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ETHICAL AND LEGAL ISSUES IN REPRODUCTIVE HEALTH

Ethical and legal aspects of noninvasive prenatal genetic diagnosis

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ABSTRACT

The new technology that will allow genetic testing of a fetus within the first trimester of pregnancy by isolating cell-free fetal DNA (cffDNA) in the mother's blood raises a range of ethical and legal issues. Considered noninvasive, this test is safe and reliable, and may avoid alternative genetic testing by amniocentesis or chorionic villus sampling, which risks causing spontaneous abortion. Ethical and legal issues of cffDNA testing will become more acute if testing expands to fetal whole-genome sequencing. Critical issues include the state of the science or diagnostic art; the appropriateness of offering the test; the implications of denying the test when it is available and appropriate; disclosure and counseling following test results; and management of patients' choices on acquiring test results. A challenge will be providing patients with appropriate counseling based on up-to-date genetic knowledge, and accommodating informed patients' legal choices.

1. Introduction

A means to detect a range of fetal genetic anomalies by testing maternal blood has been developed, described as cell-free fetal DNA (cffDNA) testing [1]. This is considered a minimum risk, noninvasive test, in contrast to fetal genetic and related testing by amniocentesis and chorionic villus sampling (CVS). However, the test raises a spectrum of ethical and legal issues. These include the state of the science or diagnostic art; the appropriateness of offering the test; the implications of denying the test when it is available and appropriate; disclosure and counseling following test results; and management of patients' choices on acquiring test results.

Resort to maternal serum to screen for fetal characteristics is not new. Alpha-fetoprotein testing of maternal blood has been used as a screening technique for over 30 years [2] to determine whether the more invasive amniocentesis is indicated. Amniocentesis may detect fetal neural tube defects such as spina bifida and anencephaly, in addition to some single-gene chromosomal abnormalities. The new test offers and promises to detect a wide range of genetic fetal anomalies and is considered to achieve high levels of sensitivity for trisomies 21, 18, and 13 in high-risk populations, with a 98% probability of correct diagnosis and a specificity above 99.5%, meaning that the proportion of non-affected instances—the true negative rate—would be very reliably determined [1].

The new noninvasive means of fetal genetic diagnosis may appeal to practitioners and expectant parents. Unlike amniocentesis and CVS, it presents no risk of causing spontaneous abortion and can be undertaken earlier in pregnancy: at 9 weeks of gestation, compared with 16 weeks plus a further 2 weeks for culture results in amniocentesis and 10–13 weeks for CVS, which is more complicated and carries twice the risk of spontaneous abortion [3] (p. 65).

In its December 2012 Committee Opinion on noninvasive prenatal testing for fetal aneuploidy [4], the American College of Obstetricians and Gynecologists (ACOG) cautiously approved cffDNA testing for women at high risk of bearing fetuses affected by trisomies 13, 18, or 21, but as a primary screening test rather than as a replacement for the precision obtained with CVS or amniocentesis. The test is also approved as a follow-up test for women with a positive first- or second-trimester screening test result. The Committee Opinion notes the limitation of the lack of outcome data for testing with low-risk populations, for which it cannot therefore be recommended. With high-risk populations, pretest counseling regarding current limitations of the test is recommended, with referral for genetic counseling for pregnant women with positive test results.

The ACOG Committee Opinion has been welcomed by companies that offer the technology for the test. They anticipate its improvement and sufficient cost reduction for widespread application, not limited to high-risk populations. Similarly, popular news media have indulged their appetite for scientific innovation with an immediate personal impact by publicizing not only the primary medical purposes but also some secondary social effects, with such article headings as "Prenatal testing: earlier and more accurate than ever" followed by the subheading "Parents-to-be can now safely determine their baby's gender, father, and certain chromosomal abnormalities during the first trimester" [5].

Popular reactions went beyond reassuring women in high-risk populations that they could enjoy the prospect of delivering healthy children. They speculated on a reduction close to elimination of births of children with Down syndrome and related genetic conditions, rendering parents who favor the births of affected fetuses and the born children themselves anomalous and stigmatized in their communities,

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and an increase in sex-selective abortion. Whether the new test offers a preponderance of social benefit over risk or vice versa is placed in the eye of the beholder.

2. State of the diagnostic art

The ACOG Genetics Committee Opinion [4] presents a balanced assessment of the current utility of cffDNA testing; its values and limitations; how it may be appropriately offered and undertaken; and how it fits within existing resources for fetal genetic diagnosis. A surge of enthusiasm to offer and provide improved diagnosis by cffDNA testing is understandable, driven by clinicians' intentions to serve their patients better and by patients' hopes that early testing will provide the reassurance of a reliable negative result or time to consider difficult options in the face of diagnosis of fetal anomaly. Promotion of cffDNA testing is also driven by aggressive advertising by test technology suppliers keen to develop a market for their product and to maximize their market share.

A cautious note has been sounded, however, against premature or excessive resort to the new technology. It has been observed, for instance, that "the diffusion of [cffDNA] testing into routine prenatal care may be occurring too quickly. Professional societies do not recommend these tests for normal-risk pregnancies because their clinical utility in the general population is not well established" [1] (p. 499). Concern has been raised regarding tests with high-risk populations because sensitivity and specificity tests were conducted on "collections of archived samples with known karyotypes that intentionally included a large proportion of specimens from women with known aneuploid fetuses" [1] (p. 499). This biasing of samples may be justified on scientific grounds related to the effectiveness of the test but it leaves questions about the generalizability of the outcome conclusions, even among high-risk populations for whom the test is considered most appropriate.

The limited evidence about the performance of testing in the general population and in twin pregnancies [6], and about the positive predictive value of the tests [7] underscores concerns about overselling and overuse of cffDNA testing. Its cost may be a restraint on present use because costs of the 4 versions of the test currently available in the USA range from $795 to more than $2000 [1] (p. 501) but, should costs fall significantly, routine resort to cffDNA testing will become a concern that reproductive health professionals and funders of reproductive healthcare services, both governmental and private, will have to address. Several biotechnological procedures such as in vitro fertilization and stem cell treatments have been criticized for having moved prematurely from research into therapy without the necessary intermediate stage of disinterested clinical evaluation—a move propelled by the hope that they will satisfy patients' needs and demands, and by commercial agents' incentives to create markets and reap returns on investments.

3. Appropriateness of offering testing

Ethical concerns raised by prospects of cffDNA testing include, but transcend, clinical diagnosis of trisomies in fetuses at high risk of abnormality. They arise more gravely because easy, safe access to fetal DNA might make fetuses amenable to techniques that test for a much broader range of genetic abnormalities such as susceptibility to breast cancer and late-onset disorders, and even extend to whole-genome or whole-exome sequencing. What was once a cavernous divide between the outer reaches of imaginative science fiction and the reality of the limited capacity of prevailing biotechnology is becoming progressively narrowed, making it foreseeable to achieve complete gene sequencing of an early fetus in utero by resort to cffDNA testing.

Initial concerns are more mundane and immediate. If cffDNA testing were to become relatively inexpensive and routine, women offered the test as part of their prenatal care might give consent as to any other request for blood sampling. Anecdotal hazards of routine blood drawing extend to thrombophlebitis, pulmonary embolism, and death but complications such as infection are rare, and associated mild bruising is usually transient. The law of informed consent to medical procedures requires disclosure of significant hazards, including low risks of severe consequences, but blood sampling is often taken as the legal paradigm of a minimum-risk procedure. Accordingly, little beyond brief discomfort and mild bruising is usually disclosed, and patients give consent to the procedure without much or any counseling.

However, as the ACOG Committee on Genetics observes, "[t]o offer a cell free fetal DNA test, pretest counseling regarding these [described] limitations is recommended. The use of a cell free fetal DNA test should be an active, informed choice and not part of routine prenatal laboratory testing" [4]. Concern has been expressed that offering cffDNA testing on a wide scale would undermine informed consent [8] and risk trivializing a procedure that might compel exceptionally difficult decisions to be made, with lifelong consequences. A related concern is that, because the "chances of an affected pregnancy ending in miscarriage decrease with gestational age, early testing will more often burden women with 'unnecessary' decision making concerning pregnancies that may spontaneously miscarry" [8] (p. 273).

Noninvasive prenatal testing of fetal characteristics has been advanced to identify significant chromosomal abnormalities, but as genetic diagnosis becomes refined the potential emerges to identify minor abnormalities, genetic features of unknown significance, and normal features of sex and inheritance—particularly paternity—that patients may disfavor for the children they might deliver. Disclosure of fetal inheritance of genes predisposing, for instance, to breast cancer may provide opportunities for parents to seek to control their future children's lives to an extraordinary degree and to terminate pregnancies on irrational and alarmist grounds. In pediatric genetics, it is often considered inappropriate to test minors for their liability to experience late-onset disorders, notably Huntington's disease [9] (p.232–3), lest disclosure may cause parents to limit their children's opportunities for enjoyment of their lives. However, disclosure may allow parents the advantage of time to make suitable plans. This raises concerns about whether there should be guidelines or limits for what tests and disclosures are appropriate regarding cffDNA testing.

A key ethical concern with prenatal genetic testing of more minor inheritance is that disclosures may precondition parents' expectations of their children's capacities and personalities, and trigger "genetic determinism:" that is, the belief that individuals' genes exclusively or primarily determine their capacities and characteristics. This belief revives the historical, unresolved debate about the interaction of nature (meaning genes) and nurture (meaning upbringing and social environment) in shaping an individual's character and personality [9] (pp. 281–299). A related concern is that, as children mature, they may be unduly influenced by what they perceive, and/or what their parents indicate, to be their genetic destiny. They may accordingly attempt to pursue, or to resist, their genetic predestination, rather than any independent choices or chance opportunities. They may be denied the freedom to flourish as their instincts and circumstances allow, and to express an independent personality.

They may also be compelled to forfeit an alleged right that has been recognized particularly in the context of genetic diagnosis: the right not to know [8] (p. 275). Ethics and law applicable to healthcare have come to emphasize informed consent, requiring health service providers' disclosures of information material to patients' choices. The obligation, however, is not to impose information but to offer it. The goal is to serve individuals' choices not only of treatment options but also of receipt of information. Patients may accept the offer and make an informed choice, or forgo the information and either accept the recommended treatment on trust or decline the treatment. Individuals may choose not to take an opportunity to learn their medical prognoses based on genetic or other tests. Parents who obtain cffDNA testing, or other genetic testing, of their fetuses may deny the children they rear the right of choice to be free of this knowledge.