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Ethical considerations in prenatal testing: Genomic testing and medical uncertainty

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A B S T R A C T

Prenatal diagnostic testing has recently progressed from karyotype to routinely available chromosomal microarray, and the potential for fetal whole exome sequencing, both through invasive diagnostic testing and, in some cases, non-invasive prenatal testing. These tests bring beneficence through providing a higher diagnostic yield, often with lower risks of miscarriage than previously available testing, but also raise the question of harms related to an increase in uncertain and unknown results. Some parents-to-be report a desire to learn as much information as possible prenatally, and there may be beneficence in providing them with this information. However, the potential uncertainty these tests may create may raise anxiety and may complicate pregnancy decision-making for both patients and providers. This article reviews current prenatal technologies and the growing research on the clinical and ethical aspects of uncertainty as it relates to expanding prenatal testing options.

1. Introduction

In the past few decades prenatal diagnostic testing has progressed, from karyotype and rapid fluorescent in-situ hybridization testing, to routinely available chromosomal microarray (CMA), and the potential for whole exome sequencing (WES). With this increasing test availability and higher diagnostic yield, more detailed genetic information is available to expectant mothers and their partners than ever before. Practice guidelines have evolved to support more detailed testing in the prenatal setting [1], and in the USA, insurance and state-run screening programs are increasingly covering the cost of more detailed prenatal testing.[1] A summary of widely used genetic testing, and screening and testing, is shown in Table 1.

Some parents-to-be report a desire to learn as much information as possible prenatally, and there may be beneficence in providing them with this information [2]. The advances in test technology, increased public awareness of hereditary disease, and somewhat more affordable test prices have allowed for prenatal diagnoses not previously possible. However, this expansion in testing and screening has, in many cases, led to increased uncertainty in terms of predictive test results and their use in pregnancy decision-making for both patients and providers. Initial research on these ethical issues has been conducted [2–5], and lessons from other disciplines can be considered to guide providers in this new age of perinatal medicine.

2. History of prenatal testing

The purpose of prenatal genetic testing and screening is to provide information about the health of the fetus to prospective parents and their healthcare providers. In some cases, this is so that parents can make informed decisions about pregnancy termination when an anomaly is identified. In others, it can guide care for a pregnant patient and her neonate, and help parents be emotionally ready for a complicated delivery or neonatal course [2–4]. Other benefits of prenatal testing extend beyond the current pregnancy, and can include clarifying recurrence risk for future pregnancies and extended relatives [5]. Genetic information can be an important aspect in pregnancy decision-making processes, although these types of decisions are inherently influenced by personal factors such as beliefs, prior experience, and perceived expectations.

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[1] Services Covered by the California Prenatal Screening Program at State-Approved Prenatal Diagnosis Centers (PDCs) Decision Tree, 2016 (personal communication). Websites of major US healthcare insurers including Aetna, Blue Cross, and Kaiser Permanente report coverage for prenatal microarray in certain situations as of May 2017.

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Table 1
Categorization and description of widely used prenatal genetic tests.

Name	Screening or diagnostic	Sample for testing	Description
Prenatal analyte screening (also called "maternal serum screening" and "nuchal measurements")	Screening	Maternal blood and ultrasound	Interpretation of biochemical analysis and early ultrasound resulting in risk estimates for frequently occurring conditions such as Down syndrome and neural tube defects.
Non-invasive prenatal testing (NIPT)	Screening	Maternal blood	Analysis of circulating cell-free DNA from the placenta. Initially used for risk estimate of frequently occurring trisomies such as Down syndrome; now routinely includes fetal sex, changes in the number of X and Y chromosomes, and other smaller chromosome anomalies. Has a higher sensitivity and specificity than prenatal analyte screening, but is not considered diagnostic.
Karyotype	Diagnostic	Fetal DNA obtained via CVS or amniocentesis	Cytogenetic analysis of chromosome structures. Can detect extra or missing chromosomes (including the frequently occurring trisomies), and partial chromosome difference (missing or extra) that are as small as 5–10 Mb.
Chromosome microarray (CMA)	Diagnostic	Fetal DNA as above	More detailed chromosome analysis than karyotype. Detects smaller extra (microduplication) or missing (microdeletion) pieces of genetic information, also known as copy number variants (CNVs).
Single gene analysis	Diagnostic	Fetal DNA as above	Testing of one disease-causing gene by sequencing, (reading through the DNA), or deletion/duplication analysis (detection of tiny missing or added sections within a gene). Sometimes referred to as Next-Gen testing when both analyses are completed at the same time.
Multi-gene panel	Diagnostic	Fetal DNA as above	Similar methodology to single gene testing, but involves testing several (up to hundreds of) genes related to a single or group of conditions. Multi-gene panels having higher detection rates, but because many genes are sequenced at the same time, there is also an increased chance to detect a variant of uncertain significance (VUS).
Whole exome/genome sequencing (WES/WGS)	Diagnostic	Fetal DNA as above	Sequencing of all genes that encode proteins (WES), or all DNA (WGS) to identify variants that alter protein sequences. Identified variants must be carefully analyzed to correctly identify normal single nucleotide polymorphisms (SNPs), and possibly disease-causing genetic changes. VUS and unexpected findings are relatively frequent occurrences.

CVS, chorionic villus sampling.
More information about these tests is available at the following websites: https://geneticsupportfoundation.org/genetics-and-you/pregnancy-and-genetics/pregnancy-and-genetics-tests; https://www.obgproject.com/category/the-genome/; http://genomicseducation.net/.

Since the 1960s, karyotype analysis has been available for prenatal diagnosis, identifying alterations in the total number of chromosomes, such as Down syndrome, and structural chromosome rearrangements including visible deletions or duplications of genetic material [6]. Karyotypes may be used to evaluate a specific set of genetic conditions (primarily those that are relatively frequent and with high likelihood that a person with that genetic change will express features of it, also called 'penetrance'), and, by extension, the counseling and interpretation of karyotype results is generally straightforward. Occasionally, unexpected results are obtained through prenatal karyotype; for example, identification of a translocation in the fetus that leads to evaluation and identification of the same structural rearrangement in a parent [7]. Other uncertain scenarios include mosaic findings, such as the fetal diagnosis of 45,X/46,XY karyotype, which remain difficult for providers to counsel families about due to mixed reports on outcomes and ascertainment bias from postnatal diagnosis. Prospective reports of postnatal outcomes stemming from prenatal diagnosis has led to clarification of a more mild phenotype for 45,X/46,XY in particular [8], and to the clarification of expected phenotypes for many chromosomal mosaic disorders generally [9–11].

After the emergence of more comprehensive genetic testing in the pediatric and adult populations, similar testing methodologies were applied to prenatal testing. Chromosome microarray (CMA) detects microdeletions and microduplications of genetic material too small to be identified by conventional karyotype [1,12,13]. CMA results may include clinically significant copy number variation (CNV), variants of uncertain significance (VUS), or no detectable variants [12]. Two microarray platforms are currently used clinically: array comparative genomic hybridization (aCGH) and SNP array analysis. Array CGH compares the sample to a standard reference sequence. SNP arrays use millions of long oligonucleotide probes to analyze the sample, and therefore can also detect regions of homozygosity (ROH), and mosaicism at a lower percentage than aCGH [12]. Using either platform, 'incidental' or 'unexpected' diagnosis, pathogenic variants outside of the primary indication for testing, may be identified [1,13].

Wapner et al. found that in ~6% of fetuses with an identified structural anomaly, a clinically relevant diagnosis was made using CMA that would not have been detected by karyotype alone [13]. Additionally, in ~1.7% of pregnancies (1:60 frequency) with normal karyotypes and no ultrasound findings, relevant submicroscopic anomalies were detected using CMA [13]. Currently, the American Congress of Obstetricians and Gynecologists (ACOG) recommends prenatal microarray after identification of a structural fetal anomaly [1]. Any patient pursuing invasive prenatal diagnosis, such as chorionic villus sampling or amniocentesis, regardless of maternal age should be offered microarray in place of karyotype analysis [1]. Validation studies on fetal interventions, for example the Management of Myelomeningocele Study (MOMS) which examined the benefit of in-utero repair for myelomeningoceles, used strict inclusion criteria for the fetus and mother. However, the genetic inclusion criteria for this study was karyotype analysis, not microarray [14]. The original study criteria have largely been applied to clinical practice; however, 73% of fetal intervention centers surveyed in 2016 favored using microarray over karyotype in their selection criteria for fetal intervention [15].

In an effort to provide prenatal genetic testing without the need

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