

# Establishing a Non-Invasive Prenatal Testing Program in Practice

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**T**raditional prenatal screening for fetal aneuploidies (see **Box**) involves screening via a combination of ultrasound analysis and serial detection of maternal serum markers, including hCG and PAPP-A, in the first and second trimesters, with follow-up diagnosis by invasive procedures such as amniocentesis or chorionic villus sampling (CVS). Large, multicenter, first-trimester prospective screening studies revealed detection rates for trisomy 21 ranging from 79% to 90%, with false positive rates of 5%.<sup>2</sup> Detection of trisomy 18 and 13 with traditional non-invasive methods is less effective than detection of trisomy 21. Positive screens require confirmatory testing via a diagnostic invasive procedure, which is associated with a procedure-induced pregnancy loss risk of up to 1 in 300 to 500.<sup>3</sup> Furthermore, most sex chromosome aneuploidies are typically only detected by invasive procedures, since traditional non-invasive screening methods are not designed to detect these aneuploidies.

**The 3 most common aneuploidies are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome). According to the US Centers for Disease Control and Prevention, trisomy 21 is the most frequent chromosome abnormality, with an incidence of 14.5 cases per 10,000 live births, compared with 2.7 and 1.3 for trisomy 18 and 13, respectively.<sup>1</sup>**

## THE TREND TOWARD NON-INVASIVE PRENATAL TESTING

Because of the inherent risks associated with amniocentesis and CVS, there has been a big push toward non-invasive prenatal testing (NIPT) for fetal aneuploidies. NIPT utilizes cell-free DNA (cfDNA), present in maternal circulation, which can be isolated from maternal plasma. CfDNA is a mixture of maternal and fetal cfDNA and the average "fetal fraction" (the fraction in fetal cfDNA with respect to the total amount of cfDNA) at 10 to 20 weeks gestation is 10% to 15% (but can range from <3% to >30%).<sup>4</sup> There are mixed reports about the effects of race or ethnicity, maternal age, and aneuploidies in fetal fraction.<sup>5,6</sup> However, there is a strong negative association between fetal fraction and maternal weight, with overweight women far more likely to have low fetal

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**Dr. Marks** reports that he has nothing to disclose.

**Dr. Mancuso** reports that she is a speaker for Natera, Inc.

**Dr. Nudelman** reports that he has nothing to disclose.

**TABLE** Comparison of non-invasive prenatal testing research studies<sup>6,10-20</sup>

<b>Sensitivity False Positive Rate</b>	<b>Sequenom MaterniT21™<sup>10-12</sup></b>	<b>Verinata Verifi™<sup>13,14</sup></b>	<b>Ariosa Harmony™<sup>6,15,16</sup></b>	<b>Natera Panorama™<sup>17-20</sup></b>
Trisomy 21 (Down syndrome)	99.1% 0.2%	>99.9% 0.2%	>99% 0.1%	>99% (83/83) (CI: 95.6-100%) 0%
Trisomy 18 (Edwards syndrome)	>99.9% 0.3%	97.3% 0.4%	98% 0.1%	>99% (27/27) (CI: 87.2-100%) <0.1%
Trisomy 13 (Patau syndrome)	91.7% 0.9%	87.5% 0.1%	80% 0.05%	>99% (13/13) (CI: 75.3-100%) 0%
Monosomy X (Turner syndrome)	94.7% 0.5%	95.0% 1.0%	96.7% Unreported	91.7% (11/12) (CI: 61.5-99.8%) <0.1%
Female	97.9% 0.5%	97.6% 0.8%	>99% Unreported	>99% (469/469) (CI: 99.2-100%) 0%
Male	99.4% 2.1%	99.1% 1.1%	>99% Unreported	>99% (533/533) (CI: 99.3-100%) 0%
Triploidy	Unable to detect	Unable to detect	Unable to detect	>99% (8/8) (CI: 63.1-100%)

Abbreviation: CI, confidence interval.

fractions.<sup>4</sup> This is problematic because performance of first-generation NIPT suffers at lower fetal fractions.

Identification of fetal aneuploidies using maternal plasma-derived cfDNA requires cfDNA amplification and subsequent bioinformatics analysis. Thus far, there are 2 main bioinformatics approaches that are commercially available: the first-generation quantitative “counting” approach (including both massively parallel shotgun sequencing [MPSS] and targeted sequencing of non-polymorphic loci) used by most cfDNA-based tests, and the second-generation approach that targets single-nucleotide polymorphisms (SNPs) and incorporates parental genotypic information. This SNP-based approach is only utilized by the Panorama™ NIPT (Natera, Inc., San Carlos, California), and allows testing from as early as 9 weeks gestation—one week earlier than is possible with counting methods. In the first quarter of 2013, Natera, Inc. commercially launched Panorama, offering detection of fetal trisomy 21, trisomy 18, trisomy 13, monosomy X (Turner syndrome), and, if requested, fetal sex.<sup>7</sup> In addition, Natera, Inc. has recently appended Panorama to include screening for fetal triploidy.

### ADVANTAGES OF THE PANORAMA SNP-BASED APPROACH

Panorama is the only available method that analyzes SNPs. A SNP is a variation in the DNA sequence where a single base-pair is altered within an otherwise identical region

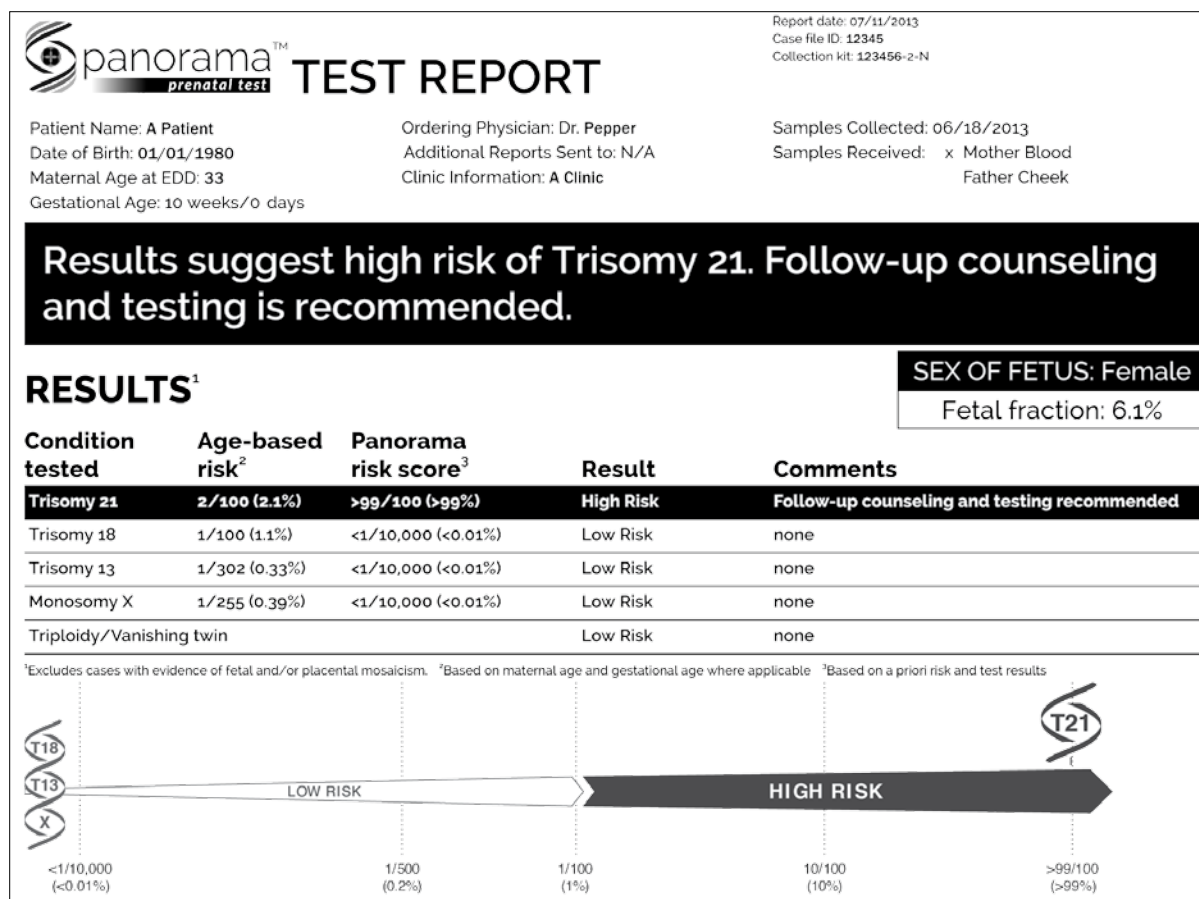
of DNA; for example, one individual may have a cytosine-guanine (CG) base-pair and another individual may have an adenosine-thymine (AT) base-pair.

Panorama’s technology utilizes the Next-generation Aneuploidy Test Using SNPs (NATUS) algorithm and is able to extract the maximum amount of information from the SNP measurements, resulting in more accurate results even at low fetal fractions. There are several distinct advantages of Panorama’s SNP-based approach that translate to unparalleled performance.

**The demonstrated accuracy of Panorama is higher than any other test.** In validation studies, Panorama demonstrated sensitivities and specificities of >99% for autosomal trisomies and fetal sex and 91.7% sensitivity with >99% specificity for monosomy X.<sup>8</sup> This is a direct result of the higher quality data produced from analyzing SNPs, when compared with methods that do not. Additionally, the NATUS algorithm incorporates parental genotypic information, meaning Panorama is also uniquely able to discriminate between maternal and fetal DNA, allowing for highly accurate identification of the fetal-specific signal.

**Panorama is the only test that can detect triploidy.** First-generation counting methods based on analysis of non-polymorphic loci require the use of a reference chromosome to identify fetal chromosome copy number; this precludes triploidy detection. However, the SNP-based

**FIGURE** An example of a Panorama test report suggesting a high risk for Trisomy 21



approach obviates the requirement for a reference chromosome and therefore is uniquely capable of detecting triploidy.

**Panorama is accurate even at low fetal fractions.** At present, the lower limit for NIPT detection of fetal chromosome copy number is around 4% fetal fraction. Additionally, accurate copy number calling is more challenging in the low fetal fraction range of 4% to 8%. Because fetal cfDNA cannot be physically separated from maternal cfDNA, accurate NIPT results are dependent on the ability to discern changes in the fetal levels of cfDNA from the predominantly maternal cfDNA signal. Panorama's use of SNPs, incorporation of parental genotypic information, and unique bioinformatics approach allow the fetal signal to be accurately identified even in the presence of an overshadowing maternal signal. Indeed, test performance is unaffected by low fetal fractions.

**The use of SNPs allows Panorama to utilize more quality control metrics, thus avoiding miscalls where cases contain abnormal biology.** Because Panorama analyzes SNPs, it generates significantly more information than first-generation methods and is thus able to include

an increased number of quality control metrics. These metrics include the singular ability to identify vanishing twins and other anomalies that might result in an incorrect call using counting methods. Additionally, Panorama generates a sample-specific accuracy that determines the reliability of the result. Together, this ensures Panorama is accurate across fetal fractions—even in the 4% to 8% range and as low as 3.8% fetal fraction. This is a significant improvement over counting methods that suffer from reduced sensitivity at fetal fractions below 8% and which cannot evaluate sample-specific validity at lower fetal fractions.<sup>4,9</sup> Panorama's accuracy at these lower fetal fractions allows testing from as early as 9 weeks gestation, when fetal fractions are typically lower.

A comparison of the autosomal trisomy sensitivities of counting approaches with those of Panorama is shown in the **TABLE** (page S2).

### CLINICAL STUDY DATA

An externally-blinded clinical study validated Panorama as a novel and effective method for accurately detecting fetal aneuploidies at an early stage of pregnancy.<sup>18</sup> In this

prospective study, 242 singleton pregnancies underwent CVS at 11 to 13 weeks gestation.<sup>18</sup> Maternal blood was collected prior to invasive testing and sent to Natera. Total (fetal + maternal) cfDNA, as well as maternal-specific genomic DNA from the mother's white blood cells, were isolated from maternal plasma. The cfDNA was analyzed at 19,488 SNPs covering chromosomes 13, 18, 21, X, and Y using a targeted multiplex polymerase chain reaction followed by sequencing. The NATUS algorithm then determined the fetal chromosome copy number and generated a sample-specific accuracy for each of the chromosomes of interest. Laboratory personnel were blinded to fetal karyotype.

Results were provided for 229 (94.6%) of the 242 cases.<sup>18</sup> All 32 aneuploid and 197 euploid calls were correct, including trisomy 21 (n = 25; sensitivity, 100% [confidence interval (CI), 86.3%-100%]; specificity, 100% [CI, 98.2%-100%]); trisomy 18 (n = 3); trisomy 13 (n = 1); monosomy X (n = 2); and triploidy (n = 1), with no false positive or false negative results. Median sample-specific accuracy was 99.9% (range; 96.0%-100%).

### USING THE PANORAMA TEST

Panorama consists of a simple maternal blood draw (2 tubes of ≥16 mL total volume) and can be performed without any risk to the fetus from as early as 9 weeks gestation—earlier than any other test. The test also includes an optional buccal (cheek) swab from the father. The father's sample maximizes the chance that a sample will return a result, but is not required as it does not impact the accuracy of results.

For sample collection, special blood tubes are used that protect the cfDNA, which are then sent at room temperature to Natera's CLIA-certified laboratory in San Carlos, California. After samples are processed, a report is generated that contains personalized risk scores for each of the tested aneuploidies (FIGURE, page S3). If requested, fetal sex is reported. Turnaround time is 5 to 10 calendar days. For patients identified as high risk for a fetal chromosomal abnormality, follow-up testing is recommended.

The American College of Obstetricians and Gynecologists' opinion from December 2012 recommended cfDNA-based NIPT, such as Panorama, as an option for screening women with an increased risk of aneuploidy and/or a positive first or second trimester traditional screening test result.<sup>21</sup> A patient with a positive NIPT result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of results.

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## PRACTICE CASE STUDIES

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### PRACTICE CASE STUDY 1: JEFFREY MARKS, MD

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#### NIPT is recommended in both low- and high-risk patients

The American College of Obstetricians and Gynecologists suggests fetal cell-free DNA (cfDNA) non-invasive prenatal testing (NIPT) for patients only at high risk of aneuploidy, including patients of advanced maternal age, patients with a prior chromosomal aberration, and patients with abnormal first or second trimester test results. Our center was a beta site user and Natera allowed us to use the test with any type of patient; there were no restrictions. We offered it to all patients that wanted non-invasive testing to either supplement or replace the other non-invasive advanced prenatal testing. Patients could either choose Panorama or First Screen, as First Screen tests for cystic hygroma. If they wanted the alpha-fetoprotein (AFP) test for spina bifida, or if they wanted a Level 2 sonogram, we would still offer Panorama.

#### Panorama enhances a practice

The reason we like Panorama is because it does not have the false positives and the lower accuracy and detection rates seen with First Screen, AFP, and even Level 2 sonogram testing. You have a detection rate of approximately 80% if you use the First Screen and AFP and still only up to 90% if you are using all 3 tests. By using fetal cfDNA NIPT, we can avoid a lot of unnecessary chorionic villus sampling (CVS) and amniocenteses, which may involve fetal risk or loss, patient anxiety, and the expense associated with those types of screens.

#### The next step for a patient who receives a high-risk Panorama test result

If the patient is early in her pregnancy, we recommend a CVS. If she is later in her pregnancy, we recommend amniocentesis. This is another advantage of Panorama because you can test at 9 weeks. The turnaround for Panorama test results is 5 to 10 calendar days. So if we test a patient at 9.5 weeks, we are early enough for a CVS.

If an aneuploidy is found and the patient opts to terminate the pregnancy, her options would be safer and easier the earlier this information is provided. You could do a sharp or suction dilation and curettage instead of a more invasive, dangerous, and expensive termination technique (such as dilation and evacuation or actually admitting the patient for delivery and induction—which can have such consequences as retained placenta and other complications).

#### Genetic counselors are available for physician questions at Natera

We refer patients with a high-risk/positive test result to a maternal-fetal medicine group that staffs a genetic counselor. One of the nice things about working with Natera is the readily available genetic counselors to address any questions or concerns. We call and talk with them fairly frequently.

In our group, we have done approximately 60 Panorama tests in 7 months and have had only 1 high-risk result. Interestingly, it was a non-advanced maternal age patient and it was early enough for her to have a CVS, which confirmed the positive results of the Panorama test.

#### The value of the Panorama reports

We like Natera's reporting because it gives you the percent fetal cfDNA fraction, as well as the probability of risk. This type of reporting is more useful, more reassuring, and less ambiguous for both the doctor and the patient. We have had experience using this type of NIPT modality from several different companies and have found that we prefer Panorama for several reasons.

Natera uses single nucleotide polymorphism (SNP) technology, rather than counting methodology, providing a more precise result with lower false positives or negatives at lower fetal fractions. We also think that it is vital that Panorama includes the percent fetal fraction in their result. If this percent is too low for an accurate result they will call a "no result" and ask for a redraw of the patient. Not every company performing cfDNA NIPT testing does this. We found that some companies will give a result no matter how low the percent fetal fraction, which can lead to an increase in false negative and false positive rates of their reporting. We also think it is important that Panorama includes monosomy X results in the report, another aspect that separates Panorama from other testing options.

Overall we feel that the Panorama test is the most precise option with the highest predictive value and has better success at lower fetal fractions. The advantage of Panorama over other types of testing is that it can be performed very early in the pregnancy, has low false positives/negatives, has no associated patient risks, and the patient can still proceed with other testing if needed once results are obtained.

### **PRACTICE CASE STUDY 2:** MELISSA MANCUSO, MD

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#### **NIPT and the maternal-fetal medicine geneticist**

We deal with the majority of prenatal testing and diagnosis in our region (Akron Canton). We receive referrals from both local and regional centers when there is a suspected birth defect or abnormality, or welcome any patients who may be interested in prenatal diagnosis. While we are the only center in our area offering chorionic villus sampling (CVS), many of our patients elect not to undergo invasive testing. Non-invasive prenatal testing (NIPT) has really begun a new era for us and more people are choosing this option.

#### **The genetic part of NIPT, the methodology behind the testing, and how Panorama compares to other tests used**

We offer NIPT to patients who are at high risk—those who are at advanced maternal age or have abnormal serum screening, abnormal ultrasound findings, history of prior affected child, etc. They are given the option of having invasive testing if they prefer. Most of our patients elect NIPT as a first-line test. Panorama uses the single nucleotide polymorphism (SNP), which can genotype both the mother and the fetus. A benefit of SNP technology is that it can detect triploidy. In addition, the test methodology gives us more confidence in a high-risk and low-risk result.

A very simplified explanation of the test is that the plasma, which has both maternal and fetal DNA, is genotyped independently from the buffy coat, which is all maternal DNA. The maternal genotypes are then subtracted, leaving only the fetal genotype. This information is put through the Next-generation Aneuploidy Test Using SNPs (NATUS) algorithm, which assigns a risk category to each chromosome of interest. We feel that this test methodology makes the most sense scientifically.

#### **The accuracy of the Panorama test**

We counsel all of our patients about the potential for false positive and false negative test results, which is very low with any of these tests. Panorama has a high detection rate, greater than 99%. That high detection rate has been very

helpful for our patients when they are deciding whether or not they want NIPT versus a CVS or an amniocentesis.

#### **The protocol for a patient who has a high-risk NIPT test result**

At this point, NIPT is still considered a screening test. We recommend confirmation of all high-risk results with either CVS or amniocentesis. Every patient who has this type of testing in our practice also will have formal genetic counseling prior to the screen. Such counseling adds an extra level of education so that the patient knows exactly what tests she is having and what type of results she can expect. She also can receive post test counseling from a genetic counselor.

#### **The potential concern of the relative fetal DNA fraction in the overweight patient**

We are learning more about maternal weight as a contributing factor in terms of fetal fraction, which can be lower in the heavier patient. We counsel these patients that there may not be a result based on the fetal fraction, depending on which test you are using. If a patient is morbidly obese, especially now as we are learning that obesity can affect the fetal fraction, we discuss that a result may not be obtained.

#### **The percentage of positive results using the Panorama test**

We have been using Panorama for about 6 months. Of the tests we have ordered, there has been a high positive rate, approximately 20%. The rate is higher than average because we are offering it only to high-risk patients right now. Many of these women have abnormal ultrasound findings such as cystic hygroma.

#### **Both doctors and patients are happy with Panorama**

Our patients have been very happy with this test, especially since they feel there is another option when they do not want invasive testing. They have been satisfied with the results. We think Panorama is a great test and our facility has also been very happy with it.

### **PRACTICE CASE STUDY 3:** MITCHELL NUDELMAN, MD

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#### **The evolution of prenatal testing**

Our practice has been around for more than 30 years, so we have experienced the gamut of how testing is done in general and how far technology has taken us. We started with just maternal age and progressed to the triple screen,

quad screen, first trimester screening (which includes nuchal translucency), and then, most recently, the sequential screen.

The cell-free DNA (cfDNA) evaluation test—one of which is the Panorama test—has changed the way we

approach our patients. We no longer feel compelled to refer patients that are of advanced maternal age, that is, over 35 years, to the perinatologist to discuss amniocentesis. We will counsel those patients within our practice and give them the options of choosing sequential screening, cfDNA testing, or referral for amniocentesis.

### Counseling patients on their options

The intake prenatal visit is usually done at 8 weeks. I cover both the genetics of chromosome abnormalities with the patient and the genetics of autosomal recessive disorders, for which I use a different test. I ask the patient about her knowledge of Down syndrome. If she is familiar with Down syndrome, I will start with the options for testing: doing nothing, having an invasive test, or having a non-invasive test. Then, I describe what an invasive test would be and the risks associated with it and the option of a non-invasive test, such as biochemical testing with the sequential screen or one of the newer cfDNA tests, such as Natera's Panorama test.

I do not tell a patient what to do. I try to understand what her needs might be. She may ask, "Why would I have a certain test?" I would tell her, "If you absolutely cannot live with partial knowledge, if you are the kind of person who really does not do well with risk assessment, and you need to have an absolute answer and you are willing to take on some risk of losing the pregnancy, then maybe amniocentesis is the best thing.

"On the other hand, if you are not going to use the information one way or another, if it does not matter to you what the outcome is, if you would not consider termination, if it would not benefit you to have information before the birth, then maybe the best option is just observation and not doing any testing."

The vast majority of patients, however, fall somewhere in the middle and I believe these patients are candidates for non-invasive prenatal testing.

### Recommending non-invasive prenatal testing to patients, especially those at high risk

My general modus operandi throughout my practice is to give patients information, to try and ascertain what additional information they need, and to give them options. Then I observe the patient's reaction. Is she still looking

confused? Does she have a real direction that she is heading? Does she feel strongly about one aspect of our discussion or another? If the patient really does not know what to do, then I offer my recommendation, based on her risk level, age, family history, and so on. If the patient wants to have some kind of evaluation done, and if I feel it is most appropriate to have the cfDNA test, then I recommend it.

I had a patient who had an amniocentesis in a prior pregnancy that wasn't necessarily indicated for medical reasons. She did it because she was anxious. She wasn't of advanced maternal age, but she wanted to have an amniocentesis. She unfortunately went on to have a second trimester loss at 17 weeks gestation that was temporally related to the procedure. With her second pregnancy, she was, by then, advanced maternal age, and was even more anxious. When she found out that the Panorama test had become available, she was appreciative of the fact that she could get reliable information from a blood test that was comparable to amniocentesis. She was thrilled that she could have her anxiety relieved and not have to go through a procedure that put her pregnancy at risk. It gave her great peace of mind and she went on to deliver a healthy baby.

### Patients who test positive according to a cfDNA test

If I have a high-risk patient, the protocol is the same as any other test that comes back to indicate a high risk for a genetic abnormality. If the cfDNA test comes back positive, I refer her to the perinatologist for a confirmatory amniocentesis.

### The Natera reporting system

I like the way that the Panorama test reports are presented and I believe Natera has been very responsible in their reporting. The idea of assigning a risk and telling patients qualitatively that this is a high-risk or low-risk result, as opposed to either positive or negative, I believe, is a responsible approach. Panorama is such a good test that the results really are significant and I feel comfortable with them.

One of the difficult things is determining which test to use. I tell patients that there are 4 tests available—MaterniT21, Verifi, Harmony, and Panorama (all coming from good companies). Having done research on them, I believe, at the current time, that Panorama is the better test, and that is why I have chosen to offer it to patients.

## PANORAMA ROUNDTABLE

Moderated by Dr. Jeffery Marks, this roundtable was held on August 8, 2013

**Dr. Marks:** How is the Panorama prenatal genetic testing method being incorporated into your clinical practice?

**Dr. Mancuso:** Right now we are offering it to all of the high-risk patients who come in that are either of advanced

maternal age, have a positive marker, or have a prior child with a fetal abnormality; basically we are adhering to the American College of Obstetricians and Gynecologists (ACOG) guidelines. I am sure you are all aware that amniocentesis and invasive testing are falling in numbers and

so many of our patients here in the Midwest are declining invasive testing. However, they feel like Panorama is a good option in terms of having a second reassuring test to get them through the rest of the pregnancy.

If anyone has an abnormal ultrasound finding but does not want invasive testing, we are offering Panorama to them as well. We are still recommending amniocentesis and invasive testing, but as a sort of second-tier approach to those patients who are declining other types of testing.

**Dr. Nudelman:** I second that. I basically follow the ACOG recommendations, which do not include low-risk individuals at this point. I will offer Panorama or invasive testing to all of my high-risk patients, meaning anyone of advanced maternal age, abnormal screening, or abnormal ultrasonographic findings that would suggest the possibility of aneuploidy. Thus I am using Panorama after positive biochemical testing, thickened nuchal translucency, or ultrasonographic markers of aneuploidy instead of, or prior to, amniocentesis.

**Dr. Marks:** Currently, ACOG's suggestion is to use this type of non-invasive chromosomal testing for only those at high risk. We have taken a slightly different approach because the cost was so affordable, at least in our practice. And just to get as much experience as we could, we were offering it across the board, even though I know that in the long term there are going to be more specific guidelines to which we will need to adhere.

I think for us, Panorama has decreased patient anxiety. Patients really have responded well to it and enjoy having that opportunity, even those at younger maternal ages or without positive markers, to avoid the false positives of the other markers.

**Dr. Marks:** As initial beta site users, have you limited Panorama to high-risk patients rather than offering the test more broadly in your practice?

**Dr. Mancuso:** I speak only for myself, but in our practice I have really refrained from making Panorama a universal option for everyone because the ACOG guidelines are limiting it right now to only high-risk patients. Even though we are a beta site, I did not want to experiment with the test on every patient at this point. But I look forward to the possibility that Panorama will eventually be something that we can offer to everyone and avoid the biochemical screening.

**Dr. Marks:** Right, because 90% to 95% of the amniocenteses we are doing are coming back normal. We are doing a great number of unnecessary amniocenteses.

**Dr. Mancuso:** I might have a slightly different practice situation because we do not see very many low-risk

patients. The majority of the people we see have some indication to have Panorama. However, we have also expanded it to women who have congenital adrenal hyperplasia. Therefore, we look for the Y chromosome and we are able to discontinue dexamethasone if they are carrying a male fetus.

I have a feeling that eventually ACOG will take the position that Panorama is indicated for all low-risk patients.

**Dr. Marks:** I think we will have a lot fewer false positives with Panorama than we would with the other markers that we have right now.

**Dr. Marks:** What do you think the important advantages of Panorama are over the other prenatal genetic testing methods and options?

**Dr. Nudelman:** I think that cfDNA tests such as Panorama carry significantly better accuracy with fewer false positives and false negatives than biochemical screening. That is certainly a benefit. There are some patients who like the idea that we are non-invasively looking directly at fetal DNA. I think this just sits well with them. We also have patients who like the idea of finding out the fetal sex as early as possible; something unique and not reliably available non-invasively to this point.

**Dr. Mancuso:** I agree with you. I think Panorama by far has many different advantages. I like that the test will identify triploidy and that the results are relatively independent of fetal fraction. I think that is really important, especially here in the Midwest, where many of our patients are larger and thus will have decreased fetal fraction. I think Panorama is the way to go in terms of screening for chromosome abnormalities. I do not think that the nuchal translucency should not be part of a screening protocol because it is valuable for detecting other issues, such as congenital heart defects or other genetic conditions, but I do think that the sensitivity and specificity of Panorama are much better. I think if I have a high-risk Panorama test result, I am more confident in telling a patient, "Yes, your baby probably really does have Down syndrome." I do not feel that we have the same confidence with serum screening, especially if only a second trimester screen is performed. I usually tell patients that we need to look a little closer with ultrasound or consider further testing.

**Dr. Marks:** The only other thing I would add is that you can test earlier with the Panorama—as early as 9 weeks. All of us have attested to the very accurate results and high sensitivity and predictive value. Panorama has the ability to perform well under low fetal fraction. The final point is that Panorama allows earlier, safer testing. If it is a positive result, an earlier, safer, and easier decision can be made by the patient.