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Decoding news and trends for the medical genetics community

By Deborah Levenson

LEGISLATIVE UPDATE

ADVOCATES CALL FOR LONG-TERM EXTENSION OF THE FDA'S RARE PEDIATRIC DISEASE PRIORITY REVIEW PROGRAM

Federal voucher program considered instrumental in shortening drug review, approval period

After the November 2016 elections, pediatric rare disease patient advocates and pharmaceutical companies were working to extend a U.S. Food and Drug Administration (FDA) program that gives companies an incentive to develop treatments for rare pediatric diseases.

The Advancing Hope Act, passed by Congress in October 2016, extended the FDA's rare pediatric disease priority review voucher program for only three months, until December 31, 2016. Advocates and companies then began lobbying lawmakers for a long-term extension during the lame-duck session of Congress. Several organizations, including the National Organization for Rare Disorders (NORD) based in Danbury, Connecticut, and the Washington, D.C.-based Kids v Cancer, have also begun lobbying Congress to extend the program beyond its 2016 expiration date.

Under the voucher program—created in 2012 and previously reauthorized in 2015—the FDA gives developers of treatments for rare pediatric diseases a voucher for priority review in which the agency endeavors to make a decision about a treatment approval within six months as opposed to the 10-month standard review period. After the FDA grants a voucher, it may be transferred or sold to another company.

"Vouchers are incentives for industry to shift resources to drugs for rare diseases. It's a carrot created by Congress," explains Alexander Varond, JD, an associate with the law firm Hyman, Phelps & McNamara in Washington, D.C. Most companies who have received FDA vouchers have sold them to larger companies for $67.5 million to $350 million, he notes. "The idea is that bigger, richer companies with drugs that would not otherwise receive priority review buy the vouchers from smaller companies."

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Congressional lawmakers who extended the FDA priority review voucher program only through December 31, 2016 are being lobbied to prolong the program.

The company that uses the voucher pays the FDA a user fee of $2,706,000 for fiscal year 2017, which began October 1, 2016. However, the FDA says this is not enough to offset the monetary and time costs of the voucher program.

The New Law

In addition to extending the voucher program, the most recent reauthorization law changes the definition of rare pediatric disease to account for disease burden and include diseases with serious or life-threatening manifestation that primarily affect between birth and age 18. This definition better accounts for children who die from their disorders.

Previously, the FDA largely focused on disease prevalence to define rare pediatric disease and did not apply the term to pediatric cancers and single-gene disorders such as sickle-cell anemia and Friedreich's ataxia, which begin in childhood, cause severe symptoms, and often kill patients in their 20s, says Paul Melmeyer, NORD's Associate Director of Public Policy.

Notably, the recent reauthorization law newly requires companies to apply for vouchers. "Before, FDA had to be proactive to see if applications from companies qualified for vouchers," Melmeyer adds.

NORD is lobbying for a 10-year extension of the voucher program through its inclusion in the 21st Century Cures Act, a massive bill that seeks to speed translation of research advances into treatments. The act also contains several

LEGISLATIVE UPDATE CONTINUED

other provisions relevant to rare genetic diseases. "Companies may not invest in drugs [for rare pediatric diseases] if they don't know [whether the] vouchers will be there or not," Melmeyer explains. "A 10-year window gives regulatory certainty for companies."

NORD had advocated for a 10-year extension prior to passage of the recent reauthorization legislation, but lawmakers rejected this proposal. Senators then successfully brokered a compromise calling for the three-month extension.

The FDA's View

The FDA has expressed concerns about the voucher program. Agency officials say they want incentives for companies to develop therapies for rare pediatric diseases but are worried that "the program adversely affects the agency's ability to set its public health priorities," says FDA spokesman Kristofer Baumgartner. Another concern is that some new drug applications submitted with vouchers do not treat serious conditions or provide significant safety or effectiveness over existing products. "We also have said that the additional workload from the program strains the agency's resources," he adds.

Baumgartner refers to a March 2016 U.S. Government Accountability Office report that notes FDA officials have complained that the voucher program lacks a pool of review staff who can be moved between divisions on an ad hoc basis and that the one-time user fee does not cover the cost of new long-term staff to assist with priority reviews. The report also details FDA officials' complaint that vouchers allow sponsors to effectively "purchase" a priority review at the expense of other important FDA work, undermining the FDA's public health mission and diminishing staff morale.

Other FDA programs aim to speed development and approval of new drugs and treatments for serious and life-threatening conditions that meet an unmet medical need, including those with a demonstrated substantial improvement over available therapy. Drugs being developed to treat rare diseases may also be eligible for grants and tax credits for clinical testing and may be exempted from applicable user fees, Baumgartner points out.

Program Extension?

It is too soon to tell if the voucher program is effective. Drug development typically takes more than 10 years, and not enough time has passed to fairly judge the program.

"Any sponsors motivated by this relatively new program to attempt to develop drugs for such [rare pediatric] disease would likely be years away from submitting their new drug applications to FDA," the report adds.

David Ridley, PhD, who first proposed the voucher program and is Faculty Director of the Health Sector Management program at Duke University's Fuqua School of Business in Durham, North Carolina, says members of Congress are wise to evaluate the results of the program before reauthorizing it. "However, it's problematic in this case," he notes. "Investors are reluctant to fund drug development for a rare pediatric disease if they aren't confident that success will lead to a return on their investment because the pediatric voucher program might no longer exist. For the program to be effective, it needs to be renewed long-term."

"If we don't extend the program fully and [instead] do piecemeal extension, we will never know if the program works and if it's incentivizing companies to develop new therapies," Melmeyer adds.

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TESTING UPDATE

GENETICISTS, HEALTH PROFESSIONALS SUGGEST RECASTING REQUESTS TO TEST CHILDREN FOR ADULT-ONSET DISEASES

New study explores parents' reasons for seeking predictive genetic testing

Geneticists and health professionals should reframe parents' requests to test their children for adult-onset diseases as broader discussions about optimal timing for testing and other concerns, a recent paper suggests.

These requests are best handled as starting points for conversations between parents and health professionals to explore the pros and cons of testing, the reasons parents want results, and at what point children should be involved in the decision-making process, write researchers from the United Kingdom's University of Southampton in the *Journal of Genetic Counseling* (Fenwick et al, 2016).

"We have found that this approach gives parents the space to consider why they are asking for a test and what might be the reasons for not doing it immediately," says senior author Anneke Lucassen, MD, PhD, Professor and Consultant in Clinical Genetics at the University of Southampton and England's National Health Service.

Based on in-depth, semi-structured interviews with 34 healthcare professionals, including 26 genetics professionals and eight other healthcare providers, the researchers examined how providers view and talk about the preservation of children's future autonomy, children's best interests, and testing's lack of medical benefit with other factors.

Autonomy and Best Interests

Although study participants generally agreed that adult-onset disease testing diminished children's future autonomy and should be avoided, some participants thought preserving autonomy was less important in the case of carrier testing, researchers say. These participants reasoned that because positive carrier test results have no medical implications for the carriers, getting this information differed from burdening children with the knowledge that they would be likely to develop a disease in adulthood.

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Discussions around the timing of adult-onset disease genetic testing in children should cover a range of topics, say healthcare professionals.

Some participants said carrier status testing is appropriate as soon as children can understand the implications of test results, while other participants said they thought carrier testing should be administered only when it would aid reproductive decisions. These findings highlighted researchers' contention that "these decisions were more complex than a 'yes' or 'no' response to testing requests and that the age of the child played an important part in any decision," Dr. Lucassen says.

All participants noted the importance of acting in the child's best interests when considering adult-onset disease testing, but many reported difficulty making this assessment. Some participants said medical criteria were the only factors they felt qualified applying to a situation, in contrast to parents, who rely on a wider concept of best interests to justify their requests.

Discussions with parents "should not be based on a narrow interpretation of best interests," the researchers write. But discussions that lead to wider interpretations depend on healthcare professionals' comfort with making this call, they add.

Participants who considered criteria besides medical utility when thinking about a child's best interests included the psychological and social impact testing for the child, parents' experience with the genetic condition, and whether parents understood that testing reveals future and not current risks.

Respondents also took into account parents' anxiety. One participant told researchers she agreed to test a child because the mother's anxiety level was so high that refusal seemed unhelpful. Others said not knowing genetic status can affect bonding with young children.

Some respondents considered their need to maintain positive relationships with the family. For example, participants pointed out that administering a test might keep the family engaged in medical follow-up it would not receive if they sought testing from a commercial lab.

Reaction

Discussing pros and cons of testing for adult-onset disease with parents is "what any expert genetics professional would do in that situation," says David Flannery, MD, Medical Director at the American College of Medical Genetics and Genomics (ACMG) in Bethesda, Maryland.

Dr. Flannery suggests pointing out to parents that if a child carries a variant associated with a high risk for an adult-onset disease, one of the parents most likely has that variant and is also at risk. He suggests telling parents, "Consider how you would feel if you're facing this burden. How do you think the child would handle this information?"

ACMG's statement on ethical and policy issues in genetic testing and screening of children does not prohibit predictive testing of minors but emphasizes it should occur after proper counseling that results in an understanding of its limitations and risks by parents and minors.

"People rarely seek this information [divulged by testing] purely out of intellectual curiosity. There is usually an emotional motivator, like fear or need for control," says Jehannine Austin, PhD, CGC, President of the National Society for Genetic Counselors (NSGC) in Chicago and Associate Professor in the Departments of Psychiatry and Medical Genetics at the University of British Columbia in Vancouver. Noting that the NSGC encourages parents to defer testing of children for adult-onset diseases, counselors can help "uncover the psychological, emotional issues that drive the request," Dr. Austin notes.

Healthcare providers who are uncomfortable weighing non-medical factors in determining a child's best interest and whose patients lack access to genetic counselors could also consider a hospital ethics consult to examine the context of the test request, says Kelly E. Ormond, MS, CGC, LGC, Professor in the Department of Genetics and Co-Director of the Human Genetics and Genetic Counseling master's program at Stanford University in California.

"Over the past few years, the newer professional guidelines and empiric data that's evolved are demonstrating a more context-based assessment of when to offer predictive testing during childhood," says Ormond. "This paper demonstrates the challenges medical professionals face in trying to weigh the context issues."

Reference

Fenwick A, Plantingna M, Dheensa S, Lucassen A. 2016. Predictive genetic testing of children for adult-onset conditions: Negotiating requests with parents. J Genet Couns Sep 28. [ePub ahead of print].

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IN THIS ISSUE

QUALITY OF LIFE EXAMINED AMONG FAMILIES AFFECTED BY ROBIN SEQUENCE

Health-related quality of life (HRQoL) in children with Robin sequence (RS) is comparable to a Dutch norm population, write Basart et al (p. 54, DOI: 10.1002/ajmg.a.37968). The disorder involves an undersized jaw and upper-airway obstruction caused by downward displacement or retraction of the tongue, with or without a cleft palate.

In this issue, the researchers report results of a patient-reported outcome (PRO) study involving online questionnaires answered by 102 Dutch children with RS and their parents. Questionnaires asked about differences in HRQoL depending on treatment, whether children have isolated or syndromic RS, consequences of facial appearance, and parental distress.

On HRQoL measures, children with RS scored similarly to the Dutch norm population. There was no marked difference in HRQoL between children with syndromic and isolated forms of the disease, especially regarding satisfaction with their appearance.

However, children with RS ages 5 and younger scored lower on lung function, sleep, motor functioning, and communication. Their perception of physical functioning was better than the Dutch norm population among children ages 6–7 and 13–18. School performance was lower among the children with RS ages 6–12, but emotional functioning was higher among teens with RS.

On average, the HRQoL of children with RS and their parents was comparable with the HRQoL of norm groups. However, parental distress was higher among parents of children with syndromic forms of the disease. The researchers suggest that larger studies are needed to more reliably compare PROs among patients enrolled in various treatments and to incorporate PROs in guidelines that physicians can use to achieve optimal patient care.

SYMPTOMS, CONCERNS OF NF1 PATIENTS WITH PLEXIFORM NEUROFIBROMAS ASSESSED

In this issue, Lai et al (p. 79, DOI: 10.1002/ajmg.a.37987) report on a conceptual framework they developed to better understand and assess the symptoms and concerns of patients with neurofibromatosis type 1 (NF1) plexiform neurofibromas (pNFs) and their effect on patients' quality of life (QOL). The qualitative study aimed to identify the most important treatment outcomes based on the perspectives of patients, families, and clinicians.

In all, eight clinicians, 31 patients, and 17 parents of patients ages 5–17 participated in semi-structured interviews about the disorder's affect on QOL. Researchers analyzed data using an iterative coding procedure that tabulated the frequency with which participants mentioned symptoms and concerns and assessed the importance of them.

The most frequently reported concerns raised by patients across all age groups were pain, appearance and disfigurement, social activity participation, stigma, and anxiety. For parents, physical functioning was the primary concern, followed by pain, social activity participation, appearance and disfigurement, and social relationships.

The resulting conceptual framework includes five domains representing the most important identified symptoms and concerns, including pain, social functioning, physical function impact, stigma, and emotional distress. Lai and colleagues note that their research might help identify symptoms of the disorder that merit referrals to clinicians.

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA CHARTS DETAIL POOR GROWTH

In this issue, Duker et al (p. 108, DOI: 10.1002/ajmg.a.37961) present growth charts for children with rhizomelic chondrodysplasia punctata (RCDP) that can be used to help parents and physicians set expectations and choose optimal feeding interventions for patients with RCDP.

RCDP is a class of peroxisomal disorders characterized by defective plasmalogen biosynthesis. It is caused by autosomal recessive inheritance in five genes and involves several medical and developmental issues, especially postnatal bone growth failure. The severity of bone growth problems correspond with the degree of plasmalogen deficiency, the researchers note.

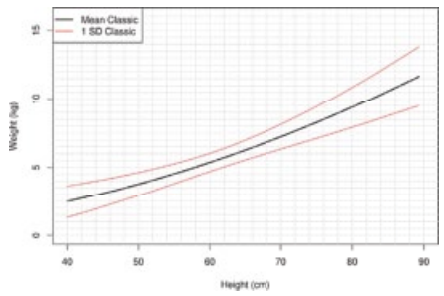

Figure 1. Weight for height chart for children with classic RCDP. Classic data are from individuals <0.05 for C18:0 DMA/C18:0 fatty acid.

In their study, Duker and colleagues provide the first detailed growth curves for length, weight, and head circumference for infants through children up to age 12 affected by RCDP. The researchers derived their charts using retrospective data from 23 individuals with RCDP types 1 and 2 and stratified growth curves by age and plasmalogen level.

Children with classic RCDP were universally microcephalic, with effectively no head circumference growth after age 3, the charts show. The charts also reveal marked growth restriction throughout the lifespan for all children with RCDP. However, children with higher plasmalogen levels, dubbed as non-classic RCDP, grew more than patients with lower levels who were associated with the classic RCDP phenotype.

Although measurable lengths were less than typical and affected by contractures, children's linear growth was more robust than their weight gain. For children ages 3–12 with the classic form of the disease, weight-for-age grids show a lack of meaningful weight gain over any 12-month period. For these classic RCDP patients, weight gain was no more than 1–2 grams per day after age 3. For infants with classic RCDP, expected weight gain dramatically dropped after the first few months of life.

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