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Research Into Rare Diseases of Childhood

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The acceleration of clinical trials studying rare diseases over the past 3 decades has occurred largely because of the Orphan Drug Act, which was enacted in 1983 as a result of patient advocacy groups working with congressional sponsors.[1] This act facilitated the development and commercialization of products (drugs, vaccines, and diagnostic agents) to treat populations with rare diseases, defined as those affecting fewer than 200 000 US residents, or those without reasonable expectation that drug development costs will be recoverable by US sales. The act has resulted in more than 3900 orphan product designation requests to the US Food and Drug Administration (FDA) with the approval of more than 450 products to treat approximately 250 rare disorders, of which approximately one-quarter in the past decade have been for pediatric diseases.[2,3]

The National Institutes of Health (NIH) has provided significant support for clinical research studying rare diseases,[4] including the development of the Rare Diseases Clinical Research Network (RDCRN). This initiative is supported and administered by the NIH Office of Rare Diseases Research in the National Center for Advancing Translational Science with participation of 8 other NIH research institutes. The purpose of this program is to promote (1) collaborative clinical research in rare diseases, including longitudinal studies, clinical studies, and clinical trials; (2) training of clinical investigators in rare diseases research; (3) proof-of-concept clinical research projects; and (4) access to information related to rare diseases for researchers, physicians, health care professionals, patients, and the general public. Seventeen consortia presently comprise the RDCRN, including 10 focused on rare diseases that include pediatric populations.

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Although individually uncommon, there are more than 6400 rare diseases that are estimated to affect 18 million to 30 million US residents. About 80% of rare disorders have a genetic origin and about half affect children. Examples of rare diseases in children studied by the RDCRN consortia are urea cycle disorders; Angel-man, Rett, and Prader Willi syndromes; lysosomal storage disorders; genetic disorders of mucocillary clearance; primary immune deficiencies; and mitochondrial diseases. As genomic medicine advances, not only will new rare diseases be identified but many common disorders will likely be found to be composites of a multitude of genetic mutations. For example, mutations in certain tumor suppressor genes in the homozygous state cause rare familial cancer syndromes (eg, retinoblastoma), while sporadic mutations in the same gene combined with mutations in other genes can give rise to more common cancers. To address the increasing importance of rare diseases, there will be a need for more clinical trials with improved methods and novel study design approaches for small sample sizes.

Rare diseases research in children is of particular importance as genomic medicine becomes more established as a discipline. For many rare disorders, early treatment can lead to markedly improved outcomes and associated quality of life. The classic example is phenylketonuria, for which dietary therapy instituted during infancy can result in normal development, whereas a significant delay in treatment is associated with severe intellectual and physical disabilities.[5] Success of early treatment of phenylketonuria was the primary impetus for the development of universal newborn screening, which now detects more than 50 rare disorders.[6] Soon, current tandem mass-spectrometry methods will likely be complemented by DNA sequencing. These methods will enable the diagnosis of hundreds of rare inherited disorders, some of which are potentially treatable. However, because of the complexity of newborn screening, followed by delays in case finding, the treatment of newly discovered inborn errors of metabolism have not always demonstrated clinical benefit.

In addition, any mass screening program, especially one that relies on biochemical markers, is likely to identify a large proportion of subclinical cases that may never develop symptoms of disease. These biochemically detected asymptomatic cases in infants represent an unavoidable consequence of the need to minimize false-negative tests. Although this adverse effect of expanded newborn screening creates transient stress and anxiety in affected families, it is a price that society has decided to pay to prevent death and disability for those families who are truly affected by devastating yet treatable disorders. In anticipation of this new method, it is important to move forward with the development of novel treatment approaches that can begin in childhood. Furthermore, research into rare genetic disorders has uncovered previously unknown biological mechanisms that have contributed to the treatment of more common disorders. For example, research on familial hypercholesterolemia ultimately led to the development of statins to treat high cholesterol in the general population.

The Urea Cycle Disorders Consortium (UCDC) of the RDCRN illustrates some lessons that can be learned from clinical research into rare diseases of childhood. Infants with a complete block in 1 of the 8 urea cycle–related enzymes commonly present in infancy with elevated ammonia levels and coma. Fewer than half of neonatal-onset cases survive to childhood and those who do survive commonly sustain severe neurocognitive deficits.[7] The UCDC

longitudinal study taught researchers that the development of research consortia to study rare diseases is essential for rapid advancement in clinical research because single institutions do not have sufficiently large patient populations of specific rare disorders to perform clinical trials efficiently and effectively. In urea cycle disorders research, previous longitudinal studies and clinical trials have involved fewer than 50 patients, whereas the UCDC is currently following up more than 600 individuals in 14 sites within the United States, Canada, and Europe. This has permitted investigation on the overall morbidity, mortality, and developmental outcomes of individuals with urea cycle disorders that could not have been accomplished without this large sample size of enrolled patients.

A second lesson is that although recruitment into treatment trials can involve many approaches, contact registries, referrals from patient advocacy groups, and enrollment of existing patients at consortium sites appear to be most successful. Third, the support and involvement of patient advocacy groups is critical. These groups successfully advocated for the Orphan Drug Act and the creation of the RDCRN, and they are invaluable in providing investigators with patient perspectives on research studies and information about the types of studies in which their members will more likely participate.

In addition, the consortia serve as an incentive for industry to enter the rare diseases drug development domain. When the UCDC was inaugurated in 2003, only a single pharmaceutical company had been developing drugs for urea cycle disorders; in 2013, there are 9. In its 10-year existence, the investigators and collaborative infrastructure of the UCDC have contributed to clinical trials that have led to FDA approval of 3 new medications. As a recent example, glycerol phenylbutyrate (Ravicti, Hyperion Therapeutics), approved in 2013, had a reported bench-to-market cost that was 10% of that of a typical drug, which, according to Hyperion, was largely the result of its collaboration with the UCDC and the National Urea Cycle Disorders Foundation.[8]

In summary, research in rare diseases in children is likely to provide important informtion that will have benefits beyond the populations studied. In recognition of this, the recently passed Prematurity Research Expansion and Education for Mothers who Deliver Infants Early (PREEMIE) Reauthorization Act[9] contains language to create a national pediatric research network to help children with rare genetic diseases. This would be another important step in the direction of promoting rare diseases research in children.

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