REPLY

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We thank Xu et al for their interest in our paper and their support of our opinion that noninvasive prenatal screening (NIPS) will miss some pathogenic copy number variants (pCNVs), especially those <5 Mb, in high-risk pregnancies that chromosomal microarray can detect.[1] Figure 1 illustrates the frequency of pCNV detected relative to aberration size and potentially what NIPS would miss.

The decision on whether to screen for pCNVs in all pregnancies is multifactorial. The direct extrapolation of incidence rates from enriched high-risk populations in the meta-analysis to the general population can be misleading. First, only 35.6% of women at high risk are positive for aneuploidy screening test and accounted for only 14% of cases with pCNV. The majority of cases (83.3%) were, however, referred for abnormal ultrasound or family history.[1]

Second, the clinical utility of NIPS for pCNVs in all pregnancies as opposed to targeted testing based on presence of ultrasound abnormalities, high-risk down screening test or family history can be assessed only by a population-wide assessment. All women, however, would have to undergo a diagnostic procedure with its potential procedure-related associated risks to determine NIPS performance. Any such study would be both expensive and questionable because NIPS for pCNVs does not have the same false-positive rate and detection rate as NIPS for trisomy 21 screening.

At best if we assume that pregnancies referred by maternal anxiety are representative of the general population, then the incidence rate of pCNV would be 0.5% based on our meta-analysis. This incidence rate would be similar to 0.43% and 0.76% reported by others.[2,3] Among the 18 pCNVs identified in these pregnancies, 15 were <5 Mb and thus are potentially not identifiable with standard NIPS.

Xu and colleagues would be aware that increasing read depths are required because the size of the pCNV to be detected decreases and the scope of the pCNVs of interest increases. These are all factors that can influence costs as well as can have a direct impact on the detection rate, specificity, and test positive predictive values. Xu and colleagues are currently assuming that NIPS would be able to detect pCNVs present, irrespective of their aberration size, in other words, that NIPS for pCNVs in all pregnancies will have close to 100% sensitivity and specificity. Notwithstanding, a recent study on expanded NIPS panels including the most common microdeletion syndromes would still miss almost half of the abnormal findings (47.4%).[2]

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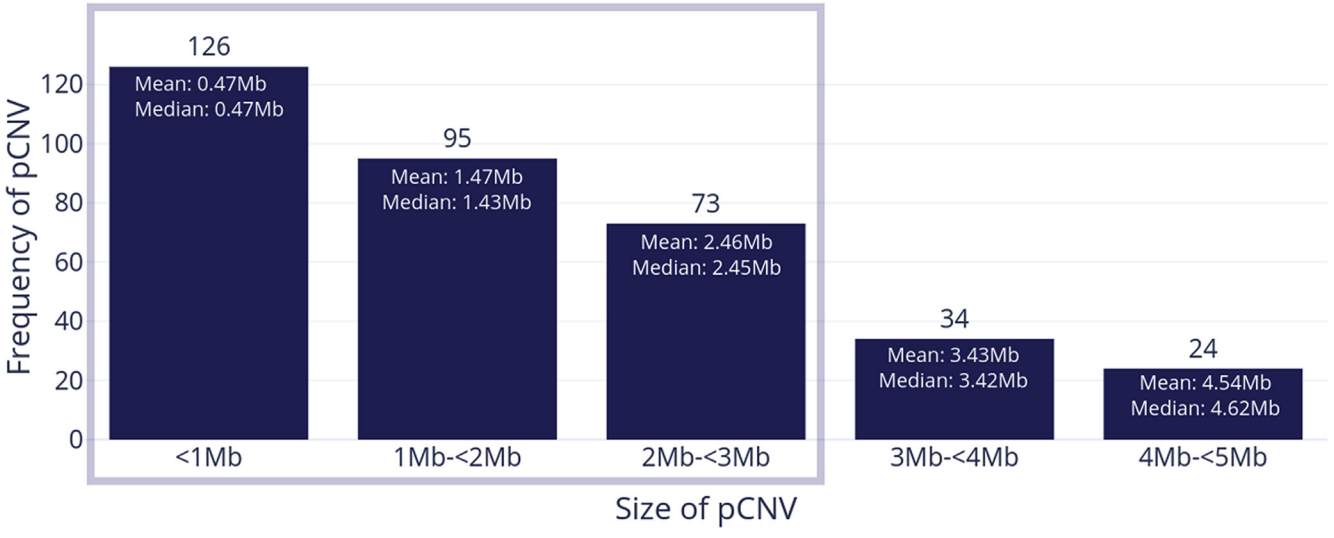
FIGURE 1

The size characteristics of 352 pathogenic copy number variants (pCNVs) of <5Mb in size detected in 23,385 fetuses undergoing invasive prenatal testing with chromosomal microarray analysis, stratified into 1Mb bins. This data illustrates even current high-resolution NIPS panels claiming a genome-wide resolution as high as 3Mb would still miss a vast majority of these pCNVs, highlighted in the grey box



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Unexpected term NICU admissions: a marker of obstetrical care quality?

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TO THE EDITORS: We want to comment on the terminology used to describe the study design of the recent paper, Unexpected term NICU admissions: a marker of obstetrical care quality, which analyzed data from the Consortium for Safe Labor.[1] The study abstract identifies the study as a retrospective cross-sectional study. The defining feature of cross-sectional studies is that they do not have a temporal direction (ie, retrospective, prospective, or ambidirectional). This is because they involve data collection at just 1 point in time about things that may exist in the past or present, and study eligibility is not based on whether a study outcome has already occurred.[2]

The term, retrospective cross-sectional study, is thus an oxymoron. The word retrospective lacks a consensus definition in epidemiology,[3,4] but it has been used at various times to mean the following: (1) de novo collection of exposure data after outcome occurrence; (2) the case-control study design in general; or (3) the feature of historical cohort studies that distinguishes them from other cohort studies: the temporal ordering of follow-up of exposed and unexposed individuals before initiation of research (ie, in the past).[2,4] In the current situation, we suspect that the term retrospective was intended to mean a study in which preexisting data were used to address a question not specifically envisioned at the time the data were collected.

The distinction between prospective and retrospective was clearer in the era when information on exposures and confounders was usually collected by direct interview of participants. However, it has become blurred in the present era of widely available electronic records of clinical interactions, insurance claims, vital records, environmental monitoring, etc, particularly when those records can be linked at the individual level. Therefore, in the current era, these terms "do not readily convey a clear message about the study" (page 96).[2]

Because of the substantial challenges in accurately applying study design categories to modern data resources, when study design distinctions must be made, we advocate dividing only between experimental and observational studies. Even this distinction is not simple and is vulnerable to classification error: for instance, when randomized controlled trials are analyzed for secondary purposes to study only exposures that were not randomized, they are effectively observational studies. However, focusing on this distinction might provide the most crucial information while also enabling accurate designation of study designs and, in turn, facilitate the identification of potentially important biases. ■

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