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

TO THE EDITORS: The pathogenesis of nonimmune hydrops fetalis (NIHF), a severe fetal condition defined as abnormal fluid collection within the fetal extravascular compartments and body cavities, is incompletely understood. The causes can be structural, hematologic, chromosomal, infectious, syndromic, or idiopathic. With the advances in genetic technologies, exome sequencing is being increasingly used in prenatal settings. The question that now arises is what is the preferable approach for unexplained NIHF: a targeted panel or an exome?

A recent article by Norton et al\(^2\) compared the diagnostic yield of exome sequencing with the simulated application of commercial targeted gene panels in 127 NIHF fetuses. Exome sequencing identified a (likely) pathogenic variant in 37 of 127 (29%) cases in a total of 29 genes, whereas the use of 64 available targeted gene panels would have detected a (likely) pathogenic variant in 11% to 62% of the same 37 cases that received a genetic diagnosis with exome sequencing. The authors concluded that exome sequencing for NIHF is a superior alternative to targeted gene panel testing. However, although fetal hydropic changes are nonspecific features, some concurrent anomalies may give a clue to a genetic condition. For example, thanatophoric dysplasia (Case H034) has a specific sonographic phenotype of micromelia and a small thorax, which is suitable for a skeletal dysplasia panel or even a targeted FGFR3 sequencing. Chandler et al\(^3\) reported that definitive molecular diagnosis was made in 81% of prenatal cases, where a multidisciplinary review considered skeletal dysplasia as a likely etiology, using a 240-gene panel related to skeletal dysplasias. Another group of NIHF caused by fetal anemia has a specific abnormal Doppler with an increased peak velocity of systolic blood flow in the middle cerebral artery.\(^4\) These cases may be suitable for a congenital anemia panel (Laboratory 3). Targeted gene panels are ideal for analyzing limited variants that have suspected associations with diseases at a much higher depth, a shorter turnaround time, fewer uncertain variants, and a relatively lower cost.

NIHF is an end-stage status of a variety of fetal conditions and by itself constitutes a poor prognostic factor for any particular disorder. Exome sequencing, combined with other investigative approaches, including autopsy (Figure), is used in NIHF cases to inform prognosis and establish the recurrence risk. For most cases, a multidisciplinary team is required so that the family can receive comprehensive messages and optimal management. It is important to relay to parents that most of the time a birth does not mean survival, even with extensive resuscitation.

The authors report no conflict of interest.

This study did not receive any funding.

REFERENCES

---

**FIGURE**

Diagnostic workup of nonimmune hydrops fetalis

(Explaned nonimmune hydrops fetalis) Detailed ultrasound + echocardiogram Maternal syphilis serology Karyotype/microarray

Anemic (middle cerebral artery-peak systolic velocity >1.5MoM)/specific features indicative of genetic conditions

Only hydropic changes with/without nonspecific features

Targeted gene panels

Exome sequencing

Neonatal extensive examination/autopsy

MoM, multiple of median.

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

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 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
Mary.Norton@ucsf.edu

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 (SK12HD001262-18, 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