Inherited Retinal Disorders: Using Evidence as a Driver for Implementation

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Abstract

Incremental advances in the field of retinal genetics have transformed our understanding of inherited retinal disorders and have led to the development of powerful diagnostic tests and promising gene-based therapies. Despite this, successful integration of these developments into routine healthcare is frequently ineffective. Providing robust evidence of benefit can accelerate the implementation of clinical genetic interventions. For example, the adoption of a genetic test is much more likely when the test's clinical utility (i.e. its ability to influence management and health outcomes) has been clearly demonstrated. However, accruing such evidence for rare conditions like inherited retinal disorders is challenging. Conducting sufficiently powered studies requires both efficient study designs and large-scale, international collaboration. Reaching all populations and as many affected individuals as possible is key. Equally important are efforts to precisely and consistently capture pheno-

typic information, including natural history data. This article summarizes some of the current obstacles to implementation and discusses approaches to overcome these barriers.

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Susceptibility to human diseases is typically influenced by the complex interplay between genetic, environmental/lifestyle and stochastic factors. The relative contribution of genetic alterations to disease predisposition is variable, and genetic disorders form a continuum: on the one end of the spectrum are common conditions (e.g. age-related macular degeneration and diabetic retinopathy) that are influenced by multiple factors to the degree that the direct effect of individual genetic changes is blurred; on the other end of the spectrum, there are conditions like rod-cone dystrophy, for which the identification of defects in a single gene can predict disease development with relatively high accuracy (Fig. 1) [1–3]. The term monogenic or Mendelian is used to describe the latter group of disorders. Although each individual condition in this group is rare (defined in the EU as affecting less than 1 in 2,000 individuals [4]), collectively they are common, and their cumulative impact on affected fami-

Fig. 1. Spectrum of inherited disorders on the basis of heritability and genetic complexity. Monogenic disorders like Sorsby fundus dystrophy are highly heritable and have a simple genetic aetiology; in these conditions, alterations in a single gene are responsible for most of the disease risk (with possible minor contributions of modifier genes or environmental factors). In multifactorial disorders like age-related macular degeneration, multiple variants, each with a relatively small effect, contribute to disease risk along with environmental and lifestyle factors [54, 55].

Fig. 2. Graph showing the number of genes reported to be linked to inherited retinal disorders (IRDs) over time (modified from [13]). The first four genes to be described/cloned are highlighted (RB1 [7], OAT [9], RHO [10], CHM [11]). Four additional genes associated with particularly prevalent IRD subtypes are also shown (PRPH2 [56, 57], RPGR [58], ABCA4 [59], USH2A [60]). The two major highlights in the field of genomics over the past three decades are indicated [61–68]. The author significantly contributed to the discovery of the IRD-associated genes in white [69–74].

lies and healthcare systems is substantial [5, 6]. This article focuses on monogenic retinal disorders and discusses the importance of building a strong evidentiary foundation for genetic ophthalmology.

The modern era of retinal genetics began in 1986 with the identification and cloning of RB1, the gene associated with retinoblastoma [7, 8]. Two years later, mutations in the OAT gene were found to cause gyrate atrophy [9] and, in 1990, the rhodopsin (RHO) gene was linked to dominant rod-cone dystrophy [10] and the CHM gene was linked to choroideremia [11, 12]. In the three decades that followed these early breakthroughs, over 270 genes have been associated with retinal disorders (Fig. 2) [13]. These discoveries have ushered a new era for the field of retinal genetics and catalysed the development of powerful genomic tests that have revolutionised diagnostics for monogenic retinal disease [14, 15]. It has also been possible to translate this growing genomic knowledge into targeted

interventions. Notable examples include gene augmentation therapies [16], anti-sense oligonucleotide treatments [17] and pre-implantation genetic screening [18].

Contemplating such progress is gratifying, but the challenges lying ahead remain considerable. A central problem is that of integrating research findings into healthcare practices and policies [19–21]. Important considerations include the cost, the benefit and the evidentiary basis of each proposed intervention. Genetic testing is discussed here as an example: although the importance and value of genetic testing for monogenic retinal disorders has been repeatedly highlighted over the past decades [22–24], variation in the current provision of testing remains significant [25, 26]. Considering economic factors is necessary but insufficient. Two important questions that need to be answered are how beneficial are these tests and how strong is the evidence that supports their routine use?

Table 1. Glossary

Genetics	The study of genes, genetic variation, and heredity in living organisms [27, 75]
Genomics	The study of genomes; the term genome refers to all the nucleotide sequences (including genes, regulatory sequences, and noncoding DNA segments) that are found in an organism, tissue sample or cell; genomics includes the study of not only single genes, but also of the functions and interactions of all the genes in a genome [27, 76, 77]
Monogenic disorders	Disorders that result from altered function of a single gene; the disease-associated gene may be located on an autosome or on a sex chromosome and the related disease phenotype may be dominant or recessive; the terms monogenic disorder, Mendelian disorder, and single-gene disorder are often used interchangeably [78]
Rare disorders	Defined differently in several legislations; in Europe, diseases with prevalence of $\leq 5/10,000$ inhabitants are considered rare [4]; in the USA, diseases affecting fewer than 200,000 people, approximately equivalent to $\leq 6/10,000$ inhabitants, are considered rare [79]; in Japan and Taiwan diseases with a prevalence of $< 1/10,000$ inhabitants are considered rare [80]; while some rare disorders are close to these prevalence thresholds, 10–20% are ultra-rare; the distinction between rare and ultra-rare diseases is important because of its implication in the assessment of the value of orphan medicinal products [36]
Genetic testing	A type of medical test that aims to identify changes in DNA, RNA, chromosomes or proteins; it can be performed for diagnostic, predictive or reproductive purposes. Diagnostic testing aims to identify, rule out or confirm the diagnosis of a suspected inherited condition. Predictive testing aims to identify changes associated with increased risk of developing an inherited disorder before any symptoms or signs appear; this includes population screening, such as newborn screening. Reproductive testing aims to identify people who are at increased risk of having a child with a genetic disorder or to identify an affected embryo or fetus; this includes carrier testing, prenatal genetic testing, and pre-implantation testing. Different methods for assessing the validity and usefulness of a genetic test have been described, but the three principle measures are: analytic validity, clinical validity, and clinical utility. Importantly, each genetic test evaluation should start by defining the clinical scenario for testing (including the target condition, the target population and the purpose of the test); for example, the validity and usefulness of a genetic test for Usher syndrome will be different if the target population includes all newborn children or if it includes just individuals with combined rod-cone dystrophy and hearing loss [27]
Analytical validity	The ability of a test to accurately and reliably identify the specific entity that it was designed to detect (e.g. a genetic variant of interest); it often reflects the robustness of the assay and it is typically described in terms of analytical sensitivity (<i>i.e.</i> how often the test is positive when a variant is known to be present) and analytical specificity (<i>i.e.</i> how often the test is negative when a variant is known to be absent); notably, a test will not be considered suitable for clinical use unless it meets acceptable standards for analytic validity [27, 81]
Clinical validity	The ability of a test to accurately and reliably identify a clinically defined disorder or phenotype of interest; it corresponds to the diagnostic yield, accuracy or pick-up rate and it is typically described in terms of sensitivity (<i>i.e.</i> how often the test is positive when a condition is present) and specificity (<i>i.e.</i> how often the test is negative when a condition is not present) [27, 82]
Clinical utility	The ability of a test to influence clinical outcomes and patient management; it evaluates the health benefits and potential harms that accrue from both positive and negative results of the test; it often reflects the utility of the intervention guided by the test rather than the test itself; narrow and broad sense definitions have been described – please see the main text for further details [27, 30–32, 81–84]

Table 1 (continued)

Clinical actionability	The ability to intervene and thereby avert a poor outcome due to a previously unsuspected high risk of disease; it is often used in the context of secondary/incidental genetic findings in certain genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated [85–87]
Clinical trial	A study carried out according to a prospectively defined protocol that is intended to discover or verify the safety and effectiveness of a procedure or intervention [27]
Evidence-based medicine	The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients; it integrates clinical experience and patient values with the best available research information [88, 89]
Genomic medicine	A medical discipline that involves using genomic information about an individual as part of their clinical care [90, 91]
Precision medicine	An approach to disease treatment and prevention that takes into account individual variability in environment, lifestyle and genes; the terms precision medicine and personalised medicine are often used interchangeably [92–95]
Implementation science (healthcare)	The study of methods to promote the integration of research findings and evidence into healthcare policy and practice [19, 20, 96]

In 2017, the US National Academies of Sciences, Engineering, and Medicine released a report titled “An Evidence Framework for Genetic Testing” [27]. This document discusses the clinical applications and usefulness of genetic tests, and examines how relevant evidence is generated, evaluated and synthesised. A key concept in this report is that of clinical utility defined as “the ability of a test to improve clinical outcomes measurably and to add value for patient management decision making compared with current management without genetic testing” [27, 28]. This term has been used in the context of genetic testing for over 20 years and, over this period, it has been construed both narrowly and broadly [29–31]. Scholars who refer to clinical utility by its narrowest definition focus on the ability of a screening or a diagnostic test to lead to an improved health outcome (impact on mortality, morbidity, disability; e.g. excising a Wilms tumour detected following a genetic test for aniridia). Conversely, broader definitions may include any change in management (e.g. preventing additional investigations or introducing personalised surveillance measures) or any outcome that is important to the affected individual or family (e.g. early resolution of uncertainty, better understanding of condition, effect on reproductive or life planning) [31]. It is noteworthy that other test parameters such as analytical validity (i.e. the ability to accurately identify variants of interest) and clinical validity (i.e. the diagnostic accuracy) are related but not overlapping with clinical utility (Table 1). Also, clinical utility is not tied to cost-effectiveness as the latter can be only evaluated at the

site level. At present, rigorous evidence on the clinical utility of genetic testing for monogenic retinal disorders is lacking – as indeed it is lacking for most other monogenic disorders (i.e. it is unclear who should be tested, with what test and when). Notably, there is no consensus on what constitutes sufficient evidence to justify implementation of genetic testing – are randomised trials required, or can observational studies aligned to mechanistic reasoning suffice? Clearly, randomised trials are expensive and hard to justify if there is no genuine uncertainty among experts (principle of equipoise) [32]. In any case, evidence gaps need to be identified and addressed.

Conducting clinical research/trials in rare disorders like monogenic retinal disease poses unique challenges. A key issue is how to avoid conducting underpowered studies. Two evident obstacles are disease heterogeneity and geographic dispersion of affected individuals. The paucity of natural history data poses another important barrier; without a firm understanding of disease progression, choosing meaningful outcome measures and designing and powering clinical trials is challenging [33–36]. Furthermore, many monogenic retinal disorders primarily affect children adding further complexity to potential study design [34]. It is apparent that to overcome these hurdles, stakeholder engagement at an unprecedented level will be required [37].

In recent years, several initiatives have focused on improving our ability to conduct research on rare diseases in general and on monogenic retinal disorders in particular. A notable example is the European Reference Net-

Table 2. Examples of measures that could accelerate the translation of our growing genetic knowledge into effective interventions for inherited retinal disease (IRD)

Data collection	
<i>Harmonising the collection of phenotypic data</i>	Reduction of unnecessary heterogeneity can be facilitated by: <ul style="list-style-type: none"> the wider adoption of standardized terminologies/ontologies (like HPO [39]); supporting a guideline development group that would define a “minimum clinical dataset” (<i>i.e.</i> the specific phenotypic information that should be collected in all individuals with IRD).
<i>Developing a health informatics infrastructure to capture and exchange data</i>	The establishment of a multicenter, international IRD database/registry that includes variant- and individual-level data would require: <ul style="list-style-type: none"> addressing the associated ethical and legislative issues, and navigating the relevant country-specific regulatory barriers; adopting standards for responsible, accountable and transparent sharing of clinical-grade data (e.g. as per GA4GH [21]).
Evidence generation	
<i>Facilitating timely and adequate recruitment of eligible clinical trial participants</i>	The prevalence and heterogeneity of IRD makes obtaining sufficient sample sizes for research challenging; addressing this would require: <ul style="list-style-type: none"> reaching as many affected individuals as possible and actively encouraging their recruitment in international registries and research cohorts; incentivising and promoting a model of large-scale international collaboration.
<i>Optimising clinical trial design</i>	Incomplete understanding of disease natural history is common in rare diseases like IRD. When natural history data is lacking, choosing appropriate outcomes and designing and powering clinical trials is particularly challenging [34]; addressing this would require. <ul style="list-style-type: none"> promoting and supporting high-quality natural history studies; long-term grants ensuring continuity in these efforts would be required. organising interactive workshops that would initiate a multi-stakeholder dialogue around clinical endpoints and outcome measures that are both sensitive and patient-centred [34–36].
Education	
<i>Increasing workforce capacity and capability</i>	Initiatives should be taken to expand the workforce of professionals that are trained to understand/incorporate genetics into the care of individuals with IRD; courses and other educational resources that can be broadly accessed should be developed.
<i>Appreciating data privacy issues and social implications of genetic research</i>	Building public trust in genetic research and its clinical application is paramount; potential genetic privacy risks should be appreciated and particular care should be taken to avoid misinterpretation and misuse of scientific results.

work on Rare Eye Diseases (ERN-EYE), an initiative with a leading role in the development of key infrastructure such as international patient registries and computational tools to standardise terminology [38, 39]. Another example is a forum/workshop organised by the Association for Research in Vision (ARVO) and Foundation Fighting Blindness in 2016 with the goal of identifying appropriate trial endpoints for inherited retinal disorders [40]. Outside ophthalmology, substantial efforts have been put on rethinking clinical trial design for small populations, de-

fining core sets of patient-centred outcome measures, optimising error rates when there are constraints on the available sample size and identifying models of “real-world” evidence collection [33, 35–37, 41–43]. However, a standardised framework integrating all these elements is still missing.

In December 2017, the US Food and Drug Administration (FDA) in a landmark decision approved the first gene augmentation therapy for an inherited disorder. The drug was voretigene neparvovec, and it can be used to

treat *RPE65*-associated retinal dystrophy in adults and children [44]. In November 2018, approval by the European Medicines Agency (EMA) was also obtained, and many European countries are presently conducting Health Technology Assessments to decide whether the therapies should be approved for reimbursement [45, 46]. Numerous other gene therapies are presently under development or undergoing benefit-risk assessment. There is little doubt that some of these ongoing trials will demonstrate safety and efficacy. However, how many will meet the required standards of evidence for reimbursement bodies remains to be determined [47]. Nonetheless, it only is by conducting high-quality trials and by gathering as robust evidence as possible that we can resolve clinical agnosticism and ensure a significant impact [48].

To obtain sufficient sample sizes for research, we need to engage geographically, socially and economically diverse patient populations. To reach as many affected individuals as possible, the effort of all ophthalmologists who see patients with monogenic retinal disorders will be required. A few steps that could accelerate the translation of our growing genetic knowledge into effective interven-

tions include: (i) ensuring that all individuals with monogenic retinal disorders that come to medical attention receive an accurate diagnosis [49]; (ii) capturing clinical information efficiently [14, 50] and collecting natural history data in a rigorous and systematic way (e.g. in registries [51]); (iii) appreciating the statistical challenges and focusing on optimising research designs [33–36, 52, 53] (Table 2).

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