Published in final edited form as:
Am J Ophthalmol. 2010 January ; 149(1): 10. doi:10.1016/j.ajo.2009.08.038.

From the Laboratory to the Clinic: Molecular Genetic Testing in Pediatric Ophthalmology

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Types of Genetic Testing Available

Ever since the first genes for genetic eye diseases were discovered, DNA testing for diagnostic purposes has been available to some patients. In 1989 a method was reported for laboratory differentiation between germline and non-heritable retinoblastoma [1] and soon after, rhodopsin mutations were noted to be the cause of some autosomal dominant retinitis pigmentosa. [2] Seemingly overnight, a new era began in ophthalmology. A specialty that was formerly based largely on clinical diagnosis, and often on subtleties of appearance, morphed into a field where retinopathies that appeared identical with the ophthalmoscope were found to be caused by different mutations in the same gene, or even by mutations in different genes altogether. In addition, some ocular disorders that appeared to be completely different from each other clinically have been found to be caused by mutations in the same gene.

While a clinical diagnosis would have sufficed for most patients a generation ago, the explosion of molecular discoveries during the past two decades has fueled many patients' desire for a rapid and accurate molecular diagnosis of their disease. As a result, clinicians will need to acquire a new level of understanding about how molecular biology is used to understand and ultimately impact the pathophysiology of these diseases. Like much of ophthalmology, this is a constantly changing landscape. This review will discuss why genetic testing is important, and how active clinicians can incorporate it into their practice in a practical and effective manner.

In the past, many dedicated ophthalmologists sent their patients' blood samples to research laboratories only to find that they rarely received any results from these investigations. While some patients did receive a genetic diagnosis, the physician was often required to field many requests for updates on the status of their testing with the answer, “I don't know.” Patients and

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Financial disclosures: None.

Contributions of Authors: Design of Study (SRL); Conduct of Study (AVD, SRL, EMS); Collection, management, analysis, interpretation of data (AVD, SRL, EMS); Preparation, review and approval of manuscript (AVD, SRL, EMS).

their doctors had an unspoken “fee for service” expectation of performance from the research labs, while in fact the research labs had insufficient personnel, instrumentation and/or communication strategies to deliver test results with this degree of customer service. Fortunately, clinicians and patients are gaining a greater appreciation for the complexity of genetic testing at the same time that research and commercial laboratories are gaining a greater understanding of their collaborators' and clients' needs. Thus, the expectation gap is closing for many genetic tests for eye diseases.

All fee for service testing, and some research testing, is performed using validated laboratory procedures specified by the Clinical Laboratory Improvement Act (CLIA). Currently available fee for service testing for inherited eye disease is very different from the research testing clinicians may have experienced in the past. First, there is a fee for the testing that is payable either by the patient or by their insurance carrier. More importantly, there is a written report, either positive or negative, that is generated and sent to the referring physician and/or patient in every case. Because many different genes can cause some inherited eye diseases, a negative report is usually not nearly as helpful in patient management as a positive one. In addition, because genes are still actively being found and certain alleles are observed only in certain populations, even “positive” results require more validation and qualification than a more routine lab test like a white blood cell count or liver enzymes. This will be discussed more fully below. Here, it is sufficient to emphasize the point that in order for a test to be offered in a fee for service manner, that test must be validated and performed in a laboratory that is certified to meet CLIA standards.

Today when a clinician suspects a genetic eye disease based on examination and testing in the office, an excellent first resource is the website www.genetests.org, managed by Roberta Pagon, MD, at the University of Washington, Seattle. This site is user-friendly, and allows the physician to query for testing for various diseases. There are links to laboratories at which fee for service testing for each disorder is done, as well as detailed information on how to send a sample. The site states what type of testing is offered, and whether carrier and prenatal testing is offered at each laboratory. Labs offering fee for service testing must be CLIA certified. Information on laboratories that offer research-based testing is also available on this site.

For patients with insurance, printing the forms for the laboratory of choice, having the physician fill out the appropriate fields, and taking the forms to a phlebotomy lab, are often all that is required. However, many insurance carriers will not pay for testing without pre-certification. Patients and/or physician office staff should call the carrier prior to having blood drawn to avoid surprise bills. In addition, as with all bills sent for payment to insurance carriers, each insurer has their own policies about which tests will be covered and which denied. In our experience, with appropriate attention to precertification, insurance companies will cover genetic testing for inherited eye disease about 80% of the time. However, it still behooves the physician to tell patients that each insurance plan is different, and that it is always safest to get a precertification number before even having the blood drawn. Because of the recent proliferation of fee for service genetic tests for all types of genetic disorders, many certified genetic counselors and genetic nurse specialists have become expert at getting precertification and coverage for genetic testing. For many clinicians, the most efficient way to obtain testing for a given patient is to refer them to a general genetics clinic with their suspected ocular diagnosis and paperwork for a lab offering testing in hand. This collaboration between ophthalmologist and geneticist/genetic counselor is ideal because the ophthalmologist can provide the clinical diagnosis, then the genetics clinic can organize DNA testing, interpret the results, and offer genetic counseling.

In many academic medical centers genetic eye disease clinics are being formed, which include an ophthalmologist with a specialty in genetic eye disease, in collaboration with a geneticist

and/or genetic counselor. These combination clinics can provide the best of both worlds in just one visit for the patient.

Fee for service laboratories will generally send the results to the ordering physician so he/she can discuss those results with the patient. The ordering physician must have a plan in advance for who will discuss and interpret the results with the patient. Many ophthalmologists prefer to work with a geneticist who will meet with the patient once the results of testing are obtained, since the discussion may be very complex. Recurrence risk in offspring, risk to other family members, reproductive options, and how to interpret both positive and negative results are outside the scope of many ophthalmologists' realm of practice. It is important to remember that essentially all genetic eye disease is heritable, but not all genetic eye disease is inherited. Spontaneous new mutations are not uncommon. In these patients there is no family history, but the genetic mutations may be passed on to subsequent generations. Some diseases have protean manifestations that only a very careful family history or examination of additional family members can elicit.

What the ophthalmologist can and should do is identify patients with likely genetic eye disease and make a tentative clinical diagnosis to direct genetic testing. Other members of the team can perform the genetic test, help explain it to the patient and help counsel the patient and their family. Thus a good working relationship between the patient, ophthalmologist, the laboratory, and the counselor is key to taking maximal advantage of genetic tests that are currently available.

Why is molecular genetic testing important in pediatric ophthalmology?

Molecular genetic testing is important for children with ocular diseases for a number of reasons. First, it is it critical for accurately diagnosing certain diseases. While a number of ocular diseases in children can be diagnosed based solely on clinical findings, there are certain diseases that cannot be diagnosed with confidence without molecular genetics. For example, in children without a family history of optic atrophy, it is only possible to definitely diagnosis Kjer's optic atrophy (OPA1) using molecular genetics.[3] There are other diseases in which molecular genetic testing can confirm the diagnosis in a situation in which the clinical findings are suggestive of one disease, but there is some overlap with other diseases. For example, a child may have findings suggestive of autosomal dominant familial exudative vitreoretinopathy (FEVR) caused by the frizzled-4 gene 4, but because of the overlap with other diseases such as persistent fetal vasculature and retinopathy of prematurity, molecular genetics may be necessary to definitely establish the diagnosis.5 While a positive test may be diagnostic, a negative test is not helpful in this disorder since there are several different genes and different modes of inheritance; it is estimated that only about 20% of index cases of FEVR are caused by currently detectable frizzled-4 gene mutations while another 20% are caused by mutations in LRP5, making the genetic diagnosis rate about 40% overall.6,7

Molecular genetic testing can often more accurately establish the risk of the disease occurring in future pregnancies as well as in the offspring of the child than can clinical diagnostics alone.

Obtaining a molecular genetics diagnosis is also important in terms of enrolling patients in clinical trials. Mutations in more than 14 different genes have been shown to cause Leber congenital amaurosis (LCA) and many of these affect retinal function in very different ways.[8] lt is not usually possible to distinguish between these different genetic subtypes on the basis of clinical findings alone. About 8% of patients with LCA have mutations in the retinal pigment epithelium-specific 65-kDa protein gene (RPE65).9 This gene encodes a protein that is required to isomerize all-trans-retinyl esters into 11-cis-retinal. Patients with the RPE 65 genotype have been shown to have a modest improvement in retinal function after the subretinal injection of adeno-associated virus carrying wild type RPE65 complementary DNA. 10,11,12 Because

there is a treatment available for at least one form of LCA, it seems incumbent on ophthalmologists to determine if a patient with LCA has RPE65-associated disease. For patients whose LCA is not caused by mutations in RPE65, accurately establishing the correct molecular cause may give them the opportunity to participate in new treatment trials as they become available for other genetic subtypes of the disease.

Molecular genetic testing can also be helpful in predicting future problems. If a child is known to be at risk for certain ocular or systemic diseases, the intervals for screening can be adjusted accordingly. For example, one of the authors was recently referred a 2 year old child with the 6p deletion syndrome. Because the deletion involved the FOXC1 gene which is one of the genes that has been shown to be associated with Axenfeld-Rieger anomaly [13,14], he was referred for an ocular examination. On examination, he was found to have posterior embryotoxon and subtle corectopia consistent with Axenfeld-Rieger anomaly. While he did not having any findings suggestive of glaucoma at that time, given that as many as 50% of patients with Axenfeld-Rieger anomaly develop glaucoma 15, he will be screened at more frequent intervals.

Molecular genetic testing can also be invaluable in assigning a risk to a patient with an ocular disease for developing certain systemic diseases. An example of this is sporadic aniridia. Autosomal dominant aniridia is caused by inactivation of one copy of the PAX6 gene at 11p13. Most patients with aniridia have an intragenic mutation, but as many as 18% of patients with sporadic aniridia have a deletion involving the Wilm's Tumor Suppressor gene, WT1, which is located near the PAX6 gene.16 While only one in 10,000 typical children develops Wilms tumor 17, the risk of developing Wilms tumor increases 67 fold in patients with sporadic aniridia.[18] Like retinoblastoma and the RB1 tumor suppressor gene, Wilms tumor is believed to arise from a loss of function of both WT1 tumor suppressor genes (i.e. the “two-hit” hypothesis). Abnormalities in the WT1 gene can be identified by chromosome analysis of 11p13 using fluorescence in situ hybridization (FISH). [19] Children with sporadic aniridia therefore benefit from referral to a genetist for DNA testing and should be screened on a regular basis for Wilms tumor if confirmed by genetic testing.

Another example of medical surveillance being guided by a specific genetic subtype is CEP290-associated LCA. We now know that different mutations of the CEP290 gene can cause isolated LCA, Joubert syndrome, Senior Loken syndrome, or Meckel Gruber syndrome [20,21]. Children diagnosed with CEP290 associated LCA should therefore have a screening renal ultrasound and regular urinalysis, and brain MRI should be considered at diagnosis.

Since the advent of genetic testing, it has become apparent that many diseases exhibit genetic heterogeneity. This means that a single phenotype (clinical presentation) can be caused by many different genes and/or different mutations in the same gene. Conversely, there can be phenotypic heterogeneity. This means the same gene, and in some cases even the same mutation, can cause different clinical appearances in different people. Genetic heterogeneity was initially a surprise, because ophthalmic diseases had been divided and subdivided by the best means possible at the time—ophthalmoscopic or slit lamp appearance. However as our understanding of these diseases grows, it is clear that genetic heterogeneity makes sense. Different gene malfunctions can easily lead to the same final common pathway of photoreceptor cell dysfunction and death, and the characteristic pigmentary changes seen in retinal degeneration, or to the loss of corneal or crystalline lens cell clarity resulting from abnormal cells in these tissues. For example, mutations in the ABCA4 and the RDS genes can cause very similar fundus changes that most clinicians would call retinitis pigmentosa. Yet other mutations in the ABCA4 and RDS gene cause only maculopathy which clinicians would call Stargardt disease or pattern dystrophy.

Bardet Biedl syndrome (BBS) is a multisystem disorder characterized by the unusual constellation of extra digits, obesity, renal disorders, reproductive disorders, developmental delays, and a progressive severe early onset retinal dystrophy. With such an unusual combination of features, one might think there would be only one gene in the human body that could cause this. Yet BBS is now known to be caused by at least 12 genes.[22] How can this be? A recent discovery shows that most of these genes contribute to a protein complex called the BBSome 23, which is important in cilia throughout the body. Now it makes perfect sense: if any one of the very different genes that contribute a piece to this BBSome complex is not working, the result is the same no matter which one of them it is: a cilia disorder. And many organs with cilia—such as brain, retina, gonads, kidney, olfactory receptors, hair cells of the ear—may be affected, linking the seemingly unrelated aspects of the disease. Of interest, CEP290 is also important in cilia.

In cases in which the same mutation causes different clinical presentations, it is likely that other modifying genes are involved that have not yet been discovered, or that there are environmental factors that play a role in how the gene is expressed. Two examples of this are the finding that variations in the Rpe65 gene modulate light damage susceptibility in mice, and influence the progression of retinal degeneration in transgenic mice with retinitis pigmentosa,[24] and that at least 2 loci on the X chromosome appear to influence how the 11778 mitochondrial mutation causes Leber Hereditary Optic Neuropathy [25].

For which ocular disorders is fee for service testing available?

Since the list of diseases for which fee for service testing is available lengthens daily, ophthalmologists should become familiar with www.genetests.org to determine which testing is available. For certain disorders there may be both research and fee for service testing options. At www.retinoblastomasolutions.org non-profit fee for service testing is offered for retinoblastoma. Bilateral and unilateral retinoblastoma patients and their families can be tested. Another non-profit genetic testing laboratory can be accessed at www.carverlab.org. Physicians can order fee for service testing for Leber Congenital Amaurosis, as well as many other disorders. Patients and families with LCA can also enroll in Project 3000, an initiative to genotype all 3000 people estimated to be living with LCA in the United States. Patients may opt to be contacted regarding research studies for this disorder as they become available, and can stay up to date with research progress.

Some disorders seen frequently in pediatric ophthalmology practice for which fee for service genetic testing is currently very useful are listed in Table 1. This list is not comprehensive.

For which ocular disorders is research testing available?

At www.clinicaltrials.gov patients and families can search for clinical trials for any disorder going on anywhere in the world.

The National Eye Institute has a program called eyeGene which accepts samples from patients with genetic eye diseases. Samples are analyzed at laboratories across the country and results are reported to the requesting doctor. Samples are then banked as a research repository. EyeGene can be accessed at eyegeneinfo@nei.nih.gov.

Limitations of Currently Available Genetic Testing

Are there some patients for whom genetic testing is not recommended? Patients who do not want a definitive diagnosis should not undergo genetic testing. Patients who do not wish to know their prognosis or who do not want to know their carrier status should not have testing. An estimate of the patient's chance of getting a useful result from each test should be part of

the discussion with the patient when one is deciding whether to order a genetic test, and if the patient feels the chance of a positive result is too low, they may opt against testing. At www.genetests.org, each disease for which testing is offered has a “GeneReview” section which discusses the current detection rates for different types of testing. For example, according to information on genetest.org at this writing, more than 90% of patients with oculocutaneous albinism type 1 (OCA1) will have at least one allele found with current testing, while the rate of detection for OCA2 is difficult to calculate due to the very large number of polymorphisms in this gene. The detection rate for neurofibromatosis type 1 (NF1) depends on the technique used to screen this very large gene; a multistep mutation detection protocol identifies about 95% of pathologic mutations. For NF2, where deletions as well as point mutations are fairly common, the detection rate is greater than 90% for familial cases but 72% for singleton patients. For Leber Congenital Amaurosis the detection rate is 50-60%. This information is rapidly changing and is updated frequently. The chance of obtaining a definitive result is steadily improving for most tests and if one has not ordered a specific test for several months it is wise to review this before talking with a patient.

In our experience, most patients want a definitive diagnosis, and are interested in testing if there is at least a 50% chance of getting a meaningful result. Each patient is different, so careful explanation and counseling about the state of genetic testing must be individualized for each person's disorder.

Some disorders for which genetic testing is available may not have a high enough detection rate to make testing useful for most patients. Many disorders require advanced knowledge of the clinical characteristics of the disorder, the inheritance pattern and the known molecular causes, to correctly interpret the results. For example, in autosomal recessive diseases, two copies of the abnormal gene must be found to be certain that the variations discovered are disease causing. However, some common recessive disorders, such as Stargardt disease and autosomal recessive albinism, have a very high rate of finding only one of the two mutations with current technology. Now that many convincingly disease-causing mutations are known for both diseases, meaningful reports can be generated in some cases based upon the finding of only a single allele. In most other autosomal recessive disorders, the finding of a single allele would be interpreted as equivocal, or not involved with the disease in question at all. Most genes will be found to contain multiple non-disease-variations when they are evaluated in a large number of individuals in the population. It requires constant vigilance by the laboratory to distinguish variations that actually cause disease from those that are incidental findings [26, 27] and physicians should always be a bit skeptical of a novel molecular result in a patient whose clinical findings are atypical.

Another complexity is that every individual harbors several autosomal recessive alleles in the heterozygous, or carrier state. During testing for a genetically heterogeneous disorder, one may discover the carrier state of an allele in one gene while the true disease-causing mutations for that patient actually lie in another gene. This fact underscores the desirability of identifying both disease alleles in a patient before issuing a positive report and the additional desirability of demonstrating those alleles to segregate as expected in additional family members.

Some disorders that are almost always inherited in an autosomal recessive manner do have rare forms that are dominant. For example, most cases of Stargardt disease are inherited in an autosomal recessive manner (caused by mutations in the ABCA4 gene 28) but a few percent are inherited in a dominant fashion and are caused by mutations in ELOVL4 29. Similarly, a few percent of cases of LCA are inherited in a dominant fashion (caused by mutations in CRX 30) while the recessive form of the disease is caused by mutations in at least 13 other genes.

Isolated congenital cataracts are estimated to be autosomal dominant in 50% of cases in Western countries and many genes have been found which, when mutated, cause this disorder. But at present no fee for service testing exists to allow us to routinely diagnose children and their families.

Congenital glaucoma can be inherited in an autosomal recessive fashion in some families. Mutations in the CYP1B1 gene have been found to cause up to 50% of primary congenital glaucoma worldwide, but the rate varies widely based on ethnicity. Close to 100% of congenital glaucoma cases in patients from Saudi Arabia and some Gypsy groups have been reported to be due to CYP1B1 mutations[31], but only 17-30% of cases in Chinese, German and Spanish populations are due to this gene[32,33]. Because of this ethnic variability, some families have a higher chance of getting a diagnostic result than others. In addition, even if CYP1B1 is negative, this does not rule out autosomal recessive inheritance since there are as yet undiscovered genes. A commercial test is available to test CYP1B1, but families must be carefully counseled both before and after testing. If the test is positive, very precise genetic counseling can be given, family members can be tested and pre-implantation genetic testing can be offered. However if the test is negative, the recurrence risk to the parents must still be assumed to be 25%, and yet pre-implantation testing would not be possible in these cases.

Usher syndrome is the most common cause of deaf-blindness. It is autosomal recessive and is caused by at least 9 genes [34]. Because children are born deaf or hard of hearing and only later start to develop RP, many parents and patients do not know the child will have multiple sensory issues until later in life. Knowing that this is a deaf-blind syndrome may affect important decisions, such as whether to perform cochlear implantion early in life, which is controversial in the deaf community, as well as for family planning and educational planning. In addition, many Usher patients suffer from not understanding why they are having difficulty with certain activities for a long time before diagnosis, which causes added anxiety. For all of these reasons, genetic testing for children born deaf or hard of hearing would be a positive development. Testing for Usher syndrome is available and currently detects approximately 50% to 80% of mutations depending upon which gene is involved and the exact mode of testing [35].

The Mechanics of Genetic Testing

Clinicians who order and interpret genetic tests quickly learn that all genetic tests are not alike. Some tests are designed to rapidly examine multiple genes for mutations that have been previously identified in other patients (allele specific tests) while other tests are designed to examine the entire coding sequence of one or more genes in search of disease-causing mutations that may have never been previously observed. There are strengths and weaknesses with both strategies. Allele specific tests are often less expensive and have a shorter turnaround time than similarly complex tests involving DNA sequencing. In addition, mutations that have been observed to properly segregate with the disease in many different families are more likely to be clinically meaningful than missense mutations observed for the first time in an isolated patient. However, some disease-causing genes have a relatively high rate of novel mutations identified even many years after their initial discovery. Some laboratories attempt to provide patients the best of both worlds by offering an allele specific test for a given disease as an initial step with the idea that more extensive DNA sequencing approaches can be used subsequently if the allele specific test is only partially revealing or does not detect any mutations.

One situation in which this tiered testing approach is particularly effective is for genetically heterogeneous autosomal recessive disorders like Bardet Biedl syndrome, Usher syndrome, LCA and recessive RP. In extensively outbred populations such as those of North America and Europe, most patients affected with an autosomal recessive disease will be compound heterozygotes – that is, they will inherit different disease-causing alleles in the same gene from

their mother and their father. By definition, one of these mutations will be more common than the other and therefore more likely to be represented on an existing allele specific test for that disease. When this more common allele is detected by a rapid and inexpensive allele specific test, it allows the lab to focus the remaining testing effort (to find the other less common allele) on a single gene. For many genetically heterogeneous recessive diseases this combination of approaches will often reach a final answer more rapidly and less expensively than either testing method alone.

Regardless of the specific method used to identify disease-causing mutations in a given proband it is almost always a good idea to also obtain samples from additional family members to help with the proper interpretation of the findings. The observation of two novel, plausible disease-causing mutations in a patient with a recessive disease is a much weaker molecular result than the same observation coupled with evidence that one or both of his parents are heterozygous for one of the patient's alleles. A surprising number of plausibly disease-causing variants turn out to lie on the same chromosome when family members are examined to determine the segregation of the alleles. For recessive disorders, 2 mutations on the same allele will not cause disease; both alleles must have at least one mutation. A side benefit to such segregation testing is that it dramatically lessens the likelihood that an error has occurred anywhere in the chain of sample handling.

Prenatal diagnosis is in theory possible for all diseases that can be diagnosed by direct analysis of DNA. However, many laboratories that offer genetic testing for eye diseases are not set up to provide results with sufficient speed to make prenatal testing practical. If a patient is considering prenatal testing for an eye disease as part of a family planning strategy, a laboratory should be engaged before the pregnancy occurs to make sure that all of the necessary reagents and personnel are in place to perform the test in the compressed time scale necessary for this type of testing.

Preimplantation genetic testing is also possible for virtually every disease that can be diagnosed by direct analysis of DNA. With this approach, a couple pursues in vitro fertilization much as one would in an infertility setting. Then, single cells are removed from the resulting embryos and tested for the presence of the family's disease-causing mutation(s) and these testing data are used to choose which embryos are transferred to the mother's uterus.

Testing of the female relatives of patients with X-linked diseases for the presence or absence of the family's disease-causing allele is one of the most powerful uses of molecular testing in clinical practice. When one makes the diagnosis of an X-linked disease in a patient, there are often several women of child-bearing age who are at significant risk of having an affected child. Moreover, when these women are distantly related to the affected individual (e.g., female cousins whose mother is the proband's aunt) they often are unaware that their future children might be affected with an eye disease. When a disease-causing mutation is known in the proband, carrier testing is relatively inexpensive to perform. Informing the proband (or his parents if he is a minor) of the availability of such testing is an important part of counseling regarding X-linked disease.

Many parents of minor children at risk for an inherited eye disease will seek genetic testing for the children before any evidence of the disease is manifest. In almost all cases, unless a preventive treatment for the condition is known, one should confine one's examination to clinical and electrophysiological modalities and pursue molecular testing only after clear signs of the disease are evident. There are many reasons for avoiding presymptomatic testing of minors. Most diseases exhibit some degree of variable expressivity such that a disease genotype does not definitively predict a disease phenotype. For example, 5-10% of patients who harbor true disease-causing mutations in bestrophin never develop a visually significant Best disease

macular lesion [36,37]. Thus, in these patients, ophthalmoscopy is actually more predictive of clinical outcome than molecular testing. When a patient reaches 18, and the disease is still not evident clinically, he or she may choose to undergo presymptomatic testing both to better understand their risk of future disease but also for planning of their own families. Performing such testing earlier robs them of their right to choose not to know, if indeed that would be their choice as an adult.

Perhaps the most common question asked by doctors who order and interpret genetic tests of those who perform them in the laboratory is why it takes so long to complete and report tests. Patients and doctors are accustomed to routine tests which are reported within days or even minutes. Unfortunately, the human genome is a very large and noisy place with millions of non-disease-causing variations competing for a geneticist's attention with the one or two that are truly responsible for a patient's disease. Perhaps the greatest difficulty is the relative coarseness of our current diagnostic nomenclature compared to high resolution reality in the genome. As just one example, the clinical finding of “retinitis pigmentosa” can be caused by more than 50 genes that collectively span millions of base pairs of genomic sequence. The solution lies partially in the continuous recognition and teaching of genotype phenotype correlations so that doctors can focus their laboratories' energies into relatively high yield activities. This, coupled with tiered testing (with interim reports given at the end of each tier) will lessen the sense that testing is not progressing, and better convey (to the doctor and the patient) the true complexity of the laboratory task. At the same time, molecular methods and bioinformatic strategies are becoming more powerful so that the costs and turnaround times for even the most complex tests should continue to decrease.

Conclusion

Genetic tests with reasonably high sensitivity, high specificity, moderate cost, and a turnaround time often measured in weeks are now available for dozens of inherited eye diseases. Insurance companies are increasingly willing to pay for them. In the coming few years, these tests will get steadily better and more numerous. The bottleneck to more widespread use of this technology is gradually shifting from the laboratory to the clinic. Where once no tests were available, now there are tests but an insufficient number of doctors who are knowledgeable enough to order them and interpret them. Ophthalmologists should see this as a tremendous opportunity to convert the negative messages of past decades, which essentially were that nothing could be done, into a message of realistic hope: with a blood test the exact cause of a child's vision problem may be diagnosed, and eligibility for the current treatment trials can be determined. Doing so will not only contribute to the discovery of additional disease-causing genes, it will also make possible the clinical trial of many exciting new therapies.

Acknowledgments

Funding/support: This work was supported in part by funding from the Foundation Fighting Blindness, the Howard Hughes Medical Institute, the National Institutes of Health, The Grousbeck Family Foundation, and Hope for Vision.

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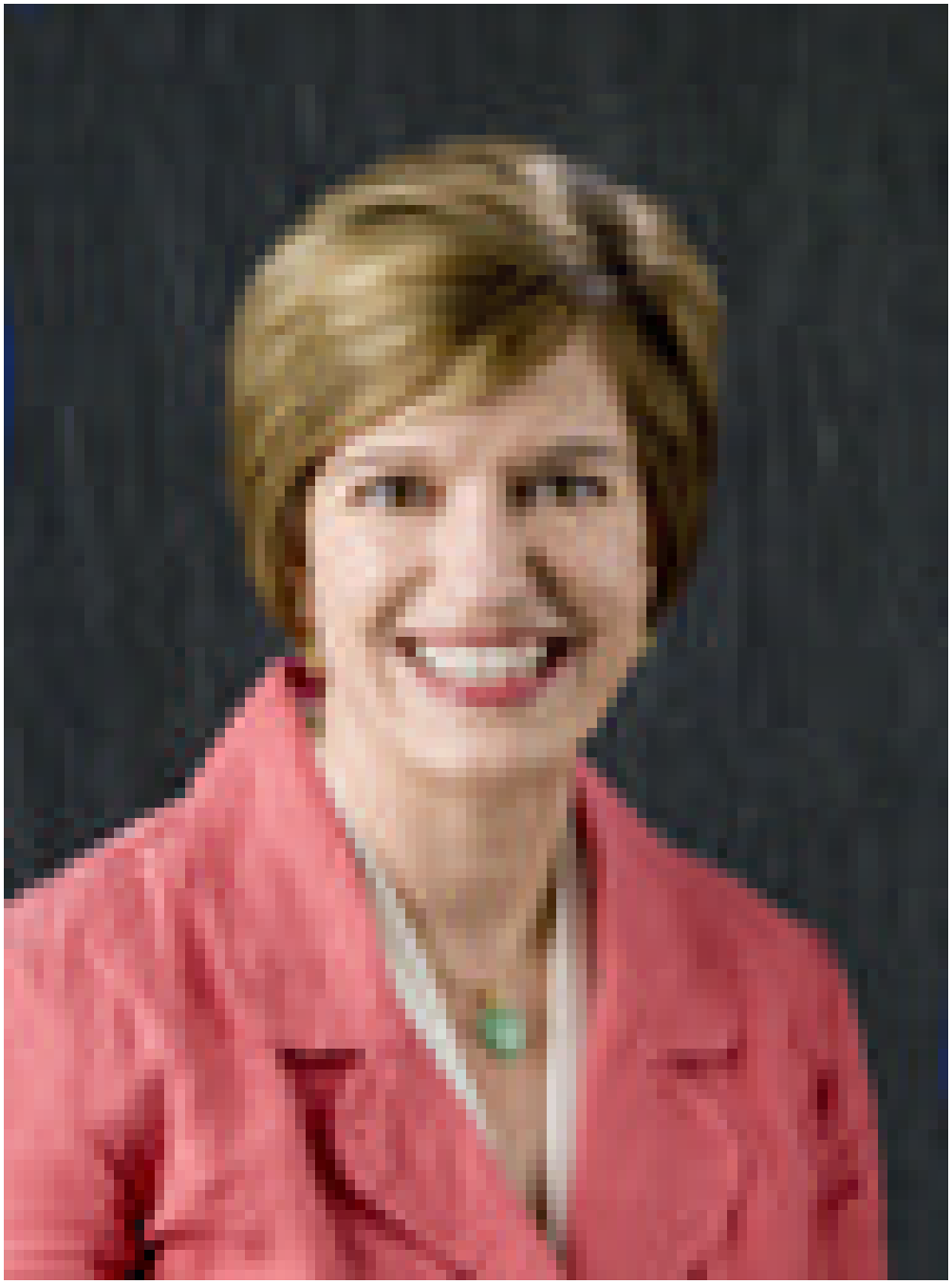

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Table 1

Some Pediatric Genetic Eye Disorders for which Fee For Service Testing is currently available

Leber Congenital Amaurosis
Achromatopsia
Autosomal Dominant Retinitis Pigmentosa
Stargardt Macular Dystrophy
Best Disease
Bardet Biedl Syndrome
Usher Syndrome
Retinoblastoma
Tuberous Sclerosis
Albinism (OCA1, OCA2, X-Iinked)
Neurofibromatosis (NF1, NF2)
Anterior Segment Dysgenesis (PAX 6)
Reiger Syndrome
Aniridia/Wilm's Tumor