Genetic counselling for predictive retinal imaging?

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Inherited retinal diseases are amongst the commonest causes of blindness in the working age population.[1] Genetic testing has become a diagnostic pillar in investigating and managing inherited retinal diseases, which may aid in patient counseling with regards to the risk of family members being affected, expected natural disease course and therapeutic options.[2] The latter has become increasingly important with the advancement of gene therapy and a rising number of other gene- or pathway-specific therapies.[3]

Predictive genetic testing may be used to determine future risk of developing a monogenic disease. This is particularly important if preventive treatment is available to reduce morbidity and burden of disease, or if it allows an individual to make plans for the future, such as lifestyle and professional adjustments. In predictive testing, a clinically healthy and asymptomatic family member of a patient diagnosed with a monogenic disease, is tested for the presence of the specific genetic variant that is thought to cause disease in their family. However, although genetic testing is highly accurate, there may be still be uncertainty with regards to whether, when and how

severely the disease may develop due to incomplete disease penetrance and variable expressivity often being a feature of inherited retinal diseases. Predictive testing may be particularly useful for diseases with autosomal dominant inheritance and onset later in life, or for testing younger siblings of patients affected by an autosomal recessive disease. However, in the absence of interventions with proven benefit to delay onset or improve severity of disease, benefit of such predictive testing remains limited to family and personal planning. In addition, there are usually strict guidelines with respect to counseling before testing due to the potential resulting impact on an individual's well-being.

High-resolution retinal imaging has improved significantly in recent years due to improved camera systems and novel imaging modalities. Using state-of-the-art retinal imaging modalities, very early disease manifestations of some monogenic retinal diseases may now be detected many years – in some cases possibly decades – before occurrence of any symptoms and before routine clinical examination shows any obvious changes. This leads to ethical implications similar to those of molecular genetic testing.

Very early detection of disease may be apparent using imaging modalities such as a simple optical coherence tomography (OCT) scan, for example in *IMPG2*- or *RP1L1*-related macular dystrophy. Widefield autofluorescence imaging, which is routinely used in most inherited retinal disease clinics, may detect pre-symptomatic retinitis pigmentosa and often demonstrates characteristic findings in carriers of X-linked disease such as retinitis pigmentosa, choroideremia or ocular albinism,[4] and in these cases retinal images can be so characteristic that they alone are often sufficient to diagnose carrier status and hence the familial inheritance pattern. Other

examples include autosomal dominant disease such as Sorsby fundus dystrophy where late-phase indocyanine green angiography may illustrate characteristic changes,[5] or Stargardt-like disease where quantitative autofluorescence imaging may detect increased lipofuscin accumulation in absence of any other retinal changes.[6] Some of these outcome measures are better established than others, and certain imaging methods are widely available whereas others are currently only used in research. Importantly, such predictive retinal imaging may sometimes be informative even if the genetic defect borne by an affected family member is not known, or if genetic testing identified a variant of unknown significance. Moreover, phenotypic severity may inform on individual disease burden and hence the likelihood of becoming symptomatic. Therefore, retinal imaging may have greater predictive power than genetic testing in some families.

When individuals attend an inherited retinal disease clinic, frequently visual acuity measurement, pupil dilation and retinal imaging are performed before a patient is seen by a clinician. We have encountered some cases where relatives of individuals with an inherited retinal disease have been referred for discussion of pros and cons of genetic testing, but their retinal imaging (undertaken prior to reaching the clinician) clearly indicates presence of pathology or carrier status in the relative. The clinician is then faced with an ethical dilemma: the individual may be unsure whether they want genetic testing to know if they carry a disease-causing variant, and has requested counselling regarding this, whereas the clinician may already know their status.

Another situation arises when the patient affected with an inherited retinal disease is a child: clinicians will often examine or request imaging in an

asymptomatic parent to inform the child's diagnosis, and this is especially helpful in suspected autosomal dominant or X-linked disease. However, in these situations the parent might not receive counselling prior to imaging, and might leave the clinic with an unexpected diagnosis themselves, possibly with inadequate support to process this.

We therefore propose that some form of counselling or discussion should precede retinal imaging in asymptomatic individuals in such situations, and not solely be reserved for prior to genetic testing. Depending on resources and facilities in clinic, a separate face to face or telemedicine appointment could be considered, for example with a genetic counsellor prior to these patients seeing their ophthalmologist, or the team could actively identify such individuals prior to undertaking imaging. Retinal imaging should be given similar thought and consideration as genetic testing in asymptomatic individuals, and with the advent of further developments in retinal imaging on the horizon, such situations are likely to be more frequently encountered.

References

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