

# *AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report*

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## **Priority Area 12: Pregnancy Including Preterm Birth**

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## **Statement of Funding and Purpose**

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS A290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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## Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to [effectivehealthcare@ahrq.hhs.gov](mailto:effectivehealthcare@ahrq.hhs.gov).

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# Executive Summary

## Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 11,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas and one cross-cutting area.

## Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are

sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

## Results

The table below lists the six topics for which (1) preliminary phase III data were available for diagnostics and procedures and pilot data were available for programs; (2) information was compiled by April 15, 2012, in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and April 26, 2012. (Fourteen topics in this priority area were being tracked in the system as of May 2012.) We present four summaries on four topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

### Priority Area 12: Pregnancy and Preterm Birth

Topic	High Impact Potential
1. CDB-2914 (ulipristal acetate) for treatment of uterine fibroids	No high-impact potential at this time
2. *Cell-phone-based educational program (Text4baby) to improve outcomes for pregnant women and infants	High
3. *Donor human milk program for very-low-birth-weight infants	High
4. Endoglin urine test for preeclampsia screening	No high-impact potential at this time
5. *In utero surgery to repair myelomeningocele (spina bifida)	High
6. *Trisomy 21 fetal DNA test for first-trimester detection of Down syndrome	Moderately high

## Discussion

Relatively few new developments in interventions or programs and services in the area of pregnancy and preterm birth have been identified as meeting criteria of the Healthcare Horizon Scanning System. Of the topics identified that have received expert comments, two programs, one surgical procedure, and one prenatal test emerged as having a potentially high impact. While the programs that emerged as potentially high impact do not employ novel technology, one takes advantage of a mass communication tool in a different way with the target patient population in the hope of influencing behaviors that could improve health outcomes, and the other leverages a scarce resource, unused breast milk, to support unrelated (from the mother) very-low-birth-weight infants. The new diagnostic test identified to detect Down syndrome marks an approach that could significantly affect the care model for prenatal testing for this condition.

## **Cell-Phone-Based Educational Program (Text4baby) To Improve Outcomes for Pregnant Women and Infants**

- **Key Facts:** Statistics from the Maternal and Child Health Bureau indicate that infants born to mothers who received no prenatal care are 3 times as likely to be born at low birth weight and 5 times as likely to die as infants born to mothers who received prenatal care. Therefore, a significant unmet need exists for ways to encourage expecting mothers to seek prenatal and newborn care. Text4baby is an educational program developed by the National Healthy Mothers, Healthy Babies Coalition that is intended to promote maternal and child health. The program employs expectant mothers' cell phones to deliver three text messages (available in English and Spanish) per week, free of charge, during pregnancy and through the first year of the newborn's life. The mobile platform is provided by Voxiva, Inc. (Washington, DC). Free messaging services are provided by participating wireless service providers. The U.S. Department of Defense and U.S. Department of Health and Human Services are both conducting formal evaluations of the Text4baby service program. Since February 2010, more than 281,000 pregnant women have enrolled in Text4baby, which is now available in all 50 States and Washington, DC.
- **Key Expert Comments:** Overall, experts providing comments were extremely divided in their assessment of this intervention's potential to improve health outcomes, care access, and costs. Several experts, particularly those with clinical backgrounds, thought the program has potential to prompt expecting women to seek prenatal care who otherwise might not access care, which in turn may improve health outcomes, reduce health disparities, increase staffing and infrastructure requirements for pregnant women, and affect costs of care associated with pregnancy. However, several experts with health systems and research backgrounds were highly skeptical about the potential of text messages to affect patient behavior to seek care, especially if a patient has no access to care to begin with or has limited health insurance.
- **Potential for High Impact:** High

## **Donor Human Milk for Very-Low-Birth-Weight Infants**

- **Key Facts:** Very low birth weight (VLBW) is defined as a newborn weight of <1,500 grams (3 lb, 5 oz) at birth. Data from the U.S. Centers for Disease Control and Prevention indicate VLBW and extreme prematurity (infants born at fewer than 32 weeks gestation) are factors predicting a higher risk of death during the first month of life if an infant is not born at a level III hospital. Child Health USA reports that infants born at such low birth weights are about 100 times as likely to die in the first year of life as infants of normal birth weight (>5 lb, 8 oz). VLBW infants who survive are at significantly increased risk of severe cognitive impairment and pulmonary and vision problems, requiring increased levels of medical, educational, and parental care. Many mothers who give birth to premature VLBW infants are unable to provide breast milk at all or in sufficient quantities. Donor milk from other lactating mothers could be a novel option to significantly improve patient health outcomes. Lactating women can pump and donate their milk to milk banks. Similar to standard practice at blood banks, lactating donors are screened for communicable diseases, alcohol consumption within a specified period, medication use, and vitamin supplement use, and donors must be nonsmokers. Milk is frozen and transported to the milk bank, where it is pasteurized, cultured for bacteria, and shipped overnight to hospitals and homes. A prescription is needed for the milk to be dispensed. The U.S. Food and Drug Administration (FDA) does not regulate human milk banking but offers

guidelines and provisions if mothers choose to feed infants with human milk other than their own.

- **Key Expert Comments:** Experts thought that human donor milk programs had potential to reduce rates of disease and infection in neonates, and they were eager to see additional studies to determine this intervention's impact on neurodevelopment. Experts agreed that this intervention had potential to reduce health disparities and thought that increasing accessibility of donor human milk programs to African-American and socioeconomically disadvantaged babies might significantly improve infant health outcomes
- **Potential for High Impact:** High

## **In Utero Surgery To Repair Myelomeningocele (Spina Bifida)**

- **Key Facts:** Myelomeningocele, the most serious form of spina bifida, occurs in approximately 3.4 of every 10,000 births, and 10% of affected infants die. In this condition, the protrusion of the spinal cord through an opening in the vertebral column may change the flow of cerebrospinal fluid (CSF) and pull the brain stem into the base of the skull (hindbrain herniation). As the circulation of CSF is affected in the brain, a life-threatening buildup of CSF requires postnatal surgical insertion of a shunt (typically 24 to 48 hours after birth) into the brain to drain excess fluid into the abdominal cavity. In utero surgical correction of myelomeningocele involves a highly specialized multidisciplinary team, and the procedure is intended to correct the defect in the fetus before the 26th week of pregnancy. With the mother under general anesthesia, an incision is made across her abdomen to expose the uterus, which is then opened to rotate and expose the myelomeningocele on the fetus' back. A pediatric surgeon removes the protruding myelomeningocele sac and closes the tissue around it, including skin. Once covered, the spinal cord is no longer exposed to the potential detrimental effects of the amniotic fluid. After closing the uterus and abdominal wall, a maternal-fetal specialist uses ultrasound to ensure that the placenta and fetus are in the right position, and a fetal cardiologist examines fetal cardiac function. Adzick and colleagues (2011) presented data from a study of 183 patients whose fetus had spina bifida who either had prenatal surgery before 16 weeks of gestation or had standard postnatal surgery. The trial was stopped for efficacy of the prenatal surgery after recruitment of 183 of a planned 200 patients. This report was based on results in 158 patients whose children were evaluated at 12 months. Researchers reported that the prenatal surgery significantly improved the composite score for mental development and motor function at 30 months and improved several secondary outcomes, including hindbrain herniation (by 12 months) and ambulation (by 30 months). The surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery. This surgery is not subject to FDA regulatory approval.
- **Key Expert Comments:** Overall, experts commenting on the procedure agreed that in utero surgery has potential to significantly improve patient health outcomes and reduce complications of postnatal surgical repair of myelomeningocele. The 2011 results of the Adzick et al. study provided the kind of data experts sought to indicate that this intervention could be an effective alternative to postnatal surgical repair with high potential for high impact.
- **Potential for High Impact:** High

## Trisomy 21 Fetal DNA Testing for First-Trimester Detection of Down Syndrome

- **Key Facts:** Currently, pregnant women are offered a series of screening tests, including blood markers and invasive diagnostic testing (e.g., chorionic villus sampling, amniocentesis) for fetal aneuploidy if a combination of maternal age, ultrasound results, and biochemical marker results indicate that the woman is at high risk of carrying an affected fetus. However, this screening algorithm has a false-positive rate of about 2%, which results in about 16 women being offered an invasive diagnostic test for each woman who is actually carrying an affected fetus.<sup>1</sup> Therefore, for each diagnosis of Down syndrome, about 15 women are subjected to an unnecessary invasive diagnostic procedure. Chorionic villus sampling and amniocentesis carry a small but significant risk of miscarriage. Several companies have developed a new fetal-DNA-based blood test that detects fetal DNA in the maternal blood to detect Down syndrome and two other trisomies. Such testing is intended to help women avoid unnecessary, invasive followup testing that could pose a risk of miscarriage.
  - The first company to make such a test available in the U.S. is Sequenom, Inc. (San Diego, CA), which markets a laboratory-developed test and is in the process of developing a test kit to gain FDA marketing approval. This test uses Fetal Nucleic Acid Technology to detect and isolate circulating fetal DNA from a maternal blood sample. Repeated parallel sequencing can detect an excess of chromosome 21 DNA of fetal origin, which indicates trisomy 21. Sequenom states that circulating fetal DNA can be obtained from a maternal blood sample very early in pregnancy and could benefit pregnant women by helping rule out trisomy 21 abnormalities during the first trimester, thereby avoiding more invasive testing. In October 2011, the company announced the launch of the test in 20 major metropolitan areas as a laboratory-developed test to be performed on samples sent to its Sequenom Center for Molecular Medicine. The cost of the MaterniT21 PLUS test has been reported at \$1,900 per screening. The additional cost associated with the addition of the MaterniT21 PLUS test to the prenatal aneuploidy screening algorithm could be offset to some extent by the potential for the test to reduce the number of invasive diagnostic procedures performed.
  - Other companies that have followed suit to develop a similar laboratory-developed test include Verinata Health, Inc. (Redwood City, CA) and Ariosa Diagnostics (San Jose, CA). Verinata Health, Inc. (Redwood City, CA) developed a test (the verifi™ Non-Invasive Prenatal Test) that is also based on massively parallel shotgun sequencing of circulating cell-free DNA from the mother and fetus in maternal blood and is intended to identify trisomies 13, 18, and 21 as early as 10 weeks into pregnancy.<sup>2</sup> The test was scheduled to become available beginning March 1, 2012, but no confirmation of this launch can be verified as of this writing (May 2012). Like the MaterniT21 and verifi tests, Ariosa Diagnostics' Harmony test is based on identification and quantification of sequences from cell-free DNA isolated from maternal blood; however, unlike the other tests, Harmony involves targeted sequencing of only specific regions of interest from the genome, potentially increasing test scalability and/or reducing the cost per test. In May 2012, the company announced the prenatal test's commercial launch in the United States and Canada.
- **Key Expert Comments:** Overall, experts commenting on maternal blood-based fetal DNA testing viewed such tests as having potential to meet a significant unmet need for a noninvasive screening methodology that avoids risk of miscarriage and provides information earlier in a pregnancy. While availability of a noninvasive screening test for trisomy 21 and other trisomies

has potential to disrupt diagnostic paradigms and care delivery methods and increase patient acceptance, it is likely that it will initially displace only the current use of other noninvasive blood markers, rather than invasive testing; therefore, its overall impact initially would be incremental. However, a negative result could help some women avoid more invasive testing.

- **Potential for High Impact:** Moderately high

# **Pregnancy, Including Preterm Birth, Interventions**

## **Cell-Phone-Based Educational Program (Text4baby) To Improve Outcomes for Pregnant Women and Infants**

Statistics from the Maternal and Child Health Bureau indicate that infants born to mothers who received no prenatal care are 3 times as likely to be born at low birth weight and 5 times as likely to die than those whose mothers received prenatal care.<sup>3</sup> Therefore, an unmet need exists for educational programs that coach expecting mothers about the importance of prenatal care and newborn well-baby care.

Text4baby is an educational program developed by the National Healthy Mothers, Healthy Babies Coalition that is intended to promote maternal and child health. The program uses expectant mothers' cell phones to deliver three text messages (available in English and Spanish) per week, free of charge, during pregnancy and through the first year of the newborn's life. The short- and long-term goals of the program are to prevent pregnancy-related complications or maternal morbidity (diabetes and hypertension are among the most commonly reported conditions), poor birth outcomes, and early childhood morbidities to reduce infant mortality.

The mobile platform is provided by Voxiva, Inc. (Washington, DC). Free messaging services are provided by participating wireless service providers. The U.S. Department of Defense and U.S. Department of Health and Human Services (DHHS) are conducting formal evaluations of the Text4baby service program.<sup>4,5</sup> Message topics include prevention and intervention strategies to promote health of mother and child, such as information on prenatal care, smoking cessation, breastfeeding, childbirth, and developmental milestones. These messages are appropriately tailored to the baby's due date or child's birth date. Intervention text messages are covered by CTIA–The Wireless Association and free to all participants.<sup>6</sup>

According to the U.S. Centers for Disease Control and Prevention, since February 2010, more than 281,000 pregnant women have enrolled in Text4baby, which is now available in all 50 states and Washington, DC. The program is being adopted by more than 700 partners from National, State, business, academic, and nonprofit entities.<sup>7</sup> Johnson & Johnson, Inc., has made a multimillion-dollar, multiyear commitment to Text4baby, helping with the program's goal of diffusion to underserved mothers and service to 1 million mothers by 2012.<sup>5</sup> In February 2012, the U.S. Centers for Medicare & Medicaid Services (CMS) announced it will promote Text4baby to individuals enrolling newborns in Medicaid and the Children's Health Insurance Program.<sup>8</sup>

On November 23, 2010, the DHHS Health Resources and Services Administration (HRSA) requested public comments on the proposed project, titled Evaluation of the Text4baby Program. According to HRSA, "The goal of this program evaluation is to examine the characteristics of women who utilize the Text4baby mobile phone-based program, assess their experience with the program, and determine whether Text4baby is associated with timely access to prenatal care and healthy behaviors during pregnancy and through the first year of the infant's life."<sup>9</sup> Currently, two large studies are under way that are evaluating the effectiveness of Text4baby. Final data will not be available later in 2012.<sup>10</sup>

The National Latino Research Center at California State University San Marcos and the Department of Reproductive Medicine at University of California San Diego were expected to present initial study results from the Text4baby program in November 2011. Preliminary reported results were:

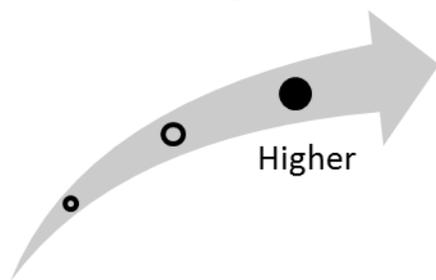
Women reported high satisfaction with Text4baby, with Spanish speaking women reporting even higher satisfaction scores than English-speaking women. Sixty-three percent of women reported that Text4baby helped them remember an appointment or immunization that they or their child needed. Seventy-five percent reported that Text4baby messages informed them of medical warning signs they did not know.

Seventy-one percent reported talking to their doctor about a topic that they read on a Text4baby message. Thirty-eight percent reported that they called a service or phone number that they received from Text4baby.<sup>11</sup>

## Clinical Pathway at Point of This Intervention

Once pregnancy is confirmed, periodic prenatal care visits are typically scheduled to provide an opportunity to discuss pregnancy-related health issues, such as the role of nutrition and physical activity, the impact of diabetes and high blood pressure on pregnancy, expectations during the birth process, and basic skills for caring of newborns.<sup>12</sup> The Text4baby educational intervention is intended to begin when pregnancy is confirmed and is intended to complement, or encourage the use of, prenatal care. The educational program may compete with Web-based platforms, such as the Mayo Clinic’s “Pregnancy week by week,” which is a Web-based information venue requiring fast Internet connectivity. The site provides images and a media gallery with topics related to the three pregnancy trimesters and pregnancy complications. Partial two-way communication is possible via blog forums and “Ask the expert” features.<sup>13</sup> Another potential competitor is the March of Dimes’ “Pregnancy” program, a Web-based platform with partial two-way communication (blogs, “Ask the expert”) that is limited to the mother’s health. There is no child health information specifically addressing the first year of life.<sup>14</sup> These interventions do not use an electronic cell-phone platform.

**Figure 1. Overall High Impact Potential: Cell-phone-based educational program to improve outcomes for pregnant women and infants**



Overall, experts were extremely divided in their opinions about this intervention’s potential impact on health outcomes, care access, and costs, signaling high controversy over such a program. Several experts, particularly those with clinical backgrounds, thought the program has potential to prompt pregnant women to seek prenatal care who otherwise might not access care, which in turn could improve health outcomes, reduce health disparities, increase staffing and infrastructure requirements for services for pregnant women, and affect costs of care associated with pregnancy. However, several experts with health systems and research backgrounds were strongly skeptical about the intervention’s potential to improve outcomes for two main reasons: the absence of any data indicating such a program could improve health outcomes and the program’s dependency on patient willingness and ability to seek care after text messages are received. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with backgrounds in clinical work, health systems, or research, offered their perspectives on this program.<sup>15-21</sup> These experts generally agreed that an unmet need exists for educating expectant women on the importance of prenatal care and newborn care and that addressing this unmet need with a text-message-based program is a novel approach. One clinical expert believes

in the program's novelty because social media and mobile devices have become the "primary source of communication among women of childbearing years. Low income and socioeconomically challenged women are high users of text messaging interactions."<sup>21</sup> A different clinical expert stated, "Most women desire more information than they can easily get from their health care providers, and may not come up with the questions to ask. Text messaging is a technology that the public—especially those young enough to be of reproductive age—has largely accepted. This provides a great opportunity to harness this technology to increase the reach of attempts to close the gap mentioned."<sup>15</sup>

However, experts were divided in their opinions on whether this program has the potential to improve patient outcomes. Some experts thought that, as one put it, "This program could have a tremendous impact on a child's morbidity and mortality in the first year of life, as well as the pregnant mother's well-being."<sup>18</sup> Other experts questioned whether receiving text messages would translate into mothers actually seeking care if they had not already tapped into a prenatal program. One health systems expert commented: "Receiving text messages will unlikely change outcomes. Those unlikely to seek medical attention during pregnancy will likely continue to avoid [seeking care] regardless of receiving text messages. In fact, there may be negative consequences, [in that] receiving messages could encourage people to not seek attention when it would otherwise be warranted."<sup>16</sup> One of the clinical experts was slightly less skeptical, but skeptical nonetheless, that this program could "result in a more 'activated' and prepared patient who can better negotiate the health care system, [but] it remains an entirely unstudied area whether this will result in significant benefit in the health outcomes measures relevant to pregnancy and childbirth."<sup>15</sup>

Experts were similarly divided on whether this intervention can change current patient management paradigms. One clinical expert believes that patient management through text messaging or social media communication might foster behavior change and believes that, because the messages are delivered on a relatively impersonal level, patients may more readily receive health information and, therefore, personally apply it. While some experts noted that this intervention might foster continual communication with patients, and possibly prompt patients to seek more care, an expert with a research perspective opined, "The technology is intended for expectant women who don't have access to prenatal care. If they become more aware that their baby is at risk, will they then have more access to care?"<sup>17</sup>

Experts who were optimistic about this intervention's potential to improve outcomes stated that it may affect health care operations if more patients seek care in primary care physicians' offices, women's health centers, and emergency departments, and the staffing and infrastructure required to deliver care would likewise increase.

If the intervention is proven to prompt better prenatal care, this program will affect costs, experts thought. On one hand, costs could increase because more patients might seek more prenatal care. Because the intervention is targeted toward women with barriers to health care access, such as a lack of insurance, costs to the patient could increase if patients are prompted to seek more care. However, costs might decrease over time because, as one clinical expert stated, "Prevention is usually less expensive to manage than actual disease processes. If the information stimulates behaviors to seek out medical care that addresses conditions early (e.g., pre-diabetic states, chronic hypertension, etc.) or prevents complications, the cost is reduced for third-party providers, self-insured patients, hospitals, and physicians."<sup>19</sup>

Because text messaging is so widely used, and because the texting program is free to patients, most patient acceptance of the messaging system will be high, experts thought. However, several experts pointed out that the program's purpose is not only to disseminate information but to encourage patients to take a more active role in their prenatal care process, and that long-term data will be necessary to

determine whether patients comply with this aspect of the program. One expert noted that for an optimal number of patients to adopt the program, messages would need to be developed for different cultures and literacy levels.

Some experts anticipated that this intervention has the potential to reduce health disparities. One expert with a research perspective believes that the intervention would have a significant impact for some patients of minority populations who currently delay prenatal care and counseling until the later stages of pregnancy, if they receive any care at all. One expert with a clinical perspective noted that, “My poorest patients with access issues have cell phones. The outreach potential for this novel patient education tool is immense.”<sup>19</sup>

## Donor Human Milk Program for Very-Low-Birth-Weight Infants

Very low birth weight (VLBW) is defined as a newborn weight of <1,500 grams (3 lb, 5 oz) at birth. Data from the U.S. Centers for Disease Control and Prevention indicate VLBW and extreme prematurity (infants born at fewer than 32 weeks' gestation) are factors predicting a higher risk of death during the first month of life if an infant is not born at a level III hospital.<sup>22</sup> Child Health USA reports that infants born at such low birth weights are about 100 times as likely to die in the first year of life as infants of normal birth weight (>5 lb, 8 oz). VLBW infants who survive are at significantly increased risk of severe cognitive impairment and pulmonary and vision problems, requiring increased levels of medical, educational, and parental care.<sup>23</sup> Many mothers who give birth to a premature infant are unable to provide breast milk at all or in sufficient quantities. This signals the need for an intervention aimed at improving physical and neurodevelopmental outcomes in these infants.

Donor milk from other lactating mothers is a potential intervention for mothers facing challenges to breastfeeding their VLBW children, such as lingering complications from pregnancy, anxiety regarding the infant's health, lack of privacy that curtails initiation of milk expression, dislike of breast pumps, and daily travel to the neonatal intensive care unit from home or work after delivery.<sup>24</sup> In human milk donation, lactating women pump breast milk and donate it to milk banks. Similar to blood donors, lactating donors are screened for communicable diseases, alcohol consumption within a specified period, and medication and vitamin supplement use; they must be nonsmokers. Human donor milk processing involves multiple steps, commencing with pasteurization (PST) team members scrubbing their hands before applying gloves required to handle donated milk. They transfer milk from the donation container to a glass flask, mixing samples from about three to five donors and distributing evenly. PST workers then distribute the milk evenly into smaller glass bottles and prepare the samples for PST. The smaller milk bottles are gently pasteurized to kill bacteria while preserving most of the milk's nutritional components, including digestive enzymes, immunologic factors, growth factors, and hormones.<sup>25</sup> Once the PST process is completed, workers check for bacterial contamination and discard the milk if bacteria are detected. Milk samples that have passed inspection are frozen and stored until delivered to a recipient's hospital or home.<sup>26</sup> Research indicates breast milk may reduce risk of necrotizing enterocolitis, urinary tract infections, and retinopathy of prematurity while improving IQ and visual development.<sup>25</sup>

In 2010, Sullivan and colleagues presented data from a study evaluating the efficacy of an exclusively human-milk-based diet (at 2 intake levels) compared with a diet of both human and bovine milk-based products in extremely premature infants. The authors concluded, "The 3 groups (total n=207 infants) had similar baseline demographic variables, duration of parenteral nutrition, rates of late-onset sepsis, and growth. The groups receiving an exclusively human milk diet had significantly lower rates of necrotizing enterocolitis (NEC),  $p=0.02$ , and NEC requiring surgical intervention ( $p=0.007$ )."<sup>27</sup>

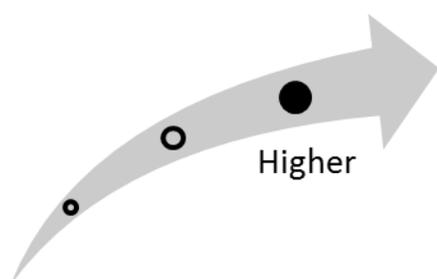
In 2009, Valentine and colleagues presented data from a study of 38 donor milk samples to evaluate the free amino acid profile for donor milk after PST. They reported, "only two free amino acids were significantly different ( $p<0.0027$ ) after PST of which Arginine was higher and Aspartate was lower. When comparing our PST samples to previous published amino acid means, our PST samples had significantly lower Glycine, Aspartate, Valine, Phenylalanine, Proline, Lysine, Arginine, Serine, whereas Histidine and Tyrosine were higher."<sup>28</sup> A study is ongoing evaluating the safety and efficacy of donor human milk regarding neurodevelopment in VLBW infants, with results expected in 2016.

FDA does not regulate human milk banking.<sup>29</sup> FDA, however, recommends against feeding with breast milk acquired directly from individuals or through the Internet and recommends that if, after consultation with a health care provider, a mother decides to feed an infant with human milk from a source other than her own, only milk from a source that has been screened to ensure its safety should be used.<sup>30</sup>

## Clinical Pathway at Point of This Intervention

Premature VLBW infants require specific management of fluids, electrolytes, and nutrition. Information from the prenatal and neonatal history may assist neonatologists in identifying conditions affecting neonatal fluid and electrolyte balance. Nutrition needs may include parenteral and or enteral modalities. Enteral feeding depends on the infant's ability to coordinate sucking, swallowing, and breathing. In general, human milk is preferred for infant enteral nutrition, but mothers of premature VLBW infants are sometimes unable to provide breast milk.<sup>31</sup> Human milk donated by other mothers and prepared for VLBW neonates is being investigated to support VLBW nutrition when the infant's mother is unable to provide any or sufficient breast milk.

**Figure 2. Overall High Impact Potential: Donor human milk program for very-low-birth-weight infants**



Overall, experts commenting on this intervention viewed donor human milk as having high potential to meet a significant unmet need for supplying breast milk to VLBW infants. While experts agreed that providing human donor milk might result in reduced rates of disease and infection, they thought that additional studies are needed to determine this intervention's impact on neurodevelopment. Experts generally agreed on this intervention's potential to impact health disparities and that increasing accessibility of donor human milk to African-American and socioeconomically disadvantaged babies may significantly improve patient health outcomes. Overall, experts believe this intervention might highly impact health outcomes for this patient population. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this intervention.<sup>32-38</sup> All experts saw a significant unmet need for more innovative ways to supply VLBW patients with the nutrients needed to avoid potential health complications, and they agreed donor human milk could be a sound intervention aimed at mitigating these complications. One research expert opined that if a mother is unable or unwilling to breastfeed her infant, donor human milk banks would provide a viable alternative to meet the needs of VLBW infants. One expert said that while this intervention might fulfill an unmet need, a question arises as to the number of mothers unwilling or unable to breastfeed their infants.

All experts agreed that donor human milk banks have the potential to significantly improve patient health outcomes, pointing to its potential impact on reducing rates of asthma, diarrhea, ear infections, necrotizing enterocolitis, pneumonia, and sepsis in VLBW infants. While some experts believe long-term studies are needed to properly evaluate this intervention's impact on neurodevelopment, one research expert stated that randomized control trials or other direct comparison controlled studies "seem unnecessary though payers will likely demand them."<sup>33</sup> This research expert continues, "What is the effect of pasteurization on survival of immunoglobulins etc? This seems like the greatest threat to the health benefits."<sup>33</sup>

Most experts agreed that donor human milk banks have the potential to significantly impact health disparities, with one research expert stating that "African Americans and socioeconomically disadvantaged babies are most likely to be born prematurely. Not having access to the health benefits of breast milk when their mothers cannot provide it (whether for health or economic reasons) will put the babies at further long-term disadvantage if their development is impaired."<sup>33</sup> Another research expert stated, "With the use of banked [human donor] milk, babies born to mothers with HIV, drug addiction, or health problems who are unable to provide breast milk for their infant will be able to receive the health benefits, therefore reducing disparity."<sup>34</sup> One research expert did not believe in this intervention's ability to reduce health disparities, citing the fact that health insurance does not currently extend coverage for human donor milk, therefore widening the barrier for the economically disadvantaged.

Experts generally agreed that this intervention's potential to disrupt the current health care delivery infrastructure and how this patient population is currently management would be low. A research expert mentioned that special facilities may need to be in place to process and store donor milk for distribution. Experts also agreed that both clinician acceptance and patient acceptance of this intervention would be significantly high, given the awareness of the health benefits of breast milk for infants, particularly VLBW infants. One clinical expert stated, "While there will be concern over infectious transfer I think this will be countered by the perceived benefits to the infant."<sup>36</sup> A research expert listed potential costs and "convenience of use" as a barrier to clinician acceptance.<sup>34</sup> The same expert also cites the education of the health care team responsible for screening, storage, and administration of donor human milk as critical to the acceptance of this intervention. Many experts believe while there may be an initial increase in costs, the reduction in costs stemming from long-term complications of health issues for VLBW infants might ultimately significantly lower costs for this patient population.

Overall, experts agreed that while more safety and efficacy studies must be performed to determine its effect on neurodevelopment outcomes, donor human milk has potential for high impact among this patient population, providing an efficacious and safe alternative to maternal breast feeding for VLBW infants. One clinical expert stated, "This is an important intervention with large potential to improve the health and development of VLBW infants as well as reduce the costs to the health care system and society. Additional research in this area should be of high priority."<sup>36</sup> Another expert believes providing another nutrition option for VLBW infants could be critical to improving long-term development in this patient population.

## **In Utero Surgery To Repair Myelomeningocele (Spina Bifida)**

Myelomeningocele, the most serious form of spina bifida, occurs in approximately 3.4 of every 10,000 births, and 10% of affected infants die.<sup>39</sup> In this condition, the protrusion of the spinal cord through an opening in the vertebral column may change the flow of cerebrospinal fluid (CSF) and pull the brain stem into the base of the skull (hindbrain herniation).<sup>39</sup> As the circulation of CSF is affected in the brain, a life-threatening buildup of CSF requires postnatal surgical insertion of a shunt (typically 24 to 48 hours after birth) into the brain to drain excess fluid into the abdominal cavity. These shunts are replaced several times during the patient's lifetime.<sup>39</sup> Other issues with this postnatal surgical procedure is that it does not obviate the incidence or severity of neurologic effects or the need to reverse the hindbrain herniation component of a Chiari II malformation.<sup>39-41</sup> A surgical procedure further mitigating complications of myelomeningocele is needed to provide this patient population with improved health outcomes and quality of life.

In utero surgical correction of myelomeningocele involves a highly specialized multidisciplinary team, and the procedure is intended to correct the defect in the fetus, typically between the 19th and 26th week of pregnancy. With the mother under general anesthesia, an incision is made across her abdomen to expose the uterus, which is then opened to rotate and expose the myelomeningocele on the fetus' back. A pediatric surgeon removes the protruding myelomeningocele sac and closes the tissue around it, including skin. Once covered, the spinal cord is no longer exposed to the potential detrimental effects of the amniotic fluid. After closing the uterus and abdominal wall, a maternal-fetal specialist uses ultrasound to ensure that the placenta and fetus are in the right position, and a fetal cardiologist examines fetal cardiac function. The mother stays in the hospital for several days, after which bedrest is recommended to reduce the risk of preterm labor. For the remainder of the pregnancy, weekly ultrasound monitoring and prenatal care are provided. At 37 weeks, a planned cesarean section is performed.<sup>40</sup>

Adzick and colleagues (2011) presented data from a study of 183 patients whose fetus had spina bifida who either had prenatal surgery before 16 weeks of gestation or had standard postnatal surgery. The trial was stopped for efficacy of prenatal surgery after the recruitment of 183 of a planned 200 patients. This report is based on results in 158 patients whose children were evaluated at 12 months. The first primary outcome (fetal or neonatal death or the need for a cerebrospinal fluid shunt by the age of 12 months) occurred in 68% of the infants in the prenatal-surgery group and in 98% of those in the postnatal-surgery group (relative risk [RR], 0.70; 97.7% confidence interval [CI], 0.58 to 0.84;  $p < 0.001$ ). Actual rates of shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group (RR, 0.48; 97.7% CI, 0.36 to 0.64;  $p < 0.001$ ). Prenatal surgery also resulted in improvement in the composite score for mental development and motor function at 30 months ( $p = 0.007$ ) and in improvement in several secondary outcomes, including hindbrain herniation by 12 months and ambulation by 30 months. However, prenatal surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery.<sup>42</sup>

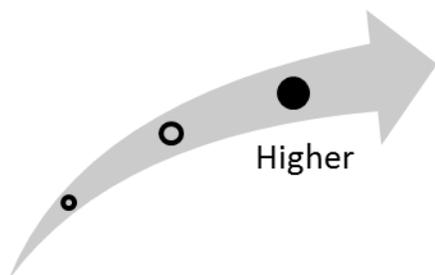
Because of the nature and complexity of this surgical intervention, experts recommend this type of surgery should be performed only at hospitals with a multidisciplinary team comprising experienced staff trained in pediatric surgery, neurology, and maternal-fetal medicine who have some experience with the procedure.<sup>39</sup> This surgery is not subject to FDA regulatory approval.

### **Clinical Pathway at Point of This Intervention**

An abnormal maternal serum alpha fetoprotein (AFP) test (usually done in the 16th week of pregnancy) may suggest a fetus with spina bifida and is an indication for additional testing. A

presumptive diagnosis made with AFP is confirmed with amniocentesis and assay of the amniotic fluid for AFP and acetylcholinesterase. Fetal ultrasonography, imaging, and radiographs usually follow. A cesarean section before rupture of amniotic membranes and labor is advocated to prevent rupturing the myelomeningocele sac and possibly reduce the risk for paralysis in the child. Depending on the presence of CSF, closure of the myelomeningocele is typically performed immediately after birth or within 48 hours if no CSF leakage is present.

**Figure 3. Overall High Impact Potential: In utero surgery to repair myelomeningocele (spina bifida)**



Overall, experts agreed that in utero surgery has high potential to significantly improve patient health outcomes and reduce complications of postnatal surgical repair of myelomeningocele. All experts agreed this intervention has potential to significantly disrupt the current health care infrastructure, given the need for a comprehensive medical team to perform in utero surgery compared with postnatal surgery. Experts thought in utero surgery might also reduce the need for care teams to manage complications of myelomeningocele or complications of ventriculoperitoneal (VP) shunt placement. Experts agreed while initial per-patient costs may increase, reducing long-term health complications could ultimately reduce costs associated with this condition. Recent study results reported in 2011 provided evidence that suggests that this intervention shows improved efficacy compared with postnatal surgical repair. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and/or health administration backgrounds, provided perspectives on this topic.<sup>43-49</sup> All experts saw a significant unmet need for a more effective surgical intervention to repair myelomeningocele, citing in utero surgical repair's potential for reducing the need for VP shunts and associated neurological complications from replacement. All experts agreed this surgical intervention would significantly improve patient health outcomes, with one researcher explaining, "Preliminary data supported a nearly 50% reduction in the need for VP shunt placement in the first year of life."<sup>47</sup> The same expert considered the potential for impact "huge," particularly if the risk of preterm delivery and the associated outcomes remain low.<sup>47</sup> One clinical expert shared the same optimism regarding in utero surgery and its potential to affect patient health outcomes "as long as the incidence of premature delivery remains sufficiently low."<sup>49</sup>

Some experts believe this intervention would not have a significant impact on health disparities, believing, as one put it, that it will not offer better access to care as the subgroups that "don't have access to current treatment modalities may not have any greater access to this new treatment."<sup>48</sup> Experts believing this intervention would significantly affect health disparities opined that in utero surgery would increase health disparities based on patient access to this intervention and affordability of this surgery. One research expert stated, "There might be a significant population of sufferers [who]

may not have access to insurance that can help in payment for this treatment and the treatment is potentially more expensive than the current treatment available as well.”<sup>44</sup>

All experts agreed this intervention has potential to significantly disrupt the current health care delivery infrastructure for this patient population, citing the need for a specialized medical team to perform surgery. Several experts opined that in utero surgical intervention could lessen the need for the support team required with current postnatal surgical intervention because neurological complications might be significantly reduced. Experts generally agreed this intervention could significantly disrupt the way patients are currently managed because myelomeningocele repair would be performed preterm as opposed to post-term. One clinical expert cited the complex nature of in utero surgery, stating “Tremendous resources [are] required to perform fetal surgery in a safe and skilled manner. The pregnant woman will likely have a mixed care provision utilizing both their local provider and the fetal surgery center.”<sup>49</sup> The same expert opined that postnatal intensive care teams would not be required after birth with in utero surgery, significantly impacting patient management.

All experts agreed that in utero surgery’s potential for clinician acceptance is high, particularly if studies conclude the risk for adverse events remain low. The majority of experts agreed this intervention’s potential for acceptance by patients is high, with one research expert expecting wide acceptance based on parents “wishing to decrease substantive risks of life-long developmental and neurologic issues associated with the disorder.”<sup>46</sup> Some experts thought barriers to patient acceptance and adoption would be the cost of this surgical intervention, when compared with current surgical management, and concerns over potential adverse events associated with in utero surgery for repair of myelomeningocele. Regarding per-patient costs for this intervention, five experts agreed initial costs might be high. However, several experts agreed that long-term per-patient costs might be reduced, with one expert citing the reduction of costs from “further surgeries such as ventricular shunting, hospital stays and long term disabilities which could be astronomical.”<sup>48</sup> A clinical expert remained undecided on potential impact for health care costs. Based on potential reduction in VP shunt malfunction, reduction in adverse events, and improvement in long-term patient health outcomes, experts agreed in utero surgery to repair meningomyelocele could have a high impact on the affected patient population, assuming access to the procedure.

## Fetal DNA Blood Test for First-Trimester Detection of Down Syndrome and Other Trisomies

Currently, pregnant women are offered a series of screening tests that include blood markers and invasive diagnostic testing (e.g., chorionic villus sampling, amniocentesis) for fetal aneuploidy if a combination of maternal age, ultrasound results, and biochemical marker results indicate that the woman is at high risk of carrying an affected fetus.<sup>50</sup> However, this screening algorithm has a false-positive rate of about 2%, which results in about 16 women being offered an invasive diagnostic test for every 1 who is actually carrying an affected fetus.<sup>1</sup> Therefore, for each Down syndrome diagnosis, about 15 women are subjected to an unnecessary invasive diagnostic procedure, which carries a small but significant risk of miscarriage. Several companies have developed a laboratory-developed test (LDT), and one of the companies is developing a commercial test kit for FDA approval that detects fetal DNA in the maternal blood to detect Down syndrome and other trisomies. The test that is furthest along in development is Sequenom, Inc.'s (San Diego, CA) MaterniT21™ test, which launched in late 2011.

Sequenom developed the MaterniT21 test, a DNA-based, first-trimester screening assay (blood test) using Fetal Nucleic Acid Technology to detect and isolate circulating fetal DNA from a maternal blood sample.<sup>51</sup> Repeated parallel sequencing can detect an excess of chromosome 21 DNA of fetal origin, which indicates trisomy 21. Sequenom states that circulating fetal DNA can be obtained from a maternal blood sample very early in pregnancy, and such testing could benefit pregnant women by helping rule out trisomy 21 abnormalities during the first trimester, thereby avoiding more invasive testing that poses a miscarriage risk. This test launched in fall 2011 as an LDT performed at the company's Clinical Laboratory Improvements Act-certified reference laboratory, Sequenom Center for Molecular Medicine.<sup>52</sup> Additionally, Sequenom intends to develop a test kit for marketing. In July 2011, Sequenom entered a supply partnership with Illumina, Inc. (San Diego, CA; manufacturer of the testing platform) and stated intentions of filing a premarket approval application for its test kit with FDA by the end of 2012.<sup>53,54</sup>

In August 2011, Sequenom announced that it had licensed technology to LifeCodexx to develop the trisomy 21 test for the European market, with an expected launch in late 2011,<sup>55</sup> and now LifeCodexx is not expected to compete with a Trisomy 21 test in the United States market.

Sequenom published results of a proof-of-concept study in March 2011 in the *American Journal of Obstetrics and Gynecology*.<sup>51</sup> In this study, 449 samples from a high-risk population were tested using the Sequenom assay with chorionic villus sampling or amniocentesis as the reference standard. The Sequenom assay detected all 39 cases of trisomy 21 (100% sensitivity; 95% confidence interval [CI], 89% to 100%) and misclassified one normal sample as trisomy 21 (99.7% specificity; 95% CI, 98.5% to 99.9%).

In November 2011, Palomaki and colleagues published results of an international clinical validation study of women considered to have a high-risk pregnancy in which they compared fetal karyotyping in 212 patients receiving a diagnosis of Down syndrome and 1,484 matched euploid pregnancies using the Sequenom assay to measure circulating cell-free DNA in maternal plasma. The authors reported that, "Down syndrome detection rate was 98.6% (209/212; [95% CI, 95.9-99.7]), the false-positive rate was 0.20% (3/1471; [95% CI, <0.1-0.6]), and the testing failed in 13 pregnancies (0.8%; [95% CI, 0.4-1.3]); all were euploid."<sup>1</sup>

In October 2011, the company announced launch of the test in 20 major metropolitan areas as an LDT to be performed on samples sent to its Sequenom Center for Molecular Medicine. The company reported that an insured patient's cost for the test would be no more than \$235 and that the Sequenom

laboratory would initially operate as an out-of-network provider to ensure eligible patients have coverage for the test.<sup>56</sup> The company stated that it expects reimbursement for the test to be similar to that for amniocentesis or chorionic villus sampling (i.e., between \$1,500 and \$2,000).<sup>56</sup>

Other companies reported to be planning launches of fetal DNA prenatal trisomy 21 LDTs in 2012 include Verinata Health, Inc. (Redwood City, CA) and Ariosa Diagnostics, Inc. (San Jose, CA). Verinata Health, Inc. (Redwood City, CA) has developed the verifi™ Non-Invasive Prenatal Test that is also based on massively parallel shotgun sequencing of circulating cell-free DNA from the mother and fetus in maternal blood and is intended to identify trisomies 13, 18, and 21 as early as 10 weeks into pregnancy.<sup>2</sup> Bianchi et al. (2012) presented data on a clinical trial to determine detection of fetal aneuploidies in 2,882 women undergoing prenatal testing. The authors concluded, “The study correctly identified 89 of 89 cases of trisomy 21 (Down syndrome) with 100 percent sensitivity and specificity, and had a 100 percent positive predictive value for the three most common autosomal aneuploidies, trisomies 21, 18, and 13. The study also detected monosomy X (Turner syndrome) and other chromosome aneuploidies such as trisomies 16 and 20.”<sup>57</sup> The test was scheduled to be available beginning March 1, 2012, but no news of this launch has been verified as of May 2012.<sup>2</sup>

Ariosa Diagnostics developed the Harmony Prenatal Test™ that is intended to identify common trisomies, particularly 18 and 21.<sup>58</sup> Like the MaterniT21 and verifi tests, the Harmony test is based on identification and quantification of sequences from cell-free DNA isolated from maternal blood; however, unlike the other tests, Harmony involves targeted sequencing of only specific regions of interest from the genome, potentially increasing test scalability and/or reducing the cost per test.<sup>58</sup> In 2012, Ashoor and colleagues presented results from a clinical trial assessing the detection rate of trisomy 18 and 21 in 400 women. The authors concluded, “Risk scores for trisomy 21 and 18 were given for 397 of the 400 samples that were analyzed. In all 50 cases of trisomy 21, the risk score for trisomy 21 was  $\geq 99\%$ , and the risk score for trisomy 18 was  $\leq 0.01\%$ . In all 50 cases of trisomy 18, the risk score for trisomy 21 was  $\leq 0.01\%$ , and the risk score for trisomy 18 was  $\geq 99\%$  in 47 cases, 98.8% in 1 case, 88.5% in 1 case, and 0.11% in 1 case.”<sup>59</sup> It was also revealed, “In 3 of the 300 euploid pregnancies (1%), no risk score was provided, because there was failed amplification and sequencing. In the remaining 297 cases, the risk score for trisomy 21 was  $\leq 0.01\%$ , and the risk score for trisomy 18 was  $\leq 0.01\%$  in 295 cases, 0.04% in 1 case, and 0.23% in 1 case. Therefore, the sensitivity for detecting trisomy 21 was 100% (50/50 cases), the sensitivity for trisomy 18 was 98% (49/50 cases), and the specificity was 100% (297/297 cases).”<sup>59</sup> In May 2012, the company, in partnership with Laboratory Corporation of America Holdings (LabCorp) and Integrated Genetics, announced the prenatal test’s commercial launch in the U.S. and Canada.<sup>60</sup>

The companies have filed several legal motions regarding the patent rights associated with the technology underlying these tests.<sup>61,62</sup>

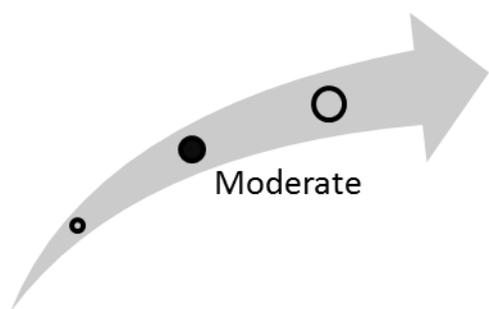
Sequenom announced that as of mid-May 2012, its laboratory had processed more than 10,000 MaterniT21 tests in 2012.

## **Clinical Pathway at Point of This Intervention**

Prenatal testing for fetal aneuploidies involves a combination of noninvasive screening tests that are used to assess a woman’s age-adjusted risk of carrying an aneuploid pregnancy and invasive diagnostic tests that are used to confirm whether a woman is carrying an aneuploid pregnancy.<sup>50</sup> Noninvasive screening can be performed in the first or second trimester or by using a combination of results from both the first and second trimester.<sup>50</sup> First-trimester screening typically consists of performing ultrasound imaging, which looks for an increased amount of fluid at the back of the fetal neck (i.e., the nuchal translucency), and assessing two biochemical markers (PAPP-A and human

chorionic gonadotropin [hCG]).<sup>50</sup> On the basis of first-trimester screening results, some women characterized as high risk will be offered diagnostic testing by chorionic villus sampling.<sup>50</sup> Second-trimester screening typically consists of assessing up to four serum-based markers (hCG, unconjugated estriol, alpha-fetoprotein, and inhibin A).<sup>50</sup> On the basis of second-trimester screening results, or a combination of first- and second-trimester screening results, some women characterized as high risk will be offered diagnostic testing by amniocentesis.<sup>50</sup>

**Figure 4. Overall High Impact Potential: Fetal DNA blood test for first trimester detection of Down syndrome and other trisomies**



Overall, experts viewed the MaterniT21 test as having the potential to meet a significant unmet need for a noninvasive Down syndrome screening methodology early in pregnancy. While availability of a noninvasive screening test for trisomy 21 and other trisomies has potential to disrupt diagnostic paradigms and care delivery methods and increase patient acceptance, it likely will displace only current use of noninvasive testing (at least initially), rather than invasive testing; therefore, its overall impact would be incremental, thought experts commenting on the test. However, that role for the test (a negative result) could help some women avoid more invasive testing. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## Results and Discussion of Comments

Eight experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on Sequenom’s MaterniT21 screening assay.<sup>63-69</sup> Although expert comments have not been provided for the other fetal DNA tests, comments provided for the MaterniT21 test would be expected to pertain to those tests as well.

Expert opinions were divided regarding the potential importance of the unmet need such a test would address. One expert noted the presence of “several combined first trimester” testing kits commercially available that are considerably effective.<sup>66</sup> This same expert, along with other experts, opined this would not completely obviate the need for invasive confirmatory testing. However, several experts acknowledged the need for more accurate noninvasive testing for this patient population, with one expert stating, “If there were less invasive tests, which could be performed earlier in pregnancy, with greater levels of sensitivity and specificity, (and not cost prohibitive), then this would be an important improvement in the current level of prenatal care.”<sup>69</sup> One research expert opined noninvasive tests and highly accurate testing platforms for Down syndrome could significantly reduce invasive confirmatory tests. Another research expert stated there was a modest unmet need, citing the potential for high-risk women, particularly older women, to be accurately screened and receive earlier diagnosis of trisomy 21 status.

Experts generally agreed this intervention has potential to improve patient outcomes, with most citing that MaterniT21 could help a mother avoid invasive screening that could potentially subject her

to serious adverse events. One research expert did not believe this would significantly improve patient outcomes, stating “best case this test will replace or be used in conjunction with current first-trimester screening tests, which won’t affect patients much.”<sup>64</sup> Additionally, experts noted given third-party payers’ likely unwillingness to cover this testing, this fetal DNA testing platform will likely not reduce health disparities.

The majority of experts do not expect a significant change in the current health care delivery infrastructure, citing this procedure involves routine blood draw and lab analysis. However, several experts pointed out the test’s potential to shift patients from invasive outpatient procedures to simple blood draws, which would shift the care setting to physicians’ offices and reduce the need for maternal-fetal medicine specialists to perform trisomy 21 screening. Experts also do not expect this intervention to significantly change the way patients are currently managed; however, one research expert noted, “It would be an improvement if it could eliminate the need for more invasive procedures such as amniocentesis, etc.”<sup>65</sup>

Experts believe that patients and physicians would readily adopt an accurate blood-based screening test for trisomy 21, citing the potential to avoid miscarriages associated with invasive tests, the increased patient comfort relative to invasive tests, and the ability of most physician’s offices to perform blood sample collection. One potential barrier to adoption that experts noted is the test’s cost (estimated at \$1,500 to \$3,000). While the majority of experts believe that such a test has the potential to reduce costs relative to invasive screening methods, experts noted that insurance coverage would be needed to promote a blood test’s use. Experts speculated that the test cost would likely be high and add to costs because it would not replace invasive methods of testing at this time.

Overall, experts saw potential for this intervention to significantly impact testing for trisomy 21 at an earlier stage of pregnancy in an effective, accurate, and noninvasive manner. One research expert envisioned the MaterniT21 screening test as potentially reducing “the number of women undergoing expensive and stressful invasive procedures that carry a risk of miscarriage.”<sup>67</sup>

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