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A flawed challenge but valid recommendation: a response to Takoudes and Hamar

We were interested in the recent article by Takoudes and Hamar[1]. They describe a sample challenge distributed to five commercial laboratories offering cell-free DNA (cfDNA) testing of maternal plasma to identify fetal chromosomal abnormalities (often referred to as non-invasive prenatal testing or NIPT). Their stated goal was to assess the reliability of NIPT. To accomplish this, they submitted non-pregnancy samples and attested that the samples were from a woman with a 12-week pregnancy.

Maternal plasma from pregnant women at 10 weeks' gestation (a general laboratory requirement) has some measurable level of circulating fetal/placental DNA. None of these laboratory-developed tests (LDTs) has been designed specifically to detect 'non-pregnancy' samples. This challenge differs from previous *ad-hoc* challenges. For example, the Government Accounting Office challenged four laboratories offering nutrigenomic tests for complex diseases with appropriate samples but with fictitious family histories[2]. They directly challenged the tests' clinical validity and found the interpretations to be 'medically unproven and so ambiguous that they do not provide meaningful information to consumers'. In contrast, the challenges by Takoudes and Hamar are not directed at clinical validity, but instead challenge the ability of the LDTs to detect an inappropriate sample. As such, the authors should interpret their results with caution. We believe the best course of action would have involved communication with the laboratories.

In our opinion, the data supplied by Takoudes and Hamar do not provide evidence that there would be discrepancies among these laboratories when the tests are used for their intended purpose. Nor have the authors provided evidence that the fetal fraction estimates in pregnancy samples differ among laboratories. Rather, this contrived study indicates that a non-pregnancy sample will not be identified by any of the laboratories. This study demonstrates the importance of providing a clinical indication for testing and an appropriate sample type to laboratories, to help ensure proper interpretation. Whether determining fetal fraction is a necessary component of testing is still an open question. As the authors admit, these tests, as they are currently configured, have demonstrated accurate performance in both the research and clinical settings[3,4].

Among the currently available cfDNA tests for aneuploidy, no two are alike. They either quantify the fetal fraction present in maternal plasma using different methodologies or have methods that do not rely on quantification of fetal fraction. When laboratories use appropriate plasma samples from pregnant women, these fetal fractions are roughly equivalent, as demonstrated by the average levels reported for control pregnancies of between 10% and 12%, independent of methodology.

We agree with the authors' recommendation to develop and enforce appropriate quality guidelines for laboratories performing cfDNA testing of maternal plasma. Towards that end, the College of American Pathologists (CAP) instituted general next-generation sequencing requirements in 2011, with additional requirements focused on cfDNA testing for aneuploidy implemented in the summer of 2012. All five of the participating laboratories are presumably CAP accredited and subject to these guidelines. We also believe that external proficiency testing using an appropriate sample type is needed for ongoing oversight of laboratories performing these widely used tests.

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