Genetics inMedicine | CORRESPONDENCE

Open

Inaccuracies and shortcomings in "Adherence of cell-free DNA noninvasive prenatal screens to ACMG recommendations"

To the Editor:

We applaud efforts to ensure that patients and providers receive reliable noninvasive prenatal screening (NIPS) results, but several of the findings of Skotko et al.,[1] which purported to analyze laboratory adherence to American College of Medical Genetics and Genomics (ACMG) recommendations for reporting NIPS results, are inaccurate or misleading, and its methods of verifying the information collected or understanding perceived inconsistencies with ACMG recommendations were lacking.

We cite three examples regarding Prelude (now Prequel, Myriad Women's Health [MWH]) that demonstrate inaccurate or misleading results. First, the authors reported that Prelude only partially adhered or had little to no adherence to ACMG recommendations 1 and 8, which suggest that laboratories clearly state detection rate (DR), specificity (SPEC), positive predictive value (PPV) (patient-specific), and negative predictive value (NPV) for the common aneuploidies in pretest marketing materials and on reports. This conclusion is incorrect. The Prelude test report has included individualized PPV and NPV (in the form of residual risk) since 2015, and sensitivity (SENS) and SPEC are stated on every report. SENS and SPEC also are included in pretest marketing materials, but PPV and NPV are not because these values are not accurate without specific patient characteristics such as maternal age and gestational age.

Second, the authors report little to no adherence to ACMG recommendation 7, which suggests that reports include DR, SPEC, PPV, and NPV for each copy-number variant (CNV) screened. This conclusion is misleading because the current state of the clinical data limit the ability to report such values for CNVs. Analytical validation data have the potential to overstate test performance in the clinical population, especially for conditions of low prevalence. We therefore do not believe it is clinically practical or responsible to include these data on the report at the present time. Rather, the Prequel report clearly notes that clinical data are currently insufficient to report PPV, NPV, SENS, and SPEC for CNVs.

Third, the authors report only partial adherence to the ACMG comment that laboratories meet the needs of providers and patients by delivering meaningful reports, engaging in education, and identifying ways to address distributive justice. The authors acknowledge "the absence of explicit benchmarks for this multifaceted comment," but then used their own benchmarks to evaluate commercial laboratories. Given the lack of specificity in ACMG's comment, it is unsurprising that the authors concluded that "[n]o laboratory fully met […or] completely failed to meet it." Though the ACMG comment is vague, we note that Prelude adheres quite strongly to the authors' benchmarks. For example, our patient and provider portals include a full suite of pre- and post-test educational materials, including some developed by the organizations mentioned in Skotko et al. MWH also provides patients and providers access to consultations with board-certified genetic counselors to explain test results at no additional charge. We have shared our experience delivering pretest education and post-test genetic consultation for NIPS via national and international conferences and in a peer-reviewed study.[2]

The authors state that they made concerted efforts to obtain all available information from each assessed laboratory. Yet, to our knowledge, no one at our laboratory was contacted to provide information about where the authors could find the information they were seeking, nor does the study's "Materials and Methods" section mention any effort to contact laboratories. The authors also did not access patient and provider portals that may contain additional interpretive and educational information. Accurate laboratory ratings require thorough investigation of all of the available resources. We also find it insufficient to simply list the materials used to make ratings and call on the authors to publish or provide links to the materials themselves. Further, it is unclear why health-system and academic laboratories offering NIPS, including those with which the authors are affiliated, were not subjected to the same evaluation.

The authors state that they do not know why some laboratories do not appear to follow the ACMG recommendations, yet also say that they are aware that some of the recommendations are out of date and do not make sense. In contrast to an incomplete snapshot of laboratories at one point in time, an examination of why laboratories do not follow certain recommendations would better educate providers and patients about NIPS testing and reporting and would be valuable for informing future recommendations for laboratories. Additionally, we have concerns about the ongoing accuracy of the information in the study. The published table is already outdated as the data were collected 15 months ago. The authors report that they plan to keep an updated version of the table on a website, yet this publication will live indefinitely in its current form in *Genetics in Medicine*, with readers potentially unaware that corrected results are (hopefully) maintained elsewhere until (and if) they reach the second-to-last paragraph of the paper.

Submitted 24 April 2019; accepted: 16 May 2019
Published online: 3 June 2019

We believe that the authors intended for this study to promote patient access to high quality NIPS, but we fear that it will have the opposite effect. It gives the false impression that patients and providers should not trust the results they receive. MWH takes laboratory quality very seriously. Our laboratory is CLIA-certified, College of American Pathologists–accredited, and New York State–approved for NIPS results. We have engaged providers and patients to ensure that our reports are closely aligned with guidelines and are as informative as possible, and we will continue these efforts. The commercial laboratory industry processes hundreds of thousands of NIPS tests annually, and without it, access to NIPS, and the extremely valuable information it provides to patients about the health of their pregnancies, will suffer.

We encourage the authors to undertake a more thorough assessment that includes interviewing laboratories to verify collected information and to understand why they may not be following every ACMG recommendation, requesting access to portals that may contain additional information, and subjecting health-system and academic laboratories to the same scrutiny. We also urge the ACMG to revisit its recommendations to identify and update those that are out of date or no longer valid.

DISCLOSURE

All authors are employees of Myriad Women's Health, which markets a noninvasive prenatal screening test.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Katherine Johansen Taber, PhD[1], *Carrie Haverty, MS, CGC*[1], *Susan Hancock, MS, CGC*[1] *and James Goldberg, MD*[1]

[1]Myriad Women's Health, South San Francisco, CA, USA. Correspondence: Katherine Johansen Taber (mwh_research@myriad.com)

REFERENCES

1. Skotko BG, Allyse MA, Bajaj K, Best RG, Klugman S, et al. Adherence of cell-free DNA noninvasive prenatal screens to ACMG recommendations. Genet Med. 2019. https://doi.org/10.1038/s41436-019-0485-2 [Epub ahead of print].
2. Arjunan A, Ben-Shachar R, Kostialik J, Johansen Taber KA, Lazarin GA, et al. Technology-driven noninvasive prenatal screening results disclosure and management. Telemed J E Health. 2019. https://doi.org/10.1089/tmj.2018.0253 [Epub ahead of print].

Advance online publication 3 June 2019. doi:10.1038/s41436-019-0555-5