Genetic Testing for Inherited Retinal Disease
Anthony T. Moore, FRCOphth, FMedSci - San Francisco, California

The report by Stone et al1 in this issue (available at www.aaojournal.org/article/S0161-6420(17)30460-8/fulltext;) is a timely reminder of the revolution under way in molecular genetic testing for inherited retinal disease (IRD). The new approach to testing involves the use of next-generation sequencing (NGS), a term used to describe a number of different technologies that use a common strategy of the parallel sequencing of millions of short segments of DNA that are then aligned bio-informatically with a human reference genome. Each fragment is sequenced multiple times, allowing improved sequencing accuracy. Next-generation sequencing can be used to completely sequence an individual’s DNA (whole genome sequencing), sequence the protein coding regions (exome sequencing), or confine the sequencing to the coding regions of panels of genes known to cause specific disorders such as IRDs. The technology has advanced to the stage that whole exome sequencing and whole genome sequencing can be performed in a short time frame and the costs of such testing continue to decrease. Next-generation sequencing testing of panels of all known retinal disease genes is already in clinical use.3,4 Whole genome sequencing further increases the diagnostic yield5 and, as the cost of whole genome sequencing continues to decrease, such testing is likely to be moved to the clinic and affect clinical practice, particularly in the field of single gene disorders.

Parallel advances are being made in the understanding of genetic risk factors for complex disease, such as age-related macular degeneration. Advances in sequencing technology and reduced costs also will affect this area of research. There is currently no evidence that molecular genetic testing for age-related macular degeneration is of any value clinically,6 and the recommendation from the American Academy of Ophthalmology is to avoid routine genetic testing for age-related macular degeneration7; the same advice holds for other complex ocular disease. However, with further advances in our understanding of the interplay among genetic variants, environmental risk factors, and response to therapy, it is possible that molecular genetic data may be useful in identifying patients at increased risk of disease progression and may eventually influence the choice of therapy. However, there is still much research to be carried out in this area, and clinical trials will need to demonstrate that clinical outcomes are influenced by genotypic information before routine testing can be recommended.6

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The authors are to be congratulated on their detailed analysis of genetic testing in 1000 patients with IRD in their clinic. They used a tiered approach to molecular genetic testing using clinical diagnosis to guide testing; for example, there is little point in testing multiple genes in an NGS panel when a clinical diagnosis of Best disease or congenital stationary night blindness can lead to targeted testing of a single gene or a small group of genes. Stone et al1 developed their own clinical algorithm involving 62 diagnostic categories, which guided testing. Such an approach proved to be effective in their clinical setting because they were able to identify the precise molecular diagnosis in more than 75% of patients at a cost they estimated was lower than using an NGS panel. However, this approach requires a high degree of clinical expertise and a laboratory that has the capacity to modify testing according to such clinical criteria. This has proved to be an effective but personalized approach, which is perhaps unlikely to be followed by other specialists who are more likely to use NGS panels for the majority of retinal disorders for which there is significant genetic heterogeneity. However, an important message of this article is that testing should be directed by clinical findings, and equally important, molecular genetic findings need to be carefully evaluated in the context of the clinical phenotype to avoid errors in molecular diagnosis.

Inherited retinal dystrophies affect approximately 1 in 3500 individuals in North America and Europe and are an important cause of blindness in children and adults of working age. Most affected individuals will not see a specialist in IRD, at least initially. The diagnosis is likely to be made by a comprehensive ophthalmologist, pediatric ophthalmologist, or retinal specialist. A number of questions will arise at diagnosis. Who should have genetic testing? What difference will the results of molecular genetic testing make to clinical management? Who will pay for testing?

Molecular genetic testing provides a very specific diagnosis, which will aid genetic counseling in the patients and the wider family members. Approximately 50% of patients with retinitis pigmentosa, for example, have no known family history, and although most will have autosomal recessive disease, some will represent new autosomal dominant mutations or have X-linked disease. Molecular diagnosis will not only confirm the diagnosis but also identify the correct inheritance pattern and allow accurate genetic counseling for the patient and their family. It will
also inform prognosis, which is particularly important in younger subjects. In the case of infants and young children, molecular diagnosis will identify those children who are at risk of systemic problems, such as renal disease, and who will benefit from early diagnosis and treatment. Precise genetic diagnosis also will allow preimplantation and prenatal diagnosis in those families who want to use these services.

However, the main reason that patients request molecular testing is that they are increasingly well informed about clinical trials of new therapies. Many of these trials, particularly those involving gene therapy, require knowledge of the specific genetic mutation causing disease. Gene therapy trials are already under way for specific forms of Leber congenital amaurosis, achromatopsia, choroideremia, X-linked retinitis pigmentosa, Usher syndrome type 1, Stargardt disease, and juvenile X-linked retinoschisis, and recruitment to these trials will depend on there being sufficient numbers of patients with these rare disorders who know their specific disease mutation. Once such therapies reach the clinic, it will be even more important to identify patients who may benefit.

Insurance companies and other agencies funding healthcare are currently reluctant to fund molecular genetic testing unless there is clear evidence that the results of testing accurately predict the clinical status of the patient and will affect clinical management. Patients whose clinical situation does not fulfill such criteria may be able to obtain testing as part of a research study or will need to self pay. The current costs of molecular investigations are a significant barrier to testing, but as the costs decrease it is likely that molecular diagnosis will become more widely available.

We are on the cusp of a new, exciting era of effective treatments for patients with IRD, and then molecular diagnosis will become essential. This raises a further question as to whether we have enough ophthalmologists who are able to interpret results of molecular testing and feedback results to patients and their families. Currently, the answer is likely to be negative, and most ophthalmologists will need to work closely with their clinical genetic colleagues. In the longer term, there is a need for more young ophthalmologists to pursue a career in this exciting and rapidly changing field.

References


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Correspondence:
Anthony T. Moore, FRCSophth, FMedSci, University of California at San Francisco Medical Center, 10 Koret Way, San Francisco, CA 94143. E-mail: tony.moore@ucsf.edu.