

developing world, might help to encourage companies to spend resources on breakthrough innovation, rather than on minor modifications and lawyer fees. But whatever its implications for innovation, this much is clear: poor people around the world need better access to affordable drugs, and this decision will help to provide it.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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A New Era in Noninvasive Prenatal Testing

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A new, noninvasive prenatal test is poised to change the standard of care for genetic screening. Cell-free fetal DNA (cfDNA) testing requires only a maternal blood sample, can be performed as early as 9 weeks of gestation, and outperforms standard screening tests for trisomies 21, 18, and 13 in high-risk populations. It has a sensitivity exceeding 98% and a specificity above 99.5% (see table).

Currently, standard screening entails testing of maternal blood samples at gestational weeks 10 to 13 or 16 to 18 (or at both points) to measure serum markers associated with common trisomies and usually an ultrasound examination, including measurement of nuchal translucency, at 11 to 13 weeks. This approach identifies more than 90% of trisomies, with a screen-positive rate of 5% in the general population. Diagnostic testing for women with positive results on screening requires either amniocentesis or chorionic villus sampling, invasive procedures that carry a risk of miscarriage. Amniocentesis, which is performed far more commonly than chorionic villus sampling, is generally delayed until after 15

weeks, with a 1-to-2-week turnaround time for results.

The use of cfDNA testing may appeal to expectant parents for many reasons: it carries no risk of miscarriage, permits earlier detection, and generally provides earlier information about a fetus's sex. Earlier testing can reassure parents who have negative results, while offering those with abnormal results timely information to help them make difficult decisions. People who choose to continue a pregnancy after an abnormal result have additional time to prepare to deliver and care for their child.

Nevertheless, the diffusion of cfDNA 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. Yet because the Food and Drug Administration (FDA) is not empowered to require testing companies to produce evidence of clinical utility before receiving marketing approval, companies have been free to build consumer demand for cfDNA testing by aggressively marketing the tests,

emphasizing data that do not answer key questions. As a result, cfDNA testing seems to be drifting into routine practice ahead of the evidence.

Tests of cfDNA appear to be highly sensitive and specific in detecting trisomies, but two problems plague the evidence base. First, the sensitivity and specificity of the tests derive from studies done on collections of archived samples with known karyotypes that intentionally included a large proportion of specimens from women with known aneuploid fetuses. Evidence concerning the performance characteristics of the testing in the general population and for multiple gestations is limited.¹ Second, cfDNA-testing companies have not reported information about their tests' positive predictive value (PPV), and there is reason to question the tests' performance on this measure.² Arguably, PPV is more important than sensitivity and specificity to patients undergoing testing: it indicates the probability that a positive test result indicates a true fetal aneuploidy. Thus, PPV should be discussed in study reports and marketing materials but isn't.

Characteristics of Representative Noninvasive Prenatal Tests Available in the United States.*

| Test | Company | U.S. Launch Date | Conditions Covered by Test | Cost \$ | Sensitivity percent | Specificity |
|------------|----------|------------------|--|---------------------------------------|---|---|
| Verifi | Verinata | February 2012 | Trisomies 21, 18, and 13; optional expansion detects sex-chromosome abnormalities (monosomy X, XXX, XXY, and XYY) and may aid in stratifying the risk of X-linked disorders (e.g., hemophilia, Duchenne's muscular dystrophy, and ambiguous genitalia) | 1,200 (cost sharing capped at 200) | Trisomy 21, >99.9; trisomy 18, 97.4; trisomy 13, 87.5 | Trisomy 21, >99.8; trisomy 18, 99.6; trisomy 13, >99.9 |
| MaterniT21 | Sequenom | October 2011 | Trisomies 21, 18, and 13; sex determination | 2,762 (cost sharing capped at 235) | Trisomy 21, 99.1; trisomy 18, >99.9; trisomy 13, 91.7 | Trisomy 21, 99.9; trisomy 18, 99.6; trisomy 13, 99.7 |
| Harmony | Ariosa | May 2012 | Trisomies 21, 18, and 13 | 795 | Trisomy 21, >99.9; trisomy 18, 98.1; trisomy 13, 80.0 | Trisomy 21, >99.0; trisomy 18, >99.0; trisomy 13, >99.0 |
| Panorama | Natera | December 2012† | Trisomies 21, 18, and 13; monosomy X; antcipated detection of additional sex-chromosome abnormalities (XXX, XXY, and XYY) | 1,495 | Trisomy 21, 100; trisomy 18, 100; trisomy 13, 100 | Trisomy 21, 100; trisomy 18, 100; trisomy 13, 100 |

* Verinata and Sequenom cap out-of-pocket costs for copayments and for patients whose insurance does not currently cover the test. Sensitivity and specificity calculations were derived from noncomparable populations. The listed percentages are those reported by the companies from their marketing materials and should not be used for comparison among test options.

† Natera launched the Panorama test to a select group of partners in December 2012, with a full launch on March 1, 2013.

Studies of cfDNA testing have often been conducted on samples including a high percentage of specimens with known abnormal karyotypes. Prevalence rates for Down's syndrome in the samples are as high as 1 in 8.³ Although sensitivity and specificity are unaffected by the condition's prevalence in the test population, PPV and negative predictive value (NPV) vary considerably with prevalence. At a prevalence of 1 in 8, assuming a constant specificity of 99.7% and a sensitivity of 99.9%, the PPV and NPV are impressively high — 97.94% and 99.99%, respectively. But at a prevalence of 1 in 200 — the approximate prevalence of Down's syndrome among fetuses of 35-year-old women in the second trimester of pregnancy — the PPV drops to 62.59%.

It is worrisome that some laboratories that performed validation tests may have been aware that the samples included high proportions of specimens with known aneuploidies — but that this isn't always made clear in the studies' descriptions. Prior knowledge about the prevalence of aneuploidies in the samples may well have affected an analyst's decisions about how to classify ambiguous test results: someone who believes 1 in 8 samples is abnormal may be more likely to classify a questionable result as abnormal than someone who believes that 1 in 200 is abnormal. Not all published studies of cfDNA testing have this problem, and one study of a sample without a high prevalence of aneuploidies suggests that the false positive rate for the Harmony test (Ariosa) is low.¹ Without additional evidence, however, the clinical utility of cfDNA remains uncertain.

Given this unproven utility in the general population, the lead-

ing professional organizations, including the American Congress of Obstetricians and Gynecologists, the Society for Maternal–Fetal Medicine, and the National Society of Genetic Counselors, recommend cfDNA testing only for “high-risk pregnancies,” without specifically defining “high risk.” Furthermore, they recommend that positive results be confirmed through invasive testing. That recommendation is important for patients to understand, because if patients with positive results on cfDNA testing are counseled to wait until their diagnosis is confirmed before taking action, an important potential benefit of cfDNA testing is lost.

Patients must also weigh the benefits of earlier detection against other informational costs. Tests of cfDNA do not provide information about some disorders that are identified through standard screening, including chromosomal abnormalities other than trisomies. It is thus crucial that providers carefully counsel patients about the test’s advantages and disadvantages. Decision making is further complicated by the fact that cfDNA testing is costly and not widely covered by insurance. Four versions of the test are available in the United States, priced from \$795 to more than \$2,000 (see table). A few major insurers cover cfDNA testing if it’s accompanied by confirmatory testing for positive results, but many have yet to decide whether to cover it.

Meanwhile, testing companies have pursued various strategies to build consumer demand, including reaching out to expectant mothers through YouTube, Facebook, and Twitter. Some companies have capped out-of-pocket costs and offered “introductory

pricing” specials with costs ranging from \$200 to \$235. This strategy has had apparent success, with one company boasting a “spectacular” adoption rate of 60,000 tests performed in 2012.⁴

The companies’ marketing strategy risks building demand for tests that may not offer a substantial benefit, particularly for women with low-risk pregnancies. Expectant parents’ excitement about the opportunity to learn their child’s sex and rule out trisomies earlier may lead to discounting the tradeoffs involved, push the standard of care away from professional recommendations for confining use to high-risk populations, and contribute to higher costs. The evidentiary gaps concerning cfDNA testing, aggressive marketing, and rapid diffusion into routine practice can be traced, at least partially, to our country’s regulatory scheme for laboratory-developed tests. Under FDA regulations, commercial test kits — which are distributed to multiple laboratories and health care facilities — are subject to both premarketing assessments of analytic and clinical validity and postmarketing reporting of adverse events. No similar requirements exist for tests, like the cfDNA tests, developed for in-house use by a single laboratory.

Laboratory-developed tests are governed, instead, by the Clinical Laboratory Improvement Amendments of 1988. Laboratories must demonstrate such a test’s accuracy, precision, specificity, and sensitivity — but not its clinical validity or utility. Although companies offering noninvasive prenatal tests have chosen to perform studies in the targeted population, they aren’t obliged to do so,² nor must they design studies so as to provide robust evidence about clinical utility.

Congress’s choice to require a less onerous regulatory approach for laboratory-developed tests arguably promotes the availability of new tests, but it leaves the real-world benefits and risks of these tests more uncertain than those of commercial tests. The rapid proliferation of direct-to-consumer genetic tests and other laboratory-developed tests has led to controversy, culminating in two unsuccessful congressional attempts to strengthen oversight.⁵ For now, as with many medical innovations, it will fall to physicians to hold the line against pressures promoting diffusion of cfDNA testing beyond the boundaries of available evidence.

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