

Commentary (Series editor: David Taylor)

Genetic testing—swings and roundabouts: a view from the United Kingdom

“With this profound new knowledge humankind is on the verge of gaining immense new power to heal. Genome science will have a real impact on all our lives, and even more on the lives of our children. It will revolutionise the diagnosis, prevention and treatment of most, if not all, human diseases.” Ex-President Bill Clinton, announcing the completion of the first draft of the human genome, 26 June 2000 with Prime Minister Blair.^{1 2}

Ignoring the hype, this was a genuinely monumental achievement, notwithstanding that the map remains in draft form. However, many clinicians remain sceptical about the real benefits for patients. Molecular geneticists have been predicting “significant advances” for years and, despite identifying numerous genes underlying rare disorders, their efforts have shed little light on commoner disorders such as heart disease, glaucoma, and macular degeneration. Sadly, the impact of recent genetic advances on the general ophthalmic community *has* been small, in spite of rising expectations on the part of the media and patients. Sceptics would argue that much has been done for the glory of research and researchers rather than for the furtherance of patient care.

So what are the possibilities for the future? Have expectations been raised unreasonably or will genuine clinical benefits accrue in due course?

There have been many real achievements in recent years. We have learned more in the past 5–10 years than in the preceding 100 about the biological basis of inherited disorders such as the retinal and corneal dystrophies,^{3 4} as well as “sporadic” disorders such as basal cell carcinoma, Peters’ anomaly, and Coats’ disease.^{5–7} However, the more we have discovered, the more complex such disorders have seemed to become. Usher’s syndrome, a relatively rare and, we thought, specific condition, is not one disease but at least 10.⁸ Even a seemingly “simple” disorder such as albinism has continued to throw up unexpected molecular twists.⁹ So it is not a surprise that the impact of this new knowledge on clinical management is limited—at least for the moment.

The situation is even more confusing for complex conditions. An example is glaucoma, a common, “treatable” group of conditions with a significant genetic basis. Here, the phenotypes remain as difficult to define as ever and as a result the susceptibility factors important for each subgroup remain undefined. While such fundamental questions remain unanswered the design of novel and targeted therapies is likely to remain unsuccessful. In this regard ophthalmology is no different from other branches of clinical medicine. However, recent work on genetic therapies for retinal dystrophies in animal models allows us a slightly firmer basis for our hopes for the future.^{10–12} Nevertheless, although novel treatment options remain limited, there is still enormous clinical utility in defining the molecular basis of disease. Precise genetic categorisation informs clinical management, genetic counselling, and research. Genetic testing when correctly applied, has already been proved to be of value in guiding clinical management—for example, in families with inherited cancers, neurological disease, and inborn errors of metabolism. Yet implementation of such testing in clinical ophthalmic practice has been slow and has lagged behind what is currently possible.

Molecular genetic testing in a nutshell

An increasing number of genes responsible for inherited ophthalmic conditions are being cloned. It is often assumed—in particular by patients and their families—that gene identification is followed by routinely available genetic testing; this is not the case. The time lag leads to a significant gulf between the expectations of patients and the ability of the clinician to fulfil these expectations. There are a number of factors to consider:

- Screening for mutations in most genes is currently a labour intensive and time consuming process which requires an analysis of the whole gene. Exceptions to this are TIMP3 (Sorsby dystrophy) and BIGH3 (stromal corneal dystrophies), where the range of mutations is limited. In the majority of cases therefore screening may take several months.
- In conditions where a broad range of genes may cause an identical phenotype (retinitis pigmentosa is the most obvious example) there is no way to choose one from a number of genes: this may make testing impractical in a clinical setting using current techniques.
- Mutation detection procedures are not 100% sensitive. Many methods of identifying mutations within a gene are around 70% successful. Thus, in many cases molecular analysis will not produce a “definitive” result.
- Where mutation screening is appropriate it is usually only undertaken on blood samples from an affected member of the family. Mutation testing of an unaffected family member is only of use once the family mutation has been found.
- Genetic testing has come to mean gene mutation testing for most people. However, it should not be forgotten that *chromosome analysis* (karyotyping) is an important tool, particularly in individuals with complex phenotypes. A chromosome abnormality may point towards the location of specific genes.

Genetic testing—if not now, then when?

Genetic services in the United Kingdom, as in some other parts of the world (for example, the Netherlands and Australia), are organised regionally to provide services for families (as opposed to individuals) with genetic disorders. The regional genetic centres encompass multiple professional and scientific groupings (clinical geneticists, cytogeneticists, molecular scientists, and genetic counsellors) and serve populations of between two and six million.¹³ Through these centres, genetic testing for a wide variety of genetic disorders such as cystic fibrosis, Duchenne muscular dystrophy, and myotonic dystrophy is undertaken. The genetic laboratories, which are subject to formal accreditation and quality assurance procedures, follow recognised

protocols for molecular diagnosis. The clinical team is experienced in dealing not only with the molecular and technical aspects of the work but also with the ethical, legal, and social issues that arise within families where a rare genetic condition is segregating.

In the past, a major problem in the development of a service for testing for uncommon genetic disorders has been the absence of a central funding mechanism to cope with conditions which are too rare to be tested for within each region. A recent report on laboratory services for genetics has proposed that a national mechanism be put in place for testing for rare disorders *for which there exists a clinical demand*.¹⁴ For each condition, testing would be available in one or, preferably, two centres (to enable a back-up service to operate in times of difficulty) within accredited laboratories. These would lie within an appropriate clinical environment.¹⁵ The implementation of this initiative was announced by the secretary of state for health in April 2001. Broadening genetic testing is useful both for the clinician (precision of diagnosis is fundamental to determining management, prognosis, and inheritance pattern) and for the patient (knowledge facilitates decision making, planning life choices, and defining risk to family members).

Genetic testing in ophthalmology: the need for communication

The challenge facing those seeking to implement molecular testing for ophthalmic disorders will be to integrate these within the national mechanism. There are potentially numerous genes which could be tested and careful prioritisation will be needed in order to set achievable, and affordable, goals. One major hurdle is the high degree of genetic heterogeneity among inherited ocular conditions—a single clinical entity may be caused by defects in many genes. For example, over 30 distinct dominant, recessive, and X linked forms of retinitis pigmentosa (RP) are now recognised, with more still to be characterised. Even the commonest RP genes, rhodopsin (which accounts for less than one third of dominant RP) and the RP GTPase regulator (RPGR, which causes the commonest form of X linked RP) may each account for only 5–10% of cases. Since each gene is generally only an infrequent cause of disease, effective mutation screening strategies for a patient with isolated (“simplex”) RP will require the analysis of numerous genes. This same situation is also likely to be encountered in the fields of glaucoma and congenital cataract.

In the past, an additional complication for a system based specialty such as ophthalmology arose as a result of its general isolation from regional genetic services. It has been difficult to develop a rational and effective strategy when those calling for a molecular diagnostic service (ophthalmologists and their patients) and those delivering it (clinical and molecular geneticists) have had so little opportunity to interact. The challenge will be to foster sufficient consultation between the two communities to develop a network of services which meets the demands of all without being either unwieldy or impractical. Such a network will need appropriate staff and funding in order to offer the support required to cope with the consequences of testing such as prenatal diagnosis, diagnosis of relatives, and counselling follow up. Those professionals within clinical genetics who already have considerable experience in such areas could be usefully exploited in developing and implementing new ophthalmic genetic services. Yet this can be no one sided affair. Ophthalmologists have a clearer understanding of the implications of vision threatening diseases; the targeting of testing must ultimately rely upon their diagnostic expertise and clinical judgment. Furthermore, future therapies will fall to them to administer.

Handle with care

When finally we get our hands on it, the Pandora’s box of widespread genetic testing will need to be opened with care as there are many potential dangers to be found within.

Predictive or presymptomatic testing of those who have neither symptoms nor signs of a disease is a delicate area to approach.¹⁶ Within ophthalmology this applies in particular to adult onset disorders such as the macular and retinal dystrophies. Guidelines for predictive testing for late onset neurological disorders and inherited cancers are well documented within the genetics community¹⁷ and need to be considered when dealing with ocular conditions. The price that an individual will pay for finding out that he or she carries a faulty gene may be high and may include not only psychological disadvantage but also could lead to problems with employment or insurance.¹⁸ It is important to examine and test genetically only those who after counselling actually want to be investigated.

Consent for genetic testing both in formal service and in research is something we must all approach with care, sensitivity, and openness. No longer can samples be stored at the whim of the clinician and patients must be fully involved in all stages of research and testing.

Hope for the future?

“Genetic advances can be a force for good. But that requires active preparation. The genetics revolution has already begun. It is not going to go away. It is time we started preparing today for the opportunities of tomorrow.” Alan Milburn (secretary of state for health) on NHS preparations to cope with the “genetic revolution,” 19 April 2001¹⁵

In the past expectations arising from molecular genetic advances were raised prematurely. In part this resulted from a misunderstanding of the complexity of the task and of the complications that would be encountered. However, it is certain that genetic knowledge, testing, and treatment will continue to expand. The questions of when and to what extent remain unanswerable. Currently, for a small number of conditions where genetic testing is directly relevant to management (for example, retinoblastoma), this is already in place as an effective adjunct to traditional clinical practice. For more rare conditions (retinal dystrophies, congenital cataract), where testing could alter diagnosis and counselling, testing will hopefully begin to filter into practice within the next 3–5 years. As for novel therapies it is unlikely that many of the “untreatable” developmental conditions—*aniridia* or *Norrie disease*, for example—will ever become treatable. However, reports demonstrating that virally mediated therapy in an animal model of *Leber congenital amaurosis* can actually restore visual function are a proof of principle, and a genuine ray of hope.¹⁰ It is likely to be some time before such therapies do become available and they will not be for a large number of inherited conditions. However, at last, we can *with justification* talk about “when” and not “if.” For this reason, as a specialty, ophthalmology must play a part in planning for these changes in practice. It will only be through dialogue between ophthalmologists and molecular and clinical geneticists that the appropriate environment can be created in which they can be developed.

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1 <http://www.number-10.gov.uk/news.asp?NewsId=684>

2 <http://www.sciencenews.org/20000701/fob1.asp>

- 3 <http://www.sph.uth.tmc.edu/Retnet/disease.htm>
- 4 Klintworth, G. Advances in the molecular genetics of corneal dystrophies. *Am J Ophthalmol* 1999;128:747-54.
- 5 Bale AE, Yu KP. The hedgehog pathway and basal cell carcinomas. *Hum Mol Genet* 2001;10:757-62.
- 6 Vincent A, Billingsley G, Priston M, *et al*. Phenotypic heterogeneity of CYP1B1: mutations in a patient with Peters' anomaly. *J Med Genet* 2001;38:324-6.
- 7 Black GC, Perveen R, Bonshek R, *et al*. Coats' disease of the retina (unilateral retinal telangiectasis) caused by somatic mutation in the NDP gene: a role for norrin in retinal angiogenesis. *Hum Mol Genet* 1999;8:2031-5.
- 8 Kimberling WJ, Orten D, Pieke-Dahl S. Genetic heterogeneity of Usher syndrome. *Adv Otorhinolaryngol* 2000;56:11-18.
- 9 Morell R, Spritz RA, Ho L, *et al*. Apparent digenic inheritance of Waardenburg syndrome type 2 (WS2) and autosomal recessive ocular albinism (AROA). *Hum Mol Genet* 1997;6:659-64.
- 10 Acland GM, Aguirre GD, Ray J, *et al*. Gene therapy restores vision in a canine model of childhood blindness. *Nat Genet* 2001;28:92-5.
- 11 Van Hooser JP, Aleman TS, He YG, *et al*. Rapid restoration of visual pigment and function with oral retinoid in a mouse model of childhood blindness. *Proc Natl Acad Sci* 2000;97:8623-8.
- 12 Ali RR, Sarra GM, Stephens C, *et al*. Restoration of photoreceptor ultrastructure and function in retinal degeneration slow mice by gene therapy. *Nat Genet* 2000;25:306-10.
- 13 Donnai D, Elles R. Integrated regional genetic services: current and future provision. *BMJ* 2001;322:1048-52.
- 14 <http://www.ast.cam.ac.uk/~douglas/GIG/policy-17-2.html>
- 15 <http://www.number-10.gov.uk/news.asp?NewsId=1995>
- 16 Evans JP, Skrzynia C, Burke W. The complexities of predictive genetic testing. *BMJ* 2001;322:1052-6.
- 17 Craufurd D, Tyler A. Predictive testing for Huntington's disease: protocol of the UK Huntington's Prediction Consortium. *J Med Genet* 1992;29:915-18.
- 18 <http://www.parliament.the-stationery-office.co.uk/pa/cm200001/cmsselect/cmsctech/174/17402.htm>



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