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Perspective

Addressing Challenges in Developing Treatments for Inherited Retinal Diseases: Recommendations From the Third Monaciano Symposium

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Over the past decade, efforts focused on developing genetic therapies for inherited retinal diseases have advanced steadily to clinical trials and the development of a treatment, fueling optimism for the potential of precision medicines to provide safe and effective therapies for these rare conditions. Although several ongoing programs remain poised for success, numerous challenges have negatively impacted the ability to obtain regulatory approvals. The present position paper briefly summarizes recent advances and challenges in developing therapeutics for inherited retinal diseases, and presents a set of recommendations for moving the field forward. The priorities identified are discussed in terms of progress made and future needs, focusing on areas including patient support, disease mechanisms, outcome measures, and therapy approvals. A key point is the potential value of restructuring collaborative interactions into broadly resourced enterprises that are comprehensive in scope across critical areas of science, business, and medicine.

Introduction

Major advances in understanding the genetics, natural history, and pathophysiological mechanisms of inherited retinal diseases (IRDs) have propelled recent progress in developing precision medicines for these blinding conditions. In 2017, in a critical breakthrough, voretigene neparvovec-rzyl (Luxturna), an adeno-associated virus (AAV)-based therapeutic targeting retinal degeneration caused by biallelic variants in the *RPE65* gene, became the first in vivo gene therapy approved by the U.S. Food and Drug Administration (FDA),[1] with approval by the European Medicines Agency (EMA) granted in 2018, and by Health Canada in 2020. After this success, a surge in research focused on developing interventions for IRDs resulted in an increased number of clinical trials building on gene-targeted and gene-agnostic therapeutic strategies.[2,3] However, despite efforts addressing a diverse group of conditions and approaches, no other potential therapies specifically targeting IRDs have so far met the threshold for regulatory approval.[4]

The inability to achieve clinical trial end points, that is, to meet predefined success criteria, has resulted in the stalling or premature termination of multiple gene therapy programs,[5] thus threatening the business model for developing therapies for IRDs and alarming the vision and rare disease communities. Importantly, the emotional well-being of patients and families, especially those affected by shuttered clinical trials, has been impacted significantly. Thus, there is an urgent

need to overcome the current challenges facing the development and deployment of therapies for IRDs.[6]

Important among these challenges are issues pertaining to improving clinical trial design, the role of preclinical studies, and the choice of outcome measures and end points meaningful to patients and acceptable to regulatory authorities. In addition, an important new challenge involves defining the factors contributing to chorioretinal atrophy in a subset of individuals treated with voretigene neparvovec-rzyl who otherwise show positive functional outcomes.[7–9] Thus, significant advances in multiple research areas will be critical for understanding both the strengths and limitations of the precision medicines being developed and for realizing the therapeutic potential of interventions targeting IRDs.

As a novel platform for providing expert guidance, and driven by an abiding interest in accelerating the development of therapies for IRDs, the Monaciano Consortium convened a third expert symposium in January 2024. The aim of the Monaciano Symposia held at 5-year intervals is to identify high-level priorities that are published as a set of recommendations.[10,11] As for previous Monaciano symposia, discussion topics were prioritized using Delphi principles to conduct a premeeting survey of questions pertaining to perceived needs in the field. Structured discussions and multivoting at the symposium were used to define the most significant issues currently impacting progress and to identify priorities for moving the field forward in the next decade. The use of this unbiased mechanism provides important potential to identify both new priorities that address new topics, as well as new aspects of priorities for which fundamental needs remain, and for which progress in the field provides a new foothold for advancing future efforts.

The six priorities now identified thus include challenges that are yet to be resolved, as well as new challenges that have come to light: (1) improving resources to lessen the impact of IRDs on patients, (2) leveraging natural history studies to optimize clinical trial design, (3) expanding and standardizing clinically relevant outcome measures, (4) establishing the clinical relevance of core and gene-specific pathogenic mechanisms, (5) creating mechanisms, incentives, and repositories to increase data sharing, and (6) establishing coalitions and mechanisms to accelerate IRD therapy development.

The present article provides an overview of the expert discussions held at the third Monaciano symposium and detailed recommendations for supporting patient needs and addressing challenges in developing treatments for this important class of rare vision-impairing conditions.

Gene-Targeted Therapy for IRDs

Advances

Since the approval of voretigene neparvovec-rzyl, a number of clinical trials focused on developing gene-targeted therapies have achieved outcomes for which safety and efficacy are viewed as promising.[3] For autosomal recessive and X-linked recessive IRDs caused by variants in relatively small genes, subretinal delivery of AAV vectors has been used for gene augmentation in clinical trials targeting a number of different genes,[6,12] including: *GUCY2D* (NCT03920007),[13] *PDE6B* (NCT03328130),[14] *RLBP1* (NCT03374657),[15] and *RPGR* (NCT03252847, NCT06333249),[16,17] as well as targeting *RS1* with AAV vectors delivered subretinally (NCT05878860) or intravitreally (NCT02317887).[18]

For IRDs with an autosomal dominant inheritance, clinical trials of antisense oligonucleotides (ASOs) designed to alter translation from mutant transcripts have been used to target mutations in *RHO* (NCT04123626)[19] and *PRPF31*-mutation associated retinal degeneration (NCT05902962).[20] ASOs have also been used to target genes larger than the capacity of AAV (~4.5 kb), with positive outcomes achieved in clinical trials targeting *CEP290* (NCT03140969)[21,22] and *USH2A* (NCT06627179, NCT03780257; NCT05158296).[23,24] In other efforts targeting *CEP290* (NCT03872479), positive clinical trial outcomes were obtained using CRISPR-Cas9 gene-editing technology delivered using AAV-spCas9 and AAV-guide RNA constructs.[25] However, neither *CEP290* program is currently being advanced by the original sponsors.

Previous strategies have also evaluated the use of lentiviral vectors for gene delivery,[26] but were limited by exacerbation of retinal pigment epithelium (RPE) atrophy and low efficacy in efforts targeting *ABCA4* (NCT01367444).[27] A related program for *MYO7A* was terminated early (NCT01505062). Additional strategies being evaluated include the development of dual AAV vectors to expand transfer capacity for gene augmentation,[28] with clinical trials currently underway for *MYO7A* variants in *USH1B* (NCT06591793). In addition, an RNA exon editing vector ACDN-01 targeting *ABCA4* variants is now in clinical trials for Stargardt disease (NCT06467344).[29]

Ongoing Challenges

Viewed together, these findings establish that the safety of subretinal delivery of AAV constructs and

intravitreal delivery of ASOs is manageable and provide evidence of the possibility of therapeutic effectiveness in individuals with IRDs. In addition, significant improvement of rod-mediated vision can be restored in adults despite a lifetime of night blindness,[30] with smaller gains in cone-mediated responses in response to voretigene neparvovec-rzyl.[31] However, improvements in best-corrected visual acuity are the exception so far, and improvements in light sensitivity after therapy may not always correspond with improvements in high-contrast spatial vision.

Few gene therapy studies targeting IRDs have advanced to phase 3 clinical trials.[6] In addition, for the trials that have progressed, choosing the right end point has presented challenges. For example, in the *RPGR* phase 3 trial, although the primary end point failed (crossed 95% confidence interval), numerous secondary end points showed improvement, including low luminance visual acuity, potentially establishing it as a clinical trial outcome measure.[32] Furthermore, for many programs currently, one of the most significant challenges is the ability to secure the patient and funding resources required to advance the programs achieving promising outcomes in phase 2 trials.

Future studies will be needed to determine the extent to which efficacy can be increased by optimizing doses, viral vectors, route of administration, management of inflammation, and timing relative to the life span and onset of IRDs.[31] There is also a compelling need to understand why voretigene neparvovec-rzyl rescue in patients with RPE65 variants works so well compared with interventions targeting other genes that are equally effective in rescuing preclinical models of IRD and why RPE65 retinopathy continues to progress in many cases, even after successful treatment.[33]

As the first gene therapy of any kind for IRD, it will also be critical to identify the risk factors underlying the chorioretinal atrophy occurring in a subset of individuals treated with voretigene neparvovec-rzyl who otherwise show positive functional outcomes. Analysis of postmarketing outcomes were critical for establishing the association of chorioretinal atrophy with voretigene neparvovec-rzyl therapy, which was not reported in registrational clinical trials, but has now been reported in multiple real-world studies.[7–9,34–40] Going forward, it will be important to establish whether the risks for chorioretinal atrophy are gene and/or therapy specific and the extent to which these observations inform our understanding of the pathomechanisms involved. In addition, advances in clinical trial design that enable better alignment with real-world efficacy and safety should be an ongoing priority.

Gene-Agnostic Therapy for IRDs

Ongoing Efforts

There is significant interest in developing gene-agnostic therapies that have the potential to treat a broad spectrum of IRD genotypes and phenotypes. Historically, most candidates evaluated in previous studies underperformed relative to expectations, including vitamin supplements, antioxidants, trophic factors, inhibitors of microglia, drugs targeting the central nervous system, blood derivatives, and transplantation of retinal progenitor cells.[41–44] A number of recent advances have served to reinvigorate efforts focused on survival factors, optogenetics, inflammation, and cell-based interventions.

Survival Factors

Efforts to identify intrinsic factors released from the retina and necessary for cone cell survival resulted in the characterization of rod-derived cone viability factor.[45] AAV delivery of rod-derived cone viability factor improved cone cell survival in preclinical models of IRDs caused by variants in genes encoding rhodopsin or PDE6A/B, and a clinical trial is ongoing (NCT05748873). In addition, AAV delivery of NR2E3, a transcription factor required for rod development and gene expression,[46] is being evaluated for efficacy in clinical trials focused on autosomal dominant retinitis pigmentosa (RP) caused by rhodopsin variants (NCT06388200).

Optogenetics

Approaches focused on the development of optogenetic forms of gene therapy involve the expression of exogenous opsins in the retina to restore light sensitivity.[47–51] In clinical trials focused on restoring light perception in late-stage IRDs, AAV delivery of red-shifted microbial opsin ChrimsonR resulted in the recovery of partial vision in patients with RP (NCT03326336).[52] In other studies focused on multicharacteristic opsin1 (MCO-010),[53,54] AAV delivery in patients with advanced RP is being assessed for effects on visual acuity, mobility performance, and shape discrimination (NCT04945772).

Inflammation

An emerging strategy with gene-agnostic potential builds on growing evidence that inflammation contributes to IRD progression and bystander death of cones. Retinal inflammation is initiated by the primary loss of rods, which triggers microglial activation and macrophage recruitment. This inflammatory response may transition to a chronic state that contributes to disease worsening, but might also constitute a viable therapeutic target.[55–60] However, it is not known whether decreasing inflammation and/or microglial activation can slow retinal degeneration, or whether therapeutic strategies should focus on acute or chronic anti-inflammatory treatments. Preclinical and clinical studies addressing these questions are expanding rapidly, driven by the potential for broad applicability of anti-inflammatory approaches, which may further benefit from potential repurposing of existing anti-inflammatory drugs.[61]

Inflammation and oxidative stress are closely linked pathophysiological processes, easily induced by one another.[62] N-acetylcysteine (NAC) is a strong antioxidant that reduces oxidative damage. An ongoing randomized, placebo-controlled multicenter trial (NAC Attack) of oral NAC designed to determine whether NAC can slow progression of RP[63] recently reached phase 3.[64]

Cell Therapies

An alternative to gene therapy involves intravitreal delivery of human retinal progenitor cell preparations that form stable cellular aggregates and act as biofactories to release critical trophic factors and preserve retinal histology.[65] Clinical trials of safety and efficacy in adults with RP have reported positive outcomes (NCT04604899), with a phase 3 trial currently being planned. More recently, a first-in-human phase 1 trial of iPSC-derived photoreceptors has started enrolling patients with advanced rod–cone and cone–rod dystrophies (NCT06789445). Still other strategies focus on the contribution of the RPE to regulating immune privilege and inflammation in the retina. These features, when combined with its accessibility from the suprachoroidal space, make the RPE an attractive alternative as a reservoir for delivering diffusible therapeutics to the outer retina. Possibilities for improved RPE targeting include the delivery of novel and engineered AAV serotypes, CRISPR/Cas9 reagents, lipid-mediated transfections, viral-like particles, as well as supra-choroidal biofactories and lipid nanoparticles.[66] Especially when targeting the RPE, the potential for inflammation may be greater compared with targeting photoreceptors.

IRD Genetics and Natural History

Genetic Diagnosis

Foundational advances in IRD genetics, coupled with large-scale screening programs, have resulted in the identification of disease-associated variants in thousands of affected individuals,[67,68] with an IRD genetic testing yield of approximately 70%. In turn, the characterization of relatively large patient cohorts sharing IRD-associated variants in the same gene has enabled natural history studies and the development of metrics of change by which to evaluate clinical trial outcomes. This includes a number of registries and natural history studies with input from multiple consortia (e.g., RUSH2A [NCT03146078],[69] ProEYS [NCT04127006], Uni-Rare [NCT05589714], and ProgStar [NCT01977846][70]). Natural history studies are also a critically important resource for supporting dialog with agencies regarding approvable end points and determining sample sizes for clinical trials.[71] Furthermore, retrospective longitudinal studies of visual function performed after treatment have important potential for evaluating the significance of therapeutic outcomes.[72]

Despite significant advances in gene identification, the genetic cause of IRD is not identified by clinical genetic testing in an estimated 20% to 30% of cases,[73–78] while the discovery of new disease genes, although slow, continues.[79] Thus, multiple strategies will be needed to identify the disease-associated variants in all IRD patients.[80] Solutions are likely to include the identification of new IRD genes, as well as new disease-associated variants in known IRD genes, such as noncoding variants that alter splicing or expression, or structural variants that impact copy number, duplications, inversions, and translocations.

Genetic Representation

For efforts to increase genetic diagnoses and natural history information, specific issues relevant to marginalized communities will need to be recognized and addressed. In particular, Black patients are more likely than White patients to decline genetic testing, even when it is offered at no cost, potentially owing to significant mistrust, stigma, and possible loss of confidentiality and discrimination associated with genetic results.[68] The resulting inequity in available genetic information confounds the interpretation of variant

classification and decreases the odds of IRD patients obtaining a molecular diagnosis (Blueprint Genetics Study, eyeGENE cohort).[81] Worldwide, there are large regions and populations in which the rate of genetic diagnosis of IRDs is quite low, including most of the African continent and many countries in Asia. Thus, there is a critical need to better inform the public about what IRDs are, the multiple benefits of genetic testing, the supportive resources available, and the therapeutic advances predicted to lie ahead.

Clinical Trials for IRDs

Outcomes and End Points

Regulatory approvals for novel therapeutics depend on well-designed clinical trials conducted according to standard protocols that address numerous aspects of drug development, manufacturing, delivery, safety, and efficacy. A significant challenge for IRD clinical trials has been the identification of sensitive testing protocols and end points that might be used to demonstrate small but meaningful changes in functional vision, as a number of standard testing measures used in the clinic have failed to show reliable improvements in response to treatment that are considered clinically meaningful by regulatory bodies, including visual acuity (doubling of visual angle as shown by ≥15 Early Treatment Diabetic Retinopathy Study letters), perimetry (≥7 dB gain that is repeatable in >5 prespecified locations), or mesopic microperimetry measures of cone function.[5,82]

Furthermore, with the exception of a few individuals with *RPE65* mutations who were treated with voretigene neparvovec-rzyl,[83–85] improvements in electroretinography outcomes have not been obtained in multiple trials of gene therapy.[86–89] These findings emphasize the many challenges of electroretinography testing, including the need for expert administration and monitoring to minimize the potential for significant recording artifacts, nonobvious tester errors, and test–retest variability. These issues can be further exacerbated when evaluating the outcomes of gene therapy in treated areas comprising approximately 20% to 25% of the total retina in which some cells may have lost the potential for rescue.

Mobility Testing

A recent advance in the analysis of IRD therapy outcomes is the development of functional vision assessment using standardized mobility testing and analysis. In clinical trials that supported the regulatory approval of voretigene neparvovec-rzyl, individuals with *RPE65* variants showed significant and sustained improvement using multiluminance mobility testing after treatment.[89,90] In addition, individuals with X-linked RP or *GUCY2D*-LCA who were treated with gene augmentation therapy showed improved performance in mobility maze testing.[13,16] Similar approaches involving the use of virtual reality to evaluate functional vision are also being developed with the goal of enhancing the reproducibility and broader applicability of performance-based testing.[91–93] However, mobility testing outcomes have yet to be widely replicated in clinical trials of therapies targeting other IRD genes, and cone-specific protocols have not yet been developed, leaving open the question of whether this approach will have broad usefulness going forward.[94]

Patient-reported Outcomes

There is an urgent need to establish sensitive mechanisms for evaluating clinical trial outcomes that are informative relative to activities of daily living and acceptable to regulatory agencies. One approach poised to play an important role is the use of patient-reported outcomes (PROs) obtained using well-designed, targeted, and controlled surveys highlighting the impact of the condition on the patients' activities of daily living.[95] Recent advances include the development of the Michigan Retinal Degeneration Questionnaire and the Michigan Vision-related Anxiety Questionnaire, now widely used in IRD clinical trials and natural history studies.[96–100] In addition, the Visual Symptom and Impact Outcomes instruments for tracking patient-reported outcomes and observer-reported outcomes, are designed to assess visual function, impacts on activities of daily living and health-related quality of life.[101]

IRD-specific surveys of health-related quality of life are also being used to evaluate various aspects of emotional, social, and physical well-being; perceived physical and mental health over time; and the issues of greatest concern to patients.[99] Similar approaches are being used to identify concerns pertaining to low vision rehabilitation, as well as sources of anxiety that are significant in this population.[96,102] Challenges associated with studies of patient-reported data include the need to accommodate factors including low-vision appropriate collection, relevance to specific IRDs, test–retest variability, mood effect, scaling, and sensitivity to change in IRD therapy. Nevertheless, there is increasing recognition of the importance of this research and significant interest in establishing the extent to which PROs can contribute to clinical trial end points.[97,100]

Structure-based Outcomes

Additional strategies are focused on developing structure-based outcomes as surrogate biomarkers in IRDs, potentially by anchoring novel end points to functional changes. Current efforts are focused on defining which anatomical features may have the greatest potential for regulatory acceptance and marketing approval. Although advanced segmentation methods require the retention of retinal lamination to some degree, structural measures have potential advantages for evaluating the outcomes of localized forms of treatment, including gene therapy.

In one approach, spectral domain optical coherence tomography evaluation of the ellipsoid zone area showed statistically significant differences in RP patients, with well-documented test–retest reliability and rates of decline amounting to a 7% mean annual rate of change in patients with X-linked RP (NCT00100230).[103] However, for USH2A-associated RP, the multicenter RUSH2A natural history study showed that the ellipsoid zone area had a significant floor effect, with a majority of patients measuring less than 3 mm^2 and exhibiting no significant change over the 4 years of the study.[69] Another analytical approach involves the use of adaptive optics-based systems that are capable of imaging rod and cone photoreceptors at single-cell resolution.[104] Although achieving stunning outcomes in research applications, this highly specialized and time-intensive technology is not yet widely available in the clinical setting.

Lessons Learned

Multiple IRD clinical trials have failed to demonstrate improvements in functional vision or positive changes to the progressive natural history of the disease. An important point to consider is that, for most clinical trials (of short duration, involving older patients), specified outcome measures may be set too high. Thus, the development of protocols with the ability to document more modest improvements could advance efforts to establish the effectiveness of a given therapy. Once a treatment is approved, more robust outcomes may be achieved in younger patients evaluated over a longer period of time.

A second point is that the primary therapeutic success in many instances may be slowing of vision loss and/or photoreceptor degeneration, and/or improved stability of visual function. Such outcomes will require new protocols to define and validate clinical trial end points that are acceptable to regulatory agencies and achievable in a fundable time frame. For efforts to demonstrate improvement within the constraints of a 2-year trial, issues of critical importance include target selection, choice of therapeutic outcomes, and patient and disease stage at intervention.[105,106]

A third point is that patients consider light perception as highly meaningful in improving quality of life,[107] in particular, with respect to gains achieved using optogenetics and retinal prostheses.[108,109] Thus, one important goal will be to determine the potential of establishing the use of full-field stimulus testing (FST) to obtain clinical measures of retinal sensitivity and photoreceptor function in IRDs. FST is currently in use as an outcome measure for evaluating patients with nystagmus or wandering eyes, as well as for those with profound levels of vision loss or severe best-corrected visual acuity reductions that may preclude adequate fixation to visual field testing, with official International Society for Clinical Electrophysiology of Vision and Imaging and Perimetry Society guidelines recently published.[110] Notably, in recent studies, patients receiving voretigene neparvovec-rzyl showed improvement in FST thresholds within 3 months.[90]

The IRD Therapy Business Model

After obtaining FDA/EMA approval of voretigene neparvovec-rzyl for biallelic *RPE65* variants, the Luxturna business model (Spark Therapeutics) was established. Using industry-based pricing determined relative to the most expensive drug currently being marketed for any eye disease, the cost of voretigene neparvovec-rzyl was set at $425,000 per eye.[1,111] This pricing strategy created considerable optimism and financial incentives for developing additional gene therapy products for various forms of IRDs. However, since the commercialization of voretigene neparvovec-rzyl, no additional forms of gene therapy targeting IRDs have been approved. Although a number of programs are ongoing, some programs were ended when commercial viability was deemed unattainable owing to small market size coupled with the high costs of development. Other programs failed to meet end points despite being based on convincing preclinical data from proof-of-concept studies, thus emphasizing the limitations and financial risk of over-reliance on current disease models and outcome measures.

Challenges

The challenges experienced in efforts to adapt the Luxturna business model to the development of therapies for other IRDs have fueled investor and patient skepticism, with many questioning the overall

approach, the rationale of the regulatory agencies, and the realities of funding IRD research and development. Feasibility concerns include managing risks associated with manufacturing, regulatory compliance, and commercialization, as well as accommodating the genetic complexity of IRDs, the delivery and timing of interventions, and the strategies needed to define meaningful outcomes. Barriers to obtaining regulatory approvals include requiring past generation outcomes and end points, with little opportunity to benefit from newly developed metrics or needed evolution in regulatory agency thinking beyond current standards. In addition, discussions with regulators consume a substantial amount of investigator time otherwise needed to advance interventional research.

Financial obstacles stem in part from overreliance on the small business model and monolithic funding sources and restrictive licensing practices that preclude technology sharing and greatly inflate the costs of good manufacturing practices needed to produce clinical-grade material. In addition, narrowly focused programs are not positioned to benefit from the financial successes of other projects in diversified portfolios. These many challenges highlight the need for significant changes and uniform guidance for decreasing inefficiencies and redundancies, and for pooling resources, increasing economies of scale, reconsidering profit models, and sharing lessons learned.

IRD Patient Needs and Expectations

As the number of individuals with a confirmed diagnosis of IRD continues to increase worldwide, a primary need is to better address the impact on quality of life, in terms of both economic costs and decreased well-being.[112] Recognizing that the toll of IRDs on individuals, their caregivers, and society is significantly larger than the health care costs alone,[113,114] there is also a compelling need to improve widespread advocacy in support of this population. In the clinical setting, there is a fundamental need to help patients acquire a clear understanding of how to access the resources and mechanisms available for getting help, including genetic testing and counseling. As precision medicines for IRDs emerge, patients will need increased access to care provided by specialists, as well as resources essential for navigating new challenges in their daily lives.

For patients and families involved in clinical trials, there are additional needs for transparency and clarity about expectations and demands, as the time needed for clinical trial participation takes a heavy toll on patients, many of whom are relatively young children. One contributing factor is the expanding use of mobility testing, for which current iterations may take several hours to complete and is available only at a limited number of sites, thus requiring the need for travel and accommodations for patients and caregivers in most cases. In addition, individuals participating in clinical studies, both in treatment arms and untreated control groups, can accrue unreimbursed financial costs and loss of productivity, as well as experience emotional challenges that further contribute to vulnerability. It follows that patients and families are profoundly affected when clinical trials fail and programs close.

Recommendations

Addressing Challenges in Developing Treatments for IRDs

Energized by progress in the field, programs focused on establishing therapies for IRDs have expanded rapidly over the past decade. However, multiple initiatives have demonstrated the difficulty of developing targeted therapies for IRDs, even those with clearly defined genetic and functional deficits. Moreover, the need to develop solutions and outcome measures suitable for diverse forms of IRDs has slowed progress further. Expert discussions at the third Monaciano symposium focused on generating recommendations for addressing existing challenges facing the development of treatments for IRDs, including issues affecting each of the stakeholder communities—patients and their families, researchers, funders, and companies. Six priorities identified by consensus at the meeting, along with strategies for achieving the recommended goals, potentially within the next decade, are presented.

Priority 1: Improving Resources to Lessen the Impact of IRDs on Patients

The complex nature of IRD genetics and the slow progress of clinical advances have created a frustrating reality for many patients who are currently unlikely to benefit from life-changing therapies. Thus, an important goal will be to develop well-resourced strategies that support the unmet needs of IRD individuals and families.

Diagnosis

Despite major advances achieved in large-scale screening programs, providing a genetic diagnosis for all individuals with IRDs remains challenging, especially for marginalized populations. Comprehen-

sive approaches are needed that include efforts to overcome societal and person-level barriers preventing under-represented minorities from opting for genetic testing. Multi-investigator sites with a proven ability to accrue under-represented minority patients will be an important resource for expanding the landscape of known and missing heritability in IRDs, with real potential to identify new genes and novel variants in these populations.[81] In addition, procedures for releasing genetic information and diagnoses should be standardized, recognizing patients' rights, as well as the need for professional interpretation at the time of disclosure.

Quality of Life

Among the most urgently needed efforts are initiatives to improve quality of life, including increased funding to support the development and implementation of low vision and adaptive technology. Natural history studies also have significant value for informing qualitative and quantitative measures of health-related quality of life, including improving the accuracy of cost-effective analysis for therapeutic interventions.[71] By including costs to caregivers, as well as the impact of disease on health and productivity across the lifespan, this analysis can contribute to efforts to define the overall costs of IRDs to individuals and society, and thereby motivate efforts to alleviate this burden. To ensure that the future needs of this vulnerable population are met, additional resources should be identified to strengthen the training pipeline for professionals providing holistic care, including mental health care, for individuals with IRDs.

Advocacy

Strategies to decrease the impact of IRDs on patients should be part of larger initiatives and lobbying efforts to increase awareness, acceptance, and advocacy for individuals with visual disabilities, particularly as pertains to their status as a vulnerable population with unique challenges. In view of the extreme burden associated with participation in IRD clinical trials, funding agencies, health care organizations, industry, and philanthropists should be called on to provide vision-related anxiety support services staffed by qualified and experienced mental health professionals. Efforts should be made to publish positive experiences of site-specific programs, such as peer-to-peer support initiatives or similar models, to provide examples of successful approaches and inspire broader implementation.

There is also a critical need to support efforts focused on formally designating IRD-associated vision loss (with or without meeting definitions of legal blindness) as a disability that fully qualifies for support services available for the severely visually impaired.

Priority 2: Leveraging Natural History Studies to Optimize Clinical Trial Design

Natural history data have enormous value for providing insights into IRD pathology relevant to therapeutic efforts and clinical trial design. An important goal will be to increase engagement and support for natural history studies focused on optimizing clinical trial design and performance needed to accelerate the approval process for new therapies.

Expanding Datasets

New technologies and increased financial support are driving the rapid expansion of large natural history datasets with important potential to benefit IRD research. The identification of sensitive changes in visual performance, retinal structure, and function have the potential to advance efforts needed to validate IRD gene-specific outcomes and end points, to inform various aspects of clinical trial design, and may also be useful for working with regulators to assess the potential to serve as surrogate outcomes. Standardizing each outcome measure and how it is acquired or measured would make data sharing easier, with the choice of which outcome measures to use individualized depending on the gene/disease, based on natural history data.

Significant investment from diverse sources will be required for developing and maintaining the necessary patient registries, recruiting patients into studies, maintaining patient engagement in natural history studies that are devoid of an intervention, performing clinical phenotyping and analysis in a standardized/certified manner, and improving dialog with regulatory agencies.

Data Management

The natural history data should be made fully available by requiring that published natural history data be deposited in accessible and curated repositories to enable the analysis of large, aggregated datasets. Data management and analysis should incorporate the use of new technologies, including artificial intelligence and deep learning, to improve the identification of sensitive variables and meaningful end points related to pathology. Support will be needed to overcome challenges including the significant costs needed for centers to provide standardized and certified testing results. Additional challenges include the need to develop robust strategies to resource and strengthen

these approaches by working to improve dialog with regulatory agencies, as well as leveraging funding from diverse sources.

Priority 3: Expanding and Standardizing Clinically Relevant Outcome Measures

The availability of outcome measures that are more sensitive, reliable, and clinically meaningful will be critical for improving efforts to evaluate therapeutic outcomes in IRD clinical trials. An important goal will be to establish testing protocols with improved ability to detect clinically meaningful changes occurring at early times after treatment in proof-of-concept studies.

Meaningful Outcomes

Continuing efforts are needed to establish the potential of new outcome measures to serve as clinical trial end points for IRDs. Strategies to develop clinical end points for very small increases in function are likely to be particularly important for testing optogenetic therapies.[52,115] Such studies should rely heavily on quality multicenter natural history data, as discussed elsewhere in this review, to identify end points with the greatest potential to detect a significant change in the largest proportion of patients over the shortest period of time, for each different category or genetic cause of an IRD. There may also be a role for composite outcome measures that prespecify possible improvements in one of several functional outcomes alongside one or more anatomical outcomes that are weighted according to the likelihood of improvement.[116]

It will also be critical to consider the extent to which clinically meaningful and meaningful to patients are likely to overlap. For example, there is growing evidence to support the use of FST, a measure of best retinal sensitivity, as an acceptable primary end point for IRD therapy.[69,117] As evaluated using PRO measures on the Michigan Retinal Degeneration Questionnaire, clear correlates of FST outcomes have been obtained showing differences between subgroups of clinical diagnosis, age, disease duration, and FST blue–red mediation.[98]

Engaging Stakeholders

In addition, engaging in dialog with regulatory agencies such as FDA/EMA early in efforts to develop new end points and metrics should be viewed as an important opportunity to include them as key partners invested in advancing therapeutic endeavors. It will be critical to optimize the balance between the need for clinical trial data and the very significant burden placed on patients, as well as for researchers and companies to publish both positive and negative results from critical trials to avoid the loss of important information. Improved understanding of the decision trees used by regulatory agencies should better guide the design and conduct of clinical trials and increase opportunities for dialogue between all stakeholders on how to improve trial outcomes.

Priority 4: Establishing the Clinical Relevance of Core and Gene-Specific Pathogenic Mechanisms

There is a fundamental need to better understand the network of interactions occurring inside the black box connecting genetic defects to photoreceptor cell death. An important goal will be to advance the basic research needed to further define both core and gene-specific pathophysiological mechanisms, including efforts to validate potential therapeutic targets.

Basic Research

Defining the biologic nodes at which IRD pathophysiological mechanisms intersect should be an important strategy for identifying disease categories with the potential to respond to similar therapeutic approaches, including gene-agnostic therapies. Basic research should also continue to play a critical role in identifying the sources, consequences, and potential treatment of disease- and therapy-associated inflammation.

Strategies will also be needed to increase the likelihood that outcomes obtained in preclinical studies can be independently reproduced and translated into therapeutic efficacy in IRD patients. An important objective should be to better define the criteria needed to predict effects on improving or maintaining functional vision, as well as cross-species translatability. Thus, future studies should provide further analysis of the relevance of current models (often murine) to clinical conditions, the predictive value of the metrics used for structural and functional assessment, and the need to develop more relevant models (e.g., human induced pluripotent stem cells or large animal models). Although likely to be limited in scope, studies in nonhuman primates are predicted to have unmatched potential for advancing these goals.

Translational Research

As studies move to the clinic, collaborative efforts and increased funding will be needed to support additional opportunities for the development of

biobanking resources to support fundamental studies of disease mechanisms and pathology. For example, vitreous samples collected at the start of gene therapy surgery have significant potential for advancing expression profiling efforts focused on identifying mechanisms that connect genetic variants to cellular dysfunction.

Another critical issue will be protocol development, especially as it pertains to gene therapy studies. For example, for studies focused on individual disease genes, studies are needed to first optimize and then establish consistency with respect to promoter, titer, serotype, capsid fill, and purity on a case-by-case basis. This work should also extend to the management of inflammatory responses with the potential to impact outcomes and interpretation. In addition, new research is needed to identify effective nonviral strategies and different modes of administration.

Priority 5: Creating Mechanisms, Incentives, and Repositories to Increase Data Sharing

In the current business climate, clinical trial data are often published only in association with therapy approvals, and comprehensive datasets of primary data suitable for further analysis are rarely provided. Thus, an important goal will be to increase access to full protocols, preclinical data, and complete clinical trial datasets, including control arms and prematurely ended studies.

Transparency

Support for increased data sharing will require significant resources to establish the necessary mechanisms, repositories, and incentives. In addition, databases for reporting adverse events, as well as overall negative outcomes from failed trials should be established to increase the visibility of this information. Critical considerations should address the realities of the small business environment, in which data sharing may be viewed as being at odds with financial interests. These efforts should include developing the infrastructure needed for data standardization, cleaning, retrieval, and analysis, as well as enlisting the expertise and support of data scientists and IRD specialists for needs assessment, design, and data analysis.

Access to Data

Participation in big data initiatives should be incentivized by increasing awareness of the power and advantages of shared big data, by providing free access to depositors while charging significant user fees to all other users, and by lobbying regulators to make data sharing a regulatory requirement for clinical trials reporting. In addition, centralized data repositories should be established and potentially managed by federal or programmatic funding, outside grants, and industry in efforts guided by expert recommendations regarding specific needs. Although an audacious goal requiring consensus building and major buy-in, precedents for data management exist, for example, for cancer clinical trials.[118]

Priority 6: Establishing Coalitions and Mechanisms to Accelerate IRD Therapy Development

A fundamental obstacle to creating approved therapies for ultrarare diseases is the high price of development relative to the small market size. Thus, a critical goal for the development of precision medicines for IRDs will be to overcome the limitations of the current business model.

Costs

To decrease the cost of clinical trials, strategies should include leveraging natural history data to develop shorter protocols, adaptive design methodology, streamlined outcomes testing, and more competitive pricing for conducting trials by contract research organizations. To improve economies of scale, modular platforms could be designed to deliver a range of gene therapy cargos. To decrease the costs of vector production, some academic and research institutions have acquired the expertise needed to produce good manufacturing practice–certified material at scale, particularly for early proof-of-concept studies that are conducted using nonindustry funding. In addition, coordinated collaborative efforts within various consortia should provide increased opportunities for streamlining focused IRD gene-specific trials with respect to protocol development, certifications, contracts, and negotiations.

Guidelines

There is an urgent need to revise the guidelines used by regulatory agencies to evaluate the efficacy of IRD interventions. An over-reliance on historically derived metrics established for disease-agnostic forms of therapy is out of step with expert assessments indicating that therapeutic success for many forms of IRDs will be best measured as the preservation of vision over time. Future strategies will need to advance beyond current thinking to define improved

metrics suitable for the pathology being addressed in the timeframes being assessed.

In this process, it will be important to engage with regulatory agencies in their roles as learning organizations that evolve with cogent data and that serve as valuable partners with vast experience in developing therapeutics to benefit patients. A key strategy will be to build extensive alliances having the gravitas needed to engage regulators in effective lines of communication that explore the full potential of the significant scientific advances being made, as well as addressing the critical interests, engagement, and support of the patient population.

Partnerships

There is a critical need to explore more durable partnerships across academia, industry, and government (as payor and as regulator and approver) in efforts to bring new technologies and therapeutics to individuals with IRDs. In this work, one successful resource has been the multicenter Foundation Fighting Blindness consortium[119] that exists to conduct natural history studies and engage with regulatory bodies. Future coalitions that include multiple stakeholders, including government and industry, have important potential for further accelerating progress. Examples include the Diabetic Retinopathy Clinical Research Retina Network (Jaeb Center for Health Research), the Bespoke Gene Therapy Consortium, the Nationwide Children's Hospital in Columbus, and the California Initiative in Regenerative Medicine.

Conclusions and Future Prospects

We have entered a new era of medical ophthalmology. Despite the many challenges of navigating this new and complex territory, remarkable progress continues to be made in efforts to develop therapies for IRDs in their various forms. Although this progress continues to reveal obstacles needing to be overcome, the potential for treating IRDs remains strong, with several new therapies currently nearing regulatory approval. On the other hand, the viability of these efforts is at risk from a range of factors, and it is often the scope and scale of resources needed to address unexpected challenges and setbacks that seal the fate of sponsored programs. Thus, critical issues moving forward will be to identify the tactics best suited to alleviate chronic under-resourcing of the translation of basic research into the IRD clinical space and to raise awareness of the unmet therapeutic need.

An important strategy will be to support the efforts needed to advance a paradigm shift in the economic model supporting IRD therapy development, which would include increased resource sharing, as well as support from a mix of nonprofit and for-profit entities. This effort will require the development of high-level strategies to coordinate consortium approaches with multiple lines of support and engagement, including government sources, commercial interests, and IRD patient groups. Motivated by the ever-increasing potential for meaningful progress, and the urgent needs of the IRD community, the aspirational goal identified by the third Monaciano Symposium is the creation of a high-level initiative supported by expert coalitions that bring together the driving forces, resources, oversight, methods and means needed to realize the promise of precision medicines for individuals with IRDs.

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