VIEWPOINT

NEXT GENERATION NEUROLOGY

Neurologist Comfort in the Use of Next-Generation Sequencing Diagnostics

Current State and Future Prospects

Guy Helman, BS
Department of Neurology, Children's National Medical Center, Washington, DC; and Center for Genetic Medicine Research, Children's National Medical Center, Washington, DC.

Joshua L. Bonkowsky, MD, PhD
Department of Pediatrics, University of Utah School of Medicine, Salt Lake City.

Adeline Vanderver, MD
Department of Neurology, Children's National Medical Center, Washington, DC; and Center for Genetic Medicine Research, Children's National Medical Center, Washington, DC.

Corresponding Author: Adeline Vanderver, MD, Pediatrics and Integrated Systems Biology, Center for Genetic Medicine Research, Children's National Health System, 111 Michigan Ave NW, Washington, DC 20010 (avanderver@childrensnational.org).

Rare diseases are an increasingly recognized source of health problems worldwide, affecting personal and community health and a creating a substantial financial burden. Although rare individually, rare disorders as a group are common, affecting 350 million people worldwide, and approximately 1 in 10 individuals in the United States.[1] Next-generation sequencing (NGS)–based approaches have improved the recognition of rare diseases and facilitated diagnostic yield of their testing.

Neurological disorders account for a substantial portion of undiagnosed diseases.[2] Studies support the early use of NGS in diagnosing unexplained neurological diseases, demonstrating improved yield, lower costs, and shorter time to diagnosis.[1,2] Rapidly achieving a diagnosis is important, allowing clinicians and families to focus on delivering clinical care rather than engaging in a prolonged diagnostic odyssey. Furthermore, even for conditions without curative therapies, identification of a specific diagnosis can lead to improved care, as has been demonstrated for disorders as varied as multiple sclerosis, cystic fibrosis, sickle cell hemoglobinopathy, and urea cycle disorders.[3] For these reasons, use of NGS, particularly for childhood neurological disorders, could offer substantial benefits of opportunity for shortened diagnostic odyssey, improved care, and, in some instances, early institution of therapy.

However, the adoption of NGS has been limited and is only used broadly at a few centers. We sought to identify why NGS is not more broadly used by pediatric neurologists. An anonymous survey of members of the Child Neurology Society, which includes most pediatric neurologists in the United States, was performed to assess frequency of use and identify barriers in implementation of NGS and presented at the 2015 Child Neurology Society Annual Meeting.[4] The survey consisted of 13 questions, requiring approximately 5 minutes for completion, and was maintained in a REDCap database. The questions posed and responses are listed in the **Table**.[4]

Sixty-seven respondents with more than 1100 years of cumulative clinical experience provided responses to the survey questions. Clinicians reported seeing an average of 9 undiagnosed cases per month. Thirty-eight percent of clinicians reported finding a diagnosis in more than 50% of the patients they evaluate by any method. Fifty-six percent of the clinicians reported considering NGS in half of the patients they see clinically. Only 29% of respondents reported that patient families had requested NGS. Sixty-seven percent of respondents reported that they often did not pursue NGS owing to difficulties in obtaining insurance coverage, and 71% reported that they had pursued NGS on a research basis owing to the difficulties in obtaining clinical insurance coverage. Most clinicians (86%) reported that about 20% of the time, reliable diagnostic answers are found for patients through NGS. Next-generation sequencing findings led to changes in care management in 55% of cases.

The survey results suggest that lack of insurance coverage is a major impediment to more widespread adoption of NGS.[4] Furthermore, the survey suggests that clinical care can be affected by NGS results, similar to what has been previously published.[1,2] Other potential barriers to the clinical deployment of NGS testing in the clinic include the potential for lack of clinician familiarity, the complexity and unclear significance of some results, and difficulties in managing identification of unrelated genetic disorders or risks.[5]

Next-generation sequencing now falls within the same range of cost as other standard diagnostic approaches for rare disorders, including tissue pathology studies, radiologic imaging studies, biochemical testing, or targeted gene sequencing, with the promise of a substantial amount of relevant data.[6] Furthermore, only about 2000 of 7000 rare genetic diseases have clinically available molecular testing and even fewer have biochemical or enzymatic testing.[6] Agnostic NGS can help bridge this substantial diagnostic gap. Additionally, concerns regarding the potential effect of incidental findings have been in part alleviated by studies within the past 5 years.[7]

The compelling diagnostic efficacy of NGS, decrease in length of time to diagnosis,[1] and the low risk of incidental findings[7] support the use of NGS diagnostic approaches to be the standard of care for diagnosis in rare disease. However, it has not yet been demonstrated whether NGS-identified diagnoses will change clinical care outcomes. The data presented by Helman et al[4] suggest that current barriers to implementation of NGS in the clinical setting include perceived inability to obtain insurance coverage and lack of clinician familiarity. These findings and our survey underscore the need for the development of standard guidelines for the use of NGS in pediatric neurology.

Table. Survey Questions and Results

Examples of Questions	No. (%)		
	Cumulative Value From All Respondents	Average Value[a]	Respondents Answering Yes, %
How many years have you spent in clinical practice?	1105[a]	~16.5	NA
How many patients with undiagnosed rare conditions do you see per month?	596[a]	~9 patients	NA
How often do you think you make a diagnosis currently?	>50	38	NA
	>30	3	NA
	>20	68	NA
How often do you consider whole-exome sequencing in the diagnosis of these patients?	>50	56	NA
	>30	59	NA
	>20	64	NA
In what percentage of cases do you get this covered by insurance?	>50	41	NA
	>30	44	NA
	>20	50	NA
In what percentage do you do it on a research basis?	>50	17	NA
	>30	18	NA
Is this because you cannot get clinical coverage?	NA	NA	71
Do you not order this because of the difficulty in obtaining approval?	NA	NA	67
Do your patients and patient's families request whole-exome sequencing?	NA	NA	29
How often have you needed to do other testing (not including Sanger sequencing confirmation) to validate a whole-exome sequencing diagnosis?	>50	29	NA
	>30	40	NA
	>20	51	NA
In what percentage of cases do you think whole-exome sequencing provides an answer?	>50	19	NA
	>30	49	NA
	>20	86	NA
In how many cases have whole-exome sequencing results led to a change in management?	NA	NA	55
Have you ever used whole-genome sequencing?	NA	NA	40

Abbreviation: NA, not applicable.

[a] Average value based on total number provided by respondents and number of respondents.

ARTICLE INFORMATION

Published Online: April 4, 2016. doi:10.1001/jamaneurol.2016.0168.

Conflict of Interest Disclosures: All authors are members of the Global Leukodystrophy Initiative Consortium. Dr Vanderver receives support from Illumina Inc for in kind donations of sequencing for clinical patients.

Funding/Support: Mr Helman and Dr Vanderver are supported by the Myelin Disorders Bioregistry Project. Mr Helman was supported by the Delman Fund for Pediatric Neurology Education.

Role of the Funder/Sponsor: The Myelin Disorders Bioregistry Project and the Delman Fund for Pediatric Neurology Education had no role in the preparation, review, or approval of the manuscript and decision to submit the manuscript for publication. Ryan J. Taft, PhD (Illumina Inc), provided comments on the manuscript, but had no role in the preparation or approval of the manuscript and decision to submit the manuscript for publication.

Additional Contributions: We thank the members of the Child Neurology Society for their participation. We also thank Ryan J. Taft, PhD (Illumina Inc), Amy Pizzino, MS CGC (Children's National Medical Center), and Florian Eichler, MD (Massachusetts General Hospital), for their advice, comments on the manuscript, and contributions to the survey design. They were not compensated for their work.

Submissions: This Viewpoint is one in a series of Next Generation Neurology Viewpoints emphasizing innovative original concepts and approaches to understanding the causation of neurological disease and providing new and effective therapies. We welcome the submission of Viewpoints that incorporate these objectives.

REFERENCES

1. Richards J, Korgenski EK, Srivastava R, Bonkowsky JL. Costs of the diagnostic odyssey in children with inherited leukodystrophies. *Neurology*. 2015;85(13):1167-1170.

2. Gahl WA, Markello TC, Toro C, et al. The National Institutes of Health Undiagnosed Diseases Program: insights into rare diseases. *Genet Med*. 2012;14(1):51-59.

3. Van Haren K, Bonkowsky JL, Bernard G, et al. Consensus statement on preventive and symptomatic care of leukodystrophy patients. *Mol Genet Metab*. 2014.

4. Helman G, Taft R, Bonkowsky J, Eichler F, Pizzino A, Vanderver A. Pediatric neurologist use of next-generation sequencing diagnostics: current state and future prospects. Paper presented at: 44th National Meeting of the Child Neurology Society; October 9, 2015; National Harbor, Maryland.

5. McGowan ML, Glinka A, Highland J, Asaad G, Sharp RR. Genetics patients' perspectives on clinical genomic testing. *Per Med*. 2013;10(4):339-347.

6. Boyd SD, Galli SJ, Schrijver I, Zehnder JL, Ashley EA, Merker JD. A balanced look at the implications of genomic (and other "omics") testing for disease diagnosis and clinical care. *Genes (Basel)*. 2014;5(3):748-766.

7. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014;312(18):1880-1887.