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New York Times
620 Eighth Avenue,
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RE: Response to New York Times Article "When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong."

The recent article "When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong" co-authored by Sara Kliff and Aatish Bhatia is misleading at best and mis-informed, mis-guided and sensationalistic at worst. At its core, the article points out the well-known limitations of all medical screening (which by definition leads to results that can be true positive, true negative, false positive or false negative). But at its worst, the article is inflammatory and will lead to an unwarranted backlash against the thoughtful utilization of a break-through medical technology that has the potential for improving pregnancy health for women and families in the present and in the future.

Firstly, the authors misconstrue the concepts of positive predictive value (PPV) and "accuracy" which we will call "sensitivity" for the purposes of this discussion. It is a well-established statistical fact that "rare" conditions with low prevalence will have a lower PPV than "common" conditions with a higher prevalence. However, one needs to take into account not just the prevalence of any one given condition but also the aggregate prevalence of ALL the conditions that one is screening for. Researchers have repeatedly suggested that the prevalence of microdeletion syndromes in the general population is approximately 1% of all births (and their relative frequency is even higher in younger women than genetic conditions such as trisomy 21 Down syndrome). Thus, one should not calculate the PPV for any one specific rare condition but rather one should calculate the PPV for all deletion syndromes combined (acknowledging that maintaining high specificity is always relevant to keeping the false positive rate as low as possible). The authors blatantly fail to report that the PPV for traditional screening strategies such as second trimester serum protein screening or maternal age is much lower than the PPV for cell free DNA technology (whether for trisomy screening or deletion screening). In the past, for every two times the old tests were right, the tests were wrong 98 times (a much lower performance than modern cell free DNA screening).

Secondly, the authors fail to recognize and acknowledge that these cell-free DNA screening tests are simply that… they are screening tests and not diagnostic tests. Screening tests

cannot be “wrong” per se; all screening tests will have false positive rates; this will always be true whether one is discussing the relative merits of screening for diabetes in pregnancy, iron deficiency anemia in pregnancy, ultrasound usage in pregnancy, or fetal genetic conditions. It is only through thoughtful and nuanced pretest education, guidance and counseling that patients and families can be informed of the potential benefits and any potential risks of these and any other screening tests that are performed during pregnancy.

Thirdly, the authors fail to acknowledge that DNA/genetic anomalies frequently contribute to significant morbidity and mortality in children and lead to significant healthcare expenditures. This type of prenatal genetic screening is NOT akin to screening for rare cancers in children (such as breast cancer) as discussed in the article; the various genetic/DNA disorders that these tests aim to screen for result in more infant mortality than any other single medical condition! Thus, screening for genetic abnormalities is warranted from both an ethical and health care cost perspective.

Fourthly, the authors seem to be suggesting that patients and obstetricians are using these tools solely for the purpose of providing abortion care. The American College of Obstetricians and Gynecologists has published strict guidance that abortions should not be performed based solely on the results of these blood screenings. While some pregnant patients may choose to terminate a pregnancy for various personal reasons, many others will use their prenatal test results to guide the decision making and clinical care of their obstetricians and pediatricians (similar to how newborn blood biochemical screening guides the provision of pediatric care for pediatricians). No one is shouting from the media that newborn biochemical screening for rare genetic disorders is problematic and “bad” because of the false positives that occur during THAT medical screening process. If anything, the opposite is true as there is a growing paradigm that genetic screening of certain ill newborns might be beneficial for the care of medically fragile children to more efficiently make an accurate and timely diagnosis, create a treatment plan and determine if any recurrence risk exists for future pregnancies.

Fifthly, the article demeans the intelligence of individual women and clinicians who understand that certain screenings such as prenatal genetic tests, pap smears and mammograms carry uncertainties and the potential for false positives that can lead to various medical interventions. Obstetricians engage with women and trust women to make careful, nuanced healthcare decision that reflect their values and balance the risks and benefits of complex healthcare decisions.

Sixthly, the authors egregiously fail to report that the largest prospective published dataset assessing the outcomes of more than 80,000 USA patients who underwent prenatal screening for sub-chromosomal abnormalities (published in the official journal of the American College of Medical Genetics in 2021) noted a PPV of >70% for clinically relevant deletions and duplications; a similar publication was released from Europe in 2019 and

described a PPV of > 30% for similar DNA anomalies. Numerous other similar articles are available for review in the published literature.

Finally, the authors inappropriately suggest that the utilization of this break-through technology is primarily being driven by the monetary greed of “corporate America”. Acknowledging that health care is “big business” in the USA does nothing to diminish the well-established fact that diagnostic error (aka failure to make a timely and accurate diagnosis and communicate that information to the patient as per the Institute of Medicine 2015 report entitled “Improving Diagnosis in Healthcare”) is a prevalent and thorny problem in modern healthcare. The thoughtful application of modern science will guide us in our goal to improve diagnostic accuracy, improve healthcare delivery, optimize health outcomes and reduce health disparities for our citizens; this technology is one more tool to be carefully and thoughtfully applied in that process.

Respectfully,

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