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## Review

# Providing comprehensive genetic-based ophthalmic care

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The diagnosis of an inherited retinal dystrophy can have a significant impact on both the physical and emotional lives of patients and their families. In order to optimize the health and quality of life for these individuals, a comprehensive approach to clinical care starting at the time of diagnosis and continuing throughout their lifespan is critical. A multidisciplinary team approach integrating ophthalmic and genetic counseling services can optimize the diagnostic process and long-term management of these patients. When vision loss is first appreciated, the diagnostic specificity of an ophthalmic evaluation can be enhanced by a detailed genetic work-up. This evaluation can help confirm the diagnosis and allow for accurate risk counseling of the patient and their family. Genetic counseling is critical at the time of diagnosis and is an opportunity to provide education about the diagnosis, discuss low-vision rehabilitation, and explore impacts on academics and employment. In addition, counseling can help patients deal with the current psychological aspects of their vision loss, prepare for the lifelong impact of their diagnosis and over time adjust to the impact of progressive vision loss.

### Conflict of interest

The authors report no conflict of interest.

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Providing comprehensive genetic-focused clinical care has always been essential for patients seen in pediatric genetics, adult genetics, prenatal, and hereditary cancer clinics. The expanded ability to make genetic-based diagnoses in a wider array of disciplines has resulted in the expansion of genetic-focused clinical care into multiple additional specialty areas including cardiology, neurology, and the focus of this article: ophthalmology. One of the largest categories of inherited eye disease seen in ophthalmology is the inherited retinal dystrophies (IRDs). This group of conditions can have a congenital to adult-onset and cause slowly progressive vision loss, which can result in legal blindness. The IRDs most commonly include diseases such as retinitis pigmentosa (RP), Stargardt disease, cone dystrophies, Leber congenital amauorsis, etc. Although collectively this group of conditions is considered somewhat rare, some conditions such as RP have a disease incidence as high as 1/3500–1/5000 (1, 2).

While a great deal of progress has been made in understanding the molecular basis of inherited eye diseases, there appears to be a gap in the provision of appropriate standardized specialized genetic ophthalmic care (3, 4). Making the diagnosis is but one step in providing comprehensive medical care for this group of patients. Collaboration between the patient, their family, the ophthalmologist, and the genetics expert can ensure that appropriate clinical care is provided and that it is personalized to the needs of the patient and their family. Once a diagnosis is made, the patient should be made aware of patient-friendly information about the disease, its impact on societal functioning, supportive resources, and reliable sources of information about the disease (5). Combined with this education is the need to provide support for the emotional impact of the actual diagnosis. One of the key issues in thinking about an IRD is the recognition that the disease is dynamic. Adjustment will occur at multiple points in time and will require

life-long education and support that explores both the current state of the disease and helps the patient and their family prepare for future stages of vision loss.

### The diagnostic odyssey

Making a genetic diagnosis in a patient affected with an inherited eye disease can be a complex process. While the ability to validate the type and extent of vision loss can be relatively straightforward, identifying the underlying cause (i.e. the pathophysiology) of the IRD is dependent on clinical diagnostic tools and expertise that are available in a small subset of ophthalmology practices. In an IRD clinic a patient's presenting symptoms may be quite broad and relatively non-specific, such as a decrease in visual acuity or nightblindness. The ophthalmic diagnostic process refines these vague symptoms to a more precise clinical diagnosis through a complex series of diagnostic evaluations and clinical examinations (Fig. 1). Subjective diagnostic evaluations such as visual field, color vision testing, and visual acuity measurements are combined with objective ophthalmic testing, such as, electrophysiology, visually evoked potential, fundus autofluorescense, angiography, and optical coherence tomography. Patients may have multiple evaluations by varied specialists before a single unifying diagnosis is obtained. It has been suggested that appropriate care requires a multidisciplinary approach comprised of integrated ophthalmic and genetic diagnostic services that can provide high quality ocular electrophysiology services, genetic testing and interpretation, genetic counseling and effective follow-up for both the patient and their at-risk family members (5). This team-based approach is critical to ensuring the visit is a success in terms of both the diagnostic evaluation and patient satisfaction (6).

Family history is also a critical diagnostic tool of the IRD clinical evaluation. A targeted family history can elicit information on other family members with a history of similar vision loss. It is essential to gather information not only on the disease in other family members but also on the age of disease onset. Asking about the age of onset may be helpful in discerning those truly affected by an IRD from those who had vision loss due to common age-related conditions such as cataracts or age-related macular degeneration. In some families sharing information about vision loss may be uncommon and uncomfortable, therefore, asking questions about the ability of that person to function in society (drive a car, read, etc) may also be useful is discerning who else in the family is affected (7). Combining the results of the diagnostic evaluations with the results of the clinical examination and a detailed pedigree can add specificity to the differential diagnosis. The tentative clinical diagnosis can then be refined through genetic testing.

When a patient and their family have had limited experiences with ophthalmology it may be a difficult and daunting task to navigate the process of getting diagnosed with an IRD. It is initially challenging to appreciate the distinctions between the various categories of eye specialist, such as, an optometrist *vs* an ophthalmologist. In addition, the limited availability of specialists with appropriate experiences with inherited ophthalmic conditions, means that for many individuals and their families the self-identification of visual impairment or vision loss may be followed by multiple evaluations by varied vision specialists before a definitive diagnosis is made (3, 8). The uncertainty that accompanies this process can leave patients both frustrated and frightened as their vision slowly declines and they have access to limited information on their future. For some patients the end of the diagnostic odyssey gives way to the larger difficulty of living with a rare diagnosis about which their physician may have limited experience in providing appropriate patient support (8). These experiences highlight the need for compassionate care at the time of diagnosis when patients may have struggled with their vision loss for a long period of time and their future is uncertain.

### Genetic counseling

Genetic counseling can be integrated into ophthalmic care for patients with diagnoses of IRDs using several different service delivery models (9). In some clinics, genetic counseling may be provided by

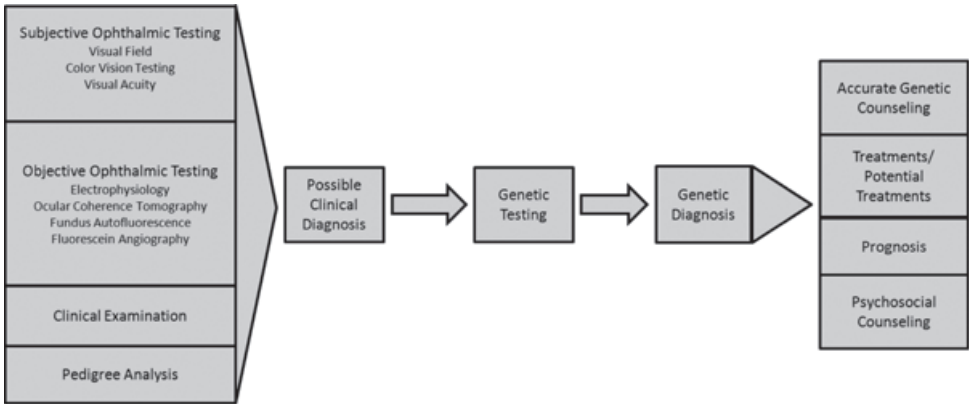


*Fig. 1.* The diagnostic process for inherited retinal dystrophies.

ophthalmologists who are board certified in both ophthalmology and genetics or have fellowship training in ophthalmic genetics. In other clinics, genetic counselors may function as a permanent member of a multidisciplinary team working directly with an ophthalmologist who specializes in IRDs. In academic centers, if the ophthalmologist is not trained in genetics or does not have a genetic counselor on staff, they may refer their patients to mainstream genetics clinics (i.e. pediatric, prenatal, or adult genetics) for this service. The referring ophthalmologist may prefer that selected or all aspects of genetic clinical care occur in the genetics clinic (9). Genetic counselors are also available through commercial companies to perform telephonic counseling for patients. When care is provided via telemedicine it overcomes geographic boundaries for people who are unable to travel to a clinic specializing in ophthalmic genetic diseases or providing genetic counseling services. Genetic counselors are trained to work with patients with all forms of inherited diseases, including inherited eye disease. However, these are a limited number of genetic counselors who have expertise in inherited eye diseases. Currently there are more than 30 genetic counselors with this expertise in the United States and Canada (K. Branham, personal communication). They are employed at university hospitals, genetic testing labs, government organizations, or businesses that provide genetic counseling via telemedicine.

Genetic counseling for patients who are blind or affected with vision loss poses unique challenges. Genetic counselors often use visual aides to explain complex medical and genetic information to their patients. These aides have been shown to improve patient recall and information retention from a counseling session (10), however, they are challenging to use during an ophthalmology session in which the patient is dilated for their examination and also has low vision. Genetic counselors who normally rely on hand motions to aide in discussing complex genetic issues with their patients, may find this is ineffective when patients have difficulty seeing. Learning to use only their spoken voice to work with patients may be challenging. Similarly, the types of written documents provided to patients with low vision may need to be modified to accommodate various forms of vision loss. When communicating with patients in written text, large fonts may be helpful for patients who have central vision loss (Stargardt disease, Best disease, etc), but would not be as useful for patients with limited visual fields (choroideremia, retinitis pigmentosa, etc). Black text on white paper is generally easier to read for a patient with low vision. Electronic formats such as PDF may be useful for patients to use with certain computer aided readers. Written summaries of clinical discussions may only be useful if patients have access to low-vision devices in their homes.

#### Genetic testing in inherited retinal disease

The recent rapid growth of genetic testing companies has improved access to both this technology and the accompanying diagnostic knowledge for both patients and clinicians in all medical specialties, including genetics and ophthalmology. Genetic testing is increasingly being seen as a critical diagnostic tool in the field of IRDs, it can be used to clarify the pattern of inheritance (and thus improve genetic counseling accuracy), clarify the diagnosis (and sometimes provide prognostic information), and optimize clinical care. Genetic counselors' specialized training makes them ideal members of the ophthalmic health care team who can ensure that prior to ordering genetic testing patients have the opportunity to discuss and evaluate the risks, benefits, and limitations of the genetic testing and can serve as a knowledgeable resource to explore the meaning of the often complicated results.

In many IRDs, there is a great deal of genetic complexity. RP is an example of an IRD which displays extreme genetic heterogeneity with autosomal dominant, autosomal recessive, X-linked, and less commonly mitochondrial and digenic forms of disease. More than 56 genes have been identified as causative for nonsyndromic forms of RP (https://sph.uth.edu/Retnet/). In some cases, careful pedigree analysis may not provide definite answers regarding the pattern of inheritance of disease in the family (11–14). Genetic testing in IRDs may also be complicated by clinical heterogeneity. There are multiple examples where mutations in a single gene result in clinically distinct form of an IRD. For example, mutations in the RDS/peripherin gene (*PRPH2*) can cause RP and several clinically distinct types of macular dystrophy (15–17).

While in most cases, genetic testing can be used to add specificity to the diagnosis of the well-phenotyped patient, in other cases, genetic testing may help provide a diagnosis for a patient in which repeated diagnostic ophthalmic evaluations have failed to identify the underlying disease. For example, Leber congenital amaurosis, achromatopsia, and congenital stationary night blindness have quite different longitudinal outcomes for patients, yet in an infant or young child, the overlapping clinical symptoms include decreased visual acuity and nystagmus (18). Genetic testing of an infant/young child presenting with these symptoms, may identify the diagnosis and provide prognostic information to both parents and patients.

Genetic testing can also optimize clinical care by allowing patients to take advantage of emerging targeted therapeutics. In some diseases, identifying the genetic basis for disease allows a patient to prepare for current and future clinical trials. Currently clinical trials are available for patients who have vision loss due to mutations in *RPE65* (19–21), *LRAT*, *MYO7A* (22), *ABCA4*, and *CHM* (www.clinicaltrials.gov). Future trials currently under laboratory investigation for several other diseases include IRDs caused by mutations in *RPGR* (23), *RS1* (24–26), *CNGA3* (27), and *CNGB3* (28, 29). Moreover, there is evidence that certain environmental factors may be more harmful in specific genetic contexts. Animal studies in *ABCA4* −/− mice showed increased lipofuscin deposits, suggesting that patients affected with Stargardt disease

should avoid vitamin A supplementation (30). Patients with *RHO* mutations are also particularly sensitive to phototoxic effects (31) and should be advised to avoid excess sun exposure.

Identifying the genetic basis for the patient's IRD, not only has implications for the patient, but impacts the entire family overall. Genetic information may be useful for other family members who wish to understand their own risk to develop the disease and/or their own risk for having children affected with an IRD. As an example, a patient presented to our clinic at age 73 having been diagnosed in childhood with a slowly progressive macular degeneration. Upon gathering family history information, we learned that his brother was similarly affected and he had a grandson, through his daughter, who suffered a retinal detachment in infancy. No unifying diagnosis had been made in this family. Although our patient's fundus findings had degenerated to the point where making a specific diagnosis was challenging, based on the clinical and family history we suspected a diagnosis of X-linked retinoshisis (XLRS). This condition is characterized by juvenile onset macular degeneration and splitting of the retinal layers (32). XLRS genetic testing was performed through the eyeGENE® study at the National Eye Institute (http://www.nei.nih.gov/resources/eyegene.asp) and identified a mutation in the *RS1* gene. Following the identification of a disease-causing mutation in our patient, other at-risk members of his family were able to have genetic testing that helped clarify their risk of developing this condition or being carriers. In this case, defining the genetic basis of the IRD helped us to not only clarify the diagnosis for our patient, but also helped individual family members define their specific disease risk. In addition, this knowledge was useful in future family planning.

Over the last 20 years, there has been a shift in the number and availability of clinical tests available for IRDs. Initially, only research labs performed genetic testing for these patients. While many of these research labs still exist, there are currently more than 12 commercial testing labs in the United States that offer genetic testing for ophthalmic eye diseases (http://www.ncbi.nlm.nih.gov/gtr/), including three labs which specialize exclusively in testing for ophthalmic disease. Numerous approaches can be used when ordering IRD testing, including targeted testing for specific mutations, panel-based testing of multiple clinically related genes, and the broadest approaches yet of whole exome/genome sequencing. Financially, it makes sense to take the most targeted testing approach available on a well-phenotyped individual (as described above) – the phenotype and inheritance pattern guide the test choice. This approach is supported by the American Academy of Ophthalmology Taskforce on Genetic Testing (33). However, for many IRD diagnoses, the extensive locus and allelic heterogeneity can make targeted testing challenging.

Despite the availability and usefulness of genetic testing, the question remains: Should genetic testing be the standard of care for IRD? The American Academy of Ophthalmology Task Force on Genetic Testing recommends that genetic testing be offered to all patients with clinical findings of a Mendelian genetic disease, for which, genetic testing is available (33). It is imperative, however, that the technology is integrated into the clinic appropriately. As a clinical tool this technology is a powerful adjunct to clinical diagnosis, however, appropriate utilization requires not only a comprehensive understanding of the pathophysiology of the disease and the varied molecular mechanisms that can result in a single clinical entity, but also careful consideration of the implications of making a molecular diagnosis for both the patient and the rest of their family. In unaffected family members it is critical to carefully consider the implications of making diagnosis in a healthy individual, that is, predictive and/or presympomatic testing before ordering the test. Patients and their families should be aware of the medical and psychosocial implications of a diagnosis and genetic counselors can have an active role in this process.

### Living with the diagnosis of an IRD throughout the life span

Multidisciplinary team members who care for patients affected with IRDs should be aware of the many challenges which can affect this group of patients. As potential members of these teams, genetic counselors can provide a comprehensive perspective on an IRD to an affected patient that helps them understand the impacts of the diagnosis on both their current and future health. Counseling in this context can include providing short-term psychosocial support which helps the patient adjust to the vision loss, identifying resources that can improve their quality of life, and helping them to appreciate the value of this type of assistance. Numerous community, state, and national resources exist for this patient population (Table 1). Their support can augment that of the multidisciplinary health care team. These government services, non-profit organizations, and clinic-based services can provide patients with long-term psychosocial support, low-vision rehabilitation, and vocational training or retraining. It is critical that patients with an IRD develop a network of resources that help them adjust to the both the physical and psychological ramifications of their diagnosis.

Following the identification of an IRD, patients should be aware that their visual impairment may impact their education, employment, mobility, socialization, psychosocial development, utilization of assistive technologies and mental health status (34, 35). However, not all individuals with an IRD will need the same accommodations or encounter the same challenges related to their vision. Due to variability in the types (central *vs* peripheral) and rates of vision loss (blindness as a child *vs* an adult), low vision, rehabilitation, and educational needs must be targeted to the specific needs of an individual and adjusted over time (36).

It is critical to recognize that a diagnosis of vision loss also results in varying degrees of stress and the emotional consequences must be acknowledged,

Table 1. Support resources for patients with inherited retinal dystrophies

| Level of resource | Type | Local examples | Roles |
|---|---|---|---|
| Community based resources | Non-profit organization | Support groups | Psychosocial support, patient education |
| | Clinical | Low Vision Clinic | Low vision sides, life skills training |
| State based resources | Government | Bureau of Services for Blind Person (Michigan) | Vocational training, advocacy |
| | Non-profit organization | Michigan Parents of Visually Impaired | Support, advocacy |
| National resources | Government | National Eye Institute | Research, education |
| | Government | eyeGENE | Research |
| | Non-profit organization | National Federation for the Blind | Advocacy, education, research |
| | Foundation | Foundation Fighting Blindness | Fundraising for research, education, advocacy |
| | Non-profit organization | National Organization for Albinism and Hypopigmentation (NOAH) | Support, education, advocacy |

accepted and accommodated. Both quantitative and qualitative studies have found that patients need time to react to the trauma of the diagnosis itself. A diagnosis of vision loss often negatively impacts psychosocial and social well-being, and patients need assistance coping with their diagnosis (37). In individuals with a diagnosis of RP it has been reported that the increasing threat of vision loss and the resulting loss of mobility and independence are sources of considerable stress (38–40). The level of emotional trauma is higher than that experienced by individuals who are adjusting to a more common diagnosis such as diabetes. For those with vision loss, this trauma appears to be reinforced by a lack of information about the diagnosis that is leading to their vision loss, limited support from health care providers, and fear of increasing physical dependence on others (friends and family) who may not fully understand the diagnosis and the continuous need to adapt and adjust to progressive vision loss (41). The ability to use assistive technology and the hope that research will help find a cure are critical to the process of actively fighting the disease. Overall, there often appears to be a high degree of resiliency that is grounded in the perspective that there are other diagnoses or life situations that could be worse. Individuals with RP have been found to use a variety of coping strategies to manage the stress associated with vision loss. These include humor, social support and communication from others with a similar diagnosis and the ability to learn to 'let it go' (38).

When hereditary vision loss is diagnosed in children, it is critical to consider the impact both on the child with the vision loss and their family members. For children who have experienced a period of normal vision, the issues are quite similar to those that are experienced by adults with vision loss and include implementing accommodations in educational settings, independence as related to driving and the ability to live outside the family home, disclosure of vision loss to friends, life partners and coworkers and identification of appropriate employment (42). The issues are also similar for children with congenital vision loss. For both groups of children with vision loss there are also challenges in social domains. Studies of Canadian youth who are blind or visually impaired have suggested that it may be particularly difficult for visually impaired children as they compare themselves directly to sighted peers and they struggle with disclosure of their impairment to their peers (42). When hereditary vision loss is considered as a chronic health problem, the impact on parents and family can include guilt over the inherited nature of the diagnosis, fear of recurrence and concerns about caring for children with vision loss (4, 41, 42). Studies of the health related quality of life (HRQoL) and psychosocial impact of an IRD on children and their families found that affected children in the study had lower HRQoL scores than other children with chronic systemic disorders (42). They also found that that their self-assessed quality of life did not correlate with objective measures of visual acuity and that in general parents assessed their child's HRQoL as lower than that reported by the child themselves. This pessimism mirrors that seen in other studies of parents of children with disabilities and highlights the importance of actively engaging parents so that they do not lower their expectations of their child's engagement in daily living activities. In addition it is important to acknowledge the stress of having a child with a chronic disability and identify ways of alleviating this burden.

In total the studies to date highlight the importance of working with all patients with inherited progressive retinal disease to acknowledge current and future vision loss and to accept their disease but limit the attempts to aggressively define when a patient will go blind. It can be very helpful to reassure patients and their families when possible that a diagnosis of an IRD does not mean that they will necessarily go completely blind (43). Concomitantly it is critical to be honest with patients about activities that will need to be altered or curtailed and help them identify resources to help deal with these changes, that is, the potential need for accommodations at school and/or work and the

utility of assistive devices and low-vision rehabilitation to help with reading and mobility. The progressive nature of vision loss requires that regular follow-up and counseling is provided. This support is particularly important in light of the varied sources of stress, both physical and emotional, that a diagnosis can evoke. Using approaches grounded in decision-making can be helpful in working with patients as they endeavor to accept their diagnosis and alter their lives to accommodate their vision loss (44, 45). The study on patient adjustment to progressive vision loss by Hayeems et al. (46) highlights a number of practical steps that can help patients adjust to their diagnosis including (i) work with the patient to understand why they believe they have their disability and normalize their search for meaning; (ii) let the patient know that the diagnosis has changed their identity and that it may be difficult to share this information; (iii) normalize the patient's reaction and help them to understand similar reactions in others with the diagnosis; (iv) help the patient think about possible lifestyle changes and identify and weigh the risk and benefits of these lifestyle changes; (v) help the patient to tailor their decision to their current vision and their psychological readiness; (vi) provide positive support by acknowledging the patient's progress in discussing these issues and (vii) anticipate future issues by providing guidance and supportive resources.

## Conclusions

A diagnosis of an IRD has significant physical and emotional impacts that occur both at the time of diagnosis and regularly through a patient's life as their vision degenerates. Making a diagnosis that is within this category of conditions, can be challenging, and patients will benefit from the input of multiple health care providers, including ophthalmologists, genetic counselors, and support staff. Taking a multidisciplinary team approach to the diagnostic process, the genetic testing process, and throughout the lifelong management of the diagnosis is critical to ensure that patients have the necessary level of support. Managing the diagnosis of an IRD requires assistance that considers both the physical and emotional dimensions of vision loss. In addition, the fact that the vision loss is inherited means that the diagnosis directly affects both the patient and their family. The ways in which genetics is integrated into ophthalmology is a useful paradigm for understanding how it might be integrated into other medical specialties.

With the rapid development of new genetic technologies (such as exome and whole genome sequencing) and swift integration into clinic care, it is increasingly challenging to determine the optimal ways of utilizing molecular diagnostics to serve our patients. Concomitant with these new advances is the responsibility to ensure that the translation from research discovery to clinical tool is appropriately integrated. As we continue to learn more about the genetic basis for inherited retinal diseases it will be critically important to ensure that a multidisciplinary team composed of physicians and genetic counselors is a standard of care for all patients.

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## References

1. Bunker CH, Berson EL, Bromley WC, Hayes RP, Roderick TH. Prevalence of retinitis pigmentosa in Maine. Am J Ophthalmol 1984: 97: 357–365.
2. Haim M. Epidemiology of retinitis pigmentosa in Denmark. Acta Ophthalmol Scand 2002: 233: 1–34.
3. Burton H, Alberg C, Moore AT. Genetics in ophthalmology: equity in service provision? J Public Health (Oxf) 2010: 32: 259–266.
4. Hamblion EL, Moore AT, Rahi JS. Incidence and patterns of detection and management of childhood-onset hereditary retinal disorders in the UK. Br J Ophthalmol 2012: 96: 360–365.
5. Sutherland JE, Day MA. Genetic counseling and genetic testing in ophthalmology. Curr Opin Ophthalmol 2009: 20: 343–350.
6. Morad Y, Sutherland J, DaSilva L et al. Ocular Genetics Program: multidisciplinary care of patients with ocular genetic eye disease. Can J Ophthalmol 2007: 42: 734–738.
7. Stroh E. Taking the family history in genetic disease: a guide for ophthalmologists. Curr Opin Ophthalmol 2011: 22: 340–346.
8. Greenberg G. Beyond the blindfold: my life with retinitis pigmentosa. Clin Dermatol 2005: 23: 640–642; discussion 642–643.
9. Cohen SA, Gustafson SL, Marvin ML et al. Report from the National Society of Genetic Counselors service delivery model task force: a proposal to define models, components, and modes of referral. J Genet Couns 2012: 21: 645–651.
10. Smerecnik CM, Mesters I, Verweij E, de Vries NK, de Vries H. A systematic review of the impact of genetic counseling on risk perception accuracy. J Genet Couns 2009: 18: 217–228.
11. Branham K, Othman M, Brumm M et al. Mutations in RPGR and RP2 account for 15% of males with simplex retinal degenerative disease. Invest Ophthalmol Vis Sci 2012: 53: 8232–8237.
12. Churchill JD, Bowne SJ, Sullivan LS et al. Mutations in the X-linked retinitis pigmentosa genes RPGR and RP2 found in 8.5% of families with a provisional diagnosis of autosomal dominant retinitis pigmentosa. Invest Ophthalmol Vis Sci 2013: 54: 1411–1416.
13. Neveling K, Collin RW, Gilissen C et al. Next-generation genetic testing for retinitis pigmentosa. Hum Mutat 2012: 33: 963–972.
14. Daiger SP, Sullivan LS, Bowne SJ. Genes and mutations causing retinitis pigmentosa. Clin Genet 2013 (in press).
15. Boon CJ, van Schooneveld MJ, den Hollander AI et al. Mutations in the peripherin/RDS gene are an important cause of multifocal pattern dystrophy simulating STGD1/fundus flavimaculatus. Br J Ophthalmol 2007: 91: 1504–1511.
16. Renner AB, Fiebig BS, Weber BH et al. Phenotypic variability and long-term follow-up of patients with known and novel PRPH2/RDS gene mutations. Am J Ophthalmol 2009: 147: 518–530 e511.
17. Weleber RG, Carr RE, Murphey WH, Sheffield VC, Stone EM. Phenotypic variation including retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus in a single family with a deletion of codon 153 or 154 of the peripherin/RDS gene. Arch Ophthalmol 1993: 111: 1531–1542.
18. Koenekoop RK, Lopez I, den Hollander AI, Allikmets R, Cremers FP. Genetic testing for retinal dystrophies and dysfunctions: benefits, dilemmas and solutions. Clin Experiment Ophthalmol 2007: 35: 473–485.
19. Bennett J, Ashtari M, Wellman J et al. AAV2 gene therapy readministration in three adults with congenital blindness. Sci Transl Med 2012: 4: 120ra115.
20. Simonelli F, Maguire AM, Testa F et al. Gene therapy for Leber's congenital amaurosis is safe and effective through 1.5 years after vector administration. Mol Ther 2010: 18: 643–650.
21. Jacobson SG, Acland GM, Aguirre GD et al. Safety of recombinant adeno-associated virus type 2-RPE65 vector delivered by ocular subretinal injection. Mol Ther 2006: 13: 1074–1084.
22. Lopes VS, Boye SE, Louie CM et al. Retinal gene therapy with a large MYO7A cDNA using adeno-associated virus. Gene Ther 2013. Epub ahead of print; doi:10.1038/gt.2013.3.
23. Beltran WA, Cideciyan AV, Lewin AS et al. Gene therapy rescues photoreceptor blindness in dogs and paves the way for treating human

X-linked retinitis pigmentosa. Proc Natl Acad Sci USA 2012: 109: 2132–2137.
24. Janssen A, Min SH, Molday LL et al. Effect of late-stage therapy on disease progression in AAV-mediated rescue of photoreceptor cells in the retinoschisin-deficient mouse. Mol Ther 2008: 16: 1010–1017.
25. Kjellstrom S, Bush RA, Zeng Y, Takaha Y, Sieving PA. Retinoschisin gene therapy and natural history in the Rs1h-KO mouse: long-term rescue from retinal degeneration. Invest Ophthalmol Vis Sci 2007: 48: 3837–3845.
26. Park TK, Wu Z, Kjellstrom S et al. Intravitreal delivery of AAV8 retinoschisin results in cell type-specific gene expression and retinal rescue in the Rs1-KO mouse. Gene Ther 2009: 16: 916–926.
27. Michalakis S, Muhlfriedel R, Tanimoto N et al. Restoration of cone vision in the CNGA3−/− mouse model of congenital complete lack of cone photoreceptor function. Mol Ther 2010: 18: 2057–2063.
28. Komaromy AM, Rowlan JS, Corr AT et al. Transient photoreceptor deconstruction by CNTF enhances rAAV-mediated cone functional rescue in late stage CNGB3-achromatopsia. Mol Ther 2013. Epub ahead of print; doi:10.1038/mt.2013.50.
29. Carvalho LS, Xu J, Pearson RA et al. Long-term and age-dependent restoration of visual function in a mouse model of CNGB3-associated achromatopsia following gene therapy. Hum Mol Genet 2011: 20: 3161–3175.
30. Radu RA, Yuan Q, Hu J et al. Accelerated accumulation of lipofuscin pigments in the RPE of a mouse model for ABCA4-mediated retinal dystrophies following Vitamin A supplementation. Invest Ophthalmol Vis Sci 2008: 49: 3821–3829.
31. Organisciak DT, Vaughan DK. Retinal light damage: mechanisms and protection. Prog Retin Eye Res 2010: 29: 113–134.
32. Molday RS, Kellner U, Weber BH. X-linked juvenile retinoschisis: clinical diagnosis, genetic analysis, and molecular mechanisms. Prog Retin Eye Res 2012: 31: 195–212.
33. Stone EM, Aldave AJ, Drack AV et al. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. Ophthalmology 2012: 119: 2408–2410.
34. Hahm BJ, Shin YW, Shim EJ et al. Depression and the vision-related quality of life in patients with retinitis pigmentosa. Br J Ophthalmol 2008: 92: 650–654.
35. Herse P. Retinitis pigmentosa: visual function and multidisciplinary management. Clin Exp Optom 2005: 88: 335–350.
36. Szlyk JP, Fishman GA, Grover S, Revelins BI, Derlacki DJ. Difficulty in performing everyday activities in patients with juvenile macular dystrophies: comparison with patients with retinitis pigmentosa. Br J Ophthalmol 1998: 82: 1372–1376.
37. Nyman SR, Dibb B, Victor CR, Gosney MA. Emotional well-being and adjustment to vision loss in later life: a meta-synthesis of qualitative studies. Disabil Rehabil 2012: 34: 971–981.
38. Bittner AK, Edwards L, George M. Coping strategies to manage stress related to vision loss and fluctuations in retinitis pigmentosa. Optometry 2010: 81: 461–468.
39. Kiser AK, Mladenovich D, Eshraghi F, Bourdeau D, Dagnelie G. Reliability and consistency of visual acuity and contrast sensitivity measures in advanced eye disease. Optom Vis Sci 2005: 82: 946–954.
40. Turano KA, Geruschat DR, Stahl JW. Mental effort required for walking: effects of retinitis pigmentosa. Optom Vis Sci 1998: 75: 879–886.
41. Jangra D, Ganesh A, Thackray R et al. Psychosocial adjustment to visual loss in patients with retinitis pigmentosa. Ophthalmic Genet 2007: 28: 25–30.
42. CNIB. The status of Canadian youth who are blind or visually impaired: a study of lifestyles, quality of life, and employment 2004.Retrieved, from the CNIB website: http://www.cnib.ca/en/about/Publications/research/Pages/youth-study-executive-summary.aspx. Accessed on May 2, 2013.
43. Grover S, Fishman GA, Anderson RJ et al. Visual acuity impairment in patients with retinitis pigmentosa at age 45 years or older. Ophthalmology 1999: 106: 1780–1785.
44. Zanko A, Fox M. Actively engaging with patients in decision making. In: Leroy BS, McCarthy Veach P, Bartels DM, eds. Genetic counseling practice: advanced concepts and skills. Hoboken, NJ: John Wiley & Sons, Inc., 2010.
45. Baty BJ. Risk communication and decision making. In: Uhlmann WR, Schuette JL, Yashar BM, eds. A guide to genetic counseling. Hoboken, NJ: John Wiley & Sons, Inc., 2009.
46. Hayeems RZ, Geller G, Finkelstein D, Faden RR. How patients experience progressive loss of visual function: a model of adjustment using qualitative methods. Br J Ophthalmol 2005: 89: 615–620.