Clinical and Cost Consequences of Incorporating a Novel Non-Invasive Prenatal Test into the Diagnostic Pathway for Fetal Trisomies

Susan S. Garfield, DrPH; Shannon O. Armstrong, BA

Summary

Background: Since 2007, the American College of Obstetricians and Gynecologists (ACOG) has recommended that all pregnant women be offered prenatal screening for fetal aneuploidy (i.e., trisomies 21, 18, 13). Current screening options include tests with sub-optimal sensitivity and specificity rates, while diagnostic procedures are invasive and create risk of procedure related miscarriage. The verifi™ test, a non-invasive test using circulating cell-free DNA (cfDNA), extracted from a maternal blood sample as early as 10 weeks gestation has demonstrated comparable sensitivity and superior specificity to invasive diagnostics in detecting fetal aneuploidy in chromosomes 21, 18, and 13.

Methods: A cost-model was developed to evaluate the impact of incorporating this prenatal test into routine high-risk maternal screening practice. The multi-stage transition probability model leveraged published cost estimates from Medicare as well as practice patterns and disease rates from published literature.

Results: The model demonstrates that inclusion of the verifi™ prenatal test provides clear clinical benefits. These include a 66 percent reduction in invasive diagnostic induced miscarriages and 38 percent more women receiving a T21 diagnosis. Total costs for prenatal screening and diagnosis for fetal aneuploidies are reduced by 1 percent annually.

Conclusion: Significant clinical and cost advantages are likely to occur when novel non-invasive prenatal screening tests with high sensitivity and specificity are incorporated into routine high-risk screening practice.

Key Points

• High sensitivity and specificity non-invasive prenatal testing has the potential to reshape the prenatal testing paradigm.
• When offered to women following a positive result from a screening test, these tests reduce the need for invasive testing.
• The reduction in use of invasive prenatal testing reduces number of procedure induced miscarriages and may reduce total costs of prenatal care.

Background

TRISOMIES 21 (DOWN SYNDROME, T21), 18 (Edwards syndrome, T18), and 13 (Patau syndrome, T13) are the most common live born aneuploidies (serious conditions caused by extra chromosomes).[1] Trisomy 21 is the most frequently occurring of the three, occurring in, on average, one of every 740 live births, though incidence increases with maternal age.[2] The average life expectancy for T21 individuals is 50 years. It is the leading cause of cogni-

tive impairment and affected persons also have a higher incidence of other health conditions including congenital heart disease, hearing, intestinal, and eye problems, celiac disease, leukemia, and thyroid dysfunction.[3]

Trisomy 18 occurs in about one in 5,000 live births,[4] though, like T21, incidence increase with maternal age. Due to the presence of several life-threatening medical problems, many infants with trisomy 18 die within their first month and as few as

Exhibit 1: Model Inputs and Outputs

MODEL INPUTS	MODEL OUTPUTS
Test specific reimbursement rates	Total costs for prenatal screening and diagnosis of aneuploidies
Test specific acceptance rates differentiated by normal and high risk patients	Total costs by testing modality (trip/quad screen, ultrasound, Amnio, CVS, verifi™ test)
Age breakdown of pregnant cohort	Invasive procedures (Amnio and CVS) rates
Test specific performance characteristics (sensitivity and specificity)	Miscarriage rates and costs
Miscarriage rates, by aneuploidy	Early identification of fetal aneuploidy rates
Aneuploidy prevalence by age	Total number of each testing modality (first trimester screening tests, trip/quad screen, ultrasound, Amnio, CVS, verifi™ test) Total diagnosed aneuploidies (T21, T18, T13)
Invasive diagnostic induced miscarriage rates	Amnio rate per diagnosed aneuploidy
Invasive diagnostic testing practice following initial positive screening result	Cost per diagnosed aneuploidy

5 percent survive until their first birthday.[4] The condition is associated with severe physical and cognitive disabilities including severe intellectual disability, heart defects and other major organ abnormalities, and low birth weight.[4]

Less common, trisomy 13 occurs in approximately one in 7,000 to 10,000 live births, likewise increasing with maternal age.[5,6] Similar to trisomy 18, most infants with trisomy 13 die within the first seven days of life due to severe anatomic abnormalities, and 91 percent of trisomy 13–affected infants die before their first birthday.[7] This condition is associated with severe physical and cognitive disabilities including cleft lip or palate, clenched hands and polydactyl, decreased muscle tone, hernias, severe cognitive defects, seizures, and microcephaly.[6] In addition to the above characteristics, infants with trisomy 13 may have a single umbilical artery at birth which can be a sign of congenital heart defects such as abnormal heart placement, atrial or ventricular septal defect, and patent ductus arteriosus.[6]

Though rare, each of these trisomies creates different degrees of complications for the infant, including high infant mortality with T18 and T13. Due to a host of health concerns associated with aneuploidies, knowledge of fetal status can help clinicians and parents plan for appropriate care.

Since 2007, the American College of Obstetricians and Gynecologists (ACOG) has recommended all pregnant women be offered prenatal screening for fetal aneuploidy (i.e., trisomies 21,18,13). Technolo-

Exhibit 2: T21 Incidence at Birth[23]

Maternal Age	Incidence at birth
Under 30 years old	0.0753%
30-34 years old	0.1532%
35-39 years old	0.5441%
40-44 years old	1.8226%
45-49 years old	3.2794%

gies currently used for routine screening include maternal serum screening (first and/or second trimester) and measurement of nuchal translucency by ultrasound (NT testing, first trimester). Second trimester ultrasound exam of the fetus is also used to detect anatomic abnormalities associated with these conditions and adds information to overall fetal assessment.

While these screening modalities are useful in identifying pregnancies at elevated risk for fetal aneuploidy, they are not diagnostic and their sensitivity and specificity along with high screen positive rates lead to a significant number of false positives and, consequently, the possibility of unnecessary invasive diagnostic procedures.[8,9,10] The trisomy 21 detection rate for first trimester combined screening is approximately 77 to 86 percent and is associated with a false positive rate of 3.2 to 5.6 percent.[8] Sec-

Exhibit 3: Test Performance Rates

Test	Sensitivity	Specificity
1st Trimester combined screen for T21 (serum plus NT)	81%[24]	94.1%[10]
1st trimester combined (serum plus NT) screen for T18	89%[24]	99%[25]
2nd Trimester Serum screen for T21 in women <35 years old	76.64%[24]	95.15%[24]
2nd Trimester Serum screen for T21 in women ≤35 years old	91.14%[24]	88.9%[24]
2nd Trimester Serum screen for T18 in women < 35 years old	55%[24]	99%[24]
2nd Trimester Serum screen for T18 in women ≥35 years old	55%[24]	99%[24]
2nd Trimester ultrasound T21	79.9%[26]	93.3%[26]
2nd Trimester ultrasound T18	83%[27]	99%[27]
2nd Trimester ultrasound T13	91%[28]	99%[28]
CVS	99.25%[29]	98.65%[29]
Amniocentesis	99.4%[30]	99.5%[30]

ond trimester serum screening and sequential screenings are associated with a higher detection rate (85 percent and 94 percent, respectively), but also an increased rate of false positive results (8.5 percent and 11 percent).[8]

Invasive diagnostic testing, such as chorionic villus sampling (CVS) in first trimester or amniocentesis in second trimester, often follows a positive screening test in order to confirm the results. However, these tests carry increased risk to both the pregnant woman and fetus, including an increased risk of miscarriage. While point estimates vary, data from several systematic reviews, randomized controlled trials, and national registry studies suggest a procedure-related miscarriage rate of approximately 0.5 to 1 percent following amniocentesis or CVS.[11,12,13,14]

While 95 percent of obstetricians report routinely offering screening to all pregnant patients,[15] not all women with a positive screening result elect to pursue invasive testing; and some with negative screening results still seek invasive testing. Uptake estimates of invasive diagnostic testing following a positive serum screen vary, with most studies reporting rates of approximately 60 percent.[16,17,18,19] The reasons for not having an invasive diagnostic procedure vary, but a high percentage of women report that fear of complications impact their deci-

sions. In contrast, a small proportion of women whose pregnancies are determined to be low risk for fetal aneuploidies elect to undergo additional testing, despite the associated increased risk of miscarriage. Most of these women are found to have fetuses with normal chromosomes (or karyotypes).

There is a clear unmet need for accurate, safe, non-invasive prenatal diagnostic technologies that allow for early diagnosis of fetal aneuploidies to provide more accurate information to pregnant women and their clinicians. Recent technological advances have spawned the development of novel prenatal diagnostic tests which are now poised to change the clinical and economic landscape of prenatal testing.

Specifically, technologies incorporating the analysis of circulating cell-free DNA (cfDNA) extracted from a maternal blood sample as early as 10 weeks gestation have received widespread interest from the medical community and from women.[20,21] These diagnostics have the potential to revolutionize prenatal testing by providing substantially more accurate results and reducing or eliminating the need for invasive procedures and their associated risk of fetal loss.

One recently commercialized non-invasive prenatal test that uses maternal whole blood from a single blood draw to detect aneuploidy in chromosomes 21, 18, and 13 by massively parallel DNA sequencing

Exhibit 4: Cost Inputs	
Test	**Estimated Cost**
1st Trimester combined screen	$378.50
2nd Trimester serum screen	$117.96
2nd Trimester Ultrasound exam of fetus	$330.18
Chorionic Villus Sampling	$1,669.98
Amniocentesis	$1,386.76
verifi™ prenatal test cost	$1,200

maternal plasma DNA[22] is the verifi™ prenatal test (Verinata Health Inc., Redwood City, CA). The blood sample is obtained by routine peripheral venipuncture, and the plasma is then separated from the blood cells. Total DNA in the plasma is then extracted, with the resulting mixture containing cfDNA of both maternal and fetal origin. Massively parallel sequencing (MPS) of DNA is then performed to generate millions of DNA sequence tags which are then aligned with a reference genome DNA sequence and undergo analysis with a proprietary algorithm to yield an aneuploidy classification for the sample for the chromosomes of interest (e.g., 21, 18, and 13). The result, provided within eight to 10 business days of obtaining a blood sample, is reported. The test can be done as early as ten weeks gestation.

The MatErnal BLood IS Source to Accurately Diagnose Fetal Aneuploidy (MELISSA) study was designed to demonstrate the performance of the verifi™ test (clinicaltrials.gov identifier NCT01122524). The MELISSA study enrolled patients with pregnancies at high risk for fetal aneuploidy due to at least one of the following factors: advanced maternal age (38 years of age or older in this study), a positive result from a serum screening test, soft or hard markers from ultrasound associated with fetal aneuploidy (e.g., increased NT thickness, cystic hygroma, congenital anomaly or amniotic fluid anomaly), or previous aneuploidy pregnancy. Blood samples were obtained from 2,882 women prior to their undergoing invasive prenatal diagnostic procedures at 60 sites in the United States. All singleton pregnancies with any abnormal karyotype and a random complement of subjects with euploid (normal chromosome number) karyotypes were selected by an independent biostatistician for analysis in a prospective, blinded fashion. Independent classifications of aneuploidy status were made for each sample, namely: chromosome 21,

chromosome 18, and chromosome 13 as affected or unaffected. These classifications were then compared to the corresponding fetal karyotype by the independent biostatistician to determine performance of the verifi™ test. Within the analysis cohort of 532 samples, the test correctly identified 89 of 89 (100 percent; 95 percent CI 95.9-100.0) cases of trisomy 21, 35 of 36 (97.2 percent; 95 percent CI 85.5-99.9) cases of trisomy 18, and 11 of 14 (78.6 percent; 95 percent CI 49.2-99.9) cases of trisomy 13. There were no false positives (specificity = 100 percent).[21]

Based on the clinical results obtained from the MELISSA study, an economic model was developed to evaluate the cost consequences of practice change given the results found in the study, if the test were incorporated into standard of care. The model details the expected clinical and economic impact of incorporating this test into routine clinical practice for high-risk pregnancies. The impact of test adoption was modeled using cost and assigned test performance variables from the MELISSA trial as well as accepted medical evidence in the field of prenatal screening and diagnosis. The model followed practice patterns of having positive test results followed by an invasive procedure to verify the results.

Methodology

Bridgehead developed a detailed transition state probability model in Microsoft Excel that captures the complex screening and diagnostic paradigm from both a cost and clinical practice perspective. The model takes theoretical cohort of 100,000 pregnant women at high risk for fetal aneuploidy based on either first or second trimester screening and assesses expected cost and clinical impact the introduction of the verifi™ test for Trisomy 21, 18, and 13 will have as compared to current practice. The model inputs and outputs are detailed in Exhibit 1.

Exhibit 5: Adoption Rates of Prenatal Testing

Test	Normal Risk	High Risk
1st Trimester Combined Screening	50%	65%
Triple or Quad Serum Screening	70%	80%
2nd Trimester Ultrasound	90%	95%
CVS (without a prior screen)	1%	3%
Amnio (without a prior screen)	1%	5%
CVS (following a positive screen)	22%	20%
Amnio (following a positive screen)	70%	60%

The model divides the cohort into two groups by inherent risk, and each group proceeds through a theoretical pregnancy chronologically. Women may begin prenatal care in either the first or second trimester. It was assumed that 81 percent of women begin their prenatal care in the first trimester. The first testing point offered is the first trimester screen. Under the standard of care, women with a positive from the first trimester screen may be offered either an immediate CVS or a second trimester amniocentesis. With verifi™ testing, women may receive either an immediate verifi™ test or CVS or a second trimester amniocentesis. Positives from the verifi™ test in the first trimester were eligible to receive either CVS or amniocentesis. It was assumed, using published miscarriage rates for each trisomy, that some true positive from the first trimester would miscarry before the second trimester amniocentesis.

At the conclusion of the first trimester, all women who had not previously received first trimester screening are offered the second trimester serum screen. Positives from the second trimester serum screen are offered either amniocentesis or verifi™ test followed by amniocentesis. Women are offered second trimester ultrasound independent of any previous testing, with positives from the ultrasound being offered either amniocentesis or verifi™ test followed by amniocentesis.

The model utilizes a combination of published incidence and miscarriage rates for T21, T18 and T13, sensitivity and specificity of current prenatal screens and invasive diagnostic procedures, and expected reimbursement rates to estimate the clinical and economic impact of incorporating the test into routine prenatal screening paradigms. Weighted average incidence rates were calculated using clinically acceptable risk formula cited in Cuckle et al (Exhibit 2).[23]

Test performance characteristics from the literature were used within the model (Exhibit 3). Because performance of the second trimester serum screen for T21 is dependent on maternal age, performance characteristics used within the model are weighted averages based on maternal age.[24] The verifi™ test was modeled at sensitivity/specificity characteristics of 100 percent/100 percent, 97.2 percent/100 percent, and 78.6 percent/100 percent respectively for Trisomy 21, 18, and 13 (as compared to invasive diagnostic procedures).

Costs were estimated using January 2012 Medicare reimbursement rates based on applicable CPT codes plus 20 percent, in order to estimate the actual reimbursement provided by private U.S. health insurance organizations. Costs were considered in their totality, including physician's fees, facility fees and laboratory fees for each test, with the exception of serum testing. These blood tests are provided as part of routine prenatal care. They do not require a separate or additional physician visit. Costs for serum testing were considered as the laboratory costs only. Prenatal testing costs used within the model are shown in Exhibit 4.

Finally, the adoption rate of current prenatal testing was considered, as not all pregnancies receive prenatal screening or invasive testing. The use of prenatal testing is dependent upon geography, maternal age, and maternal socioeconomic status. The uptake of prenatal testing was stratified based on inherent maternal risk (advanced maternal age or previous aneuploidy pregnancy) and was estimated using a combination of published literature and quantitative primary research with clinicians and patients (Exhibit 5). Rates of amniocentesis uptake following a positive screening test were taken from Mueller et al 2005.[17]

It was assumed that women receiving a first trimester combined screen would not also receive a

Exhibit 6: Modeled prenatal diagnostic pathway which incorporates non-invasive prenatal testing

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Positive Screening          Non-invasive                    +        Amniocentesis or CVS
Test Result         ───▶    Prenatal Diagnostic*    ──────▶
                                                        ──────▶
                                                            −         No Further Testing
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*Non-invasive prenatal test model is based on data from the MELISSA study, evaluating the performance of the verifi™ test

second trimester screen, though they may receive a second trimester ultrasound. Therefore, the rates of acceptance for second trimester screening (70 percent or 80 percent, depending on baseline risk) were applied to only the women who had not elected a first trimester screen. Similarly, women who had received a first trimester CVS were not eligible to receive a second trimester amniocentesis. The lower uptake of CVS is based on a single study of the impact of first trimester combined screening on invasive diagnostic procedure uptake, showing a preference for amniocentesis over CVS (71 percent versus 29 percent).[31] While some women receive a "fully integrated" screen, which uses both the first trimester combined screen and second trimester maternal serum screen, that screening modality was not considered within this model.

Women in the model were eligible to receive the verifi™ test in the first trimester following a positive first trimester screen. Additionally, women were eligible to receive the test in the second trimester following a positive result from the second trimester serum screen or second trimester ultrasound. It was not assumed that the test would increase uptake of prenatal testing generally. Within the model, the uptake of the test in either the first or second trimester was confined to the maximum uptake of existing prenatal screening and diagnostics. Further, it was assumed that 80 percent of women at baseline high risk and 71 percent of women at baseline normal risk would choose the test following a positive screening result. This adoption rate assumes a small increase in demand over invasive diagnostic testing for non–invasive follow-up diagnostic testing after a positive screening result due to elimination of miscarriage anxieties.

Miscarriage rates of 0.5 percent for amniocentesis and 1 percent for CVS were used to estimate ex-pected miscarriages in the two scenarios. The model explored the use of the verifi™ test both with and without a confirmatory invasive procedure following a positive test result from the test.

A sensitivity analysis was conducted to understand the impact to overall results of each component variable. The sensitivity result findings were used to identify areas of high impact as well as to determine where future work should be focused.

Results

The model demonstrates that inclusion of the verifi™ test into the prenatal testing paradigm for high-risk women will provide clear clinical benefits. The biggest benefit to women comes from a reduction in miscarriages due to invasive testing. In the modeled population of five million covered lives with 100,000 pregnancies annually, invasive diagnostic induced miscarriages are reduced from 60 to 20, a 66 percent reduction. When an invasive procedure is never used following a positive test result, miscarriages are further reduced to 18.

Another clinical benefit of the verifi™ test is an earlier and accurate diagnosis of fetal aneuploidy. Testing with this novel blood test is possible as early as the tenth gestational week. The high performance of this test, regardless of gestational age, allows more women to receive an earlier definitive diagnosis. The adoption of the novel test results in 15 percent more women receiving a T21 diagnosis (148 with the standard of care versus 170 with verifi™ testing) and 2 percent more women receiving a T18 diagnosis (44 with the standard of care versus 45 with verifi™ testing), in the modeled population of 100,000 pregnancies.

Finally, the cost impact of the verifi™ test is an important consideration for health plans. In addition to being clinically beneficial compared to the current prenatal testing paradigm, use of the test prom-

ises to moderately reduce overall costs. Total costs for prenatal screening and diagnosis for fetal aneuploidies is expected to be $59,748,721 for 100,000 pregnancies under the current standard of care. The total cost for prenatal testing which incorporates the verifi™ test is expected to be $59,228,142 for 100,000 pregnancies, a savings of $520,578 or nearly 1 percent annually. The inclusion of verifi™ testing is driven by an important assumption within the model. A higher acceptance rate for verifi™ testing has been assumed as compared to acceptance rates for either CVS or amniocentesis. It has been anticipated that more women will accept a non-invasive blood test with no miscarriage risk. While the use of CVS and amniocentesis has been reduced by 72 percent in this model through the introduction of verifi™ testing, 927 more women receive some form of follow-up diagnostic after a positive screen in the verifi™ scenario than in the standard of care.

While seemingly moderate, the 1 percent savings is accompanied by an improved clinical experience by ruling out the need for clinically unnecessary invasive testing for many women. The model shows that with this test, the number of invasive procedures necessary in order to diagnosis a single aneuploidy is reduced by 81 percent from 43 to eight.

Sensitivity analysis reveals several important drivers of overall costs within the model. The cost of the verifi™ test had a large impact on the overall cost benefit of testing. With pricing of up to $1,200 per test, adoption of the verifi™ test yields cost savings when provided to women with a positive screening test. The cost of amniocentesis is also an important determinant of total costs. As the cost of amniocentesis increases, total cost benefit of the verifi™ test also increases.

Because uptake of screening tests ultimately determines eligibility for testing, the use of screening tests is an important driver of costs. Most significant to cost outcomes is the rate of second trimester ultrasound as many fetal trisomies are first identified during ultrasound. As use of the second trimester ultrasound drops, fewer women are indicated for invasive testing, resulting in fewer diagnoses, but lower costs. Testing with verifi™ remains cost effective at ultrasound adoption rates below 40 percent.

Similar to adoption rates, the specificity of prenatal screening is an important driver of costs and outcomes as specificity determines the total number of clinically unnecessary invasive tests. Specificity of ultrasound, second trimester serum screening, and first trimester screen were impactful to overall cost benefit.

Conclusions

The availability of a highly sensitive test that identifies risk for major aneuploidy disorders (i.e., Down syndrome, Edwards syndrome, Patau syndrome) is a major change in prenatal screening. With sensitivity and specificity approaching or equaling 100 percent, the significantly improved accuracy will almost certainly lead to rapid practice change among obstetricians and maternal and fetal medicine specialists and uptake by pregnant women. Payers will be challenged to consider how to cover the verifi™ test and other novel non-invasive prenatal diagnostics, either enabling broad-based access or limiting coverage to a pre-defined population of women determined to be high risk.

The findings of the model suggest a highly sensitive and specific test that identifies trisomy 21,18, and 13 would be cost saving by offsetting costs associated with clinically unnecessary invasive tests and resulting miscarriages. The high economic and emotional costs of amniocentesis and CVS could be significantly curtailed by use of non-invasive prenatal diagnostics, leading to more rational use of health care resources.

While several non-invasive prenatal diagnostics are currently in development, tests with the highest sensitivity and specificity will have the most positive economic impact to payers by decreasing false positive rates and associated unnecessary follow-up costs for invasive tests by 71 percent. These economic savings can be considered alongside the significant decrease in anxiety and reassurance women will have with safer, earlier, and improved availability of results. These types of advancements in care are rare.

Today, the clinical evidence for most non-invasive prenatal tests recently launched or soon to enter the market focuses on high-risk pregnancies (i.e., > age 35, previous aneuploidy birth, etc.). However, as data emerge about the utility of these tests as true screeners in the general population more economic analysis will be required to fully quantify the likely impact. Preliminary assessment using the performance variables from current studies on the theoretical cohort of 100,000 pregnancies suggest that screening all pregnancies would reduce unnecessary invasive tests by 88 percent and prevent 53 pregnancies from falling victim to diagnostic induced miscarriage. This significant clinical benefit comes at some cost when broadly applied. As such, ongoing modeling efforts can be used to detail the implications of different price, utilization, and performance variables to ongoing cost-effectiveness.

Ultimately, payers and other policy makers need to work with manufacturers, clinicians, and women's health organizations to facilitate patient education about the availability of these novel diagnostics. Additionally, given the cost-effectiveness and clinically superior performance non-invasive prenatal tests provide compared to current practice, coverage

policies should be developed that enable access for all indicated women. Further study is warranted to assess patient acceptance, clinician adoption, and real–world impact on practice patterns and behavior.

Susan Garfield, DrPH a Vice President at Bridgehead International, is a health economist with expertise in market access, reimbursement and novel technologies. Prior to joining Bridgehead, she was the Director,Global Reimbursement, Policy and Economic Strategy at QIAGEN Corporation. She received her Doctorate of Public Health from Boston University.

Shannon Armstrong, BA is a Consultant at Bridgehead International. She has developed economic models highlighting the clinical and economic benefits of a range of technologies. Before joining Bridgehead, she spent six years as the Director of Research and Marketing at InfoEdge. She received a B.A. from the University of Pennsylvania.

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