Noninvasive Prenatal Diagnostics: How Much Closer to Reality?

(A#2009800209)

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Issue:	*IN VIVO* Nov. 2009
Section:	Feature Articles (Long Article)
Article Type:	Corporate Strategy; Corporate Strategy/R&D, Technology
Industry Segment:	In Vitro Diagnostics; In Vitro Diagnostics/Genetic Testing; In Vitro Diagnostics/Molecular Diagnostics, Probe-Based
Subject/Market Dynamic:	Biochips, Microarrays; Genotyping; Hereditary diseases; Home Brews; R&D Strategies; Reagent Instruments; Tool & Target Technologies; Women's Health
Market/ Customer:	Physician Specialty/Obstetrics, Gynecology
Therapeutic Categories:	Gynecological, Urological
Companies:	Columbia University; Fluidigm Corp.; Harvard University/Harvard Medical School; Helicos BioSciences Corp.; Ikonisys Inc.; Luminetx Corp.; Luminex Corp.; National Institutes of Health; PerkinElmer Inc.; Sequenom Inc.; Spectral Genomics Inc.; Stanford University; Tufts University
Summary:	Whether the astonishing missteps by Sequenom, which earlier this year disclosed it could not support its data for a non-invasive Down Syndrome test, were merely poor management or a reality check for the field of non-invasive prenatal disgnostics, the NIPD opportunity is compelling. But the profession also understandably balks at obtaining information that is not then clinically actionable -- an issue that could further amplify in importance as technologies like microarrays and direct DNA sequencing increase become more prevalent.

Further Analysis:

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Illumina Goes Consumer	*IN VIVO*	Jun. 2009	2009800118
Sequenom's Failure Highlights an Underappreciated Risk of Biotech Investing	*IN VIVO*	May 2009	2009800083
Sequenom Is Improving Prenatal Screening, in Steps	*Start-Up*	Dec. 2008	2008900259

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Noninvasive Prenatal Diagnostics: How Much Closer to Reality?

The Sequenom affair may have dented expectations and stained credibility in the emerging field of noninvasive prenatal diagnostics, but the real question is whether any technology works yet.

by Mark L. Ratner

The complicated matrix of screening followed by diagnosis suggests that in the end, the opportunities in the prenatal space will yield various combinations of solutions.

But the profession understandably balks at obtaining information that is not then clinically actionable. That issue could further amplify in importance as the use of technologies like microarrays and direct DNA sequencing increases.

Strategies around isolating whole fetal cells from maternal blood have given way to the capture of free circulating fetal nucleic acids.

That the same technologies are used to identify circulating tumor cells makes it likely that the pursuit of cancer diagnostics will be a main driver for fetal cell extraction.

It remains to be seen whether the astonishing missteps by **Sequenom Inc.**, which earlier this year disclosed that it could not support the clinical results it had claimed for a noninvasive test for Down syndrome (trisomy 21), were merely a circumstance of poor company management--and therefore dismissible as an anomaly--or a statement that a reality check for the field of noninvasive prenatal diagnostics (NIPD) is in order and that expectations should be ratcheted way back.

It's conceivable that Sequenom's test could be revalidated and even launched in early 2010, and credibility restored. Conversely, the data may ultimately prove to be so weak that the company, which analysts at one time were saying could sport a market cap in excess of $2.5 billion and some hedge fund managers had bet would go even higher (it's currently under $200 million), is sold for scrap IP. Whichever way that situation shakes out, however, the NIPD opportunity is compelling: replace the current invasive testing for genetic disorders, which entails either chorionic villus sampling (CVS) or amniocentesis, with noninvasive tests using a blood draw; extract circulating cell-free nucleic acids or even whole fetal cells; interrogate the nucleic acids to detect changes in chromosome number or gene copy number variation; and, ultimately, leverage the technology to expand the panel for tests beyond Down syndrome, the other trisomies (extra copies of chromosomes 13 or 18), and chromosomes X and Y to also include microdelection and microduplication syndromes that are too small to be detected by current cytogenetic chromosome analysis (karyotyping).

"The opportunity for noninvasive prenatal diagnostics is something that has to happen," says Lissa Goldenstein, former CEO of **Artemis Health Inc.** "There's got to be a better way."

Driving the argument are advances in methodologies for identifying and isolating fetal nucleic acids circulating in the mother's blood (cell-free DNA or RNA) and in the tools for analyzing that cell-free material for genetic mutations, including kits for isolating free nucleic acids from plasma, amplification technologies such as digital and single-cell PCR, microarrays, mass spectrometry, even direct DNA sequencing, which many argue will become routine as costs come down toward the $1,000 genome goal. (In the past four years alone, sequencing costs have decreased by a factor of 10,000.)

The use of many of these techniques was at the heart of Sequenom's development of its *SEQureDx* trisomy 21 test, and the claims it had been making for its sensitivity and specificity--at least until April 2009, when the company acknowledged serious data tampering and announced that it therefore had to revalidate all of its clinical data in new studies, ultimately leading to the dismissal of the management team in September. (*See "Sequenom's Failure Highlights an Underappreciated Risk of Biotech Investing,"* IN VIVO*, May 2009*

[A#2009800083].)

Sequenom has been focused on Down syndrome using methods for detecting cell-free RNA and also DNA, based on work done by long-time collaborator Dennis Lo, MD, PhD, of the **Chinese University of Hong Kong**. [W#200820510] [W#200720209] (*See "Sequenom Is Improving Prenatal Screening, in Steps,"* START-UP, *December 2008 [A#2008900259]*.) Those efforts mirror the discoveries made by sequencing pioneer Stephen Quake, PhD, of **Stanford University**, the co-founder of **Fluidigm Corp.**, a microfluidics specialist, and next-generation sequencer **Helicos BioSciences Corp.** Quake published his work in the *Proceedings of the National Academy of Sciences* (*PNAS*) in October 2008, two months before similar work by Lo appeared, also in *PNAS*. Stanford has licensed Quake's inventions for detecting fetal genetic characteristics in maternal plasma, including the use of a combination of digital PCR and high-throughput shotgun sequencing, to both Fluidigm, which sells PCR kits, and Artemis Health (formerly Living Microsystems Inc.), one of the handful of young companies that, like Sequenom, is developing NIPD content. [W#200920069] (*See Exhibit 1*.)

Exhibit 1

Selected Companies Developing Noninvasive Prenatal Diagnostics

Company	Genetic Material/Source	Comments
Sequenom	Cell-free nucleic acids from blood	Developing Down syndrome test using mass spec. Presumed to also be developing sequencing-based detection technology. In the process of revalidating all of its data after discovery of data mishandling by employees.
Artemis Health	Cell-free nucleic acids or whole fetal cells from blood	Initially developing whole fetal cell separation methods using microfluidics. In January 2009, added a second program to develop technology for sequencing-based detection of fetal nucleic acids for Down syndrome.
Lenetix	Cell-free nucleic acids from blood	In a clinical trial of its *PloidYX* array-based technology using DNA methylation differences to detect trisomies. A publication on the technology has been submitted and could be out as early as November 2009.
Ravgen	Cell-free nucleic acids from blood Chances are,	Treats blood samples with formaldehyde to boost proportion of fetal DNA in the sample. Preliminary study published in *The Lancet*, February 2007.
Zoragen	Cell-free nucleic acids	Detection of unpaired nucleic acids for prenatal diagnosis.
Celula	Fetal cells from blood	Isolation of cells partly based on cell-sorting technology in-licensed from Genoptix. Assumed to be using white blood cells (not confirmed by company).
Ikonisys	Fetal cells from cervical smear	Founded 10 years ago to image fetal cells, but has been unable to isolate sufficient quantities of red blood cells for analysis. Now using digital microspcopy imaging technology elsewhere—to identify circulating tumor cells in cancer. Maintaining a prenatal program using FISH probes on fetal cells isolated from a cervical smear.
Parsortix	Fetal cells from blood	Device to separate fetal cells from 1.5 mL of whole blood.

SOURCE: Interviews; Company web sites

The Search for Whole Fetal Cells

Artemis is currently in fund-raising mode and declined a detailed interview for this article. Rightly or wrongly, however, when it took a license to the Quake technology, many close to the field interpreted the move as a signal that Artemis' strategy at the time, which was based on the isolation and analysis of fetal cells in maternal blood using a size-based microfluidics sorting technology, was foundering.

The prospect of NIPD based on isolation of whole fetal cells from maternal blood, thereby capturing the whole genome for biochemical analysis or even an optical analysis of the cells, has always been enticing. Getting the entire genome from an intact cell theoretically offers up many diagnostic possibilities, even beyond Down syndrome and other trisomy testing.

But these cells are rare, and while researchers have been trying to develop methods for enriching them--basically, by a negative depletion of the maternal cells in the solution--there have been few tangible advancements. Certainly none of significance as measured by publications or by the hint of a significant flow of VC funding into companies.

To get an idea of the difficulty, **Harvard Medical School**'s Mehmet Toner, PhD, a microfluidics expert and original Artemis Health collaborator, compares detection of fetal cells to that of circulating tumor cells (CTCs)--an increasingly important diagnostic tool for cancer detection. "A CTC is like taking a salt shaker and putting in 10 pieces of salt and one piece of pepper, whereas a fetal cell is like putting in a piece of sugar." In the case of maternal versus fetal cells, he says, "they smell the same and look the same." Also, cancer cells normally spread in blood. "That's the mechanism; it's part of the physiologic process," Toner points out. The biology of fetal maternal trafficking, however, is less known. People believe that these cells are leaking into the maternal circulation as part of immune regulation, he says, "but it is not as established as the biology of circulating tumor cells."

Nucleated red blood cells (RBCs) have been one favorite target because adult RBCs are not nucleated so there is no DNA coming from them, and fetal nucleated RBCs do cross the placenta. But they are also fragile: in effect, they are dying cells. Plus, although an intact cell presumably offers the potential to obtain the entire genome, the process of preserving the cells may prevent the use of a particular analytical method on either RNA or DNA. "It's a matrix of issues," says Goldenstein. Fetal intact cells in the mother's blood may also be at different developmental stages or comprise different cell types. They are also experiencing shock because they are moving from a hypoxic environment to a relatively hyperoxic environment, notes Diana Bianchi, MD, of **Tufts University**, an advisor to Artemis Health, who pioneered much of the prenatal field's early work using whole cells and holds IP in the area. "The fetus has a low blood oxygen level and the mother a higher blood oxygen level," she points out.

It appears that one of the few stalwarts still aimed at development of NIPD based on the isolation of whole cells is **Celula Inc.** It is focused on a variety of single-cell diagnostics including tests using fetal cells from maternal blood.

"We are not in a position to talk a lot about what we are doing or how we are doing it," says Drew Senyei, MD, of Enterprise Partners, which along with Arch Venture Partners and Versant Ventures has raised $11 million for the firm. "I can tell you that we are distinct from other companies doing prenatal diagnosis using free fetal DNA. We are going after the whole cell, which provides access to the whole genome." Using genetic analysis methods, Celula expects to choose among the 150 serious genetic abnormalities where there's consensus as to cause. "Our goal is to work with doctors and patients and provide them what they want, as opposed to what we think they want," says Senyei. The emphasis will therefore be on early identification of disease risks where action can be taken, such as phenylketonuria (PKU), a genetic abnormality usually found at birth where phenylaniline is not metabolizable, leading to mental retardation. There's a simple fix for PKU--change the baby's diet.

Senyei is quick to point out that Celula's emphasis is on development of both a diagnostic and a screening test. In terms of a diagnostic, despite the risks of amniocentesis and CVS, any new test would have to be extremely accurate and meet or exceed current karyotyping standards, he acknowledges, adding that the current standard of practice "is not 100%, but is very close to it," a high hurdle for a new technology.

Yet even if the premise of replacing invasive CVS and amniocentesis is simple and obvious, mapping out how it will come about is far from that.

The State of the Art

Most of the work in prenatal diagnosis the last 30 years has focused on two broad areas: Down syndrome and fetal structural abnormalities. The enormous interest in Down has resulted in the American College of

Obstetricians and Gynecologists (ACOG) coming out with a policy statement in 2007 that all pregnant women should be offered noninvasive prenatal screening for Down syndrome irrespective of their age.

Currently, screening is done using a combination of methodologies in the first and second trimesters, often including nuchal translucency (NT, an ultrasound technique used to forecast potential for defects based on the thickness of the skin fold behind the nape of the neck of the fetus--a thick fold is suggestive but not necessarily indicative of potential neural defects). There are first trimester and second trimester immunoassays including tests for levels of alpha-fetoprotein, human chorionic gonadotropin, and the hormone estriol (the Triple Test)--sometimes adding inhibin-A, a protein secreted by the ovary, as well (the Quad Test). Confirmatory amniocentesis or CVS is performed following a positive screen for these markers. CVS can be performed at 12 weeks and amnio after 16 weeks. "The big thing for any of these [screening] technologies is to be able to perform them in the first trimester," says Risa Stack, PhD, of Kleiner Perkins Caufield & Byers.

Using karyotyping based on an invasive sampling procedure, a geneticist can see extra chromosomes, missing chromosomes, breaks, and rearrangements. But only at a certain resolution--spotting a change of less than five megabases of sequence is problematic. Thus, while adequate for identifying major chromosomal disorders such as the trisomies, karyotyping doesn't reveal minor changes, which can have clinical consequences. "There are many of these microdeletion syndromes now," says Sue Gross, MD, of the **Jacobi Medical Center** in the Bronx, NY. "Not just one gene, but several contiguous genes that you are not going to see."

The current solution is to use fluorescent *in situ* hybridization (FISH)--a technology that uses sets of probes complementary to the DNA sequences of interest. FISH is used routinely in many parts of the US to look for trisomies and chromosomes X and Y, and results are available in 24 to 48 hours. There are also probes clinically available for certain microdeletion syndromes such as DiGeorge (22Q deletion) syndrome, which is associated with cardiovascular abnormalities, endocrine and immunological problems, hair loss, learning disabilities, even psychiatric disorders. But although DiGeorge can be inherited from parent to child, in many cases it's sporadic and just happens.

If there's a family history, a cytogeneticist can simply apply the 22Q probe. Sporadic cases may show up on an ultrasound, but the signs are often missed. "If it's a heart defect you'll find it," says Gross, "but if there's something wrong with the palate--that's not easy to see by any means."

In many cases, individual labs perform tests for microdeletion syndromes using customized panels. To reduce the need for FISH, which is expensive, Gross's lab has been collaborating with **PerkinElmer Inc.** (PE) to develop a set of probes for trimsomies and microdeletion syndromes using BACs (bacteria artificial chromosomes, commonly used in sequencing) attached to **Luminex Corp.**'s plastic beads.

PE, which devised a way to attach BACs to the beads, intends to sell a generic "BACs on Beads" kit--it's currently approved in the EU and approval is pending in the US--and also plans to offer testing via its **NTD Laboratories Inc.** affiliate, acquired in 2006. [W#200610123] Gross, however, prefers to customize. Her lab determined the disorders where it felt useful information could be obtained that would have "the most clinical impact for the buck," she says. "We came up with what we feel is a very logical and important set of disorders to look at." (*See Exhibit 2.*)

Exhibit 2

A Sample Test Panel of Microdeletion Syndromes

Disorder	Description
DiGeorge	Deletion on chromosome 22 and also known as 22Q11.2 deletion syndrome, associated with cardiovascular abnormalities, endocrine and immunological problems, speech impairments, hair loss, learning disabilities, and psychiatric disorders.
Williams	Deletion on chromosome 7, characterized by mild to moderate mental retardation or learning difficulties, a distinct facial appearance, and a personality combining over-friendliness, empathy, and anxiety.
Prader-Willi	Deletion of a subset of genes on chromosome 15, associated with weak muscle tone, feeding difficulties, poor growth, and delayed development.
Angleman	Related to Prader-Willi. Absence of a functional copy of the UBE3A gene, associated with feeding difficulties, development delays, speech and movement disorders, and later, seizures.
Miller-Dieker	Deletion on chromosome 17, causing severe abnormalities in brain development and characteristic facial features.
Smith-Magenis	Abnormality in the RAI1 gene on chromosome 17, associated with mild to moderate learning disabilities, sleep disorders, delayed speech and language skills, behavioral problems, and distinctive facial features.
Wolf-Hirschhorn	Deletion on chromosome 4, associated with delayed growth, intellectual disability, and seizures.
Cri-du-chat	Deletion on chromosome 5, associated with intellectual disability, delayed development, distinctive facial features, small head, low birth weight, and weak muscle tone.
Langer-Giedion	Deletion of various regions on chromosome 8, associated with bone abnormalities, including tumors, and distinctive facial features.
DiGeorge 2	Deletion on chromosome 10, associated with cleft palate, immune system and kidney problems, and learning disabilities. Also at greater risk for many mental illnesses.

SOURCE: Sue Gross, MD, Jacobi Medical Center; Various NIH web sites

Gross' lab purposefully picked syndromes for which FISH probes are available, so that in the event the probes find something, it can be confirmed with a reflex FISH test. "We are not calling these [BACs on Beads] diagnostics. They work well to that extent, but to call something a diagnostic you need a sufficient case history to establish that," Gross says. BACs on Beads should reduce the need for FISH testing, she believes.

Indeed, as the use of test panels that rely on amniotic fluid, such as BACs on Beads, expands, the matrix of screens and noninvasive and invasive diagnostics physicians want could become even more complicated. "If I counsel a patient about a noninvasive test, I have to tell her that amniocentesis carries a relatively minimal but real risk. However, amnio can detect A, B, C, and D, whereas the noninvasive test will pick up only A and B," says Gross. As more molecular information is added into the mix, weighing the information gained with an invasive procedure versus the risk of that procedure becomes even more complicated. "It's a moving target," she says.

Arrays to the Rescue?

For all kinds of prenatal testing, there are risks related to accuracy and also utility. "Be wary of someone who says there is no risk," says Gross. "For prenatal, specifically, our profession has balked at receiving information where the implications of a particular result are not clear. That will only result in scaring women and their families." PE learned this lesson when it attempted to move a technique called array comparative genomic hybridization (array CGH) from the postnatal setting, where it can be used to help diagnose reasons for developmental delay or intellectual or emotional impairment. As with FISH, array technologies look for different breaks in the chromosome. The advantage of arrays is they can house many probes and their "real estate" can therefore be leveraged to test for many things at once, offsetting their operating complexity.

PE obtained array CGH capabilities via the acquisition of **Spectral Genomics Inc.** in 2006. [W#200610069] "We were looking at the opportunity of moving array CGH to more of a prenatal application," says Howard Grey, PhD, VP, molecular diagnostics at PE. But in going through that and talking to key opinion leaders and users, it discovered that there was nowhere near a consensus in terms of the application of a high-density array CGH in a prenatal environment. "It became clear that the clinician community was looking for less information, not more," says Grey. "They were concerned about the degree of information an array could bring that was not necessarily clinically actionable." That experience led PE to the more modest and targeted BACs on Beads approach.

Now, however, the **National Institutes of Health** hopes that an ongoing trial of microarrays will be a significant step toward better defining test utility and clinical actionability.

The NIH multicenter study is using amniocytes and therefore is not geared toward noninvasive testing. But even if the current fetal DNA comes from amniotic fluid or CVS, the goal is to demonstrate that there are better analytical methods than FISH, for example, for interrogating DNA fragments. "Have we thought of using arrays noninvasively? Of course," says lead investigator Ronald Wapner, MD, of **Columbia University School of Medicine**. "That's the chase everyone is on, but it's down the line." At least half the samples used in the trial are from chorionic villa in the first trimester, reflecting the field's trend toward first trimester diagnosis.

The NIH array has a backbone that can identify aneuploidies and also approximately 80 known disease loci for microdeletion and microduplication syndromes, according to Wapner. "It's designed to be at minimum comparable to a regular karyotype and actually to be superior," he says.

The frequency of Down syndrome is approximately one in 800 pregnancies. Adding in the probability of the other trisomies, the odds are one in 500. Then including published results that demonstrate measurement of microdeletion and other syndromes that could be measured with array technology, significant array findings may occur in approximately one in 60 pregnancies, says Wapner. "The real balance question is what patients will think about a noninvasive test that identifies something that's one out of 800," he says, assuming an NIPD for Down alone, versus an array-based test using CVS or amniotic fluid. "If using microarrays identifies things that are more common, does it make more sense to go with the invasive test and get more information? That's the question all of us are struggling with," he says, echoing Sue Gross' comments.

Then, if a noninvasive test is a screen and not diagnostic, the equation becomes even more complicated. Those who have a negative noninvasive test result for Down syndrome, for example, still would have somewhere around a 3 to 5% chance of having the disease, even assuming the sensitivity Sequenom originally claimed. Plus, with the present paradigm, you get both information about the biochemistry and, when including NT, additional information about pregnancies at risk for heart defect, a number of other things, and a view of the anatomy of the fetus. "It's not likely," says Wapner, "that those of us in the field who do all of these pieces would abandon our present screening for only an incremental improvement in sensitivity or even of specificity. The incremental advantage if you come out with free fetal DNA as a screening test probably isn't going to excite anybody very much. It needs to be a diagnostic test."

In addition to refining the techniques for identifying clinically actionable genetic mutations, the NIH microarray trial could validate the tools that will help open up the entire field of fetal functional genomics.

Bianchi recently demonstrated what may be the first correlation between a gene expression pattern from fetal mRNA and disease. Indeed, her current work is now largely focused on looking at fetal mRNA in maternal whole blood, but unlike Sequenom or Artemis Health, she is using the technology to gauge the normal development milestones in the normal fetus as a lead for the development of new therapies.

Her lab recently showed that a Down syndrome fetus exhibits fundamental differences in terms of gene expression as compared with a normal fetus, she points out. "It was remarkable," she says. All of the Down

syndrome fetuses looked alike at the molecular pathophysiological level, even at week 16. Moreover, an analysis of those differentially regulated genes indicated that in Down syndrome, the fetus is undergoing oxidative stress--"a clear hypothesis for [developing] new treatments," she says. Plus, the pattern was different from that of fetuses with other chromosome abnormalities.

"There's no reason to believe that an examination of differential gene expression in amniotic fluid can't be used for understanding any fetal condition," she adds. If that's the case, and assuming the ability to extract fetal nucleic acids noninvasively, it would broaden the scope of conditions an array- or sequencing-based NIPD could identify, giving the technologies significantly more leverage. But as Wapner points out, that's years down the road.

In NIPD, Ethics and Technology Convergence

On their own, neither invasive nor noninvasive prenatal testing opportunities have propelled technology development. Sequencing costs are plummeting because of its utility in other areas, notably as a drug development tool. And the fact that many of the technologies used to identify infrequent cells and DNA sequences in circulation, such as differences in DNA methylation patterns, are of great value to the much-larger oncology community makes it likely that the pursuit of cancer diagnostics will be a main driver for rare cell extraction and even the framework of strategies for biomarker identification in NIPD.

Interestingly, however, discussions of the issues around clinically actionable information and physicians' discomfort with disclosing information to patients that's complicated and may only be of limited predictive value sound much the same as the discussions over the ethics of direct to consumer (DTC) personal genomics--especially when it comes to the use of sequencing technology.

George Church, MD, PhD, professor of genetics at Harvard Medical School, is quick to point out that what most people mean by DTC personal genomics are SNP chips. "That's really just leveraging a research community that has driven the development of these chips and plunging it into a market to see what happens," he says. It's a far cry from acting on a recommendation from a geneticist. It's also apparent that the potential impact of obtaining some level of information about the risk of birth defect, and also making the decision on whether to risk an invasive procedure that could cause significant harm to the fetus in the process of confirming that, is a thousand times more consequential than any actions based on knowing that one has a slightly elevated risk of diabetes or heart disease because of genetic make-up. (There may be some small parallel with having the ApoE4 gene and therefore a corresponding elevated risk for Alzheimer's disease, because there's little that can be done to prepare for its onset.)

Nonetheless, in both cases, it's reasonable to expect that as technology and bioinformatics costs drop, the information will be out there for the taking. "Historically, families looked for prenatal genetic screening only after they'd had an affected child," says George Annas, bioethicist at the **Boston University School of Public Health**. "If this becomes cheap enough and noninvasive, the tendency will be to do it routinely," he says. Certainly the true believers in sequencing see it as inevitable as the $1,000 genome itself, especially as sequencing one's genome would be a once in a lifetime expense.

The difference, of course, is that very few pregnant women would self-advise and not seek out a genetic counselor and/or physician. Plus, there are the professional societies like ACOG and the International Society for Prenatal Diagnosis to monitor and issue guidelines, as ACOG did with Down syndrome screening.

Diana Bianchi cites a talk she gave at a maternal fetal medicine meeting two years ago, at which she pointed out the number of scientifically baseless OTC tests there are that offer to determine the sex of a baby--some even cited her work on their web sites as an implied endorsement of their technology. "It's very upsetting to me as a responsible scientist," she says. On the other hand, she adds, "it always surprises me in many ways how much more sophisticated pregnant women are than their healthcare providers with regard to DTC testing."

The use of arrays and functional genomics methods, analysis of fetal cell-free DNA or RNA, and potentially whole fetal cells, along with improving analytical methods, are different opportunities that will yield combinations of solutions, says Lissa Goldenstein. But it's going to take strong clinical studies, she adds, to get it to the market and to become the standard of care. "The company that will be most successful will understand that this is about the quality of the information and the delivery of that information to the clinical community," she says.

Sequenom's premature bull rush to the market showed an ignorance of that need. Chances are, it was also as much a signal of work to be done as it was of progress being made.