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COMMENTARY

The evolving role of medical geneticists in the era of gene therapy: An urgency to prepare

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Introduction

A recent report from the RARE-X consortium that reconciled multiple rare disease databases estimated that well over 10,000 rare diseases exist, far exceeding previous estimates of 5000 to 8000.[1] Less than 10% of these diseases have approved treatments,[2] and of these, nearly all treatments are medications that reduce the consequences of abnormal genetic variants but do not address the condition's root cause. The remaining 90%+ do not have viable treatment options, with management limited to supportive care, such as specialized diets, or surveillance for disease progression.

Gene therapy can directly address the underlying genetic causes of many of these diseases. However, progress has been measured. More than 40 years elapsed between 1968, when the feasibility of gene transfer using viral vectors was initially demonstrated, and the first approvals of gene therapies by the European Medicines Agency (2012) and US Food and Drug Administration (2017).[3,4] Throughout that period, gene therapy for rare genetic disorders was often touted as being just around the corner; however, early gene therapy trials encountered serious safety issues that resulted in substantial delays.[5,6]

Recent advances suggest that we may, indeed, now be turning that corner. At least 334 potentially durable,

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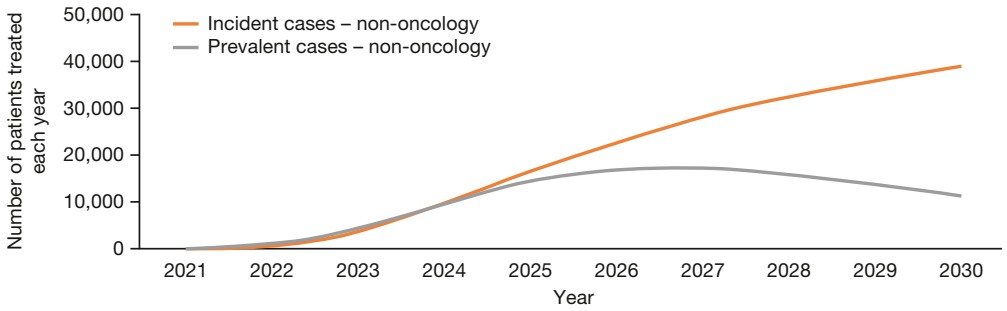

Incident cases	251	609	3,995	9,982	16,679				39,226
Prevalent cases	140	917	4,408	9,731	14,966				11,592
Total addressable cases	391	1,526	8,403	19,713	31,675				50,818

Figure 1 Estimated number of patients in the United States treated each year with durable nononcology gene and cell therapies. This figure assumes that the gene therapy pipeline is not replenished over time. (Adapted from Young et al[7]).

nononcology gene therapies are in development, including 40 in phase 2 trials or later, and ClinicalTrials.gov lists >2000 gene therapy trials as of mid-2022.[7,8] One recent analysis estimated that approximately 30 nononcology gene therapies will be approved in the United States by 2030; if approved, these therapies would become available to treat approximately 50,000 patients annually in the United States alone (Figure 1).[7] This likely represents the initial inflection point of an exponential increase in the clinical use of gene therapy.

For this discussion, the term gene therapy is defined as treatments that introduce or remove DNA sequences or change the content of the genetic code with the intention of providing enduring therapeutic benefit. Gene therapy, as defined herein, represents a change from historical management approaches—thus the potential for disruption of conventional management paradigms for genetic disorders cannot be overstated. In fact, routine gene therapy will shift how patients are screened, diagnosed, and counseled about their treatment options, how therapy is delivered, when it is delivered, who delivers it, and how patients are followed up over the short- and long-term after administration.

The role of the medical geneticist in this new treatment paradigm has not been fully elucidated or even recognized by societies and licensing boards. For example, although acknowledging the central role of medical geneticists in treating patients with hereditary disorders, the American Board of Medical Genetics and Genomics (ABMGG) does not explicitly address their role in gene therapy.[9] Similarly, the European Board of Medical Genetics does not yet recognize gene therapy as part of the core skill set for medical geneticists.[10] The American College of Medical Genetics and Genomics (ACMG) has a more expansive view of the role of medical geneticists.[11] According to its strategic plan, ACMG's goals are to "empower its members to be leaders in the integration of genetics and genomics into all of medicine and health care, resulting in improved personal and public health." This vision encompasses not only the practice of medical genetics but also the development of rigorous evidence-based treatment guidelines and care pathways, providing education and tools for medical geneticists and other health care providers (HCPs), and advocacy. These goals align with the expanding roles of medical geneticists in gene therapy as these treatments enter wider clinical use.

Medical geneticists have established roles as clinical and thought leaders in the management of many rare genetic diseases and provide support in the diagnosis and care of the handful of genetic diseases that are more common in the general population and managed by other specialists, such as hemophilia, sickle-cell disease, Duchenne muscular dystrophy, spinal muscular atrophy, and cystic fibrosis. Given the potential availability of an increasing number of gene therapies over the next decade, there is a need to better define the role of medical geneticists within this new treatment paradigm.

The current and future role of medical geneticists in gene therapy was explored in an industry-sponsored global advisory board meeting in November 2021. Attendees were selected to participate in this advisory board qualitatively based on their membership in major international medical genetics societies, including the ACMG and the European Society of Human Genetics, and their established interest in gene therapy based on their publications. Industry representatives from medical affairs also attended the meeting and participated in discussions. The focus of the advisory board was on the potential role of medical geneticists in delivering gene therapy rather than on specific disease states or products. The discussions at the advisory board meeting, as well as from follow-up conversations, were synthesized by the group at an additional online meeting and submitted to a professional medical writer to prepare a first full draft manuscript. All drafts were circulated for review and comments until consensus was reached by email on the content of this article. The content of this article represents the synthesized opinion of the meeting participants.

At this meeting and in follow-up online conversations, the authors investigated each of these topics to delineate further where and how medical geneticists can contribute their expertise to ensure the effective, safe, and durable

Table 1 Calls to action

Timeframe	Action Needed
Immediate	• Better define educational needs for medical geneticists • Better define educational needs for other members of the multidisciplinary team (other specialists, referring physicians, pharmacists, nurses, other health care provider staff, and managerial staff) who are directly involved in the care of patients receiving gene therapy or decision-making for these patients
Intermediate term (1-3 y)	• Develop models of care that apply to the growing range of gene therapies that are anticipated to become available over the next decade • Develop educational programs tailored to the needs of different stakeholders in the pathway of Gene Therapists—medical geneticists who plan to focus on gene therapy specifically o Medical geneticists involved in initial decision-making, assessments, and long-term follow-up o Multidisciplinary team members directly involved in gene therapy administration o Specialists in the broader health care community o Primary care providers • Partner with disease-state specific societies to deliver educational programs that enhance awareness and understanding of basic genetics concepts and gene therapy • Train genetic counselors to deliver basic education on gene therapy and assist in counseling patients • Incorporate opportunities for genomic screening of newborns
Long term (≥3 y)	• Incorporate basic gene therapy training into medical and health care professional school curricula • Increase the number of medical geneticists to meet evolving needs • Increase the number of medical geneticists in regions where limited numbers exist • Consider adding gene therapy to training and certification requirements for medical geneticists

implementation of gene therapies as they become increasingly available. Specific calls to action that were identified during this meeting are summarized in Table 1 and discussed in further detail below. It is important to recognize that the roles medical geneticists may play within gene therapy pathways are likely to vary depending on their country, region, and institution, as well as on the preferences and expertise of the individual clinician. It should also be recognized that organ/domain specialists have already and will continue to take the lead in gene therapy for many of the more common genetic diseases that naturally fall within their specialties.

Medical Geneticists and Models of Gene Therapy Delivery

Gene therapy has not yet reached the inflection point at which it becomes a routine and widely used modality to address genetic diseases. Given the limited number of patients who have received gene therapy to date and the relative lack of data on the long-term efficacy and safety of these treatments, the practical clinical implementation of potentially single-treatment in vivo gene therapy can be modeled on care pathways for other single treatments, clinically high-value but complex procedures, such as solid organ transplantation or stem cell transplantation, in which health care systems have developed hub-and-spoke models of care to accommodate the unique needs of these patients.

Indeed, hub-and-spoke models that coordinate the complete package of care for gene therapy delivery have been proposed for hemophilia. In 1 example, the hub is a hemophilia treatment center with experience in comprehensive care and gene therapy and the spokes are hemophilia treatment centers with little or no experience in gene therapy.[12] Alternatively, the hub may be the dosing center for a specific gene therapy/gene therapy platform, with the spoke being the management center.[12] The roles of the hub and spokes, based on a schema developed by the European Association of Haemophilia and Allied Disorders and European Haemophilia Consortium, are summarized in Table 2.[12]

A similar model can be applied to inborn errors of metabolism and multisystem genetic conditions that are managed by medical geneticists. Given the broad range of diseases that will ultimately be addressed with gene therapy, each hub would include medical geneticists with clinical and technical expertise in gene therapy for specific inherited diseases. Spokes could include medical geneticists who, although having experience in the disease state, do not manage the patient during the period immediately surrounding dosing. Instead, these clinicians and their local teams would be involved in patient identification and initial eligibility assessments for gene therapy, counseling, education of local HCPs and managerial stakeholders, and long-term follow-up. The training needs of medical geneticists at hubs and spokes differ as outlined below.

Although the hub-and-spoke model might be an appropriate model for gene therapy delivery, especially over the initial several years of clinical implementation, other models of care could evolve to better fit the needs of the health care system as gene therapy becomes more mainstream in clinical practice. Although speculative, ex vivo gene therapy could continue to warrant a hub-and-spoke pattern of care delivery

Table 2 Hub-and-spoke model for gene therapy delivery, based on a proposal by the European Association of Haemophilia and Allied Disorders and the European Haemophilia Consortium for in vivo AAV-mediated gene therapy for hemophilia

Activity	Hub	Spoke
Counseling about treatment options and discussing expectations	• Renew discussion before dosing	• 2-3 times during predosing process
Patient selection	• Review eligibility criteria	• Identifying possible candidates • Confirming eligibility
Laboratory monitoring and performance of diagnostic tests for the gene therapy program	• Required testing before treatment (eg, pre-existing AAV antibodies) • Required testing after treatment o Measurement of biomarkers	• Required testing before treatment (eg, pre-existing AAV antibodies) • Required testing after treatment o Ongoing measurement of biomarkers
Education and training	• Education of multidisciplinary team at hub-and-spoke centers on gene therapy in general and the specific therapy	• Education of multidisciplinary team at spoke
Informed consent	• Review before dosing	• Education and regular follow-up of patients and physicians
Preparation of gene therapy product and dosing	• Storage of materials and dosing	
Follow-up		
Short-term	• Counseling and collaboration • Further regular follow-up • Protocols on different strategies for immunosuppression	• Regular follow-up (weekly to monthly) at least during the first year • Initiation of immunosuppressive treatment
Long-term	• Counseling about potential long-term risks	• Regular follow-up • Liver health review
Data collection	• National and international data collection	• National and international data collection
Multidisciplinary team	• Counseling and collaboration	• Ongoing management of residual disease • Assessment for potential delayed adverse events • Information sharing with hub

AAV, adeno-associated virus.

because of the complexity and risks of these treatments. The future is less clear for in vivo gene therapies, which in practice are less technically demanding. At present, these treatments are likely to be delivered within the academic hub and community spoke paradigm to ensure that patients are appropriately selected and administration requirements and rigorous long-term follow-up requirements are met. As in vivo gene therapies become more routine and evidence accumulates on long-term efficacy and safety, establishing smaller gene therapy centers could become feasible. Such centers will expand geographic access to gene therapy for a broader range of patients and allow for routine follow-up to be conducted on site by center staff, rather than in the community, similar to how cancer treatment centers both treat and follow up patients with malignancies. The optimum model for cost effectiveness remains to be discerned.

Regardless of current or future models of care for the delivery of gene therapy, the group consensus was that it is critical that medical geneticists position themselves to play a leadership role in shaping the treatment modality. A subset of medical geneticists, perhaps with a specific designation such as gene therapists, with training that provides broad and deep experience in the implementation of gene therapy technologies may be best equipped to serve in this capacity.

Selecting Patients for Gene Therapy

The ABMGG defines medical geneticists as "clinicians who specialize in the interaction between genes and health, with the training to evaluate, diagnose, manage, treat, and counsel individuals with hereditary disorders."[9] According to this definition, patient identification, selection, and advising on eligibility by genotype and phenotype lie within the current purview of medical geneticists.

Most genetic diseases exist along a phenotypic continuum of clinical severity dictated by the nature of the genetic alterations, and the majority of patients with genetic disorders receive their diagnosis from medical geneticists, who become natural advocates for accessing and managing gene therapy. As genotype and phenotype experts, medical geneticists must be prepared to identify appropriate patients for gene therapy, which includes clinical decision-making and discussion of treatment options with patients and/or caregivers to ensure shared decision-making and set realistic expectations. As more gene therapies become available, there may be multiple options for some diseases; in these cases, the medical geneticist must clearly understand each therapy that is under consideration.

Roles may evolve as more such therapies are developed. The current novelty of gene therapy presents an opportunity

for medical geneticists to act as consultants to other specialists as new gene therapies become available, in addition to their natural role in leading the selection process for diseases that they typically manage. For some diseases with late-stage gene therapy options, such as hemophilia, these roles are already well served by other specialists. For these diseases, consultation from medical geneticists may be beneficial early in the gene therapy implementation process; as other specialists gain experience with a novel gene therapy, medical geneticists would shift their focus away from these disorders.

An increased focus must be placed on expanding the skillset of all medical geneticists to be able to fill these roles. Training should be provided to expand their general knowledge of gene therapy, including a deeper clinical understanding of gene therapy platforms, potential risks and benefits of specific gene therapies, and the need for long-term follow-up. In addition, it is important for medical geneticists to understand that some gene therapies may target some symptoms in a disease while leaving others unaddressed. Clear communication to patients and management of clinical expectations and ongoing therapy (if needed) is a natural extension of current medical genetics practice.

The Role of Medical Geneticists in Site Preparedness

Gene therapies will use many mechanisms of action, thus mandating unique site requirements for appropriate and safe administration.[13] Not all medical geneticists need a detailed understanding of these concepts. However, those involved directly in decision-making at gene therapy hubs should be well versed in the pathways and processes required for the local implementation of gene therapy.

Although medical geneticists at gene therapy hubs can have roles in all aspects of site preparedness for gene therapy, some roles are likely to be central, whereas others are better considered consultative. At least initially, medical geneticists at hubs should be involved in the detailed, comprehensive patient assessments that must be made for each gene therapy. Medical geneticists should also play a central role in supporting the proactive development of pathways and processes for short- and long-term patient follow-up. Medical geneticists can also lend their expertise in a consultative capacity to other conversations around gene therapy. For example, they can be involved in cross-departmental clinical biosafety committees with pharmacists, associated HCPs, and occupational health and biosafety/environmental safety officers. They should also be integrated into teams involved in identifying infrastructure needs/gaps and structuring gene therapy delivery pathways and care plans. As regulatory authorities approve gene therapies, medical geneticists should be included as part of national, regional, and local committees that evaluate new gene therapies for reimbursement and inclusion in formularies.

Some of these concepts are currently unfamiliar to many medical geneticists, and appropriate training is required for those who are involved at gene therapy hubs, including but not limited to relevant virology, immunology, and biotechnology concepts as well as the procedures and risks associated with gene therapy modalities used at a specific hub.

The Role of Medical Geneticists in Gene Therapy Education

The ABMGG definition of medical genetics does not encompass an educational role for medical geneticists in gene therapy programs.[9] However, medical geneticists are logical choices to help deliver such education to their fellow clinicians, including the medical community as a whole and the multidisciplinary team (MDT) directly involved in gene therapy. Thus, there is a need to prepare medical geneticists to act as educators on these topics in medical, pharmacy, and nursing schools; the broader medical community; and within the MDTs involved in the direct care of patients with addressable diseases—a role advocated for in the ACMG strategic plan. As a first step, it is important to better define existing educational gaps in medical genetics training programs and leverage this information to fill them.

An additional opportunity exists to define educational gaps of different audiences more rigorously and to leverage this information to develop training that is tailored to their needs, including for both the gene therapy MDT (other specialists, referring physicians, pharmacists, genetic counselors, nurses, and other HCPs as well as non-HCP staff) and the broader health care community.

Education of the broader medical community

At present, knowledge of gene therapy among the broader medical community is limited. Although this is likely a function of the small number of available gene therapies at present, several surveys of the broader medical community have revealed significant educational gaps that must be addressed.[14-17]

For example, a recent survey of 1472 HCPs across 14 specialty areas (87% physicians) provides insight into knowledge gaps of basic genetics and gene therapy among clinicians.[14] Although the majority reported being involved in the management of patients with rare diseases who might conceivably qualify for a current or near-term gene therapy, nearly two-thirds were uncomfortable discussing gene therapy with their patients instead preferred referring them to an expert for these discussions. Only 20% had discussed gene therapy options or clinical trials with their patients, with hematology/oncology specialists raising the topic most frequently (45%) followed by neurology/child neurology specialists (43%). The survey also suggested a lack of understanding of some genetic concepts among the physician community, such as causes of genetic alterations and somatic vs germline variants. The survey highlighted deficits in the understanding of the types of currently available gene

therapies; when asked about US Food and Drug Administration–approved gene therapies, 63% indicated that they had no knowledge of these products. Nearly one-third of participants in this survey had not received training on gene therapy, and only 26% had learned about gene therapy from attending a session at a local, regional, or national meeting.

The findings of this study were limited by its scope and methodology and may reflect the limited number of diseases for which gene therapy is currently available. Indeed, throughout this survey, hematologist/oncologists demonstrated the greatest awareness of gene therapies of any type, perhaps reflecting the availability of chimeric antigen receptor T cell therapy for hematologic malignancies and late-stage trials of hemophilia gene therapy. Nevertheless, most respondents were uncomfortable discussing these topics, suggesting a need to reinforce these concepts and update clinicians on advances in molecular genetics and genomics that have occurred since their training.

As gene therapies become more widely available, medical geneticists also can ensure that the broader medical community is aware of the availability and viability of these treatments. Because some gene therapies may have a window during which they have the greatest potential to alter disease course, it is critical to ensure specialists and primary care clinicians understand the need for early screening and testing to identify disorders amenable to gene therapy.

Medical geneticists have an opportunity to lead in developing and delivering gene therapy teaching tools and case modules for medical students, residents, and other HCPs, and there may be additional opportunities to partner with disease-specific societies to deliver large-scale educational programs that enhance awareness and understanding of these therapies. One such educational program developed by the ACMG was presented for the first time in the summer of 2022 and is available on demand through the ACMG Genetics Academy (https://www.acmgeducation.net/Public/Catalog/Main.aspx). Table 3 highlights some anticipated knowledge gaps that need to be addressed with the broader health care community and MDT.[7]

Table 3 Potential health care provider educational gaps

Knowledge Area	Knowledge Gap
Technology	• Vector design and engineering • Attributes of different gene therapy platforms • Nonintegrating vs integrating vectors • Mechanisms of action (gene transfer, gene editing, modulation of gene expression) • Gene therapy manufacturing and supply chain
Disease state	• Understanding mechanisms of genetic disease • Gene therapy development/ regulatory status and availability • Eligibility requirements for gene therapy • Gene therapy clinical trials
Efficacy	• Anticipated effects on disease symptoms • Anticipated duration of effect • Implications for need of therapy over the short- and long-term
Safety	• Potential adverse events in the peri-dosing period • Potential adverse events associated with associated therapies (eg, immunosuppressants) • Potential long-term adverse events, including cancer risk with integrating and predominantly nonintegrating vectors • Host immune responses to vector and expressed protein • Vector shedding • Implications for patient lifestyle after gene therapy
Site preparedness and administration	• Institutional requirements for gene therapy • Handling and dosing of gene therapies • Requirements for follow-up • Duration of follow-up
Other educational gaps	• General knowledge about genetics • General principles of gene therapy • Health technology assessment

Adapted from Miesbach et al.[12]

Education of the MDT

The education of MDTs who touch directly on the gene therapy pathway is a priority, whether they are involved in initial patient identification and qualification for gene therapy, the peri-dosing period, or the short- and long-term follow-up of treated patients. As experts in genetic disease mechanisms with an understanding of the range of approaches to therapy that draw upon genetic knowledge, medical geneticists can deliver this education.

With the introduction of gene therapies, educational gaps may emerge that need to be addressed by medical geneticists. At minimum, all MDT members require training on basic principles of molecular biology and genetics, gene therapy vector platforms, potential efficacy and short-term adverse events (including but not limited to viral shedding, immune responses to the capsid and the transgene, and seroconversion), durability, and long-term safety considerations for each gene therapy. With appropriate training, medical geneticists can help ensure these gaps are addressed in collaboration with other specialists and the broader health care community.

Patient and caregiver education

Clear communication to patients and management of clinical expectations is a natural extension of the current practice of

medical genetics. All members of the MDT should be prepared to educate patients and caregivers on realistic expectations for outcomes, practical aspects of gene therapy, and address any questions or misperceptions, with the goal of making a shared decision on treatment choices that is firmly based on the individual's clinical history, preferences, and treatment goals.[18] Education for patients and caregivers must be tailored to the audience, recognizing that they are often highly motivated and knowledgeable about their disease state and are likely to desire more detailed education than is delivered to general nonclinician audiences (Box 1).[18]

Because there is a recognized shortage of medical geneticists in clinical practice, efforts must be made to leverage other MDT members to provide patient and caregiver education. In particular, genetic counselors may have a role in these efforts. Most genetic counselors currently focus on assessing individual and family risk of inherited conditions and providing information and support to other HCPs, individuals, and families. Expanding their role to helping drive health-literate patient and caregiver education on gene therapy might help alleviate pressures resulting from a shortage of medical geneticists in the United States and Europe. Given the potentially important role of genetic counselors in education and operationalizing gene therapy, establishing or expanding training programs in regions and countries where few genetic counselors currently practice should be considered.

The Role of Medical Geneticists in the Follow-up of Patients Who Have Undergone Gene Therapy

The long-term efficacy and safety outcomes of gene therapy remain incompletely understood. All patients treated with gene therapy require long-term follow-up to address potential residual symptoms and monitor the durability of effect. Maintaining patient engagement during this period is a critical yet challenging aspect of gene therapy in which medical geneticists could play a central role.

Because medical geneticists outside of hubs will be responsible for many aspects of the long-term care of patients who have undergone gene therapy, they must understand follow-up requirements, including procedures and pathways for monitoring the efficacy, durability, and safety of the therapy. These clinicians must recognize when referral to a gene therapy hub is necessary for additional follow-up. Medical geneticists will also play a critical role in collecting data from their patients to better understand long-term risks and benefits of therapy.

The Role of Medical Geneticists in Laying the Groundwork for New Gene Therapies and Partnering for the Future

Medical geneticists are already key contributors to preclinical and clinical research on gene therapy. Continued discovery, development, and delivery of gene therapies will require tremendous resources and, therefore, robust collaboration and partnership among medical geneticists and patients, physicians, academic researchers, industry partners, policy makers, and payers.

For example, the American Society of Gene & Cell Therapy and the European Society of Gene and Cell Therapy are primary membership organizations for those involved in genetic and cellular therapies. Both societies include a broad range of stakeholders focused on gene therapy. All medical geneticists with an interest in gene therapy should consider joining and participating actively in such societies. Partnerships should be explored between these organizations and United States and European medical geneticist societies to create appropriate training for medical geneticists who plan to focus on gene therapy as well as education for the broader health care community. Indeed, the latest American Society of Gene & Cell Therapy strategic platform emphasizes the importance of such partnerships to deliver educational content and cross-promote program offerings of each organization.[19]

Box 1. Topics that should be considered with a patient contemplating gene therapy.

- Results from clinical trials
- The vector being used and the prevalence of pre-existing antivector antibodies
- Patient eligibility criteria
- The dose of the vector and the anticipated range of therapeutic effect
- Potential adverse events associated with the vector or transgene
- Potential adverse events associated with concomitant therapies (such as prophylactic steroids, if used)
- Duration of transgene expression, including a detailed discussion of expected outcomes and the lower limit of duration of efficacy that would be acceptable to the patient
- Degree of comfort with monitoring and commitment required (especially in the first year) and with follow-up for years or decades

Adapted from Miesbach et al.[18]

Preparing for Gene Therapy: The Time Is Now

Gene therapies have reached an inflection point at which they will, with increasing rapidity, be adopted as therapeutic options for various rare diseases. The shifts in clinical practice that this will engender must not be underestimated or ignored. As the specialty at the forefront of diagnosing and managing genetic diseases, medical geneticists have an opportunity to lead in the effective, safe, and efficient deployment of gene therapy. An opportunity clearly exists for additional training of medical geneticists. Although all clinicians in the specialty can benefit from broader education in gene therapy fundamentals, truly capturing the lead in this evolving treatment modality requires a training pathway to create gene therapists—specialized medical geneticists with expertise within all the areas outlined above who are adequately prepared to lead at gene therapy centers regardless of the model of care.

In summary, the breadth of potential roles for medical geneticists in the rapidly evolving field of gene therapy has gaps that must be addressed for them to assume a leadership role in the clinical implementation of gene therapy (Table 1). Although this opinion article outlines some of the key issues and concepts that must be addressed, a true consensus can only be built through engagement, debate, and advocacy within our clinical discipline.

Limitations

This article represents the opinion of a limited group of medical geneticists from the United States and Europe, with expertise or interest in newborn sequencing and gene therapy. The meeting was sponsored by Pfizer Inc, which has commercial interest in gene therapies, although it did not address any specific disease or gene delivery modalities. Input from a wider sampling of medical geneticists and from other stakeholders involved in gene therapy is a logical next step and a desired outcome of this report. As such, the views espoused are a first step toward building consensus on a path forward for medical geneticists to play a major role in gene therapy as they become more routinely used in clinical practice.

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