HHS Public Access

Author manuscript

Am J Obstet Gynecol. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

Am J Obstet Gynecol. 2022 February ; 226(2): 277. doi:10.1016/j.ajog.2021.09.039.

Response to "Further genetic testing in prenatal cases of nonimmune hydrops fetalis with a normal array: a targeted panel or exome?"

Mary E. Norton, MD, **Teresa N. Sparks, MD, MAS**

Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Francisco, Box 0132, 490 Illinois St., 10th Floor, San Francisco, CA

Thank you for your interest in our article, in which we compared the diagnostic yield of exome sequencing with the simulated application of commercial targeted gene panels in 127 fetuses with nonimmune hydrops fetalis (NIHF).[1] We agree that in some cases, concurrent anomalies can give a clue about a genetic diagnosis that might be adequately assessed using a targeted gene panel. However, as you note, NIHF is a nonspecific finding, and the full phenotype of some associated genetic conditions is not completely elucidated; this makes the selection of the appropriate targeted panel more difficult. For example, early in gestation, a fetus that is small with shortened long bones may not be easily categorized as affected with a skeletal dysplasia vs another type of genetic syndrome that may also present with shortened long bones. Likewise, a fetus with elevated peak systolic velocity in the middle cerebral artery may be affected with a broad spectrum of disorders; this sonographic finding is not specific for fetal anemia. The use of targeted panels further limits the discovery of additional genes associated with fetal phenotypes and of the unique fetal features of genetic diseases. Although you note that targeted gene panels have the advantages of a higher depth of sequencing, a shorter turnaround time, fewer uncertain variants, and a relatively lower cost, we did not find these purported benefits to be consistently present. Our exome sequencing had adequate depth of all the relevant exons on the commercial panels, with a mean depth of sequencing of 135× and a minimum depth of 30×. The turnaround times for targeted gene panels and STAT exome sequencing are similar; they are on the order of 2 to 4 weeks. Although the rates of uncertain variants in commercial laboratories was not clearly reported, rates as high as 58.1% have been published based on commercial hydrops panels,[2] compared with 9% in our exome cases. Finally, although targeted panels are less expensive on average, there was an overlap in the cost, with some targeted panels costing more than exome sequencing. Even though we agree that the prognosis of NIHF in general is guarded, providing a precise genetic diagnosis can guide pre- and postnatal treatment, whether that includes more specific interventions or the redirection of care. At the end of the day, making a diagnosis is what is most important for the families when faced with these complex pregnancies.

Mary.Norton@ucsf.edu .

Acknowledgments

M.E.N has received research funding from Natera and is a consultant for Invitae. The other author reports no conflict of interest.

This study was supported by the University of California San Francisco (UCSF) Center for Maternal-Fetal Precision Medicine, the Brianna Marie Foundation in collaboration with the Fetal Health Foundation, Ultragenyx (for studies conducted through the UCSF Center for Maternal-Fetal Precision Medicine), and grants (5K12HD001262-18, supporting T.N.S., and U01HG009599, to M.E.N.) from the National Institutes of Health. The funding sources had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

REFERENCES

1. Norton ME, Ziffle JV, Lianoglou BR, Hodoglugil U, Patrick Devine W, Sparks TN. Exome sequencing vs targeted gene panels for the evaluation of nonimmune hydrops fetalis. Am J Obstet Gynecol 2021. [Epub ahead of print].
2. Leach NT, Wilson Mathews DR, Rosenblum LS, Zhou Z, Zhu H, Heim RA. Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions. Genet Med 2019;21:417–25. [PubMed: 29907801]