

POSITION STATEMENT

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The need for widely available genomic testing in rare eye diseases: an ERN-EYE position statement

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Abstract

Background: Rare Eye Diseases (RED) are the leading cause of visual impairment and blindness for children and young adults in Europe. This heterogeneous group of conditions includes over 900 disorders ranging from relatively prevalent disorders such as retinitis pigmentosa to very rare entities such as developmental eye anomalies. A significant number of patients with RED have an underlying genetic etiology. One of the aims of the European Reference Network for Rare Eye Diseases (ERN-EYE) is to facilitate improvement in diagnosis of RED in European member states.

Main body: Technological advances have allowed genetic and genomic testing for RED. The outcome of genetic testing allows better understanding of the condition and allows reproductive and therapeutic options. The increase of the number of clinical trials for RED has provided urgency for genetic testing in RED. A survey of countries participating in ERN-EYE demonstrated that the majority are able to access some forms of genomic testing. However, there is significant variability, particularly regarding testing as part of clinical service. Some countries have a well-delineated rare disease pathway and have a national plan for rare diseases combined or not with a national plan for genomics in medicine. In other countries, there is a well-established organization of genetic centres that offer reimbursed genomic testing of RED and other rare diseases. Clinicians often rely upon research-funded laboratories or private companies. Notably, some member states rely on cross-border testing by way of an academic research project. Consequently, many clinicians are either unable to access testing or are confronted with long turnaround times. Overall, while the cost of sequencing has dropped, the cumulative cost of a genomic testing service for populations remains considerable. Importantly, the majority of countries reported healthcare budgets that limit testing.

Short conclusion: Despite technological advances, critical gaps in genomic testing remain in Europe, especially in smaller countries where no formal genomic testing pathways exist. Even within larger countries, the existing arrangements are insufficient to meet the demand and to ensure access. ERN-EYE promotes access to genetic testing in RED and emphasizes the clinical need and relevance of genetic testing in RED.

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Keywords: Genetic and genomic testing, Rare eye diseases, ERN-EYE, Position statement

Background

Technological advances have allowed genetic and genomic testing for Rare Eye Diseases (RED). The outcome of genetic testing allows better understanding of RED and allows reproductive and therapeutic options. Despite these advances critical gaps in testing remain in European member states, especially in smaller countries. Even within larger countries, the existing arrangements are insufficient to meet the demand and to ensure equity of access. The European Reference Network (ERN) initiative, a cross-border cooperation between healthcare providers and researchers from across the European Union, has been created to improve diagnosis and treatment of complex or rare medical conditions that require specialised treatment, knowledge and resources [1]. ERN-EYE promotes access to genetic testing in RED and emphasizes the clinical need and relevance of genetic testing in RED.

Main text

There are 24 thematic ERNs, including ERN-EYE, whose focus is on RED [2]. The ERNs seek to aggregate healthcare providers in order to improve patient access to healthcare information and thereby increase treatment options. They aim to do this by (i) creating innovative care models, in particular using digital technologies, (ii) enhancing research through the increase of the size and power of clinical studies as well as epidemiological registries and (iii) enabling sharing of costly resources which ultimately leads to more sustainable national healthcare systems. The overarching objective is to improve health outcomes for the large numbers of patients in the EU suffering from rare and often complex conditions.

RED are the leading cause of visual impairment and blindness for children and young adults in Europe [3, 4]. This heterogeneous group of conditions includes over 900 disorders ranging from relatively prevalent disorders such as retinitis pigmentosa (estimated prevalence of 1 in 4,000) to very rare entities described only once or twice in medical literature [5]. ERN-EYE is structured around 4 clinical thematic working groups (Retina, Neuro-ophthalmology, Paediatric, Anterior segment) and 6 transversal working groups (Low vision, Genetic diagnostic, Registries, Research, Education / Training, Communication) [2]. Notably, the ERN-EYE has organised workshops on diverse areas ranging from clinical terminology standardisation (Mont Sainte-Odile workshop, 2017) to genomic testing (Florence workshop, 2018) and clinical trials (Strasbourg workshop, 2019) [6].

The advance towards personalization of medicine is accelerating [7]. For rare diseases, including RED, there is now a general understanding that patients often experience delayed diagnosis, which in turn leads to poor access to appropriate treatment and management protocols. For RED, a significant number of patients have an underlying genetic etiology. Effective and individualized approaches to clinical management are consequently dependent upon a comprehensive means of delivering genetic or genomic testing [8]. Genomic testing allows a precise diagnosis of highly heterogeneous disorders, improves counselling (e.g. understanding prognosis; facilitating reproductive decision-making) and is increasingly important in directing treatment options [9].

Genomic approaches can improve diagnosis and management of RED

There are now numerous examples demonstrating clinical benefit of genomic testing in RED. For example, for oculocutaneous albinism, genetic diagnostic approaches provide a positive diagnosis in over 75% of cases. This not only achieves a diagnosis in early life for individuals with reduced vision but also allows identification of syndromic forms including the 1 in 30 cases of apparently uncomplicated albinism that represent unsuspected cases of Hermansky-Pudlak syndrome implying specific surveillance and care [10].

Leber Congenital Amaurosis (LCA) is the earliest onset and most severe form of inherited retinal diseases (IRD) [11]. This group of conditions is caused by genetic alterations in over 20 genes and is also the field where most clinical research is performed to date [12–14]. Some examples are given where comprehensive genomic testing leads to a molecular diagnosis and offers therapeutic perspectives. A first example are pathogenic variants in the RPE-specific gene *RPE65* encoding a protein member of the visual cycle that regenerates retinal. The recent FDA and EMA approval of *voretigene neparvovec-rzyl* for the treatment of LCA patients with biallelic *RPE65* mutations, as a landmark of novel gene-directed therapy, paved the way for successful treatment [15–18]. A second example is a recurrent deep-intronic pathogenic variant in *CEP290*, a gene encoding a key component of the connecting cilium. There are promising clinical studies suggesting potential for intravitreally delivered antisense oligonucleotide (AON) therapy and for gene editing using CRISPR/Cas9 [19–21]. Pathogenic variants in *CEP290* and other cilia-related genes (e.g. *IQCB1*) can predispose for multi-systemic complications including renal failure

[22, 23]. Other examples requiring an early diagnosis are *AILP1*- and *GUCY2D*-associated LCA given the ongoing therapeutic efforts [24–27].

Moreover, *CLN3*-associated Batten disease, first diagnosed by ophthalmologists, is another example where early diagnosis is critical to direct management, counseling, and support for young patients and their families. The systemic therapeutic options for this disease in early-phase clinical trial benefit from a start at the earliest stage of disease [28, 29].

Other examples are pathogenic variants identified in disease genes implicated in achromatopsia [30], choroideremia [31], Stargardt disease (STGD1), X-linked retinitis pigmentosa and other IRD [33, 34] that are eligible for the huge range of clinical trials being undertaken currently [12–14]. Specifically, rare and recurrent deep-intronic pathogenic variants (total: 355) in *ABCA4* associated with STGD1 in ~10% of cases allow the design of novel RNA splice modulation therapies using AONs [35–37].

Patient groups, clinicians and scientists together recognize an urgent need for widespread availability of genomic testing for RED to avoid the so-called ‘diagnostic odyssey’ - an extended and distressing period, often unsuccessful, characterised by multiple sequential investigations. By providing a definitive molecular diagnosis this can strongly facilitate clinical and personal decision-making [38, 39].

What is the current picture of genomic testing in RED?

Adoption of genomic testing for RED has accelerated considerably over the past 10 years due to the availability of ‘next generation sequencing’ (NGS), a technological advance allowing massively parallel sequencing of multiple nucleic acid targets [38]. This technique is increasingly being deployed in the clinical diagnostic setting and it has allowed affordable analysis of complete genomes [40, 41].

A survey of countries participating in ERN-EYE demonstrated that the majority are able to access some forms of genomic testing. However, access is still far from universal and there is significant variability of delivery, particularly in the degree to which different countries are able to provide testing as part of clinical service. It is not uncommon for clinicians to have to rely partly or completely upon either research-funded laboratories (for example in the Czech Republic) or private companies. Notably, some member state relies mainly on cross-border testing either by way of an academic research project. For example, research-based sequencing of the entire *ABCA4* gene for variants associated with STGD1 in the Netherlands and Belgium has yielded bi-allelic variants in ~500 probands ascertained worldwide, including many

undiagnosed families from Eastern European countries [35–37]. Currently 2,000 STGD1 and STGD-like maculopathy probands have been sequenced for mutations in *ABCA4* and *PRPH2*, solving ~50% of the cases.

In the US, *Invitae* has announced a free sequencing service for RED probands from the US based on a partnership with *Spark Therapeutics* [41]. The Foundation Fighting Blindness, in partnership with *Blueprint Genetics* and *InformedDNA*, offers free genetic testing and counselling to individuals living in the US or US territories and clinically diagnosed with an IRD [42].

In Europe, some countries have a very well delineated rare disease pathway (summarized in Table 1). In France for example, there is a long-standing national centralized organizational plan for rare diseases (*Plan National Maladies Rares*) [43] now combined with a centralized national plan for genomics in medicine (*Plan France Médecine Génomique*) [44]. In the UK, a small number of Genomic Laboratory Hubs and a highly productive national initiative (100,000 Genomes; Genomic England) allow relatively frictionless access to testing [45]. In Belgium and the Netherlands there is a well-established organization of genetic centres with good access to reimbursed genomic testing of RED and other rare diseases. In Germany, academic genetic centres, private genetic laboratories but also industrial laboratories offer this service. Other member states such as Italy rely on regional organisation where University centres have, over time, developed significant expertise in specific RED fields.

Within this overall picture, critical gaps in testing remain, especially in a number of smaller countries where no formal genomic testing structures exist. Notably, even within larger countries, the existing arrangements are insufficient to meet the demand and to ensure equity of access. Consequently, across the EU there are large numbers of clinicians and affected families who are either unable to access testing or who have to wait for considerable periods of time to receive results. Overall, while the cost of genomic sequencing has dropped at an extraordinary rate over the past decade, the cumulative cost of providing a comprehensive genomic testing service for populations remains considerable. Importantly, the majority of EU countries reported healthcare budgets that limit testing despite the fact that increase in demand (i.e. numbers of patients requiring testing) is inevitable [46].

Clinical utility: making the argument to justify genomic testing

It is perhaps not surprising that translation of clinical, technological and research advances into routine

Table 1 Rare disease pathway summary and access to genetic testing by country

Questions to ERN-eye members? (October 2018 with March 2020 update)	BE	CZ	DK	ES	FR	GE	IT	LV	LT	NL	UK	PL	PT
Are there national initiatives for genetic testing (GT) such a National Plan?	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	N	N
Is there a unique national model for the consent form? (thus HCP specific)	N	N	Y	N	Y	N	N	Y	N	N	Y	N	N
Are most of the GTs done with academic hospital laboratories?	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	Y	Y
Are GTs done by industrial partners?	N	Y	N	Y	N	N	Y	95%	rare	N	N	Y	Y
Are there samples sent abroad for GT?	Y	Y	Y	Y	Y	Y	Y	N	N	Y	rare	Y	Y
Can ophthalmologists prescribe the GTs?	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	N
Are there national rules for the prescription of GTs?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Are there multidisciplinary meetings in the GT course?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Do you have access to Sanger sequencing?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Do you have access to panel-based testing?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Do you have access to whole exome sequencing (WES) for GT in your country?	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	N	N
Do you have access to whole genome sequencing (WGS) for GT in your country?	N	N	N	N	N	N	N	N	N	Y	N*	N	N
Do you have access to WES for research only?	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	N
Do you have access to WGS for research only?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
Is the patient reimbursed for GT (gene panels, Sanger)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Is the patient reimbursed for WES?	Y	-na	-na	-na	Soon	Y	N	N	-na	Y	Y	N	N
Is the patient reimbursed for WGS?	N	-na	N	N	N	N	N	N	Y	N	N	N	N
Are there enough specialists in genetic ophthalmology in your MS?	Y	N	Y	Y	N	N	N	N	N	Y	Y	N	N
Is there a national genetic database?	N	N	N	Y	N	N	N	Y	Y	Y	N	N	N

*Due to be available from April 2021

Abbreviations used: BE: Belgium; CZ: Czech Republic; DK: Denmark; ES: Spain; FR: France; GE: Germany; IT: Italy; LV: Latvia; LT: Lithuania; NL: Netherlands; UK: United Kingdom; PL: Poland; PT: Portugal

healthcare is slow. Undoubtedly, the adoption of a clinically relevant intervention—in this case, genomic testing—is more likely where its ability to influence management and health outcomes has been clearly demonstrated. Therefore, a focus on clinical benefit ('clinical utility') of genomic testing remains an urgent requirement to provide a clear evidence for widespread implementation [47, 48]. To date, compiling such evidence for RED has been slow. However, evidence of clinical utility has been demonstrated for small groups of patients [49–53]. Additional, well-designed studies of broader scale are becoming available [7, 54].

Training and mainstreaming of genomic medicine

Genomic testing is only one of the barriers that exist for effective diagnosis and management for individuals with RED. It is clear that the number of healthcare professionals and genetic counsellors who specialise in ophthalmic genetics is another important limiting factor, even in settings where genomic testing is readily available. Notably, at present, care for families with RED is generally delivered by a few "super-specialists" in ophthalmic genetics who work within a relatively small number of academic centres. Given the cumulative prevalence and overall number of RED, and the increasing recognition of clinical need, this dependence of small groups of experts is likely to be unsustainable.

Broadening access to genomic testing will require an expansion of the group of clinicians who are willing and able to order such diagnostic tests. Since this requires specialist knowledge, training of a wider group of clinicians at all strata of seniority will be necessary. While in the longer term this sits within medical schools and professional curricula, in the shorter term it will be critical to provide professional development that enables up-skilling of existing clinical workforces. There will be different levels of skills required for different groups of clinicians. Paediatric ophthalmologists and medical retina specialists who encounter RED more frequently are perhaps the first who need to acquire these new skills and to enhance their understanding of the care pathways, consent issues and utilisation of genomic knowledge in clinical management. However, it is expected that in the not-so-distant future, broader applications of genomic medicine such as pharmacogenetics and complex genetics will be increasingly important to all clinicians.

Technological advances of DNA sequencing technologies have tremendously expanded the ability of healthcare systems to diagnose RED. This gives great hope to affected families. Harnessing the motivating power of patient groups and hearing the patient voice is critical in promoting systematic change in healthcare provision. The ERN-EYE initiative has been strongly influenced by

patient bodies and advocates. These interactions have greatly enhanced our understanding of how a definitive genetic diagnosis can promote closure, lead to early resolution of uncertainty, allow better understanding of the condition and, crucially, inform reproductive and life planning. However, ultimately, implementation of such advanced diagnostic strategies will require considerable increased investment. Thus, there is an urgent need for professionals to provide broad evidence of clinical benefit and utility. The extraordinary acceleration in the number of clinical trials for RED in general and for inherited retinal disorders in particular, has provided considerable urgency and impetus.

Conclusions

- Technological advances have allowed genomic testing for RED.
- Despite these advances critical gaps in testing remain, especially in smaller countries where no formal genomic testing structures exist. Even within larger countries, the existing arrangements are insufficient to meet the demand and to ensure equity of access.
- The outcome of genetic testing allows better understanding of the condition and allows reproductive and therapeutic options. The increase of the number of clinical trials for RED has provided considerable urgency for genetic testing in RED.
- ERN-EYE promotes access to genetic testing in RED and emphasizes the clinical need and relevance of genetic testing in RED.

Abbreviations

ASO: Antisense oligonucleotide; Cas9: CRISPR associated protein 9; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; EMA: European Medicines Agency; ERN: European Reference Network; ERN-EYE: European Reference Network for Rare Eye Diseases; FDA: Food and Drug Administration; LCA: Leber Congenital Amaurosis; IRD: Inherited Retinal Diseases; RED: Rare Eye Diseases; STGD1: Stargardt disease type 1.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

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