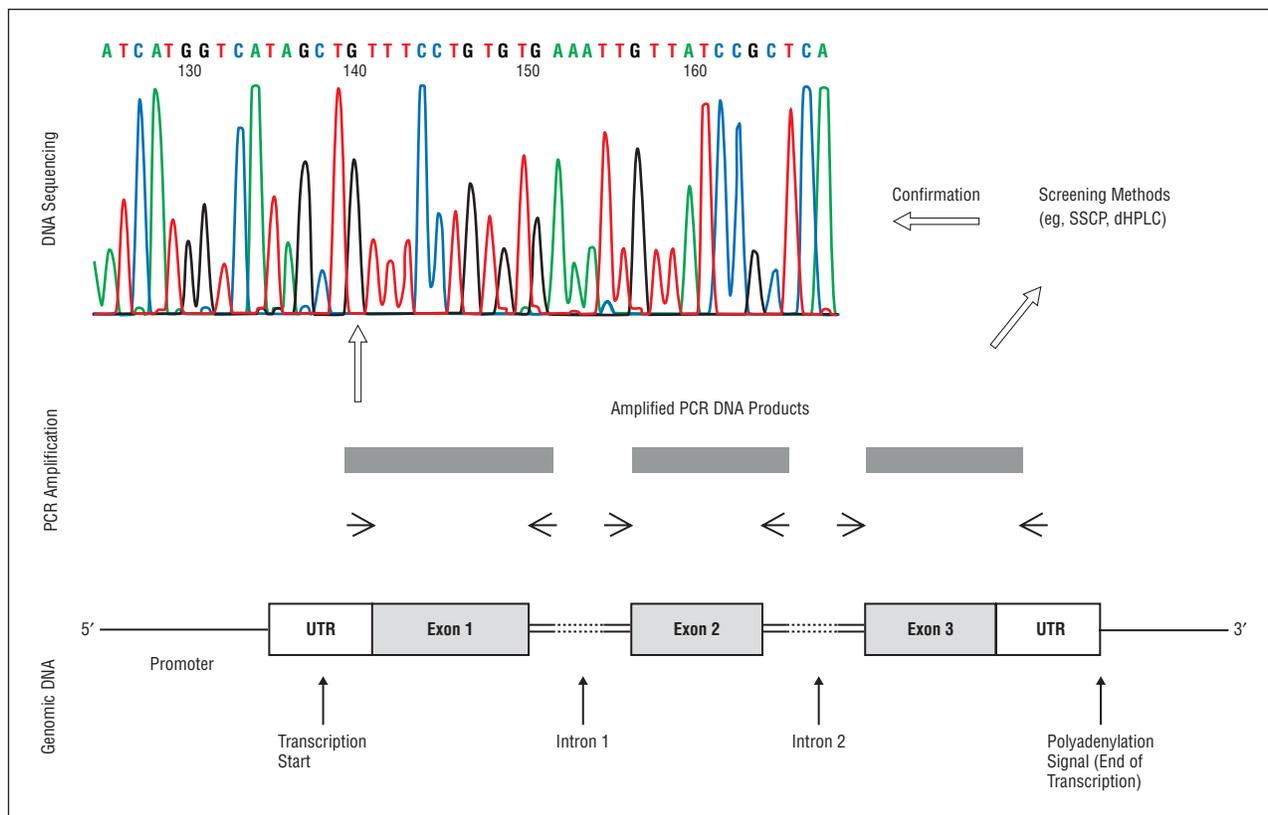
#### DNA Sequence Analysis

Many times, however, genetic disease is not caused by the relatively large changes in DNA content or arrangement amenable to cytogenetic analysis; the changes in DNA responsible for disease may be as "small" as a change in a single DNA nucleotide base pair. These changes are best analyzed with DNA sequence analysis.

Genes are composed of several functional components (**Figure 4**).<sup>11</sup> The DNA sequence that is initially transcribed into messenger RNA (mRNA) is composed of both intron and exon sequences. Through a complex, regulated process of splicing, the intronic sequences are removed and a mature mRNA results. This mRNA is, in turn, translated into



**Figure 3.** Fluorescent in situ hybridization (FISH) can be used to detect chromosomal deletions too small to be resolved using classic cytogenetic techniques. In the technique, fluorescently labeled DNA sequences complementary to chromosomal areas of interest are hybridized to patient DNA. In this example, the green probe hybridizes to the center (centromere) of chromosome 11, while the red probe hybridizes to an area that includes the *PAX6* gene. Although a cytogenetic abnormality was detectable with G-banding in patient A, this deletion was too small to detect in patient B without the aid of FISH. Arrows indicate the deleted chromosome 11 (absence of red signal). Because the Wilms tumor suppressor gene, *WT1*, lies in the same genomic region as the *PAX6* gene, patients with such cryptic deletions also could have *WT1* deletion and require tumor surveillance. Images have been digitally enhanced to show banding patterns of chromosomes in addition to FISH signals. Karyotypes were kindly provided by John Crolla, PhD, and Veronica van Heyningen, PhD. Images were prepared by Viv Maloney, "PhD."



**Figure 4.** A hypothetical, 3-exon gene. Recall that genes are composed of exons (light gray boxes) and intervening DNA sequences are removed by the splicing process (introns, double lines between exons). The rate of transcription of messenger RNA from DNA is regulated by other noncoding sequences of DNA (eg, promoters and enhancers). Specific DNA sequences can be amplified using specific primers (denoted by open arrows) via the polymerase chain reaction (PCR). In most cases, the sequences that are amplified in molecular diagnosis are exons and the exon-intron boundaries (dark gray rectangles). These PCR products are then either directly sequenced or screened for mutations using technologies such as single-strand conformational polymorphism (SSCP) analysis or denaturing high-performance liquid chromatography (dHPLC). Any abnormality detected with these screening methods is then confirmed by direct sequencing. If a mutation were to occur deep within an intron or in the promoter region, it would go undetected. Therefore, negative results from this kind of molecular analysis need to be interpreted with caution. UTR indicates untranslated region.

protein. The transcription of these sequences is regulated by other DNA sequences (ie, promoter and enhancer sequences).

A typical scenario for molecular diagnosis is presented in Figure 4. Primer sequences complementary to sequence flanking the exons of a gene suspected to cause disease are used in the polymerase chain reaction to amplify exonic sequences (ie, transcribed and translated into a protein product) and the area of the exon-intron boundaries (ie, the areas where splicing of the mRNA occurs). These sequences are chosen to pick up changes that might affect the corresponding protein sequence or mRNA splicing. Mutations (changes in the normal DNA sequence of a gene) can then be detected in the amplified DNA segments directly with standard DNA sequencing techniques. Alternatively, if a large number of polymerase chain reaction products are to be analyzed, screening (indirect) techniques such as single-strand conformation polymorphism analysis or denaturing high-performance liquid chromatography analysis can be used to screen for a change; direct sequencing can then determine the exact nature of the change. While convenient for handling a large number of samples, these indirect sequencing methods are neither as sensitive nor as specific as direct sequencing. Typically, promoter, enhancer, and deep intronic DNA sequences are not amplified and are therefore not analyzed. Reasons why a pathological sequence change is not detected using this technique could therefore include: (1) the gene studied is not the gene responsible for the condition; (2) the sequence change is outside of the region of the gene that is ascertained; or (3) the patient is heterozygous for a chromosomal deletion or rearrangement, such that 1 allele (ie, the specific DNA sequence at this position on one of the chromosomes) does not amplify with the polymerase chain reaction primers used.

Once a sequence change has been identified, how do we know that it is truly causative of the disease in our patient?<sup>12</sup> In general, sequence changes that are predicted to result in premature truncation of the cor-

responding protein (ie, nonsense or frameshift mutations) are pathological. Changes that are predicted to change 1 amino acid to another without otherwise affecting protein primary sequence (missense mutations) and those that are around splicing junctions can be more difficult to interpret. Supportive evidence that a missense sequence change is pathological includes: (1) it cosegregates with the disease in a family where more than 1 member is affected, such that those who are affected have the sequence change and those who are unaffected do not have the change; (2) the protein primary sequence is well conserved across different species and/or across other members of its protein family, suggesting that evolutionary pressures have preserved this residue; (3) it is not found in unaffected controls of the same ethnic population; (4) it has been previously reported in other unrelated affected individuals; (5) it changes the nature of the amino acid drastically (eg, from an amino acid with a small side chain to one with a bulky side chain); and (6) it has been shown to have functional significance in a cellular or animal model system.

Direct sequencing to identify mutations can be quite time-consuming and costly, especially if a disease can be caused by mutations in any one of a number of genes (eg, retinitis pigmentosa or Leber congenital amaurosis). Hierarchical testing strategies have been proposed for genetic testing to improve efficiency and reduce cost.<sup>12</sup> As mentioned previously, screening methods such as single-strand conformation polymorphism analysis and high-performance liquid chromatography are useful when screening the same exons repeatedly in multiple samples. The use of high-throughput microarray technology also allows for the interrogation of multiple genes for a disease (eg, retinitis pigmentosa or Leber congenital amaurosis) in a single experiment.<sup>13,14</sup> Some microarray technologies test for the presence or absence of specific, previously identified mutations, whereas others test for any change across the entire sequence of a gene (resequencing chips). Because the former may miss new mutations, negative re-

sults on this platform should be interpreted with caution.

## GENETIC COUNSELING IN OPHTHALMOLOGY

The diagnosis of an inherited and/or congenital ophthalmic condition often comes “out of the blue” for families. Such diagnoses generally evoke powerful feelings, such as fear, anxiety, helplessness, fatalism, loss, and guilt. Even with a long-standing diagnosis or a known family history, deciding to pursue genetic testing comes with emotional and practical ramifications. These should be addressed prior to and as a follow-up to testing, as part of genetic counseling.

### Conceptual Framework

According to the National Society of Genetic Counselors,

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.<sup>15(p77)</sup>

It may first be useful to review some guiding principles of genetic counseling because these provide the framework in which genetic testing is offered to date. Walker<sup>16</sup> cites 7 genetic counseling principles, many derived from principlism—an ethics theory based on the principles of autonomy, beneficence, nonmaleficence, and justice, used as guidelines to analyze specific ethical cases. While testing may be a favored option for a health care professional, the first principle remains that of voluntariness: patients ought to decide for themselves and their families whether genetic testing is indeed their best option. Two other related principles are those of education—patients should have sufficient information at hand to make a reasonable decision for themselves—and complete disclosure of all relevant information by the health care

professional since selectively withholding information is viewed as going against a patient's autonomy. In the same spirit, counseling should be both nondirective and empowering: options should be presented in a neutral manner, and patients should be given the ability to best use this information by the health care professional eliciting and exploring the patient's personal circumstances. The last 2 principles of Walker are more universal, namely equal access to genetic services and protection of patient privacy and confidentiality.

Genetic testing may be carried out for different purposes. These include to (1) confirm a diagnosis in an affected individual and sometimes assess the prognosis for that individual when phenotype (the observed characteristics of a person)-genotype (the genetic makeup of a person) correlations have been recognized; (2) determine the carrier status of an individual, either for an autosomal recessive or an X-linked condition; (3) ascertain a predisposition to a late-onset disease or establish a presymptomatic diagnosis; and (4) assist with preimplantation diagnosis, prenatal diagnosis, and newborn screening.<sup>17</sup> In the next subsection are considerations common to all testing purposes and a few topics circumscribed to specific forms of testing. Such considerations ought to be discussed with the patient prior to testing because genetic testing generally requires informed patient or parental consent (newborn screening being an exception). The extent of the discussion with the patient will, however, depend on factors such as information availability, receptivity and interest of the patient, and time constraints. Some of this information should be revisited with the patient when results become available. Because of these complexities, we recommend that a professional well versed in genetics and genetic counseling (eg, a clinical geneticist, a genetic counselor) be involved when molecular testing is being considered.

#### Possible Areas for Discussion

**Test Specifications.** The discussion should first establish what will be tested (gene[s], chromosomes,

biochemical marker) and the rationale for doing so. This should include a clear explanation of whether and how test results will influence disease management. It should address which method will be used and what its benefits and limitations are. A piece of information sometimes requested by patients is test sensitivity (the proportion of individuals with a specific diagnosis whose test results are positive). When available, such information is important in anchoring patients' expectations as to possible test results. A different concept, the positive predictive value of a test (the probability of being affected given a positive result), is equally useful in setting expectations. What these results may be (positive, negative, of unknown significance) and when they may become available should also be provided to the patient. Patients should understand that not all genetic tests can give immediately useful information; in some cases, patients may be handed a result that cannot be interpreted. Even in the presence of a known mutation, it may be difficult to predict disease severity in an individual (variable expressivity). Testing costs and whether they are covered by insurance should be clearly ascertained because some genetic tests can cost several thousands of dollars. Patients should be aware that if an insurance company pays for a test, that company is entitled to the test results. The risk for human error or possibility of test failure should be raised, however small it may be. This may prevent patient confusion if a new blood sample is needed, for instance. Finally, alternatives to genetic testing, whether they be clinical testing or no testing at all, should be presented to the patient; this should include the right to change one's mind and not receive test results in the end.

**Nonpaternity and Adoption Disclosures.** Patients and their families should be made aware of the possibility to uncover nonpaternity and adoption in cases of linkage analysis or DNA testing involving several family members. These are non-trivial issues not only involving family dynamics but also influenc-

ing test usefulness and interpretation. The commonly quoted nonpaternity rate is 10% to 15%, with estimates ranging from 1.4% to 30%.<sup>18</sup> From 2% to 4% of American families include an adopted child.<sup>19</sup>

**Privacy and Discrimination.** Patients may be interested in testing and sharing results with close relatives, but at the same time, patients may be concerned with the privacy of their genetic information and fear discrimination from employers or insurers.<sup>20,21</sup> This issue may be particularly salient for patients seeking testing for predictive purposes. The current policy landscape provides inconsistent protection against genetic discrimination.<sup>22</sup> At the federal level, the Americans with Disabilities Act,<sup>23</sup> the Social Security Act,<sup>24</sup> and the Health Insurance Portability and Accountability Act<sup>25</sup> offer limited and often untested protections. The Health Insurance Portability and Accountability Act prohibits health insurers in the group market only from using genetic information in determining insurability. Federal employees are protected against employment discrimination based on genetic information under Executive Order 13145.<sup>26</sup> At the state level, laws are diverse, with 41 states having enacted laws related to genetic discrimination by health insurance companies and 32 states having laws against discrimination in the workplace.<sup>27</sup> Comprehensive federal legislation is being considered; in February 2005, the Genetic Information Non-Discrimination Act of 2005<sup>28</sup> passed 98 to 0 in the Senate. An identical bill was introduced in the House in 2005. This bill, which now has more than 240 sponsors, is currently under consideration by 3 committees.<sup>29</sup> The National Society of Genetic Counselors has created a brochure for patients about genetic discrimination, which can be downloaded from their Web site ([http://www.nsgc.org/consumer/genetic\\_discrimination\\_resource.cfm](http://www.nsgc.org/consumer/genetic_discrimination_resource.cfm)).

**Psychosocial Ramifications of Testing.** Learning about one's genetic makeup may evoke many feelings in patients and, in the terms of Rolland and Williams, raise "devel-

opmental challenges.”<sup>30</sup> It is not uncommon for patients and their families to express their eagerness to learn as much as possible about themselves; information gathering is a known coping mechanism to regain personal control over a situation seen as uncertain and threatening.<sup>31</sup> Others, however, may see little value in knowing the molecular underpinning of their condition. It is the health care professional’s role to “cue in” on some feelings patients may have or may develop and offer anticipatory guidance. The following are possible reactions to test results that may be discussed either during pretest or posttest counseling. This is not implying that they are always present; rather, these examples serve to raise awareness of reactions that will need attention. Determining that a mother is a carrier for an X-linked condition or has a mitochondrial disease or that a parent has a mutation causing a dominant condition can evoke powerful feelings of guilt and shame.<sup>32</sup> Obtaining a positive test result may make a diagnosis concrete for patients, thereby eliminating any hope that they might have a more benign condition; denial and its variations, disbelief, deferral, and dismissal, are coping mechanisms commonly used by patients reacting to the bad news of a clinical diagnosis.<sup>33,34</sup> Test availability may change family dynamics; there may be those who want to know and those who do not want to know but feel obliged to take action, and resentment may emerge. Test results may reveal information on many other family members, such as those with a mitochondrial DNA mutation, and issues of communication with relatives may be at stake. Given issues of confidentiality, deciding who should provide information to other family members is a complex matter that should be handled with care in collaboration with a genetics professional. Finally, the pretest discussion may uncover signs of maladjustment or depression in the patient. This is to be expected in the realm of ophthalmology because low vision has been associated with lower quality of life and emotional distress.<sup>35,36</sup> In such a context, a discussion should be engaged with the

patients as to their readiness for genetic testing. Indeed, studies have shown that pretest emotional state is a strong predictor of posttest distress for predictive testing.<sup>37</sup>

**Predictive (Predisposition, Presymptomatic, and Asymptomatic) Testing.** In conditions with incomplete penetrance or variable expressivity, testing may bring to light that an apparently healthy individual nonetheless carries a pathogenic dominant mutation, such as in some forms of retinitis pigmentosa. In other circumstances, testing may reveal that one carries a genetic change that may make one more susceptible to developing a condition, like with complement factor H and age-related macular degeneration, or that one will almost certainly develop a disease later in life, like spinocerebellar ataxia 7.<sup>38</sup> Predictive genetic testing has clear benefits, such as reducing uncertainty, creating knowledge and therefore a sense of control, or avoiding unnecessary surveillance. Research consistently indicates that individuals undergoing predictive testing within an adequate testing protocol do not seem to have long-term emotional distress,<sup>39-41</sup> provided they do not come to testing with psychological issues.<sup>37,42-44</sup> Such testing can sometimes pose challenges, however. Concerns about privacy and potential discrimination may arise because a positive result could be defined as a preexisting condition. While some may specifically seek testing for planning purposes, others may feel pushed into unanticipated decision making about their lifestyle or profession or communicating potentially life-altering information to siblings and/or children. Patients might also wrongfully construe positive results to predisposition testing as a certainty to develop disease, since it has been shown that individuals tend to see risk in a binary fashion.<sup>45</sup>

**Testing of Minors.** Testing in children and adolescents raises several ethical and legal considerations. When is a child mature enough to have a say in testing? How do you balance the right of the parents and the future right of the child to make

an autonomous decision? How can you reconcile helping a child know about and adjust to genetic risk and preserving that child from possible stigmatization?<sup>46</sup> Guidelines by the American College of Medical Genetics<sup>47</sup> and the National Society of Genetic Counselors<sup>48</sup> recommend testing only in cases where an obvious medical or psychosocial benefit exists. Some have argued that, while medical benefit can generally be easily sorted out, the psychosocial benefit is often reduced to autonomy issues. Consequently, a more global, family-centered approach may be more beneficial in determining whether testing is justified in a minor rather than strictly following guidelines.<sup>46,49</sup>

**Prenatal Testing.** Prenatal testing is available for a subset of eye conditions regularly tested in clinical and research laboratories. When faced with a request for prenatal testing, the health care professional ought to first verify testing availability and modalities; custom testing may be available when a mutation has been ascertained in a family. GeneTests,<sup>50</sup> a reference Web site funded by the National Institutes of Health and sponsored by the University of Washington, offers an easy way to determine testing availability for a large variety of genetic conditions. It is also essential to have a discussion with the parent(s) to clarify the reasons for requesting prenatal testing and explore the possible decisions the parent(s) may face with a positive result, such as financial planning or abortion. The goal is not to encourage or deter testing; rather, it is to help parent(s) make as informed a decision as possible and be comfortable with their choice.

**Posttest Counseling.** Studies have shown that patients receiving positive test results not only expect some information about what the test results mean but also want social support and a discussion of options.<sup>51,52</sup> In other words, patients want the health care professional who delivers the test results to show some empathy and acknowledge any painful news. They also want suggestions for next steps. These may include a roadmap for screening or preventive mea-

tures, meeting with a counselor or receiving referral to psychological services, or being given contact information for support groups. The latter information may be found on the Genetic Alliance Web site.<sup>53</sup> The Genetic Alliance is a nonprofit organization that represents many advocacy groups in the genetics community.

### INTEGRATING MOLECULAR DIAGNOSIS IN YOUR PRACTICE

We would like to end with a few practical suggestions for integrating molecular diagnosis in your practice. First, identify and develop a relationship with local genetics professionals; their familiarity with the counseling issues and the mechanics of testing will expedite the process. A list of board-certified geneticists can be found at <http://genetics.faseb.org/genetics/abmg/abmg-listings.html>. Similarly, directories of genetic counselors can be found at <http://www.nsgc.org/resourcelink.cfm> and [http://www.abgc.net/genetics/abgc/abgc\\_diplomates.htm](http://www.abgc.net/genetics/abgc/abgc_diplomates.htm). The Online Mendelian Inheritance in Man database<sup>54</sup> provides a current overview of genes, clinical syndromes, and mutations. Fan et al<sup>55</sup> provide a useful table of additional Web-based resources in their recent review of molecular diagnosis of eye disease.

As previously mentioned, the GeneTests Web site<sup>50</sup> provides links to current review articles about a broad range of inherited diseases, lists of research and clinical laboratories performing molecular testing, and links to patient resources. Testing laboratories often provide useful links that describe the details of sample collection, cost, and shipping. For a test to be used in the clinical care of a patient, the laboratory must have been accredited by a government organization known as CLIA (Clinical Laboratory Improvement Amendments). Tests done on a research basis are generally considered preliminary and must be confirmed before results can be given to a patient. One such CLIA-approved laboratory, The Carver Laboratory at the Univer-

sity of Iowa,<sup>56</sup> is specifically dedicated to providing nonprofit genetic testing for a broad range of inherited eye diseases.

The National Eye Institute has recently established The National Eye Disease Genotyping Network.<sup>57</sup> The purpose of The National Eye Disease Genotyping Network is to create a repository of DNA samples from patients with specific inherited eye diseases that is coupled with anonymous phenotypic information; this effort will hopefully accelerate the pace of our molecular understanding of these diseases. As part of this endeavor, patients will have the option to have CLIA-approved molecular genetic testing for numerous disorders. It is our hope that a "side effect" of this project will be to make molecular diagnosis an integral part of the practice of ophthalmology and that it will provide an entrée to patients with inherited eye disease into important clinical studies.

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