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Gene-Targeted Therapies in Pediatric Neurology: Challenges and Opportunities in Diagnosis and Delivery

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Abstract

Background: Gene-targeted therapies are becoming a reality for infants and children with diseases of the nervous system. Rapid scientific advances have led to disease-modifying or even curative treatments. However, delays and gaps in diagnosis, inequitable delivery, and the need for long-term surveillance pose unresolved challenges.

Objective and Methods: The goal of the Child Neurology Society Research Committee was to evaluate and provide guidance on the obstacles, opportunities, and uncertainties in gene-targeted therapies for pediatric neurological disease. The Child Neurology Society Research Committee engaged in collaborative, iterative literature review and committee deliberations to prepare this consensus statement.

Results: We identified important challenges for gene-targeted therapies that require resource investments, infrastructure development, and strategic planning. Barriers include inequities in diagnosis and delivery of therapies, high costs, and a need for long-term surveillance of efficacy and safety, including systematic tracking of unanticipated effects. Key uncertainties regarding technical aspects and usage of gene-targeted therapies should be addressed, and characterization of new natural histories of diseases will be needed. Counterbalanced with these obstacles and uncertainties is the tremendous potential being demonstrated in treatments and clinical trials of gene-targeted therapies.

Conclusions: Given that gene-targeted therapies for neurological diseases are in their earliest phase, the pediatric neurology community can play a vital role in their guidance and implementation. This role includes facilitating development of infrastructure and guidelines; ensuring efficient, equitable, and ethical implementation of treatments; and advocating for affordable and broad access for all children.

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Child neurology; Disparities; Diagnosis; Gene therapy; Rare disease; Ethics; Health economics; Antisense oligonucleotide

Introduction

Gene-targeted therapies provide new treatment options for people affected by formerly incurable conditions, including rare and orphan diseases. Many of these diseases affect the brain and nervous system, onset of symptoms is often in childhood,[1,2] and many cause progressive symptoms and disability or death before adulthood. Childhood genetic diseases of the nervous system impose disability, chronic health problems, and substantial health care burden.[3] Children with chronic medical needs, often from genetic conditions, are the single largest group of patients admitted to children's hospitals.[3–5] Among the thousands of genetic diseases that affect the nervous system of infants or children, there are currently only a handful of gene-targeted therapies available for use in clinical practice.[6] However, more than 900 additional gene-targeted therapies are now in development or clinical trials.[7] These treatments may improve quality of life, modify disease severity or course, or even be curative.[8–10]

The disease burden as well as the transformative potential of gene-targeted therapies are profoundly apparent to the pediatric neurology community. Treatment of spinal muscular atrophy (SMA), for example, has been transformed by three Food and Drug Administration (FDA)–approved gene-targeted therapies in the past five years. Instead of dying from a rapidly lethal disease, children with SMA can now not only have a halt of disease progression but also acquire developmental milestones never previously achieved by children with SMA.[11] Treatments for even the rarest of diseases are becoming feasible, which is critical for pediatric neurological conditions which may have unique genetic variants found in only a few or individual patients. For example, milasen, an antisense oligonucleotide (ASO), was developed for and administered to a single patient with a unique CLN7 mutation.[12] The milasen strategy demonstrated that an "N-of-1" or "bespoke" approach (single patient, single unique treatment) to therapy development is feasible.[13,14]

With excitement surrounding new treatment possibilities come important considerations for diagnosis, delivery, and access to therapies. New therapies may alter the natural histories of neurologic diseases, and novel medical problems related to the altered disease trajectory, or to the therapies themselves, are likely to become apparent. Finally, given the novelty of these gene-targeted therapies, and vulnerability of the developing nervous system, it is critical to develop infrastructure and metrics to track and analyze the long-term impacts.

The National Institutes of Health (NIH) recently issued a request for information regarding facilitation of early diagnosis and equitable delivery of gene-targeted therapies to individuals with rare diseases (NOT-TR-21-027). The Child Neurology Society Research Committee developed comments in response to the request for information, which we have expanded upon in this manuscript. For the purposes of our comments, we consider gene-targeted therapies broadly, including genetic correction or editing, gene replacement (viral or

transplantation), and oligonucleotide or other therapies that target the gene or aspects of RNA expression. Many of our recommendations are not unique to pediatric neurology; however, we highlight areas in which particular aspects related to neurological disease of infants, children, or adolescents merit special attention.

Developing infrastructure for the efficient, effective, and equitable distribution of gene-targeted therapies

Rules and regulations

Rules and regulations regarding the use of gene-targeted therapies in children must be developed and applied equitably.[15] These rules should include definitions of "best practices": expectations for vector choice and preclinical standards, standards for evaluation of efficacy in animal models and in humans, and requirements for long-term follow-up of outcomes, efficacy, and effects (both intended and unexpected).

Over 20 years after the death of Jesse Gelsinger during a gene therapy trial for ornithine transcarbamylase deficiency,[16] ongoing consideration of ethical issues remains critical. This is particularly true in the case of children or infants, who have limited or no decision-making capacity. Gene-based therapy must have a clear prospect of significant benefit to the child because children with neurologic disease have limited capacity for assent and are unable to provide informed consent.[17] Problematic situations include scenarios such as a treatment that is life-saving but has a negative impact on subsequent fertility, treatment of a disease where the child is already severely affected before administration of therapy,[18] or that a therapy has no "undo" once administered if issues are uncovered in subsequent years.

Consideration of the impact as well as the duration of therapies on the still-developing nervous system is also needed. For example, if a gene-based therapy has an efficacy duration of 15 years, a single course of treatment might be appropriate for a patient in their 60s, but the same treatment for a five-year-old child would require consideration of repeat or additional treatment when the patient reaches their 20s. Or, if a therapy is affected by developmental processes, for example, ongoing myelination and oligodendrocyte generation, this will require planning both for the administration of therapy as well as the clinical and research follow-up.

Issues related to fetal/in utero technologies need to be evaluated, with specific regulations and ethical considerations developed for therapies that can cause germline or other heritable genetic changes. In particular, the potential for off-target genome editing (i.e., unintended genetic modifications) must be considered and every effort made to minimize this risk before use in humans. Also, it is important to consider use of gene-targeted therapies currently only for treatment of pathogenic variants, as opposed to therapies intended for modification or alteration of normal variation, such as augmentation of intelligence.[19]

Technical and resource infrastructure

Technical and resource infrastructure should be arranged. Currently, there is no guidance on what molecular reagents (such as an antisense oligonucleotide backbone) would or

would not be permitted or on where specifically approved reagents could be obtained. Resources could include “modular” vector backbones available through certified providers or promoters preapproved for clinical trials and clinical practice. Careful consideration is needed regarding diversifying available vector-based therapies. For example, if a patient has antibodies against a particular viral vector subtype, then availability of an alternative vector subtype is needed.

New methods for assaying long-term efficacy and bio-distribution of gene-targeted therapies will be needed. For example, it is critical to develop methods that permit a clear understanding of expression levels in hard-to-access tissues such as the brain. Investment in shared infrastructure could help reduce development costs and costs to patients. Collaboration across networks is crucial to enhance strategic development priorities and efficiency by avoiding gaps or duplicative efforts.

Data on outcomes must be recorded, stored, and made publically available. Optimally, such databases would be served by partnerships between academia, industry, and government. Longitudinal follow-up is particularly important for children; as effects of unintended mutagenesis (“genotoxicity”) might not manifest until years after therapy administration, any genotoxicity would be highly relevant across the life span of a pediatric patient.[20]

Infrastructure for clinical care delivery

Gene-targeted therapies require new clinical delivery consideration. Currently, the specialized knowledge related to diagnosis, prognosis, phenotypic and genotypic spectrum of disease, appropriate timing for intervention, and management of post-administration complications is limited to few specialists. Furthermore, the specialized surgical experience for tissue-targeted therapies or routes of administration (such as via intra-cisternal magna) is also very limited.[21] A framework for clinical programs that provide specialized, skilled delivery and follow-up of gene therapy should be developed and supported. This support should be made broadly available, with linkage of centers and development of billing and regulatory frameworks that bridge individual state Medicaid programs (or Provincial health insurance programs), to allow consultation, care, and guidance to the patient’s local community providers. The existing NIH Center for Clinical and Translational Science sites could be leveraged to provide a practical approach to develop comprehensive and integrated scientific and clinical programs. A national framework of programs must take into account differences in accessibility across geographic regions, including urban and rural settings, so that specialized services are equitably available across the range of geographic regions.

Funding for clinical infrastructure should include support for clinical registries as well as for training programs. Clinical registries are needed to monitor shifts in natural history and track efficacy and adverse effects of gene-based therapies. Such registries should track both gene-targeted therapy recipients and comparable non-recipients. Training programs in gene-targeted therapies are needed, such as subspecialty fellowships, focused medical genetics education for medical students and residents, and continuing medical education for currently practicing clinicians. Of critical importance is the training of clinicians and funding of infrastructure for transition programs to adult care for people whose diseases were previously incompatible with survival to adulthood.

New financial models are needed to support the added clinical complexity of gene delivery. Currently, gene-targeted therapy reimbursement pays only for the costs of the medication and does not pay for the clinical infrastructure, expertise, and time involved to safely administer the treatment, or to monitor or manage the patient in the short or long term.

Scientific infrastructure

Additional efforts should be developed to clarify natural history of diseases for which penetrance or expressivity of phenotype is uncertain or unknown. This information is needed before therapy delivery, to determine who are appropriate candidates for gene-targeted therapies. For example, careful studies should focus on whether all types or severities of a given disease would benefit from a gene-targeted therapy or if such treatments are only appropriate for certain types, or at certain ages or disease stages. This scientific information depends in part on regulations around genetic testing to establish variant pathogenicity (e.g., insurance coverage, or lack thereof, for testing the proband as well as the parents). Additional resources to develop comparative effectiveness evidence and guide best practices regarding selection of appropriate first- and second-line therapies, and use of novel trial design such as N-of-1 models,[22] would assist in efficient delivery of the most effective treatments.

As new gene-targeted therapies offer disease-modifying effects for previously life-limiting diseases, new natural history studies are urgently needed as part of a program of careful follow-up and long-term surveillance. Long-term follow-up for a duration of ≥20 years is essential for assessment of treatment stability, efficacy, cost-effectiveness, and evaluation for genotoxicity effects.[23] This requires novel infrastructure, such as national databases for collection of short- and long-term follow-up data (i.e., across the lifespan), structured with care transitions and functional mobility in mind. This infrastructure is of particular relevance for therapies developed for pediatric disorders, because of the potential for side effects that might manifest over decades, as a child’s brain and other organ systems mature, and because of the risk of genotoxicity that might have late effects (e.g., insertional mutagenesis leading to cancer). Not only toxicity but also long-term efficacy needs to be tracked; for example, some data suggest potential concerns for long-term efficacy of SMA gene replacement therapy.[24,25]

New natural history trajectories for treated patients (derived from clinical, imaging, and neurophysiologic biomarkers) must be defined as gene-targeted therapies become widely used in clinical practice. This necessitates development of validated, age-appropriate and developmental -stage–appropriate instruments for objective measurement of growth and development while also including disease-specific parameters. Databases should be required for both private and public ventures, be transparent with regards to data collection processes and sharing, utilize common data elements and sharable interfaces, and have sufficient granularity to include common as well as rare events. Such data should be openly accessible for review (with appropriate research ethics review board and Health Insurance Portability and Accountability Act [HIPAA] protections). Funding should also be designated for determination and documentation of unanticipated or rare events, such as adverse effects in the offspring of recipients of gene therapy, or evidence of neoplasms in individuals

who receive gene-targeted therapy. Sharing safety information may reveal otherwise-cryptic patterns, for example, if certain vectors or treatments have adverse or long-term effects.

Careful consideration with a multistakeholder process is needed to develop procedures for timely and equitable access to gene-targeted therapies

Diagnosis

Many of the new gene-targeted therapies are effective only when given early in the disease process; any delay in diagnosis or implementation of the therapy can result in irreversibly devastating outcomes. Yet, access to diagnosis and treatment are inequitably distributed to those in need of these therapies.[26–29] For example, diagnosis rates of treatable leukodystrophies are lower in minority groups.[30] The advantages of colocating diagnosis and treatment at centers of excellence must be balanced with the need to provide widespread availability of therapies. Instead of support being directed to only a few locales not accessible to many patients,[31] geographic and population-based center support models should be considered.

Funding to support research into improved diagnostic strategies, such as prenatal genetic carrier screening panels or expanded newborn screening with next-generation sequencing, should be prioritized. Newborn screening programs can provide equitable access to diagnosis, are necessary for early diagnosis of some treatable diseases, and will become increasingly cost-efficient as sequencing costs decrease and costs of adding additional treatable diseases to biochemical-based screening expand. In the United Kingdom, for example, there is public support for use of next-generation sequencing in newborn screening[32] In the US, an additional hurdle is the need to standardize screening that is often discrepant between states.[33]

As novel therapies are developed and applied in routine clinical practice, education of primary care providers and general neurologists will be critical. The rapid evolution of genome sequencing and clinical genomics over the past decade presents many barriers to the efficient and effective application and interpretation of genetic testing (e.g., the ubiquitous and dreaded “variant of unknown significance”). Greater involvement of genetic counselors as well as increased genetics education requirements in residency and through continued medical education is essential to overcome these barriers. Mandating insurance coverage of genetic counseling visits could be a cost-effective approach to provide prenatal and postnatal genetic counseling to families. The concept that neurological diseases do not require precise diagnoses because they are rarely treatable is outdated and incorrect.[34] Efficient diagnosis and facile referral to appropriate specialists and/or clinical centers are key, particularly for treatable disorders. Improved triage strategies must be developed both at the institution level and by professional societies to minimize unnecessary delays in evaluation and treatment in newly treatable diseases.

Finally, with expansion of diagnostic approaches, it will be important to support research studies and then implementation of evidence-based recommendations regarding impacted ethical, legal, and societal domains.

Funding models

Given the currently high costs of gene-targeted therapies, support and concerted efforts are urgently needed to develop funding models that are sustainable and equitable.[35] Different models will likely be needed in countries with universal health care (such as Canada or the United Kingdom) compared with the strategies developed for the US, where coverage is provided through a matrix of private or public insurance and philanthropy. Given the high monetary cost of the currently approved gene-targeted treatments, there is an urgent societal need for regulations that address ethical distribution and availability of these therapies. Consideration must be given to health care savings provided by a gene-targeted therapy that are spread over a lifetime, such as reducing hospitalizations or need for intensive care or technology dependence. For example, the annual cost of care for a patient with Duchenne muscular dystrophy is ~$50,000[36]; after 10 years, a highly effective and durable therapy that costs $500,000 may be dominant in a cost-benefit analysis.

Policies for funding should be drafted, reviewed, refined, and finalized in a multistakeholder process that includes physicians, scientists, patients, families, ethicists, advocacy and professional societies, payers, pharmaceutical companies, and health care systems, as well as state/provincial and federal governments. For example, a central funding mechanism from Medicare could be distributed based on a prospectively agreed-upon model, which would take into account prevalence, disease severity, disease progression, etc. Furthermore, such models need to be considered to either pay for all eligible patients or develop a centralized prioritization and allocation system, such as is used for organ transplant recipients.[37]

Evaluation and then regulatory interventions regarding the very high prices of gene-targeted therapies are needed, including review of the patent and FDA clearance systems and ethics of business practices around therapies for rare diseases. Because the technologies and scientific advances that now support gene-targeted therapies have included large investments from the government and public (via taxpayer support), it is reasonable that funding policies should be examined with involvement of all stakeholders.

Discussion of prioritization decisions for therapy development is necessary because of limited financial and time resources. For example, current therapies have targeted “low-hanging fruit”—such as more common genetic diseases including SMA or sickle cell disease. It makes sense to continue to prioritize these diseases to maximize impact. However, there are other important disease features, such as disease severity, that require careful consideration as priorities are developed.

Conclusions

The increasing availability of gene-targeted therapies for neurological disease offers new hope for affected families and new challenges for the scientific and clinical infrastructures that support the development and delivery of these treatments. Infants and children with neurological diseases could reap tremendous benefit from these advances, with potential for lifelong and life-saving cures. Despite the potential high cost, therapies might be less expensive than supportive care over a lifetime for some of these disorders. Given the historical underfunding of research for pediatric neurology compared with adult

neurology,[38] particular emphasis is needed to ensure that funding specific to pediatric neurology gene-targeted therapy programs is prioritized. Development and implementation of thoughtful regulations, clinical and scientific infrastructure, and sustainable payment models are urgent. The solutions to these challenges will be complex and must involve a very broad range of stakeholders. The urgency is underscored by the tremendous potential to avert morbidity and mortality for infants and children previous generations of pediatric neurologists could only dream of saving.

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Summary table: Key recommendations

1. Infrastructure must be developed to enable consistent assessment of efficacy, duration of treatment effect, new natural histories, and adverse effects of gene-targeted therapies across the developmental spectrum and the full life span.
2. Resources are needed to develop comparative effectiveness evidence and guide best practices regarding selection of appropriate first- and second-line therapies and use of novel trial design such as N-of-1 models.
3. Training of clinicians and funding of infrastructure for transition programs to adult care for people whose diseases were previously incompatible with survival to adulthood should be prioritized.
4. Strategies for equitable and affordable delivery of gene-targeted therapies are needed. Development of these strategies must include deliberate multistakeholder input.