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Pre-and Post-test Genetic Counseling for Chromosomal and Mendelian Disorders

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Abstract

Genetic carrier screening, prenatal screening for aneuploidy and prenatal diagnostic testing have expanded dramatically over the past two decades. Driven in part by powerful market forces, new complex testing modalities have become available after limited clinical research. The responsibility for offering these tests lies primarily on the obstetrical care provider, and has become more burdensome as the number of testing options expands. Genetic testing in pregnancy is optional, and decisions about undergoing tests, as well as follow-up testing, should be informed and based on individual patients' values and needs. Careful pre- and post-test counseling is central to supporting informed decision-making. This article explores three areas of technical expansion in genetic testing: expanded carrier screening, non-invasive prenatal screening for fetal aneuploidies using cell-free DNA, and diagnostic testing using fetal chromosomal microarray testing, and provides insights aimed at enabling the obstetrical practitioner to better support patients considering these tests.

Keywords

Genetic counseling; prenatal diagnosis; genetic carrier screening; cell-free DNA screening; non-invasive prenatal screening; chromosome microarray

INTRODUCTION

In the past five years, dramatic advances in genomic medicine have led to significant changes in the types of genetic tests available to pregnant women. New testing modalities

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such as non-invasive prenatal screening for Down syndrome and expanded carrier screening frequently move from the laboratory to clinical care after only limited clinical research, often fueled by intensive marketing aimed at commercial gains, and before clinical practice guidelines are in place to govern their use. These new tests are aimed at providing more information about potential fetal disorders in response to women's and obstetricians' general desire for information that will serve to either reassure the woman that abnormalities are absent, or to inform both the obstetrician and the pregnant woman about the presence of a potential genetic condition. This potential might signal the need for additional testing to provide more clarity, lead to changes in obstetric or pediatric management, precipitate consideration of pregnancy termination, or result in prolonged uncertainty. Although more information can be known, this information may be ambiguous, complicating decision-making and raising ethical issues.[1,2]

The use of genetic technologies in prenatal care has always presented ethical challenges[3], but debates have intensified as prenatal testing options expand to include genetic tests that are easily obtained in the obstetrical office.[1, 4–5] Discussion has focused on the extent to which the accessibility of these new tests will routinize their use, erode informed consent and stigmatize individuals living with certain disabilities.[6] It is likely that genetic screening in the future will include testing for more disorders. In the face of the common notion that "more is better", many pregnant woman may accept screening without considering the downstream consequences, including possible anxiety created by additional information, especially if it is uncertain.[5–7]

In most instances, prenatal genetic screening and carrier testing options are first offered to patients through their obstetrician, midwife, or other primary obstetrical care provider[8,9], and obstetrical care providers remain the primary initial source of information for women about new testing modalities.[10,11] Currently, numerous professional guidelines recommend that women offered prenatal screening and testing for genetic disorders be given education and pretest counseling aimed at helping them to understand and weigh the benefits, risks and limitations of various testing modalities, and then make an autonomous decision that is most consistent with individual values and preferences.[12–26] Although the general public is increasingly aware of the availability of new tests through the mass media, direct marketing or social networks, consumers frequently hold exaggerated views of the utility of genomic tests, and may underestimate their limitations.[27]

When options for genetic testing are introduced by the obstetrical care provider, some minimal information should be included in the pretesting discussion, including:

1. Genetic testing is optional and the decision to undergo or decline genetic testing in pregnancy should be based on the personal values and needs of each patient;
2. General Information about the conditions being tested for, including variability and common features;
3. Nature of the testing (screening, carrier screening, diagnostic);
4. Available alternative testing options and the risks, benefits and limitations of each;
5. Possible results of testing (positive, negative, unclear, unexpected);

6. Implications of positive results and follow-up options and available resources if the testing is positive;
7. Cost of testing and expectation regarding insurance coverage;
8. The availability of genetic counseling to provide additional information and risk assessment, to assist with decision-making about testing or discuss follow-up regarding results.

To maximize time for consideration of testing choices and to allow for appropriate follow-up, education and counseling about genetic tests should ideally be accomplished in the first or second prenatal visit, generally occurring in the first trimester of pregnancy, or in the case of carrier screening, even preconceptionally. The integration of counseling regarding optional genetic tests into early prenatal care is complicated by several factors including delays in initiating prenatal care by the patient, anxiety and uncertainty about pregnancy outcome that frequently occurs in the first trimester, and the significant volume of education and information that is necessary to discuss during a relatively short clinical encounter.[28,29] Time constraints coupled with increasing complexity of available testing options increase concerns that women are being expected to make decisions after receiving only minimal information and with poor understanding of what they are consenting to.[7,30] Furthermore, intense marketing pressure as well as concern for wrongful life suits may lead providers to encourage testing rather than supporting autonomous decisions about testing by the patient.[31,7]

In response to these concerns it has been suggested that all women should meet with a genetic counselor early in pregnancy to review personal genetic risks and available testing options.[8] Genetic counselors are typically master's degree trained professionals who work in a variety of clinical, research and commercial settings. Consultation with a genetic counselor in the prenatal setting involves review of the family and medical history of the patient and her reproductive partner; review of risks and/or test results, discussion of testing options to include overview of risks, benefits, limitations, alternatives and potential next steps; review of conditions that may be tested for; and most importantly, clarification of patient values regarding prenatal testing options. The goal of genetic counseling is to provide the risk assessment, support, education and resources needed to facilitate patient decision making that best supports the individual patient's personal needs and values.

Historically, prenatal genetic counselors have worked in academic medical centers, healthcare systems and perinatology practices. However, over the past decade, genetic counselors are increasingly working in less traditional settings including telephone based genetic counseling services as well as commercial testing laboratories. In some cases, laboratory-based genetic counselors directly interface with patients providing pre-test counseling and/or in follow-up of test results. The potential for conflict of interest associated with counseling provided by a laboratory counselor should be considered carefully, and the American College of Obstetricians and Gynecologists (ACOG) caution that neutral counseling may be compromised through "use of patient educational materials or counselors that are provided by a company that may profit from a patient's decision to undergo testing".[13]

While it would be ideal for all pregnant women to have the opportunity to meet with a genetic counselor, such a goal is not realistic given the number of trained genetic counselors and the finite number of training slots currently available.[32] As a means to provide education to women, various modalities to evaluate risk and to inform women about prenatal tests and support decision-making have been developed and evaluated,[33–36] and a method for rapidly creating and updating educational materials has been called for.[8] Such resources may support the work of the primary obstetrical care provider in providing pre-test counseling and follow-up of genetic test results.

This review will provide information to aid obstetrical care providers in providing information and support to patients regarding three very different new technologies that are being increasingly integrated into prenatal care: expanded carrier screening, non-invasive prenatal screening (NIPS) for Down syndrome and other aneuploidies using cell-free DNA (cfDNA), and chromosomal microarray analysis (CMA) for detection of copy number variants (CNVs). We will provide some brief background for each technology, focus on the specific counseling issues associated with each, and make suggestions for counseling that might be provided by the primary obstetrical providers when these tests are offered, and after test results are received.

EXPANDED CARRIER SCREENING

Carrier screening programs for genetic disease began in the 1970's with the availability of screening for Tay-Sachs disease by enzyme analysis[37] and sickle cell disease through blood cell morphology.[38] In 1989, the *CFTR* gene was discovered which opened the door for molecular genetic carrier screening for cystic fibrosis[39] and eventually for many other single gene disorders. Currently, practice guidelines for professional societies support offering carrier screening for some conditions for individuals known to be at increased risk for specific genetic conditions based on ethnic background or heritage and for certain personal and family history features.[12,14–16, 21, 23–25] For example, there are specific guidelines for offering carrier screening in the Ashkenazi Jewish and Mediterranean populations.[12,14] A family history of intellectual disability and autism should prompt consideration of carrier screening for Fragile X syndrome.[16,21,40] Current guidelines recommend offering cystic fibrosis carrier screening to all women of reproductive age.[17]

With recent developments in next generation sequencing technology however, it is now possible to screen simultaneously for mutations related to dozens of genetic conditions.[41] A number of genetic testing companies now offer expanded carrier screening (ESC) panels for the purpose of carrier screening without reference to a patent's prior risk. Expanded carrier screening panels may include analysis of mutations in several or more than a hundred genes associated with conditions presenting in both childhood and adulthood. Within each gene, carrier screening panels may look at only one specific known mutation or several mutations. More recently, some labs are now offering expanded carrier panels which sequence each of the genes included on the panel. Use of these panels has scaled up carrier screening and presents both new opportunities and new challenges in the provision of obstetrical care.

Expanded carrier screening encourages a pan-ethnic screening strategy in which all individuals regardless of ethnic backgrounds are screened for the same panel of conditions. This approach may be attractive to physicians because it bypasses following patient-specific guidelines and increases the probability of identifying carrier state. It is also may appeal to patients who want to "test for everything possible". However, ECS has important limitations, including the fact that these panels do not screen for *all* genetic conditions or may exclude mutations that might be important in certain situations such as a positive family history.[42] Furthermore, expanded carrier screening may not be time and cost efficient, and may raise anxiety for patients given the much higher likelihood of being identified as a carrier for a genetic condition when using larger panels.[43–44]

Pre-test Counseling

It is established medical practice that carrier screening for genetic conditions be presented to patients as a personal choice.[13] The elements that are required to support an informed choice need to be defined for any screening program.[45] In the case of genetic carrier screening, the amount of detail desired by each patient prior to making testing decisions will likely vary.[46] Practically, clinicians express support for patient autonomy by explicitly stating that any possible choice regarding carrier screening is appropriate: extensive carrier screening using ESC with reproductive interventions to achieve an unaffected pregnancy; screening for a limited number of conditions based on ethnicity or family history; or declining all testing and reproductive interventions.

Prior to participating in reproductive genetic carrier screening of any type, patients should understand the possible reasons to elect or decline screening. Certain key elements for informed consent to include in pre-test counseling for expanded carrier screening have been defined and include the following key points.[42]

- The results from carrier screening may be used to inform subsequent reproductive decisions
- Conditions included on expanded carrier screening panels may vary tremendously
- It is common for individuals to be identified as carriers with use of ECS panels
- Pregnancy risk assessment depends on carrier status of partner, so their partner must be available for testing to accurately assess reproductive risk
- A negative screen does not eliminate risk to offspring

When possible, reproductive options will be maximized by introducing genetic carrier screening prior to conception.[42] Couples who elect to undergo carrier screening prior to pregnancy should be informed that if they are found to be at increased risk for a genetic condition, they would have a variety of different reproductive options to consider. Some couples may elect to move forward with spontaneously conceived pregnancy as planned with or without undergoing prenatal diagnosis using chorionic villus sampling (CVS) or amniocentesis. Other options include the use of assisted reproductive technologies (ART) such as in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) or the use of donor gametes. Other options that may be considered are adoption, selection of a different reproductive partner, or electing to limit family size or not have children. While this

information in the preconception period can maximize reproductive options, decision-making can be difficult and stressful. Some pathways such as the use of ART may also be cost prohibitive for many individuals and also may not always result in successful pregnancy.

If carrier screening is performed during an established pregnancy, patients should be aware that if she and her partner are found to be a carrier for the same genetic condition, diagnostic testing through CVS or amniocentesis would be necessary to determine if the fetus is affected. With recessive conditions, in the case that both parents are determined to be carriers, the likelihood that the fetus would be affected is 25%.

Expanded carrier screening panels will very frequently identify patients as carriers, with as many as 1 in 4 individuals being found to be a carrier of at least one condition on a panel in one study.[47] Providers should prepare patients for this possibility during pretest counseling and recognize that such results can lead to patient anxiety. Further, providers offering ECS should be prepared that the process of notifying carriers and arranging testing of partners is likely to involve considerable clinical time. Being identified as a carrier for a recessive condition is only meaningful if the patient's partner is also a carrier for the same condition, and there is only a small chance of this in most cases. This likelihood of shared carrier status among partners for the same genetic condition is higher for consanguineous couples as well as for couples from certain ethnic groups such as Ashkenazi Jewish individuals.

A counseling challenge presented with some current ECS panels is that the conditions included on these panels are vastly diverse in terms of effects and severity. Conditions may include problems such as sensitivity to anesthesia, which may be useful to know but are not relevant prenatally. Including conditions that are always lethal, such as Tay-Sachs disease, on the same panel as a treatable disorder, such as isolated hearing loss, places medical providers and patients in a situation of possibly learning more information than they desired. Although the American College of Medical Genetics and Genomics (ACMGG) has recommended that only more serious genetic conditions with predictable prognosis related to genotype be included on ECS panels, many conditions on these commercially- available panels do not universally cause disease in individuals who inherit two mutant alleles, and some conditions are not generally considered to be severe.[48] The interpretation of the severity of any individual condition is subjective and individually defined. Patients and providers may wish to select a carrier screening panel which is limited to reduce the likelihood of identifying carrier status for conditions of questionable clinical significance to the fetus.

Another issue that may arise with ECS panels is that the prevalence based on ethnicity as well as the sensitivity of the screening tests for targeted mutations can vary dramatically. In order to put a carrier screening result into context for a couple's reproductive risk, one must know the carrier frequency within a population and the proportion of disease-causing alleles detected using a specific testing platform. Either one or both of these factors may be unknown for any given patient which can lead to much uncertainty in result interpretation.

Post-test counseling

If a patient is found to be a carrier for a given condition, and the detection rate of a targeted screening test in her partner's ethnic group is unknown, the usefulness of the carrier testing may be limited. One alternative may be DNA sequence analysis of the entire gene, however such extensive testing can be costly and given that it is not recommended under current guidelines, is unlikely to be covered by insurance. Furthermore full gene sequencing may result in identifying mutations for which there is little information available about anticipated prognosis, which could require patients to make important decisions based on uncertain information. Some companies do not offer carrier testing for single genes, meaning that the partner may need to have testing for the entire panel. Generally, if one member of a couple is found to be a carrier for a given condition on a screening panel and the other partner has a negative screening test, the couple should be counseled that the chance of an affected pregnancy is low, but not zero.

In rare cases, an individual learns from carrier screening that he or she may have a genetic condition such as Gaucher disease, a thrombophilia or atypical cystic fibrosis.[49–50] In such cases, referral to an appropriate specialist for medical management and genetic counseling is indicated to review the inheritance patterns, recurrence risks, clinical features and possible treatment.[42]

Additional Considerations

Notably, not all conditions for which carrier screening is recommended based on current guidelines are included on ECS panels. For instance alpha-thalassemia is not included on most ECS panels and this condition is still best screened by evaluation of red blood cell indices followed by subsequent testing by hemoglobin electrophoresis and DNA testing based on results and heritage.[12] Expanded carrier screening may appeal to providers who believe that such testing will reduce their medico-legal liability for potential wrongful birth suit that may arise if a genetic risk is not identified and a baby is born with a genetic condition. In fact, although expanded carrier screening panels may screen for over a hundred genetic conditions, for many of the conditions included on the panels only a single mutation to a handful of mutations for each condition will be evaluated. The mutations included in the panel may be the most common mutations in some but not all ethnic groups so the ability of the screening test to detect carrier status is expected to vary significantly among individuals of various backgrounds. Given the existence of over 7,000 conditions with Mendelian inheritance[51] providers and patients may overestimate the comprehensiveness of expanded carrier screening, and a busy clinician may overlook the most appropriate screening test for an individual patient situation, such as a patient with a positive family history of a particular autosomal recessive condition.

Many ECS panels include conditions for which current professional societies specifically recommend against universal population screening, for instance MTHFR (Hickey 2013) and hereditary hemochromatosis.[53] Because of complexities in interpreting Fragile X carrier screening results and predicting outcomes based on genetic screening[54] the American College of Medical Genetics, American College of Obstetricians and Gynecologists and National Society of Genetic Counselors (NSGC) all recommend against screening of Fragile

X syndrome except in circumstances were the patient's personal or family history is suggestive of Fragile X syndrome.[16,21,40] However, screening for Fragile X syndrome is commonly included on expanded carrier screening panels. Another potential challenge to implementing expanded carrier screening is cost. Although the tests themselves maybe marketed as a good value when compared to gene by gene testing, expanded carrier screening panels can be costly as are the infrastructure and human resources needed to provide appropriate education, counseling, interventions and follow-up.

Testing options should be offered with the goal of autonomous patient choice. Although expanded carrier screening may be the method of choice for some patients, currently practice guidelines do not recommend that ECS replace targeted carrier screening in general obstetrical care.[42] Obstetrical providers should be confident that it is reasonable to offer targeted carrier screening based on current practice guidelines which support testing based on ethnicity and family history indications.

NON-INVASIVE PRENATAL SCREENING (NIPS) FOR FETAL ANEUPLOIDIES USING CELL-FREE DNA (cfDNA)

Over the past three decades, prenatal screening options for Down syndrome and other common aneuploidies have moved from an assessment based on age and family history alone, to screening using maternal serum markers only, to screening using both maternal serum and ultrasonographic markers, and most recently, to include screening using circulating cell free (cf) DNA present in maternal blood. Screening was initially performed in the second trimester, but is now more typically performed in the late first trimester. As the timing, sensitivity and specificity of screening tests have improved, the utilization of invasive procedures, such as amniocentesis and chorionic villus sampling, by pregnant women has declined. [55, 56, 57, 58] These welcome advances also involve an unprecedented degree of complexity that has challenged our current approaches. [30, 59]

In 2007, ACOG updated their practice guidelines about prenatal screening for aneuploidy to recommend that all pregnant women be offered screening, and that invasive testing for chromosomal aneuploidy be made available to all pregnant women, regardless of their risk for fetal aneuploidy. [60] The 2007 ACOG guidelines along with the shift to tests that are offered in the first trimester and often in the obstetrician's office have led to the need to educate more patients about more screening options at an earlier stage of pregnancy. [29] This has fueled concerns that more women will be making decisions with insufficient education concerning the risks, benefits and limitations of various available options. [61, 62] Patients and clinicians are drawn to cell free DNA screening because of the greater detection for trisomy 21 compared with conventional maternal serum and ultrasound screening. [63, 64] However, implementation of cfDNA screening has been driven in part by market forces rather than a thoughtful integration into current test offerings. [65, 66] This has led to rapid and high uptake of cell free DNA screening for aneuploidy by high risk women when it is offered. [56] Current guidelines indicate that cfDNA screening is an appropriate choice for high risk patients within the context of other clinical factors and test results.[58] Pretest counseling by obstetrical providers, including genetic counselors, will have a major impact on utilization and efficacy of this new screening modality.

Pre-test Counseling

The number of prenatal screening and prenatal diagnostic options currently available, and the complexity of cfDNA in particular, will challenge the clinician's ability to adequately inform women of all available options, and the pregnant woman's ability to make informed decisions about their use. Current clinical guidelines concerning cell free DNA screening for aneuploidy emphasize autonomous reproductive choices and the provision of balanced pretest counseling and information to patients. [23, 66, 20, 67] In order to meet this challenge, obstetrical providers must develop new methods of pre-test counseling that present the important elements of testing options in a framework patients can comprehend. Written and web-based educational materials that are understandable and unbiased for patients will also enhance the pre and post-test counseling process. [68] The content of educational materials produced by commercial NIPS labs varies tremendously and may have an underlying message to support test uptake rather than informed and autonomous patient decisions. [69] Kloza et al (2014) [68] compared commercially available patient literature and provide an editable generic copy of a validated patient pamphlet (www.ipmms.org). More such patient oriented materials are urgently needed.

Currently, all clinical guidelines recommend that cfDNA screening for aneuploidy be accompanied by pre- and post-test education and counseling, and that it not be considered a routine obstetrical test. Professional organizations including ACOG,[23] the American College of Medical Genetics and Genomics, [26] and the National Society of Genetic Counselors [22] have made recommendations about the content of pre-test education for non-invasive screening. All three organizations recommend that education should include information about the conditions that the test screens for, the availability of follow-up, the implications of a positive results, the need for confirmatory testing following positive results, the availability of alternatives (such as invasive testing), and the possibility of false positive and false negative results.

Several sources recognize the validity of various combinations of methods and approaches to prenatal screening. [20, 66] Given the value of first trimester ultrasound, [71] and the wide availability and proven cost effectiveness of first trimester screening, [72, 73] patients may prefer to start with first trimester screening and use cfDNA as secondary screening. While first trimester screening has a slightly lower detection for Down syndrome, it will identify pregnancies with or at increased risk for other birth defects and obstetrical factors important in patient care that are not detected with cfDNA. First trimester screening also involves a two-step process involving measurement of the fetal nuchal translucency by ultrasound and analysis of biochemical serum markers prior to generating results that allows patients more time for and information about individual risk on which to make the decision about cfDNA screening. Likewise, given the provision of definitive results and relative safety of CVS and amniocentesis, [74] high risk patients should be advised that they may elect to undergo invasive prenatal diagnosis without undergoing any screening. [55] In many situations, the implementation of cfDNA into prenatal screening programs and the use of companion tests to screen for other conditions in pregnancy may depend on the resources available in the local community. [55, 66]

Patients should be informed that while cell free DNA screening has an extremely high sensitivity and specificity for trisomy 21, and only slightly less for trisomies 13 and 18, it is not diagnostic and interpretation of results requires consideration of the patient's a priori clinical risk. As this is not typically provided by the laboratory, determination of the individual's risk requires clinical interpretation. [75] The possibility of false positive results will be higher for less common abnormalities and in low risk populations. [76] Obstetrical providers offering cfDNA screening to low risk patients should anticipate a lower positive predictive value and low risk patients should be informed of this prior to testing. [77, 78]

When considering its overall ability to detect fetal anomalies, cfDNA screening does not replace first trimester ultrasound in its ability to detect other birth defects and markers for other chromosome abnormalities. [78, 79, 80] First trimester ultrasound has been shown to detect non-chromosomal abnormalities in approximately 1% of cases. [81] Approximately half of the major anomalies previously detected at 20 weeks gestation may be detected or suspected on targeted first trimester ultrasound by experienced practitioners at 12 weeks. [71]

Cell free DNA screening does not replace amniocentesis and CVS in allowing full karyotype or microarray analysis, although some cfDNA methods screen for a limited number of microdeletion syndromes. At this point in time, cfDNA screening does not routinely enable other specialized testing (eg. specific single gene DNA analysis). As with other first trimester screening options, cfDNA does not replace alpha-fetoprotein (AFP) screening or second trimester ultrasound for detection of neural tube defects. [26]

In addition to detecting the common aneuploidies trisomy 21, 18 and 13, cfDNA may currently also be used to detect fetal sex, sex chromosome abnormalities and certain microdeletion syndromes. Patients eager to use cfDNA testing to learn fetal sex should be counseled regarding the full implications of screening. Patients need to be advised that the false positive rate for screening for sex chromosome aneuploidies is relatively high and the prognosis frequently includes few clinical findings. [82] In some cases, screening for fetal sex chromosome aneuploidy may detect maternal sex chromosome mosaicism, a situation for which most patients would be unprepared. Further, they should know in advance that the clinical utility of screening for rare microdeletions in low risk populations has not been established and that the positive predictive value for these uncommon conditions is low. [66] Patients should be encouraged to consider these issues prior to undergoing cfDNA screening and be given the option to decline the test or limit what the test includes. Clinicians should be prepared that in the near future, cfDNA testing is likely to be used as a method of detecting other fetal conditions, [83] as well as certain maternal conditions. [84]

Cell free DNA screening for aneuploidy might not provide a result for all patients. Patients with "no call" results may be at increased risk and should be offered genetic counseling and repeat screening or diagnostic testing. [20, 23], Additionally, the possibility of identifying a genetic or other important heath condition in the mother or other unexpected result through cfDNA should also be a part of the informed consent process. [84, 85]

Post-test Counseling

In general, pre-test counseling should prepare patients for possible positive results. Obstetrical providers should be prepared to deliver these results, provide post-test counseling and make referrals. Women generally opt for cfDNA testing to test for Down syndrome, and are generally not familiar with other detectable conditions, such as sex chromosome aneuploidies or conditions associated with chromosomal deletions or duplications. [11] Preparing patients for possible unanticipated results has always been an important goal in genetic counseling provided prior to prenatal diagnosis using amniocentesis and CVS, and may be a factor in almost any genetic testing situation. Positive screening results are associated with considerable anxiety, and providers should be prepared to allow time for patients to react and process the implications of results. Patients should be informed about the availability of invasive testing for confirmation of findings and offered genetic counseling. More than one visit may be optimal, or the initial obstetrical providers contact may be followed by a genetic counseling visit the next day, allowing patients time to consider results and testing options. Prenatal genetic counselors can assist with interpreting results and providing follow-up that may be critical in meeting the patient's needs.

Obstetrical providers should include the concept of false positive results and explain the difference between the detection rate (sensitivity) and positive predictive value (chance that a positive result is a true positive) to patients in pre-test counseling. [67] While cfDNA testing is often advertised as being highly accurate, patients should be aware that in the event of a positive result, the likelihood that the pregnancy is affected depends on factors including her age, results of other screening tests and her pregnancy and family history. In the low risk population, the chance that a positive result is a *false positive* result may be similar to or even exceed the likelihood of a *true positive* (see Table 1).

For those with a positive cfDNA screening result, amniocentesis and chorionic villus sampling (CVS) provide near definitive results. [86] However, patients should be made aware that laboratory testing of villi obtained via CVS may occasionally differ from the fetus. In these cases, testing may reveal abnormal cells which could be present in the placenta, but not reflective of the fetal karyotype, a phenomenon known as confined placental mosaicism. It has been shown that cell free DNA in maternal blood also originates from the cytotrophoblast and is therefore of "placental" not fetal origin. The phenomenon of placental mosaicism may confound cfDNA screening in some cases. [87] In addition, "no result" cfDNA results occur in up to 8% of cases, and because such results are associated with increased risk for fetal aneuploidy, genetic counseling, comprehensive ultrasound evaluation and invasive diagnostic testing should be offered.[2367, 87]

For patients electing CVS or amnio, microarray analysis or specific DNA testing may be included in prenatal testing. Depending on the presence or suspicion of an abnormality or specific genetic condition, other specialized fetal evaluation may be indicated, such as fetal echocardiography or MRI and consultation with pediatric specialists for better prediction of prognosis and better patient counseling. Genetic counselors may be utilized in coordinating these referrals.

Additional Considerations

Integration of cfDNA into prenatal care will require significant patient and health professional education. [88] This new approach to screening for the common aneuploidies also raises ethical and societal concerns that are not being addressed in on-going research that has focused primarily on technical aspects of the test. [59] More attention is needed to optimize effective, unbiased patient and provider educational materials, approaches to offering screening and delivering test results, and delivery of care and follow-up for those with positive results. Thoughtful research investigating the impact of widespread screening on individual patients, families and society is needed. Successful implementation therefore will require research, education and a dialogue between stake holders regarding the value and application of cell free DNA in clinical practice.

Current professional guidelines recognize the validity of multiple options for implementation of cfDNA screening. [20, 66] One option would be to offer screening for Down syndrome, trisomy 13 and 18 in a two-tiered approach. [70, 88] This might involve offering first trimester and maternal serum AFP screening or serum sequential screening to low risk women. Re-evaluation of the definition of increased risk may include lowering the cut-off for offering cell free DNA screening. High risk women and women at-increased risk based on these screening results might then be counseled about all options for prenatal screening or prenatal diagnosis, either by the obstetrical provider or by a genetic counselor. Options would currently not only include cell free DNA screening, but also detailed ultrasound, perinatal consultation, prenatal diagnosis through chorionic villus sampling or amniocentesis, or other specialized testing depending in the individual circumstances. The implementation of cfDNA into prenatal screening programs and the use of companion tests to screen for other conditions in pregnancy may depend on unique characteristics of different patient populations and the resources available in the local community. [55, 66]

CHROMOSOMAL MICROARRAY ANALYSIS

Chromosome microarray analysis (CMA) is now being performed prenatally as an alternative to standard karyotype analysis obtained through CVS or amniocentesis. CMA can identify submicroscopic genomic deletions and duplications that are not detectable by traditional karyotyping. In pediatric settings, CMA testing is a first tier test for the detection of genomic abnormalities in children with neurodevelopmental disabilities where about 20% of children are predicted to test positive for a causative pathogenic copy number variant, [89] frequently leading to changes in patient management. [90, 91] Unlike chromosomal aneuploidies, the incidence of copy number variants is not associated with maternal age. In the context of a pregnancy without ultrasound anomalies, clinically significant copy number variants are seen in 1–1.7% of cases with a normal karyotype. [92] When a fetal structural anomaly is present, about 6% of fetuses carry a copy number variant of clinical significance.

Prenatal cytogenetic testing via CVS or amniocentesis is generally an option for couples who are at increased risk for having a child with a chromosome anomaly. Based on the increased yield of chromosomal microarrays compared to standard karyotyping, the American College of Obstetrics and Gynecology (ACOG) has recommended that microarray testing be offered in place of fetal karyotyping when a fetal structural anomaly is detected on

ultrasound. [19] ACOG has further recommended that for women carrying a structurally normal fetus who are undergoing invasive prenatal diagnostic testing for indications such as advanced maternal age or an abnormal first trimester screening test, either CMA testing or karyotyping can be offered. [19] CMA testing can also be considered to clarify whether an apparently balanced translocation involves the loss or gain of genetic material, to provide information about the origin of a marker chromosome, when there is an intrauterine fetal death, or to attempt to clarify any ambiguous karyotype result. [93]

Ethical concerns, counseling challenges and inadequate insurance reimbursement have tempered widespread use of prenatal CMA testing. [1, 94,95] Specific concerns include the possibility of detecting copy number variants (CNVs) of uncertain clinical significance (VOUS), the detection of CNVs associated with conditions with variable expression or penetrance, and incidental findings including CNVs associated with an increased risk for adult-onset conditions or neuropsychiatric disorders. [95, 96, 97] These findings complicate pre-test counseling and when detected, cause significant distress and difficulty with decision-making. [2]

Pre-test counseling

The challenges and limitations of prenatal CMA testing need to be addressed in pre-test counseling provided by either a knowledgeable obstetrical care provider or a genetic counselor. Pre-test counseling will focus on options available for detecting chromosomal imbalances, the couple's assessment of the risks and benefits of testing, their personal beliefs regarding testing options and attitudes towards parenting a child with disabilities. Such counseling is vital because of the possible identification of findings that are associated with a variable phenotype, and the possibility of results, including secondary findings, that are not related to the indication for testing. [93] After such counseling, some women may opt to minimize the risk of receiving incidental findings or results indicating a variant of uncertain significance by choosing a targeted array designed to test for CVNs associated with known syndromes, if available. [98] Laboratories offering CMA typically use a platform specifically designed for prenatal use that limits detection to avoid VOUS. Several have targeted array that limits VOUS further and future advances are likely to reduce their occurrence. Avoiding uncertain findings would need to be weighed against the inability to detect some pathologic CVNs that would not be detected by the targeted array.

For women opting for genome-wide arrays that are designed to cover a larger portion of the genome and detect smaller deletions or duplications, the possible detection of a variant of uncertain significance (VOUS) should be discussed in pre-test counseling. Women should be counseled that if a VOUS is detected, parental samples will be requested in an attempt to clarify the likelihood that the variant is pathogenic. Women should also be counseled that even with some well-described microdeletion/duplication syndromes, such as the 22q11.2 deletion syndrome associated with DiGeorge syndrome, there is a wide range of severity of clinical involvement. Pretest counseling is further complicated because nearly all of the disorders potentially diagnosed through CMA testing are individually rare and are unfamiliar to most patients. Women will therefore need to be told that the test identifies a wide variety of conditions, with varying clinical outcomes. They should be reassured,

however, that if an abnormality is detected, they will be able to consult with experts who will share with them whatever information is available about the expected clinical outcome for their baby, if they choose to continue the pregnancy. Finally, women should understand that even though CMA testing can identify a wide range of conditions due to deletions or duplications of genetic materials, it will not detect certain genetic conditions such as those due to point mutations or small deletions or duplications in single genes, apparently balanced chromosomal translocations or conditions associated with low level mosaicism or other types of inheritance.

Post-test counseling

When CMA results are positive, the patient should be referred immediately to a genetic counselor or medical geneticist to discuss the implications of the findings and to make decisions about the pregnancy moving forward. The obstetrician should encourage both partners to attend the genetic counseling visit when possible. The couple can be informed that the genetic counselor will provide the patient or couple with available information about implications of the finding for the baby's health and development, discuss the uncertainties surrounding the prediction, and review available options, including parental testing, additional fetal testing (if indicated), testing of family members, and the availability of pregnancy termination. Couples generally want as much information as possible about the implications of the finding. [99] However, when informed about an abnormal result, couples are generally in a state of shock, and several visits or repeated contact with the family may be needed in order to adequately educate the family about the implications of the finding.

Counseling couples about positive prenatal CMA results is complicated because the conditions detected by microarray are generally unique. [11] Moreover, for some copy number variants, no information is available about the expected phenotype. In addition, most CNVs are associated with a probability, or a range of probabilities of various potential complications, and it is generally not possible to assess the fetus for clinical involvement, especially for neurocognitive deficits. Making predictions about the expected clinical outcome after prenatal diagnosis is difficult because most of the available outcome information is usually derived from children who are tested because of the suspicion of a problem, so information generally will be skewed towards the severe end of the spectrum. Thus, couples frequently find themselves needing to make decisions in the face of considerable uncertainty. [2]

Before meeting with the couple to discuss an abnormal CMA result, the genetic counselor typically will gather all information available about the CNV detected by consulting with experts and by reviewing various databases such as the European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (www.ECARUCA.net), the Database of Genomic Variants (www.projects.tcag.ca/variation; ClinVar (www.ncbi.nlm.nih.gov/clinvar), or the USCS Genome Browser (www.genome.ucsc.edu/cgi-bin/hgGateway). In the counseling session, the genetic counselor will take a detailed family history, and discuss whether parental testing would provide additional helpful information. Parental studies may also be used to look for cryptic translocations to predict the risk for recurrence. The counselor might provide only preliminary counseling until

testing of the parents is complete and it can be determined if the variant present in the fetus is inherited or *de novo*. In the setting of a VOUS result or of an inherited CNV associated with a risk for a neurodevelopmental disorder, if the variant is found to be inherited, the counselor will evaluate whether the family history provides any clues about the phenotypic impact of the CNV. A CNV that is inherited from a phenotypically normal parent provides some evidence that the CNV may be benign, but there is growing evidence that because of incomplete penetrance and variable expressivity, complete reassurance cannot be provided, and some uncertainty about clinical outcome will remain. In addition, parents who are found to carry a copy number variant may experience guilt, stigma or uncertainty about their own health. [2, 100]

In addition to informing the couple about the clinical implications of the microarray results for their baby, the counselor will explore with the couple their attitudes towards parenting a child who may have or who may be at risk for a disability, their tolerance towards uncertainty, and their attitudes about pregnancy termination. Ideally, these issues would have been discussed as well during pre-test counseling. The counselor might suggest additional testing, such as fetal imaging or echocardiography to determine if there are associated anomalies. Consultations with pediatric providers who have expertise in the condition diagnosed, or referrals to disease organizations may be helpful to the couple, either to develop a plan for neonatal or pediatric follow-up, or to gather additional information about the child's expected health and development. The extent of the counseling, and the topics addressed in the counseling will generally be individualized to the particular needs and concerns of the couple. Frequently, the genetic counselor will follow-up with the couple to assess on-going needs, answer additional questions, and provide emotional support.

Additional Considerations

With increasing resolution of genomic testing, the probability of identifying genomic changes of uncertain significance or changes unrelated to the indication for testing increases. [95] Careful pre-test counseling can help couples understand the types of results available from prenatal CMA testing, and the uncertainties associated with many results. Unfortunately, uncertainty will be persistent as the genome is assayed more finely. Variants of uncertain significance will challenge genetic counselors. [32] and complicate the decision-making and coping processes of pregnant women. [2, 101] In addition, unexpected findings, such as the identification of a copy number variant associated with an increased risk for an adult-onset condition will occur. At present, there are few guidelines for handling such findings, and policies are needed about returning unexpected or uncertain findings that take in to account the priorities multiple stakeholders, including pregnant women and their partners. [99, 102] Clinicians should be aware of the differences in CMA platforms available from targeted panels that reduce the likelihood of a VOUS to more comprehensive high resolution, whole genome arrays.

In the future, the ability to counsel patients about expected outcomes relating to many copy number variants should improve as additional data are gathered about the expected phenotype associated with many CNVs. Policies are likely to support expanding the use of

prenatal microarray testing as evidence accumulates documenting improvements in postnatal outcomes after early detection of CNVs. [97]

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SUMMARY

The complexity of genetic testing options available to patients in preconception and prenatal care is expected to continue to grow, and likely at a rapid pace with the advent of new molecular and bioinformatics technologies. Such expanding technologies may provide beneficial information for some patients but also create ethnical quandaries and counseling challenges for obstetrical care providers. In order to provide optimal patient care, it is essential that obstetrical care providers stay up-to-date regarding available technologies as well as the overall benefits, drawbacks and limitations of various testing options. Being well-informed about rapidly-changing technologies is difficult and complicated by the limited availability of evidence-based educational materials that provide unbiased information to providers and patients.

There is a need for development of tools, resources and alternative service delivery models to support optimal care and autonomous, values-based and informed patient choices with regards to prenatal testing. While it is impractical for each pregnant women to have individual genetic counseling, collaboration between the primary obstetrical care providers and genetic counselors is essential as we develop best practices for providing high quality education and genetic counseling for all women considering reproductive genetic testing.

Table 1

Cell-free DNA Test Performance Characteristics in Patients Who Receive an Interpretable Result *

			Age 25 years	Age 40 years
	Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**PPV (%)**
Trisomy 21	99.3	99.8	33	87
Trisomy 18	97.4	99.8	13	68
Trisomy 13	91.6	99.9	9	57
Sex chromosome aneuploidy	91.0	99.6	-- †	--

Abbreviation: PPV, positive predictive value.

* This table is modeled on 25– and 40–year-old patients based on aneuploidy prevalence at 16 weeks of gestation. Negative predictive values are not included in the table but are greater than 99% for all patient populations who receive a test result. Negative predictive values decrease when patients who do not receive a result are included. Test performance characteristics are derived from a summary of published reports and as assessed and compiled in published reviews.

† The positive and negative predictive values for the sex chromosome aneuploidies depend on the particular condition identified. In general, however, the PPV ranges from 20% to 40% for most of these conditions.

Applicability to clinical practice:

Positive predictive value (defined as true positives divided by true positives plus false positives) is directly related to the prevalence of the condition in the population screened. Based on the sensitivity and specificity of the test, when a population with an overall prevalence of 1/1,000 for trisomy 21 is screened, the positive predictive value of an abnormal result is 33%—only one in three women who get an abnormal result will have an affected fetus. If the prevalence is 1/75, the positive predictive value is 87%.

Data from Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2015;45:249–66; Porreco RP, Garite TJ, Maurel K, Marusiak B, Ehrich M, van den Boom D, et al. Noninvasive prenatal screening for fetal trisomies 21, 18, 13 and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA. Obstetrix Collaborative Research Network. Am J Obstet Gynecol 2014;211:365. e1–365.12; Snijders RJ, Sebire NJ, Nicolaides KH. Maternal age and gestational age-specific risk for chromosomal defects. Fetal Diagn Ther 1995;10:356–67; Benn P, Cuckle H, Pergament E. Non-invasive prenatal testing for aneuploidy: current status and future prospects. Ultrasound Obstet Gynecol 2013;42:15–33; and Verweij EJ, de Boer MA, Oepkes D. Non-invasive prenatal testing for trisomy 13: more harm than good? Ultrasound Obstet Gynecol 2014;44:112–4.