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Expanding Use of cfDNA Screening in Pregnancy: Current and Emerging Ethical, Legal, and Social Issues

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Abstract

Purpose of Review—In 2011, screening platforms became available in the US that detect and analyze fragments of cell-free placental DNA (cfDNA) in maternal blood serum. Marketed as noninvasive prenatal tests (NIPT), cfDNA screening is more accurate than previously available serum screening tests for certain aneuploidies. The combination of a noninvasive procedure, high specificity and sensitivity, and lower false positive rates for some aneuploidies (most notably Down's syndrome) has led to broad clinician and patient adoption. New ethical, legal, and social issues arise from the increased use and expanded implementation of cfDNA in pregnancy.

Recent Findings—Recently, several professional associations have amended their guidelines on cfDNA, removing language recommending its use in only "high-risk" pregnancies in favor of making cfDNA screening an available option for women with "low-risk" pregnancies as well. At the same time, commercial cfDNA screening laboratories continue to expand the range of available test panels. As a result, the future of prenatal screening will likely include a broader range of genetic tests in a wider range of patients.

Summary—This article addresses the ethical, legal, and social issues related to the shift in guidance and expanded use of cfDNA in pregnant women, including concerns regarding routinized testing, an unmet and increasing demand for genetic counseling services, social and economic disparities in access, impact on groups living with disabling conditions, and provider liability.

Keywords

cfDNA; Prenatal screening; NIPT; Ethics; Legal issues; Social issues

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Conflict of Interest The authors each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Prenatal genetic screening and testing are a common element of obstetrical care in the United States (US). Genetic screening and testing typically are conducted for congenital conditions associated with genetic anomalies, most commonly chromosomal aneuploidy. Screening tests use low-risk and noninvasive techniques, such as a blood sample or ultrasound, to identify fetuses with elevated risks for congenital conditions [1, 2]. However, screening procedures have a false positive rate of up to 15%, depending on the combined protocol used [2–4]. Prenatal diagnostic tests include more invasive procedures that collect amniotic fluid (amniocentesis) or placental tissue (chorionic villae sampling, “CVS”) and can provide definitive results based on analysis of amniotic or placental DNA [5]. Diagnostic procedures are generally elected by pregnant women considered to be at higher risk for carrying a fetus with genetic condition: those over 35 years of age at delivery, with a family history of certain genetic conditions, screen-positive results, or a previously affected birth [6]. Invasive procedures carry a small risk of infection or miscarriage (less than 1 in 300 to 500 when performed by a well-trained clinician) [6].

In 2011, screening platforms became available in the US that detect and analyze fragments of cell-free placental DNA (cfDNA) in maternal blood serum. Marketed as noninvasive prenatal tests (NIPT), for certain aneuploidies, cfDNA screening is more accurate than previously available serum screening tests: sensitivity and specificity for Trisomy 21 (Down syndrome) is reported as above 99% with less than 1% false positive rates [7, 8, 9•, 10–12]. However, sensitivity and specificity vary significantly depending on the condition, and test performance is lower for all other aneuploidies that the test platforms cover [13]. Test panels typically offer results on the three most common aneuploidies (trisomies 13, 18, and 21) and sex chromosome anomalies, including Turner and Klinefelter syndrome; further, as of 2015, some test panels include selected microdeletions.

As of 2015, many professional societies—including the National Society of Genetic Counselors (NSGC), the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal-Fetal Medicine (SMFM), and the American Congress of Obstetricians and Gynecologists (ACOG)—had recommended that cfDNA screening be offered only to women at higher risk for fetal aneuploidy, include only the three most common aneuploidies, and include pretest and posttest counseling [14, 15, 16•, 17]. However, in 2016, SMFM and ACOG amended their guidelines to say that cfDNA screening could be offered to any woman who expressed a need for information beyond serum screens [18]. In 2016, the American College of Medical Genetics and Genomics (ACMG) also amended its guidelines to recommend that cfDNA screening for common trisomies should be offered in all pregnancies, provided that adequate counseling, decisional support, and test reporting procedures were in place [19]. It also advised that expanded screening for sex chromosome aneuploidies and microdeletions should be used cautiously, and with careful attention to the higher false positive and lower positive predictive value of these screens. At the same time, commercial cfDNA screening laboratories continue to expand the range of available test panels. In 2016, Sequenom announced that it would begin offering a “genome-wide” cfDNA screen to detect copy number variants of 7 megabase pairs (Mbp) or larger [20•]. Researchers at the University College of London began offering cfDNA screening for single

gene disorders, including sickle cell disease and achondroplasia [21•]. It seems clear that the future of prenatal care will include a broader range of genetic tests in a wider range of patients. Here, we discuss the social, ethical, and legal issues related to this shift.

Ethical and Clinical Issues

Informed Consent and Routinization

One common concern about prenatal cfDNA screening is that it may increase routinization of prenatal genetic testing and erode informed consent processes [22, 23•, 24•, 25–29]. Routinization, a process in which a biomedical innovation is transformed into routine medical practice, decreases attention to decision-making processes among both providers and patients [30•, 31]. Routinization has been well documented in other forms of prenatal screening and testing [30•, 32•, 33•]. cfDNA screening, at least partially due to its ease of use and procedural similarity to serum screening, has quickly become part of prenatal clinical routines [34]. Some scholars issued early warnings that these characteristics might also mean that pretest counseling and informed consent for cfDNA screening would resemble the routine description and acceptance of serum screens [35, 36], and these warnings appear to have been borne out. Certainly, early studies suggest that cfDNA screening receives considerably less counseling and decision-making attention than diagnostic procedures, even as the information load available from such screening expands toward that of diagnostic procedures [23•, 27, 37, 43]. Even when written informed consent is sought, informed consent documentation for cfDNA screening frequently lacks attention to recommended elements of consent—including descriptions of the conditions being screened and the possibility of inaccurate results—and rarely meets readability standards [38].

Provider and Patient Information

Concerns about informed consent go hand-in-hand with those about the education and informational materials provided to both patients and health care providers. Only recently have academic, nonprofit, and professional organizations begun disseminating educational tools and materials for providers about cfDNA screening.[1] Many clinicians have reported that cfDNA screening companies provided the majority of the information they received about cfDNA screening, via marketing materials, websites, educational seminars, and direct outreach [34, 39]. Companies also aggressively market to pregnant women and families through online advertising, participation in online pregnancy discussion boards, and print materials at clinical offices and elsewhere [40–43]. These online and print marketing materials have been assessed by researchers and neither meet readability standards for patient information materials nor offer all information about cfDNA screening recommended by professional organizations [41–43].

[1]These currently include the NIPT/Cell Free DNA Predictive Value Calculator, from the Perinatal Quality Foundation and the National Society of Genetic Counselors (NSGC) and endorsed by the American Congress of Obstetricians and Gynecologists (ACOG) (https://www.perinatalquality.org/Vendors/NSGC/NIPT/); an Abnormal Prenatal Cell-free DNA Screening Results fact sheet from NSGC, endorsed by ACOG (http://nsgc.org/page/abnormal-non-invasive-prenatal-testing-results), and a cfDNA Policy “Cliff’s Notes” chart by the Genetic Support Foundation (https://www.geneticsupportfoundation.org/providers/cfdna-for-providers).

Little is yet known about the quality of provider knowledge and education regarding cfDNA screening. A survey of maternal-fetal medicine fellows conducted in 2012 found that nearly all respondents (97%) understood that cfDNAwas non-diagnostic, but only 35% knew all validated indications [39]. While a majority of respondents reported that they learned about cfDNA screening from formal educational activities, self-review of literature, and discussions with peers, many also reported receiving information from commercial laboratory representatives (31%) and laboratory-produced materials (22%) [39]. Among frontline providers (including obstetricians, nurse practitioners, certified nurse-midwives, and family medicine specialists), an earlier survey of obstetricians found that nearly half mistook cfDNA as essentially diagnostic [44], though it must be noted that little professional guidance had been issued at the time of that survey. A more recent survey of obstetricians and certified nurse-midwives found significant gaps in knowledge and comfort with counseling about first-trimester serum screening, including aneuploidy risk and posttest reproductive options, topics that are equally important in cfDNA screening [45]. Gaps in the knowledge of these frontline prenatal healthcare providers are concerning, since a recent survey of obstetricians found that 83.3% offered prenatal genetic screening of some type, 59.6% served as patients' primary pretest counselor, 43.9% counseled patients on screen-positive results, and only 30% referred screened patients with positive results to a genetic counselor [46]. More research is needed on provider education and counseling for prenatal cfDNA screening, particularly among frontline providers.

Increased Use in Low-Risk Populations

In 2014, commercial cfDNA companies began to release sponsored academic research that suggested the sensitivity and specificity of cfDNA screening for major trisomies was comparatively high in both over 35 and general populations [47]. These findings suggested that cfDNA screening might be expanded for use in a general obstetric population, and in 2016, the American College of Medical Genetics' Noninvasive Prenatal Screening Work Group amended its guidelines accordingly (see above) [19]. Clinical uptake is still uncertain, but in a 2016 study, 8 of the 19 insurance payers examined had extended coverage of cfDNA screening to an average risk population, citing professional guidelines [48•]. This development suggests that professional guidance and payer practice are beginning to align in introducing the option of cfDNA screening to most covered pregnancies. However, the uptake by state Medicaid programs remains uneven; due to the patchwork nature of pregnancy care coverage among Medicaid plans, tracking coverage for screening can be difficult.

One of the most problematic elements of this expansion into general populations is the impossibility of providing specialty counseling and interpretation services to every woman considering prenatal screening and testing. Historically, women at higher risk of a pregnancy affected by a genetic condition were referred to maternal-fetal medicine or genetic counseling services. However, maternal-fetal medicine practices are generally restricted to tertiary care centers, and there are a strictly limited number of certified prenatal genetic counselors to counsel patients. Due to broad difficulties in receiving reimbursement for genetic counseling services, the majority of general practices cannot afford a full time genetic specialist [49, 50]. As a result, frontline providers will increasingly

be responsible for discussing screening and testing options and delivering results of prenatal genetic screens. Due to limitations on time and reimbursement, these practitioners often find it challenging to stay abreast of rapidly evolving genetic screening options, let alone adequately counsel patients about the increasing number of genetic conditions for which cfDNA screening is offered [34].

Expansion of Test Content

Concerns about expanding use of cfDNA screening in the general obstetric population increase with continual expansion of test panel content to include sex chromosome anomalies (SCA) like monosomy X (Turner syndrome) and Klinefelter syndrome; some microdeletions and subdeletions like 22q11.2 (DiGeorge syndrome) and Prader-Willi syndrome; and (on one panel) genome-wide copy number variants of 7 Mbp or larger and certain deletions that are smaller than 7 Mbp [20•].

Since any test's positive predictive value (PPV) depends on the population incidence of the condition tested, the PPV of cfDNA screening for trisomy 21 in higher-risk pregnancies remains high [51]. However, the PPV for rarer trisomies is lower, and is quite low for very rare conditions in a low-risk pregnancy, for instance between 2 and 4% PPV for the most common cfDNA-screened microdeletion, 22q11.2 (DiGeorge syndrome) [51]. As more and rarer conditions are added, inconclusive cfDNA screening results may necessitate increased follow-up testing, thus negating the reduction in invasive procedures that makes cfDNA screening appealing. Despite concerns about PPV, initial data on use of cfDNA screening indicates that it has led to a reduction in invasive follow-up procedures, with numbers of invasive procedures in California dropping from 47.2% from the year before cfDNA screening was introduced to 39.2% afterward [52]. A decrease in invasive diagnostic testing is a positive development but may also be cause for concern, as it may make it more difficult to train practitioners in techniques like amniocentesis and CVS or to keep practitioners' skills up-to-date. Finally, expanded test content presents challenges for genetic counselors and other practitioners, who must be vigilant to stay well informed about new test panels and to evaluate the clinical data available for each new result being offered so that counseling can be thorough and accurate.

Social Issues

Trends in Prenatal Screening and Termination of Affected Pregnancies

Expansions in the scope of cfDNA screening and population being offered it also have potential downstream effects socially and ethically. Several observers have raised concerns that the expansion of universal cfDNA screening will increase the number of abortions; this concern is exacerbated by existing evidence of diagnostic misconceptions among both patients and nonspecialist providers [53–55].

Another concern with expanded panels is the introduction of population-level screening for conditions that have not, historically, been the target of screening. In the US, sex chromosome aneuploidies have generally been identified in the neonatal period, if they are diagnosed at all, and many individuals with milder phenotypes are never diagnosed [56].

The introduction of cfDNA screening for these conditions, along with a high rate of false positive results, is forcing a rapidly expanding number of families and providers to confront difficult decisions about diagnostic testing and pregnancy continuation.

It is too early in the expansion of cfDNA to ascertain the impact this expansion will have on termination rates for these new conditions. Although numbers vary widely by geographic region, the historic US average rate of elective termination after a prenatal trisomy 21 diagnosis is approximately 61%, resulting in an estimated 20% decrease in live births of individuals with Down syndrome [57]. Existing data on parental decision-making following a diagnosis of sex chromosome aneuploidy indicates variation by condition but suggests an elective termination rate of 61–85% [58]. Even if the *rate* of terminations does not change with the introduction of cfDNA, its higher sensitivity and increasing popularity mean that more families will likely be offered such decisions. Thus, concern that the absolute number of terminations will increase may be realized.

Perspectives Regarding Disabilities

The high rate of elective terminations after a prenatal diagnosis may be partly due to a lack of understanding of genetic conditions and their impact on families. Indeed, a major component of the "disability critique" is that prenatal testing itself "depends on a misunderstanding of what life with a disability is like" [59•]. Phenotypes of prenatally tested genetic conditions range from very mild to fatal; people considering whether to have prenatal testing or considering test results may have difficulty distinguishing a particular condition from this wide range of possible outcomes [32•, 33•, 60, 61•]. Information regarding individual and family quality of life may be poor, and counseling to help families parse the available information is often scarce [62–66]. However, past studies of families that include individuals with Down syndrome, for example, have shown both that individuals with Down syndrome and their families generally report happiness and high quality of life, and that reported problems tended to be due to external factors like prejudice rather than the condition itself [67–70]. Significant improvements in medical care and social support services have also significantly changed the profile of living with many genetic conditions, in terms of both length and quality of life [66, 71–73].

Many scholars have also expressed concerns that prenatal cfDNA screening will erode social support for families with genetic conditions [28, 74–76]. Such concerns have been expressed about prenatal testing for decades, and there is some evidence that public attitudes toward those with prenatally detectable conditions have been shaped by the ability to predict and prevent their birth [26, 77–79, 80•, 81]. However, some families with genetic conditions have also expressed support for prenatal testing, often maintaining that prenatal information can help families prepare for a wanted child, who has special needs [74, 81–84].

Equity in Access

As cfDNA screening rapidly expands, disparities in access are another concern. As a commercial product, the cost of cfDNA panels is at the discretion of commercial laboratories that offer the test. Traditional serum screening and ultrasound protocols in the US are widely provided or reimbursed through states' Departments of Health and/or

Medicaid programs, and there is rarely a significant out of pocket cost to the patient [85]. By contrast, as of 2016, cfDNA screening was only gradually gaining acceptance and reimbursement by many private group insurance providers. Among public programs, California is the only US state to include cfDNA panels in a state prenatal screening program and then only as a contingent screen after other screen-positive results [86]. For the majority of its clinical use, therefore, cfDNA screening has mainly been available as an out of pocket expense, although in some instances, insurance companies will subsidize its use [87, 88]. Inevitably, this leads to improved access to cfDNA screening among patients with more comprehensive insurance coverage and/or higher income [89, 90]. Moving forward, it is not at all clear that either public or private payers in the US will find it cost-effective to offer universal coverage of cfDNA screening as a first-tier screen. Recent comprehensive analyses in the Canadian and UK health systems found that cfDNA screening offered cost savings when used as a contingent screen—that is, to follow up on high-risk serum screens—but not as a first-tier test [91•, 92]. For those without preexisting risk indicators, therefore, cfDNA is likely to remain a not insignificant out-of-pocket cost for the foreseeable future.

The creation of a “two-tier” health care system, in which higher standards of care are offered to those who can pay for them, is considered fundamentally unjust by many, and as perpetuating and exacerbating existing disparities in health, quality of life, and lifespan [93, 94]. Furthermore, those with lower socioeconomic status are likely to have considerably fewer resources to fully support a pregnancy and/or child with a genetic condition. The advantages afforded by earlier genetic screening are arguably higher in these populations, if they can utilize screening to access them. At the same time, increased preoccupation with newer screens is in danger of occluding the resources and support services devoted to the traditional screening protocols that disproportionately continue to serve individuals from lower socioeconomic groups. Moreover, when high-risk results are returned, it seems clear that those with private insurance will more readily enjoy improved access to follow-up care—including counseling, diagnostic testing, and social support services—than those from other groups [90, 95, 96, 97•, 98•]. The question of how and where to devote the public health resources necessary to adequately support the broad expansion of cfDNA panels and patient populations is one of the defining challenges of the translation of this technology.

Legal Issues

Intellectual Property

The technology underlying cfDNA screening has all been patented, which creates a complex patent landscape in the US. Over 100 patents have been filed regarding cfDNA screening technology, and the first four companies to enter the US market have engaged in numerous legal battles over the past several years to control access to the market [99•]. Several cases have centered on Sequenom’s 2011 patent on the method of detecting maternal cfDNA commonly used in cfDNA screening [100]. The validity of the patent was only recently decided when the Supreme Court refused to hear Sequenom’s appeal of a 2013 Federal Court ruling the patent invalid [100]. This decision may bring some stability to the volatile IP environment around cfDNA screening and also addresses issues of monopoly that a successful suit by Sequenom might have created. However, the significant costs of such

lawsuits may be passed on to consumers as companies try to recoup costs. Additionally, the intellectual property landscape is shifting as several companies, including Sequenom and Natera, pool their patents and license them out to independent labs. At least 46 labs have so far taken licenses using this underlying intellectual property [99•].

Regulatory Oversight

cfDNA screening platforms have been marketed by manufacturers as "laboratory developed tests" (LDTs), which means laboratories are monitored by the Centers for Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA) act. In 2014, the Federal Drug Administration (FDA) announced a draft guidance that would extend FDA oversight to more strictly cover "moderate" or "high-risk" LTDs, which would include cfDNA screening platforms [101]. As of publication, such regulations are yet to be finalized [101]. Under the current regulatory oversight, CLIA monitoring does not directly address patient safety concerns because CLIA neither assesses the clinical validity of tests nor validates tests prior to entering the market [102].

Abortion and Reproductive Rights: Return of Genetic Disability and Fetal Sex Information

cfDNA screening use may increase women's reproductive options and improve maternal safety in cases where a woman chooses to terminate her pregnancy. Because cfDNA screening can be used as early as 9–10 week's gestation, women may receive their results as early as 11–12 weeks. This is far earlier than traditional blood serum screens or amniocentesis results, many of which are not available until 15–20 week's gestation. While professional societies do not recommend using cfDNA screening as a diagnostic tool, screen results may enable patients and providers to schedule diagnostic tests earlier in a pregnancy [103]. In states like Arizona, Arkansas, Nebraska, and Texas (among others) where legislation restricts women's access to abortion prior to viability—in some cases as early as 20 weeks [104]—this may increase the amount of time a woman has to access abortion services. Earlier termination increases maternal welfare; complications associated with abortion, while very rare, increase with each week gestation [105].

However, some states are restricting abortion on the basis of termination for fetal sex or genetic disability, including Indiana, South Dakota, and Ohio [104]. The enforcement mechanism for these laws is questionable, as is their constitutionality, and Indiana's law was blocked in a Federal District Court because it limits access to abortion prior to viability [106]. However, clinicians must be aware of their state's laws regarding termination on the basis of genetic information.

Physician Liability

As cfDNA screening becomes more common in clinical care and expands into lower-risk populations of pregnant women, concerns about legal liability for healthcare providers also increase. Charges of medical negligence may arise if a physician does not meet the standard of care in genetic testing, resulting in a missed or incorrect diagnosis [107]. As cfDNA screening and its use change rapidly, gaps often develop between tests' advertised capabilities, professional recommendations, and actual clinical use in a given geographic area, leading to uncertainties regarding standards of care and legal obligations [108]. As

cfDNA screening technology moves into general practice, the legal obligations of clinicians without specialized training in genetics similarly become unclear. A medical negligence claim in this area may derive from omission or incorrect information given to a patient or from not properly explaining the potential error in genetic results from testing, both circumstances that may increase with increased use of cfDNA screening in nonspecialized, general practices [107, 109]. To date, no successful case regarding medical negligence and cfDNA screening has occurred, but as with all new medical technologies, as the use of cfDNA screening becomes more widespread, the likelihood increases for medical negligence cases to be brought [109].

Conclusion

cfDNA screening technologies continue to advance internationally. In 2016, the Wellcome Trust Sanger Institute in the UK announced a consortium to carry out the Prenatal Assessment of Genomes and Exomes; including the sequencing, via cfDNA, of over 1000 families for which a structural abnormality has been detected by ultra-sound, with an eye toward clinical translation [110]. The Chinese University of Hong Kong announced that cfDNA screening could detect not only the presence of malignancy in the maternal sample but also the organ system implicated, potentially bringing us closer to a liquid biopsy in oncology care [111]. Meanwhile, the same lab reported that they had advanced methods of detecting methylation status and size of DNA fragments to make cfDNA screening even more specific and expand its potential applications to the detection of thalassemia disorders [112]. Given that thalassemia disorders are the most common genetic disorders in humans—an estimated 307,900 children are born annually with a severe hemoglobin disorder—the ability to initiate noninvasive population screening for these disorders may constitute a much greater public health benefit than the comparatively rarer conditions currently screened [113]. Finally, in late 2016, Jain et al. published a study reporting the success of a method of performing cfDNA screening on trophoblast cells retrieved from the endocervical canal [114]. If validated, this technique may in the future extend the timeline of cfDNA back as early as 5 weeks gestation.

These unprecedented expansions into the scope and abilities of cfDNA screening offer the potential for enormous clinical benefit, especially as research on the future of prenatal interventions to address genetic abnormalities continues to move forward [115]. However, the rapid progress of the technology is straining the available resources for counseling and interpretation of results, and this trend is likely to continue as the number of individuals in the US and worldwide who are offered cfDNA screening continues to grow [23•]. This strain is even more prevalent in low-resources areas, including rural areas in both the US and abroad [116], raising the specter of a large number of women receiving screening on an uninformed basis and/or receiving or making incorrect interpretation of results, potentially leading to pregnancy termination they would not seek if provided accurately interpreted results and genetic counseling. It also raises the very pertinent question of the impact this widespread screening will have on the balance of social forces around wellness, maternal responsibility, and disability [26, 78, 117–120]. As more and more screening for an increasingly broad swath of the genome continues to take hold, it is realistic to assume that

the concept of what it means to have a “healthy” fetus must evolve; at a broad enough level of sequencing, *all* individuals contain genetic variants of unknown impact on the phenotype.

Meanwhile, there are difficult resource allocation decisions to be made about the best way to extend our health care energies in the prenatal period. There are strong arguments to be made that, given uneven access to basic obstetric services, it is inappropriate to continue expansion of a highly technocratic technology with unproven clinical utility [96, 121, 122]. Both public and private health insurers, providers, and policy-makers will need to grapple with the appropriate support for such a new and rapidly developing technological protocol. As discussed, there are likely to be considerable legal and policy implications of both cfDNA’s presence in prenatal care protocols and the downstream effects of our ever-growing knowledge of fetal genomic information. It remains essential to maintain a robust research agenda around the legal, public health, social justice, and psychosocial impact on the expansion of cfDNA screening on women, families, and health systems as a whole. The future of cfDNA screening is promising, but it is not yet an uncomplicated good.

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