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Original Article

Offering Prenatal Screening in the Age of Genomic Medicine: A Practical Guide

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Abstract

Aims: In September, 2015, Mayo Clinic convened a panel of national thought leaders on prenatal screening, medical genetics, and obstetrics and gynecology practice.
Results: During the 2-day symposium, participants discussed the implications of the shift toward broader prenatal screening using cell-free placental DNA in maternal serum (cfDNA screening). Key topics included challenges around the pace of change in the prenatal screening market, uncertainty around reimbursement, meeting the need for patient counseling, and potential challenges in interpreting and returning cfDNA screening results.
Innovation: Here, we describe the challenges discussed and offer clinical recommendations for practices who are working to meet them.
Conclusion: As the spread of prenatal genetic screening continues, providers will increasingly need to update their practice to accommodate new screening modalities.

Keywords: prenatal care, genetic testing, prenatal counseling

Introduction

Since its introduction in 2011, prenatal screening using cell-free DNA extracted from maternal plasma (cfDNA screening)* has expanded at a steady rate, in both scope and uptake.[1] Unlike serum screening regimes, which detect variations in maternal hormones *associated with* fetal abnormality (phenotypic markers), cfDNA provides the ability to analyze a genotypic marker DNA directly from the placenta. Direct analysis of placental or fetal DNA is only possible on samples obtained through invasive procedures such as chorionic villus sampling or amniocentesis. cfDNA screening thus offers the opportunity to more directly and expansively interrogate the genetic makeup of the fetus without a procedure-related risk.

*All references to cfDNA, in this study, refer to the mixture of both maternal and placenta-derived cell-free DNA.

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Initially, cfDNA screening was validated for detecting fetuses with possible trisomy 21 in pregnancies at high risk for aneuploidy.[2–4] Screening for trisomies 13 and 18 became available in 2012, after studies showed relatively high sensitivity and specificity (although lower than for trisomy 21) when compared with other maternal serum screening methods.[5,6] cfDNA screens can also detect sex chromosome aneuploidies (including, among others, Klinefelter and Turner syndromes) and provide fetal sex. In 2014, two commercial laboratories began reporting suspected deletions, including DiGeorge, Prader-Willi, Cri-du-chat, and Jacobsen syndromes.[7–9] In 2015, one laboratory launched a ''whole genome'' scan that claims to detect deletions of 7 Mb or larger, in addition to whole chromosome aneuploidies (https://laboratories.sequenom.com/providers/maternit-genome).

Competition between cfDNA screening companies is fierce, including a number of legal challenges regarding intellectual property and the right to use specific aspects of cfDNA screeening.[10,11] As a result, some laboratories advertise that their panel has the highest detection rates, the lowest false positive rates, the lowest failure rate, or the most comprehensive panel. Others are adding rare conditions and microdeletions to maintain a competitive advantage. Given proof of concept of whole-genome sequencing using cfDNA,[12,13] some observers are predicting that widespread noninvasive prenatal whole-genome sequencing (WGS) in the general pregnancy population is inevitable.[14–16]

While the inevitability of WGS using cfDNA may be disputed, prenatal genetic screening utilizing cfDNA is a clinical reality. Professional societies initially approved offering cfDNA screening for trisomy 21 to women considered at high risk of an affected pregnancy: patients who were of advanced maternal age (over 35), had a history of an affected pregnancy, showed abnormalities on ultrasound, or had a high-risk result from a previous screen. However, by 2015, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) issued joint recommendations that the option of cfDNA screening could be made ''available to women who request additional testing beyond what is currently recommended by professional societies.''[†] In 2016, the American College of Medical Genetics and Genomics updated its recommendations to suggest that a discussion of the availability of cfDNA screening for common aneuploidies was appropriate with all pregnant women, given stringent counseling and laboratory reporting standards, but that its use for expanded indications may be appropriate in a limited clinical circumstance.[17] Obviously, the landscape of professional recommendations is shifting rapidly.

Prenatal care providers are now faced with a myriad of decisions about how to offer cfDNA screening in ways that are appropriate to their patient population and their workflow. How this technology will best be integrated into clinical practice remains to be determined. The issues that cfDNA screening brings to the forefront are different than the issues around analyte screening that are so familiar to the prenatal community: cfDNA screening may move the locus of decision-making earlier in the pregnancy; cfDNA panels can be relatively easily expanded into new conditions; cfDNA panels are commercial panels with uneven insurance coverage; many primary care providers do not have education in genetics or genetic screening; and genetic screening demands additional clinical counseling and decisional support from an already overstretched clinical schedule. These new realities call for concrete recommendations to help frontline prenatal care providers implement cfDNA screening in ways that are clinically feasible and ethically appropriate.

Working Group

In September of 2015, the Mayo Clinic Center for Individualized Medicine hosted an interdisciplinary symposium titled ''Responsible Implementation of Expanded Non-Invasive Prenatal Genetic Screening.'' This event brought together 21 subject matter experts, from within Mayo Clinic and around the nation, to discuss the broadening trend in prenatal genetic screening. Participants were identified based on the academic literature as thought leaders who had direct professional experience with developing, offering, counseling, or studying the healthcare delivery of prenatal genetic screens.[‡] Participants represented a variety of relevant disciplines and practice settings, including medical genetics, maternal fetal medicine, obstetrics, genetic counseling, laboratory medicine, patient advocacy, medical education, epidemiology, medical screening, and bioethics.[§] During the closed-door, 2-day symposium, participants discussed clinical needs, future directions, challenges, and potential solutions. While complete consensus was neither possible nor attempted, the subgroup of participants represented in this study reached agreement through iterative discussion. We are sensitive, however, to the need to walk a fine line between offering recommendations and attempting to dictate clinical practice. We present some of the challenges discussed and provide preliminary clinical recommendations for obstetrics and family medicine practices facing this rapid and accelerating shift in clinical technologies.

Challenges Identified

Participants agreed that cfDNA screening represents a valuable technical advance in prenatal medical care. For common autosomal and sex chromosome aneuploidies, cfDNA screening offers increased sensitivity and specificity over previous serum screens. Discussion therefore centered not on whether cfDNA screening was clinically useful in any form, but rather on what form it should take and how to integrate it into existing paradigms and clinical realities.

The pace of change

Among the most frequently cited challenges was how difficult it is for prenatal care providers to keep current with the constant changes in prenatal screening offerings. These changes include the increasing number of companies offering screening; the varying performance and capability of individual screens; the different components or elements of each panel; and the fact that these elements can change rapidly and

[†]See SMFM Statement: Clarification of recommendations regarding cell-free DNA aneuploidy screening (www.smfm.org/publications/212-smfm-statement-clarification-of-recommendations-regarding-cell-free-dna-aneuploidy-screening).

[‡]Some invitees declined due to scheduling conflicts.

[§]To maintain neutrality among the many competing laboratories, representatives of the commercial laboratories offering cfDNA screening were not invited to attend.

without notice. Some laboratories offer only one prenatal screening panel; others offer three or four different panels: some including autosomal aneuploidy alone, some panels with the addition of sex chromosome aneuploidy, and others include select deletion syndromes.

Subchromosomal variation screening can be offered on an opt-in basis (the clinician has to order it specifically) or on an opt-out basis (the clinician has to explicitly decline it) and this may have implications for the cost of the test. Furthermore, as the technology is licensed to additional laboratories, the number and range of test offerings is expected to proliferate. While having a variety of options is familiar to providers, there are a large number of serum screening laboratories offering a wide variety of options (*e.g.*, quadruple testing, combined testing, integrated and testing); traditional screening has generally been provided by local laboratories and with limited commercial competition or aggressive marketing.

Choosing a screening panel. Participants emphasized that routinely ordering the broadest possible spectrum of cfDNA screening was unlikely to make sense from a clinical cost or practice management perspective. Instead, participants suggested that practices assess the level of screening that makes sense for individual patients and practice area. Relevant factors are likely to include the availability of a state-sponsored serum screening program, the payer mix, and the resources available to counsel patients and interpret results. Many practices represented by participants stressed that the choice of panel was frequently determined by the decisions Medicaid or Department of Health officials made at a state level. Broader panels usually include sex chromosome aneuploidy and/or microdeletion screening, which are not currently recommended by ACOG and SMFM. Therefore, for most general practices, a standard panel, including common chromosomal aneuploidies and an option to learn of fetal sex (Table 1), which achieves the broadest reimbursement access may be most appropriate.

Participants identified certain circumstances in which larger cfDNA screens might be appropriate. For example, in a situation with certain fetal anomalies seen on ultrasound where the patient declines invasive testing, cfDNA screening may offer some insight into fetal health. Nevertheless, providers who order cfDNA screens should be cautious about ordering expanded cfDNA screening without understanding the implications. Providers are also obligated to appropriately educate patients regarding the limitations of various panels and possible complexities in the interpretation of their results.

It is important for providers to understand the components or elements of the screening panels. Anecdotally, participants reported that some providers receiving positive screen results for a microdeletion syndrome were not even aware that the panel included such a condition, despite the fact that the inclusion of such results is frequently a selling point of particular cfDNA screens. Informed decision-making and patient trust in providers and prenatal technologies, in general, may be compromised by a lack of clear understanding of the available screening options and how to interpret the results. Participants suggested that, whenever possible, providers have explicit conversations with company representatives as to the full content of the panel they agree to order, including the full range of expected results. However, participants recognized that providers may have difficulty maintaining a secure knowledge base as screening panels evolve rapidly. It was agreed that it is incumbent on the laboratory to inform clinical practices before changing the contents of screening panels or related options. Providers who order cfDNA screens can help by setting clear expectations with company representatives.

Reimbursement and cost management

A major consideration in choosing a screen is the availability of reimbursement or the patient's ability to pay out of pocket. From 2011 to 2016, cfDNA screening has undergone rapid changes in professional and reimbursement status.

Initially available, almost entirely, on an out-of-pocket basis, cfDNA screening is now covered by many insurers, although reimbursement has been generally available only for ''high''-risk pregnancies. Recently, insurers have begun to include policy coverage for the general pregnancy population.** Nevertheless, coverage by third party payers is highly variable, as are individual patients' out-of-pocket expenses. State Medicaid programs differ in reimbursement policies for cfDNA screening: as a first-tier test versus a follow-up to serum screening, for a specific brand name versus another, and for all uses or only when a specific indication is present. Likewise, private and group insurers have highly individual policies regarding which screen can be reimbursed and under what circumstances. Navigating the complicated process of preauthorization can be especially time-consuming for patients and providers. Also, because the charges for cfDNA screening can range from $700 to over $3000,[18] unsuccessful insurance reimbursement can result in considerable out-of-pocket patient costs.

Managing costs. Participants recommended that practices have proactive discussions regarding which panels the practice will offer and to whom. In selecting a panel or panels to offer, providers need to be aware of the existing arrangements between common health insurance companies and testing laboratories, and the complex and ever-evolving process of test coding, charges, reimbursement rates, discounts, co-pays, and deductibles. Practices should implement a plan for negotiating the preauthorization process. It is important to note that some insurers (and sometimes selected policies) will only offer reimbursement for cfDNA screening for certain populations (age 35 or older) or medical indications (abnormal ultrasound and family history).

In states where Medicaid has agreed to cover cfDNA screening, it will most often make sense for practices to use the reimbursed screen. However, using the covered screens as a standard may have clinical implications because not all cfDNA panels assess the same conditions. A workflow plan should be created in advance that includes staff education about how to order testing and facilitate reimbursement. All care providers should be aware of their roles in such a plan and receive the necessary information to carry out those roles. The essential steps in the plan should revolve around

**See, for example, www.genomeweb.com/business-news/sequenom-inks-deal-anthem-blue-cross-and-blue-shield-nipt-test-coverage;www.genomeweb.com/sequencing-technology/anthem-bcbs-changes-policy-deems-nipt-medically-necessary-average-low-risk

Table 1. cfDNA and Fetal Sex

- Noninvasive fetal sex determination via cfDNA is considered a positive feature of this screening method, especially for those who are interested in learning fetal sex as early as possible in pregnancy.
- Some women report that knowing fetal sex allows them to connect with the fetus more intimately.
- However, providers should try to ensure that patients are not opting in to cfDNA screening just to learn fetal sex and are prepared for the full range of results that may be returned.
- In the event of a high-risk result for a genetic condition, some women may wish *not* to learn fetal sex as they may be contemplating termination in the event of diagnostic confirmation.
- Pretest conversations should include encouraging patients to consider whether they might wish to learn fetal sex.

communicating with the patient in a nondirective manner and helping them gain a sufficient understanding of testing options and possible outcomes to make an informed choice with which they and their family are comfortable. The plan for each practice will depend on the backgrounds of its patients and the resources available. Once a screening menu has been decided upon, it is reasonable to tell laboratories to reduce direct marketing efforts or make future contact only when there are significant changes in products. Many practices report that consistent pressure from laboratory sales staff is stressful and distracts from clinical time.

Counseling and education

One of the largest challenges participants reported was finding time to educate patients on their prenatal screening and testing options. The initial pregnancy visit encompasses a wide variety of screens, baseline health assessments, and patient education. Adding an in-depth discussion of screening and testing options for chromosomal aneuploidies is challenging. cfDNA laboratories often employ genetic counselors who may work with providers or directly with patients. However, participants echoed concerns reported in the media[19] about the potential for conflicts of interest and biases associated with laboratory employees counseling patients.

Participants were sympathetic to the patient burden of OB/GYN practices and the fact that decisions regarding prenatal screening/diagnosis may be just a small component of patient care. Because serum screening has been routine in many prenatal practices for many years, practices are familiar with referring patients to genetic counselors or maternal fetal medicine specialists who have extensive experience counseling patients about high-risk screening results, especially for rarer conditions such as microdeletion syndromes. However, the provider may be less able to provide responses to patients before them seeing genetic specialists. Participants emphasized that, while analyte screening has become routine in many prenatal practices, many providers have less experience with the kinds of conversations necessary to prepare patients to choose between multiple screening and testing modalities.

Finally, provider time constraints are also an issue. There is little current guidance on the level of detail that should be provided to patients about each condition for which they are being offered screening. As the number of conditions on screening panels increases, providers are faced with a trade-off between providing patients with in-depth information about every condition for which there is an available test or more pretest counseling about the spectrum of clinical severity of microdeletion syndromes and aneuploidies, while preserving more detailed counseling for the event of a high-risk finding.

Pretest conversations. Due to concerns about a perceived conflict of interests, participants recommended that providers offer their own pretest counseling services whenever possible and avoid relying on laboratory-employed personnel. Participants also expressed reservations about relying on pamphlets and other marketing materials provided by laboratories during the counseling process. These materials may overrepresent both the scope and quality of the information provided by a given screen. Participants perceived laboratory materials as being designed to encourage patients to undergo cfDNA screening; these materials frequently portray prenatal genetic information as ''vital'' or capable of ensuring that ''everything is alright.'' Genetic counselors, in particular, pointed out that these portrayals may be misleading.

Ideally, an independent genetic counselor directly counsels each patient about her screening and diagnostic options before she makes any decisions about screening or testing. However, participants pointed out that the limited availability of genetic counselors means that their time is generally reserved for women considered to be at high risk of fetal aneuploidy. Larger practices reported that they support multiple genetic counselors who provide a 50-minute session of counseling to women with high-risk pregnancies about their prenatal options. Some maternal–fetal medicine specialists pointed out that they generally have longer sessions with high-risk patients for discussion of screening and testing options.

Participants spent considerable time brainstorming options for helping patients explore their screening options and facilitating informed consent. Some participants reported that their practices have established group counseling sessions in which several couples can receive education and counseling at once. In other practices, pretest counseling is being shifted onto practice personnel such as nurses, who may also be the ones helping patients navigate the reimbursement process. Although there is no empirical evidence to suggest how often this occurs, participants agreed that practice personnel were more and more frequently taking on these tasks. While a complete genetic counseling session is not usually possible in the time allotted for most prenatal clinical visits, participants encouraged providers to include certain minimal content in conversations with patients (Table 2). Participants also resolved to facilitate academic/professional collaborations in which objective training and education materials could be made available to providers to assist them in offering cfDNA screening.

Interpreting and returning results

Reporting the results of cfDNA screens can be complicated by a number of factors. One factor is assay failure. Assay failure can occur if insufficient cfDNA from the placenta is

Table 2. Pretest Conversations

1. Have conversations with patients about their values regarding termination and pregnancy planning, which will help direct and personalize counseling.
2. Screening and testing are optional. Patients may have misunderstandings or incomplete information about the capability and limitations of various screens, and their ability to refuse testing.
3. Patients are being asked to choose among four options: ultrasound screening only, ultrasound plus analyte screening, ultraound plus cfDNA screening, and diagnostic testing using amniocentesis or chorionic villus sampling. The only definitive information is provided by diagnostic testing. Patients should understand that false positives and false negatives are possible.
4. If a screening test returns a high-risk result, diagnostic testing will be offered. Patients should consider their willingness to undergo diagnostic testing before undergoing screening.
5. Many patients are strongly interested in knowing fetal sex as early as possible. However, if this is the only reason the patient is selecting cfDNA screening, providers should have a conversation about the other information patients will get.
6. cfDNA screening may not be covered by private or public insurance. Analyte screening will be covered by most medical insurance plans or Medicaid.[25]
7. The numbers published by laboratories with regard to sensitivity and specificity are specific to certain populations. Patients with multiple gestations and/or high maternal BMI should be counseled that they are less likely to receive an interpretable result.
8. cfDNA screening may return an uncertain result or an incidental finding. Pretest counseling should include a discussion of these possibilities and consideration for further evaluation of incidental results.

found in the blood sample or if the ratio of placental to maternal cfDNA (fetal fraction) is too low. Failure can also occur due to unusable test results following test failure or other assay-related interpretation issues. Women with a high BMI (or body mass index) are more likely to have low fetal fraction and associated assay failure. Other reasons for low fetal fraction include the following: collection at 10 weeks or earlier, increased time between sample collection and testing, and fetal karyotype (triploidy, for example, has consistently very low fetal fraction).[20] Repeating the test with a new sample will allow successful interpretation in about 60% of test failures, and for this reason, repeat testing is common in clinical testing protocols.

Providers are also confronted with the possibility of both false-positive and false-negative screening results. The published data on the sensitivity and specificity of cfDNA screening for trisomy 21 are strong, but for other common trisomies, sex chromosome aneuploidies, and twin gestations, less data are available and the predictive value of both positive and negative test results are generally lower.[21,22] However, these predictive values are still considerably higher than for existing serum screening tests. For microdeletions, the data are even more limited, mainly due to the rarity of these conditions, and the fact that sample banks are not available as they have not traditionally been targeted by prenatal screening. The false-positive and false-negative rates of cfDNA screening for microdeletions and duplications depend on the technology used; expanded sequencing into smaller deletions will improve the detection of a wider variety of microdeletions, but will also result in increased false positives.

cfDNA screening is also based on the assumption that the mother's genome is ''normal.'' Because maternal plasma includes a mix of cell-free DNA from the mother and the placenta, abnormal characteristics in the maternal genome will complicate the interpretation, potentially producing false positives and uninterpretable screening results.[22,23] Genetic counseling can also be complicated by the possibility of an incidental diagnosis of a genetic abnormality or health concern in the mother. The most common maternal finding is variation in the X chromosome, such as Turner syndrome, but other genetic conditions and maternal cancers have also been detected by cfDNA.[23] These findings may allow for early diagnosis and management of maternal malignancy, but greatly complicate clinical management of the pregnancy.

Finally, certain laboratories use analytic techniques that can interrogate all chromosomes, even though only certain aneuploidies are reported. These techniques may allow the laboratory to identify abnormalities of chromosomes that are not the focus of the screening panel and for which the patient has not given consent and may not have received counseling. Some laboratories report these ''unofficially'' (*i.e.*, by phone to the provider), some will include them in the report,; and some will not report such findings at all.

Communicating results. It is important for providers to have a system in place that ensures the prompt return of screening results, assistance in helping them and their patients understand those results, and providing appropriate patient referrals to specialist care when necessary. If specialty genetic care is not available locally, practices may be able to form regional partnerships so that a referral to a genetic specialist can be made in the event of a high-risk result. In many cases, this referral may include a phone counseling session; some research has shown that genetic counseling by phone can be as effective as in person.[24] At least one company offers nonaffiliated genetic counseling services by phone. Practices may set up a contract with a known counseling provider so that billing is streamlined and patients have clear expectations. In addition, many organizations provide patient support materials around cfDNA screening and specific genetic conditions. Proactively partnering with these organizations so that materials, or references to materials, are immediately available when a high-risk result is received may greatly improve conversations in this space.[††]

[††]For example, see the Genetic Support Foundation (geneticsupportfoundation.org), the Perinatal Quality Foundation (www.perinatalquality.org) and the National Center for Prenatally and Postnatal Down Syndrome Resources (downsyndromediagnosis.org)

Providers may want to have a conversation with their chosen cfDNA screening laboratory/laboratories about their policy on the reporting of no-calls, assay failures, findings of uncertain significance, and fetal sex. Most laboratories will report an assay failure as a ''no-call'' and offer to retest on new blood usually at no charge. However, practices should consider whether retesting is the best option; failure of a cfDNA panel can be associated with an increased risk for aneuploidy and retesting will delay clinical decision-making.[17,25] Further consideration of diagnostic testing may be a more efficient alternative.

Conclusion

These four major themes associated with the challenges of appropriately integrating cfDNA screening into prenatal care—rapidly changing test options, cost and reimbursement, counseling and education, and interpreting and returning results—were addressed in our workshop with a particular focus on front-line prenatal care providers. These providers must attend to many aspects of reproductive and prenatal care, and cfDNA screening comprises only a small part of this overall care, but it is a part that requires careful attention to patient needs and preferences, along with increased efforts toward educating patients and guiding informed decision-making. As cfDNA screening continues to evolve, prenatal care practices will increasingly need the support of professional guidelines and expert-produced educational materials to provide the most current testing options in ways that are ethically and socially appropriate for their local patient populations.[26] Important areas for future research include developing alternative mechanisms for education and support of nonspecialist providers and patients who do not rely on the availability of specialty services such as genetic counselors. Further assessment should also be done among general practice providers about their priorities and support needs in offering prenatal screening. In addition to the recommendations in this document, our workshop has continued interprofessional collaborations aimed toward developing these supports for practices and their patients.

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