AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 12: Pregnancy including Preterm Birth

Potential High Impact Interventions Report

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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. HHSA29020100006C). 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 closer to diffusion into practice in the United States. Drafts of 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 those interventions that experts deem, 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 six 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 the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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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 target technologies and innovations in health care and to create an inventory of target technologies 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 the identification and monitoring of 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 the analysis of 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 utilization 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.

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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 identification of 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 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

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 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) 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 a profile on topics and issuing topic profile 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 high impact potential designation. 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 late-phase data were available for diagnostics and procedures; and pilot data were available for programs; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February and November 1, 2011. (A total of 14 topics in this priority area were being tracked in the system as of November 2011.) 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
1. CDB-2914 (ulipristal acetate) for treatment of uterine fibroids
2. *Cell-phone-based educational program (Text4baby) to improve outcomes for pregnant women and infants
3. *Donor human milk program for very-low-birthweight infants
4. Endoglin urine test for preeclampsia screening
5. *In utero surgery to repair myelomeningocele (spina bifida)
6. *Trisomy 21 DNA test for first-trimester detection of Down syndrome

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-birthweight 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. It 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.
- **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-Birthweight Infants

- **Key Facts**: Very-low-birthweight (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 are 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, screening of lactating donors is performed to test 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 in the event that mothers choose to feed infants with human milk other than their own.

- **Key Expert Comments**: While experts agreed that human donor milk might result in reduced rates of disease and infection, they were eater to see additional studies to determine this intervention's impact on neurodevelopment. Experts agreed on this intervention's potential to affect health disparities and that increasing accessibility of donor human milk to African-American and socioeconomically disadvantaged babies might significantly improve patient 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).[1] 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 be sure the placenta and fetus are in the right position, and a fetal cardiologist examines fetal cardiac function. This surgery is not subject to any regulatory approval by FDA.
- **Key Expert Comments**: Overall, experts commenting on the procedure agreed that in utero surgery has the potential to significantly improve patient health outcomes and reduce complications of postnatal surgical repair of myelomeningocele. Pending results from ongoing studies, this intervention could prove to be an effective alternative to postnatal surgical repair, marking its potential for high impact, experts thought.
- **Potential for High Impact**: High

Trisomy 21 Fetal DNA Test for First Trimester Detection of Down Syndrome

- **Key Facts**: The risk of having a baby with Down syndrome increases with older age at pregnancy, and as the population of women becoming pregnant in the U.S. becomes older, more women and couples have concerns about the risk of Down syndrome. Thus, an unmet need exists for a noninvasive and accurate diagnostic test that can be performed early in pregnancy for the chromosomal abnormality that causes the syndrome, so women and couples can make informed decisions. Current clinical guidelines recommend first-trimester screening for Down syndrome using a battery of biomarker blood tests (e.g., alpha-

fetoprotein, estriol, human chorionic gonadotropin beta subunit, inhibin A, PAPP-A) in combination with nuchal transparency testing by ultrasound imaging. Upon receiving a positive result from these first-trimester tests, a woman may be counseled to undergo a similar biomarker test, which, if positive, may be followed by amniocentesis (sampling amniotic fluid surrounding the fetus in utero) or chorionic villus sampling (harvesting placental tissue cells in utero), depending on the week of gestation, to confirm the result. These confirmatory tests pose a risk of miscarriage. A new blood test takes a sample of maternal blood during the first trimester in pregnant women interested in knowing whether their fetuses have a trisomy 21 abnormality. The test can be used earlier in pregnancy than other confirmatory invasive tests because it uses "Fetal Nucleic Acid Technology" to detect and isolate circulating fetal DNA from a maternal blood sample to detect an excess of chromosome 21 DNA of fetal origin, which indicates trisomy 21. Several companies are developing such a test and patent infringement has been alleged by various developers at various points in time. As of November 2011, Sequenom, Inc. (San Diego, CA), appears closest to product launch of a laboratory-developed test and a premarket approval application for a test kit. The company published results of a proof-of-concept study in March 2011 and in May 2011 announced completion of testing in a pivotal study of the test's clinical performance. In October 2011, the company announced launch of the test in 20 major metropolitan areas as a laboratory-developed test (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. 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).

- **Key Expert Comments**: Overall, experts commenting on the test viewed it as having potential to meet a significant unmet need for a noninvasive Down syndrome screening methodology that avoids risk of miscarriage and provides information earlier in a pregnancy. While availability of a noninvasive screening test for trisomy 21 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, and, 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

Intervention

Cell-phone-based educational program 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.[2] 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' cellular telephones 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, with the specific aim of reducing 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 both conducting formal evaluations of the Text4baby service program.[3,4] 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. After one year (inception in February 2010), more than 150,000 individuals had signed up for the Text4baby program.[5] The program is being adopted by more than 350 partners from National, State, business, academic, and nonprofit groups.[4,6] Johnson & Johnson, Inc., has made a multimillion-dollar, multi-year commitment to Text4baby, helping with the program's goal of diffusion to underserved mothers and service to 1 million mothers by 2012.[4]

On November 23, 2010, the DHHS Health Resources and Services Administration (HRSA) requested public comments on the proposed project entitled: 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."[7] Currently, there are two large studies under way, evaluating the effectiveness of Text4baby. The final data will not be available until the first half of 2012.[5]

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:

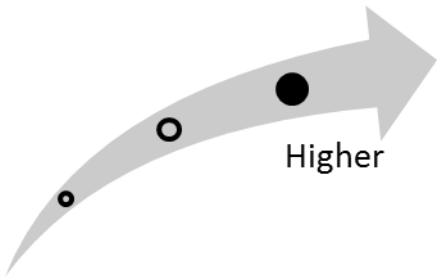
> Women reported high satisfaction with Text4baby, with Spanish speaking women reporting even higher satisfaction scores than English-speaking women. Sixty-three percent of women reported that Text4baby helped them remember an appointment or immunization that they or their child needed. Seventy-five 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.[8]

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.[9] 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 each of the three pregnancy trimesters and pregnancy complications. Partial two-way communication is possible via blog forums and "Ask the expert" features.[10] 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 especially addressing the first year of life.[11] 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.[12-18] 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 novelty of this program 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."[18] 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.[12]

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."[15] 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."[13] 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."[12]

Experts were similarly divided on whether this intervention has potential to 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?"[14]

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."[16]

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 purpose of the program 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 if 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."[16]

Intervention

Donor human milk program for very-low-birthweight infants

Very-low-birthweight (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.[19] 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.[20] 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.

Researchers are investigating the benefits of pasteurized donor human milk on infant health and development when maternal milk is not available. Researchers theorize that a donor human milk diet of nonmaternal milk for VLBW infants is associated with better neurodevelopmental outcomes at 18 to 22 months than a formula diet.[21] Typically, challenges and barriers to breastfeeding a VLBW infant include lingering complications from pregnancy, mothers' 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.[22] Thus, donor milk from other lactating mothers may 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, screening of lactating donors is performed to test 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.[23] According to the 2011 Surgeon General's Call to Action to Support Breastfeeding, breastfeeding protects infants from infections, conditions, and illnesses, including asthma, diarrhea, ear infection, pneumonia, and sudden infant death syndrome. A decreased incidence of obesity is seen in infants breastfeeding for 6 months.[24] Donor human milk may provide an effective means to better patient health outcomes.

In 2010, Sullivan and colleagues presented data from a study evaluating the efficacy of an exclusively human milk-based diet (at two 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)."[25]

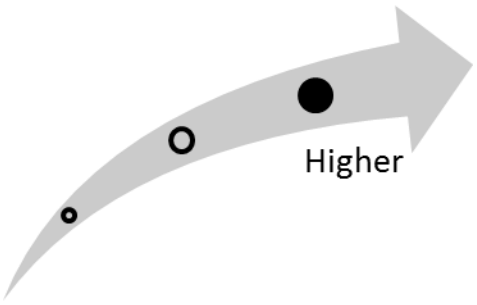
In 2009, Valentine and colleagues presented data from a study of 38 donor milk samples to evaluate the free amino acid profile for donor milk after pasteurization (PST). They reported, "only two free amino acids were significantly different (p <0.0027) after PST of which Arginine was higher and Aspartate 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."[26] A study is currently 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.[27] 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 the safety of the milk should be used.[28]

Clinical Pathway at Point of This Intervention

Premature VLBW infants require specific management of their 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.[29] 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-birthweight infants



Overall, experts commenting on this intervention viewed donor human milk as having the 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.[30-36] 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, there is a question as to the numbers of mothers who are 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."[31] 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."[31]

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."[31] 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."[32] 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."[34] A research expert listed potential costs and "convenience of use" as a barrier to clinician acceptance.[32] 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 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."[34] Another expert believes providing another option of nutrition for VLBW infants could be critical to improving long-term development in this patient population.

Intervention

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.[1] 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).[1] 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.[1] 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[1,37,38] 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 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 be sure 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 bed rest is recommended to reduce the risk of preterm labor. For the remainder of the pregnancy, weekly ultrasound monitoring and prenatal care is provided. At 37 weeks, a planned cesarean section is performed.[37]

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.

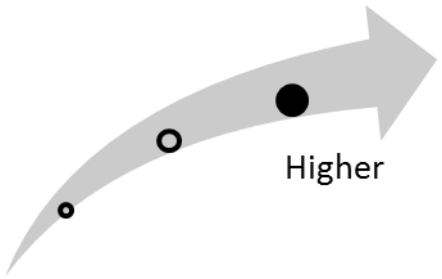
The trial was stopped for efficacy of prenatal surgery after the recruitment of 183 of a planned 200 patients. This report is based on results in 158 patients whose children were evaluated at 12 months. The first primary outcome [fetal or neonatal death or the need for a cerebrospinal fluid shunt by 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, 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 (relative risk, 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.[39]

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 comprised of experienced staff trained in pediatric surgery, neurology, and maternal-fetal medicine who have some experience with the procedure.[1] This surgery is not subject to any regulatory approval by FDA.

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 the 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 believe 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, reduction in long-term health complications could ultimately reduce costs associated with this condition. Pending results from ongoing studies, experts have determined this intervention to be an effective alternative to postnatal surgical repair, marking its potential for high impact. 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.[40-46] 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."[44] This same expert considered the potential for impact "huge," particularly if the risk of preterm delivery and the associated outcomes remain low.[44] 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."[46]

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."[45] 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."[41]

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 needed 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 postterm. 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."[46] 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 the 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."[43] 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."[45] A clinical expert remained undecided on potential impact for health care costs. Overall, experts opined further studies need to be conducted to properly evaluate the efficacy and safety of this procedure. However, 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 be considered an intervention of high impact for this patient population.

Intervention

Trisomy 21 fetal DNA blood test for first trimester detection of Down syndrome

Testing during pregnancy for Down syndrome in at-risk women currently involves invasive tests that pose a risk of miscarriage and cannot be carried out very early in pregnancy. Thus, an unmet need exists for a noninvasive and accurate diagnostic test that can be performed early in pregnancy for the chromosomal abnormality that causes the syndrome. With that information, women and couples can make informed decisions earlier in a pregnancy. Several companies are developing a blood test that detects fetal DNA in the maternal blood to detect Down Syndrome. Sequenom, Inc. (San Diego, CA), has developed the MaterniT21™ test, a DNA-based, first-trimester screening assay (blood test).[47] This test appears to be closest to product launch and was expected to launch in fall 2011as a laboratory-developed test performed at the company's Clinical Laboratory Improvements Act-certified reference laboratory, Sequenom Center for Molecular Medicine.[48] 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.[49,50]

Other companies reported to be planning launches of fetal DNA prenatal trisomy 21 laboratory-developed tests in 2012 include the European-based company, LifeCodexx (subsidiary of GATC Biotech AG, Konstanz, Germany) and Verinata Health, Inc. (San Carlos, CA).[51,52] Some companies are developing such a test and patent infringement has been alleged by various developers at various points in time.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,[51] and now LifeCodexx is not expected to compete with a Trisomy 21 test in the United States market.

The Sequenom 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.

Sequenom published results of a proof-of-concept study in March 2011 in the American Journal of Obstetrics and Gynecology.[47] 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."[53]

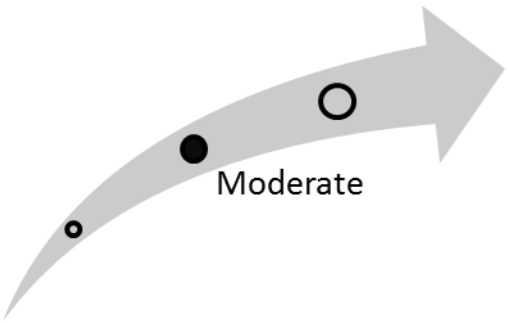
In October 2011, the company announced launch of the test in 20 major metropolitan areas as a laboratory-developed test (LDT) to be performed on samples sent to its Sequenom Center for

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. 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).

Clinical Pathway at Point of This Intervention

Current clinical guidelines recommend first-trimester screening for Down syndrome using a battery of biomarker blood tests (e.g., alpha-fetoprotein, estriol, human chorionic gonadotropin beta subunit, inhibin A, PAPP-A) in combination with nuchal transparency testing by ultrasound imaging.[54] Upon receiving a positive result (i.e., high risk) from these first-trimester tests, the woman can be counseled to undergo a similar biomarker test that, if positive, might be followed by amniocentesis (sampling amniotic fluid surrounding the fetus in utero) or chorionic villus sampling (harvesting placental tissue cells in utero), depending on the week of gestation, to confirm the result. The MaterniT21 test takes a sample of maternal blood during the first trimester in pregnant women interested in knowing whether their fetuses have a trisomy 21 abnormality.

Figure 4. Overall High Impact Potential: Trisomy 21 fetal DNA blood test for first trimester detection of Down syndrome



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 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 and, 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 this intervention.[55-62] These experts saw a significant unmet need for a noninvasive alternative to current trisomy 21 testing, citing the potential for miscarriages associated with current invasive testing and the desire of women and couples to have earlier diagnosis of trisomy 21 status. The majority of these experts stated that the trisomy 21 detection test's methodology seems plausible. One expert with a research background noted that other research groups have validated the detection of DNA from circulating fetal cells. However, a health systems expert noted the opaque nature of the genetic testing method, which could influence its adoption. Based on reported results from pilot studies, the test seems highly accurate in detecting trisomy 21 experts thought, but some questioned whether these results would hold up in day-to-day clinical application. If the Sequenom test is confirmed be accurate in routine use, experts thought, it has significant potential to alter the way in which trisomy 21 screening is performed. One clinical expert suggested that the availability of a low-risk blood test for trisomy 21 screening could shift the screening paradigm from one of testing high-risk individuals only to a screening paradigm in which all pregnancies are screened. Additionally, the

majority of experts pointed out the potential of the test 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. Several experts also noted that this care-setting shift has the potential to increase access to care and/or health disparities by allowing trisomy 21 testing to be available in a greater number of clinical settings because it involves only a blood draw.

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 any physician's office to perform blood sample collection. One potential barrier to adoption that experts noted is the cost of the test (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 coverage by insurance 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.

Many experts suggested that the MateriT21 test has the potential for controversy. Some experts note that the accuracy (sensitivity and specificity) of the test in high-risk populations may not hold true in the general population of pregnant women. Most experts' comments addressed the fact that patients receiving a positive result from the test would be making a decision regarding whether to continue the pregnancy and, therefore, could become embroiled in the general debate regarding these issues. Additionally, one clinical expert noted that the test has the potential to displace use of established screening methods and that members of the medical community who currently employ these screening tests could be reluctant to modify current practice. 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 expert with a clinical background envisioned the MateriT21 screening test being "readily accepted, adopted and utilized."[62]

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