Special issue on “Feto-Maternal Genomic Medicine”: a decade of incredible advances

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In this Special Issue, we assembled a collection of articles from experts in maternal–fetal medicine, clinical genetics, and placental biology to highlight how advances in genetic sequencing have catalyzed a revolution in screening and diagnostic tools used in clinical care across pregnancy.

Genetic testing in pregnancy dates back to the 1950s with the introduction of amniocentesis, initially for determination of fetal gender and Rh status, and by the 1960s for diagnosis of Down syndrome (Sabbagh and Van den Veyver 2019). Testing evolved to include diagnostic tools available earlier in pregnancy (i.e., chorionic villus sampling (CVS) in the 1st trimester in the 1980s), and non-invasive serum screening (late 1980s through 2000 with the number of serum markers screened and gestational age at testing improving screening performance). While karyotype was the standard genetic test used for prenatal diagnosis for decades, chromosomal microarray became first line in 2012 due to its enhanced ability to detect microdeletions and duplications beyond the resolution of standard karyotype (Wapner et al. 2012). In the last decade, the introduction of massively parallel sequencing technology [i.e., next-generation sequencing (NGS)] has allowed for an accelerated course of new test development affecting the spectrum of pregnancy care, ranging from expanded carrier screening (ECS) to cell-free DNA screening (i.e., non-invasive prenatal testing (NIPT)) for fetal aneuploidy to sequencing of fetal genomes for diagnostic testing (Sabbagh and Van den Veyver 2019).

For genetic carrier screening, practice is shifting from assessing a select number of pan-ethnic and ethnicity-based

conditions to expanded carrier screening (ECS) (Sparks 2019). ECS reduces disparities in carrier detection between ethnicities and allows for detection of a much larger number of conditions. However, there is great variation between different ECS platforms, with inclusion of conditions on many that do not meet the classic criteria (i.e., common, severe, childhood-onset conditions for which genetic variants associated with the condition are well understood) for routine carrier screening.

For aneuploidy detection, massively parallel sequencing made cell-free DNA-based aneuploidy screening (i.e., NIPT) possible with greatly improved sensitivity and specificity compared to prior serum screening algorithms (Guseh 2019). NIPT has rapidly been integrated into mainstream prenatal care, with its most inherent limitation being that cell-free DNA is from the placenta (not the fetus). Beyond detection of aneuploidy, NIPT development has recently been focused on detection of copy number variants (CNVs), in particular for common microdeletion syndromes, as well as genome-wide detection of larger CNVs and a select set of single-gene disorders.

When fetal anomalies are detected prenatally and chromosomal evaluation by microarray is normal, whole exome sequencing (WES) is increasingly being used and increases diagnostic yield by 10–30% depending on the population tested (Tayoun and Mason-Suares 2019). Parental samples greatly facilitate variant calling in prenatal samples where phenotypic information is often limited, and thus most laboratories that perform prenatal exome sequencing require trio samples. Prenatal phenotypic information is essential to optimize prenatal variant calling from WES, but can be very limited compared to postnatal phenotype information (Tayoun and Mason-Suares 2019; Sabbagh and Van den Veyver 2019). Lethal fetal phenotypes are especially poorly represented in database of fetal phenotype-genotype correlations. While chromosomal microarray is the standard of care for genetic testing following a stillbirth (fetal loss ≥ 20 weeks), work examining the diagnostic yield of

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additional genetic testing, including exome sequencing, is underway (Wilkins-Haug 2020). These strategies are likely to reveal new genotype–phenotype correlations for known genetic disorders and shed light on the human “intolerome” conditions incompatible with life resulting in fetal demise.

As diagnostics improve, women with genetic diseases are increasingly becoming pregnant requiring specialized management by high-risk obstetricians and clinical geneticists (Stone and Reed 2019). In particular, pregnancies in women with inborn errors of metabolism, connective tissue disorders, and skeletal dysplasias are increasingly common and require a multidisciplinary team approach. Management guidelines for these women remain limited and consensus recommendations still guide the majority of clinical care. Thus, larger multi-institutional studies examining pregnancy courses and outcomes would be of great clinical utility.

As DNA-based diagnostics have advanced considerably, there is now a great opportunity to assess the health of the placenta both through cell-free DNA and within the placenta itself (Del Gobbo et al. 2019). While the relationship of fetal and placental aneuploidy has been investigated, the effect of other genetic alterations including CNVs and single-gene variants on placental functioning are not well understood, nor is the role of epigenetic alterations.

Taken together, a few common themes emerge across these distinct areas of reproductive genetics. (1) There is a tremendous need for genetic counseling. Genetic counselors play an essential role in pre- and post-test counseling for ECS, NIPT, diagnostic testing (including prenatal exome sequencing), as well as preimplantation or prenatal genetic testing for women with heritable genetic conditions. Given the complexities of each of these types of tests and their rapid evolution, specialized prenatal genetic counselors, as well as novel educational tools, are critical for providing information to both patients and providers about the benefits, limitations, and implications of testing. (2) Prenatal genetic tests may reveal information about maternal health. In addition to informing about risks to a potential or developing fetus, prenatal test results can have medical implications for the pregnant woman herself. For example, ECS can uncover women who are carriers of Gaucher disease, which increases the risk for Parkinson’s disease later in life. Women undergoing NIPT for fetal aneuploidy screening may learn that they have a sex chromosome aneuploidy (i.e., monosomy X or triple X) or even an undiagnosed cancer. Prenatal ultrasound anomalies may lead to a fetal genetic diagnosis which reveals an undiagnosed maternal condition, such as Noonan

syndrome or polycystic kidney disease. These diagnoses may have implications for a patient’s siblings, parents, offspring, or extended family. (3) Improved fetal phenotype-genotype databases are needed. As the postnatal pediatric phenotype of a given genetic disorder can differ significantly from the more limited prenatal phenotype (and certain genotypes that are lethal in utero may never be observed in pediatric patients), improved fetal phenotype-genotype correlations are critical for patient counseling and decision-making following a prenatal genetic diagnosis. Collectively, advances in genetic technology have revolutionized reproductive care over the last decade and challenge all of us to continually learn and adapt to this exciting and evolving landscape.

We thank all the authors who contributed to this cultivated collection of feto-maternal genomic medicine reviews, and we thank Human Genetics for highlighting this important field.

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