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How should costs and cost-effectiveness be considered in prenatal genetic testing?

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Abstract

In January 2017, a group of experts in prenatal genetics attended a workshop at the Society of Maternal-Fetal Medicine meeting to review the evidence behind the costs and cost-effectiveness of prenatal genetic testing. Over the past decade, prenatal genetic testing options have dramatically expanded to include additional options with cell-free DNA (cfDNA) screening, as well as increased diagnostic abilities through chromosomal microarray analysis (CMA), gene panels, whole exome sequencing, and other tests. With these expanding technologies, it is important to consider the options available as well as the cost effectiveness of their use. Other important considerations are the effects of movements toward value-based health care; the role of professional societies, commercial laboratories, and insurers; disparities that exist in prenatal genetic testing; and outcomes for both patients and health care systems. Workshop participants identified key areas of research to advance our understanding of the costs and cost-effectiveness of prenatal genetic testing, which include (1) understanding the short- and long-term costs to patients and to health care systems with prenatal genetic tests; (2) elucidating the short- and long-term health outcomes for parents and children that are important to consider when comparing one testing strategy to another; (3) understanding the value underlying prenatal genetic testing to individuals and health care systems; and (4) identifying disparities in prenatal genetic testing, reasons for these disparities, and how to minimize them.

Keywords

Cost; Cost-effectiveness; Disparities; Prenatal genetic testing; Value-based care

Background

Prenatal genetic testing is a core element of obstetric care provided in the United States. Traditionally, this testing focused on detection of Down syndrome and then expanded to trisomy 18 and trisomy 13. Prenatal screening tests are offered with the goal of identifying those individuals at high risk of having a fetus with chromosomal aneuploidy, and then

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followed by diagnostic testing via chorionic villus sampling (CVS) or amniocentesis to obtain more definitive information. Over the past decade, prenatal genetic testing options have dramatically expanded to include multiple options for screening and the addition of cell-free DNA (cfDNA) screening, as well as expanded diagnostic abilities through tests including chromosomal microarray analysis (CMA) and gene panels. Critical to be conscious of, though, with these expanding technologies are the costs associated with their use relative to the diagnostic yield achieved.

Cost-effectiveness analyses are designed to evaluate the costs and clinical benefits of particular interventions in order to determine which strategy provides value for a population.[1] The value proposition in cost-effectiveness analyses usually is ascertained by comparing the incremental costs to the incremental benefits to determine whether the gain is worth the additional cost. A common threshold that is used is $100,000 per quality-adjusted life year (QALY). Cost-effectiveness analyses of prenatal genetic testing take into account choices for screening tests as well as for diagnostic testing and subsequent management of the pregnancy, ranging from procedures such as amniocentesis that enable further or confirmatory genetic testing to deciding whether to terminate a pregnancy with a known or suspected fetal condition. The risks associated with prenatal genetic tests must be considered, such as the risks of false positive or false negative results, pregnancy loss or complications following procedures such as amniocentesis, and detrimental effects on quality of life. More difficult to incorporate into cost-effectiveness analyses is the time necessary for counseling about each testing approach and the results that follow, psychosocial factors such as stigmata associated with genetic testing, and deviations from the expected paths of decision-making. Cost-effectiveness analyses have been employed to evaluate the utility of preimplantation genetic diagnosis, approach to first and second trimester serum screening, approach to carrier screening for conditions such as Fragile X and spinal muscular atrophy, and other prenatal genetic testing dilemmas.[2–10]

An inherent goal of cost-effectiveness analyses is to evaluate the costs associated with one strategy versus another, thus leading to reallocation of resources in a particular direction to optimize population health if certain strategies are found to more effectively balance cost with improved or equivalent clinical outcome. Overspending in one strategy that does not most effectively optimize population health misappropriates resources, and can lead to unmet health care needs and disparities. Cost-effectiveness research for prenatal genetic testing can inform clinical decision-making about the costs versus utility of certain testing strategies, leading to improved maternal and fetal health with relatively less cost incurred by both individuals and society. Care must be taken, though, to consider which testing results and health outcomes are most important to evaluate; what defines costs with respect to monetary value, imposed risk to health, and effects on quality of life; and the interplay of individual and cultural belief systems.

Clinical considerations and recommendations

How will movements toward value-based health care impact prenatal genetic testing?

In order to discuss the impact of value-based health care on prenatal genetic testing, one must first consider value. Value has been defined as the health outcomes achieved per dollar

spent for a full cycle of care for a patient's medical condition.[11] Value-based health care is aimed at maximizing the quality of care while minimizing cost.[12] Patients, providers, and payors are all thought to benefit when value is optimized in health care, and value should guide decisions made in health care. However, the means by which to assess value in obstetric care require further study, particularly with respect to determining the most important outcome measures and for whom these outcomes are relevant. Intrinsic value may vary with baseline health status, individual or cultural beliefs, perception of risk, and many other factors, and value to an individual may not be the same as the value to the health care system or society.

Studies evaluating the obstetric outcomes important to women have identified a multitude of factors central to increased maternal satisfaction, including the quality of information delivered by providers, perception of shared decision-making, maternal and neonatal morbidity, mode of delivery and the birth experience, mother-infant attachment, and maternal autonomy or self-esteem.[13–19] When considering prenatal genetic testing, individual beliefs and preferences as they relate to value become imperative to understand. For one woman, receiving the results of a genetic test that identifies a severe intellectual disability in her fetus might carry a very different weight than for another woman. Several studies have identified the severity of the underlying genetic problem as an important outcome to patients when they consider genetic testing, as well as the certainty of the test (false positive and negative rates) and their associated distress, coping, mood, and sense of empowerment.[20–22] Additional out-come measures that are considered useful by both patients and health care providers include the accuracy of women's risk perceptions, whether the test actually helped their decision-making, provider's knowledge about genetic conditions and the quality of patient education imparted, the degree of personal control perceived by women, and whether quality of life was affected.[23] Further studies are warranted to evaluate the outcome measures most important specifically to individuals in the prenatal setting who are evaluating genetic testing options, especially as the availability of both screening and diagnostic tests in pregnancy expand. While early diagnosis and intervention are often at the forefront of prenatal decision-making, further studies should also address both the short- and long-term outcomes following particular testing strategies, taking maternal and child heath as well as quality of life into account.

Also important to consider for value-based health care are the relevant outcomes on a larger scale from the perspective of third party payors, the health care system, and society. As with outcomes on an individual level, the outcomes through which value may be assessed in the larger scale remain under debate, particularly as the availability and types of genetic tests expand for pregnant women. Rather than the fee-for-service reimbursement model through which greater patient volumes are prioritized, focus has shifted toward value-based health care models that place the focus on quality of care.[24] Additionally, maternity care bundles have generated increasing interest as measures to potentially balance cost and quality in prenatal care, although it remains unclear which services should be grouped into a bundle, how to define an obstetric episode of care, how to ensure that appropriate and medically indicated care is delivered and disparities are not created, and how to best evaluate the quality of the care delivered by such bundles.[25–26] Finally, cost and cost-effectiveness are

essential considerations for both prenatal genetic testing and value-based health care, and are addressed in the following sections.

What outcomes should cost-effectiveness analyses consider when evaluating prenatal genetic testing?

In the setting of multiple strategies that differ in cost and effectiveness, cost-effectiveness analyses directly compare these strategies and aid in decision-making. With prenatal genetic testing, cost-effectiveness analyses have been used to compare strategies for preimplantation genetic screening, first and second trimester serum screening, carrier screening, and other genetic tests.[2–10] Important decisions that are faced with prenatal genetic testing include preimplantation screening and diagnostic strategies, screening and diagnostic strategies during pregnancy, method of diagnostic testing during pregnancy (CVS or amniocentesis), type of diagnostic test during pregnancy (karyotype, CMA, single gene testing, gene panel, or emerging broad strategies such as whole exome sequencing), and continuation of pregnancy versus termination.

There is no perfect screening or diagnostic test during or outside of pregnancy, so considering the positive and negative predictive values for each test relative to each genetic condition is essential when cost-effectiveness analyses are performed. To account for variation in test characteristics, patient population, and other components of cost-effectiveness models, sensitivity analyses can be applied to vary the test characteristics, disease prevalence, and other baseline assumptions. The genetic diagnoses uncovered by each test are crucial to evaluate, keeping in mind that although aneuploidies such as trisomy 21 have traditionally been the focus of prenatal genetic testing, there are a myriad of genetic conditions that may be of relevance to pregnant women and that may now be detected by currently available tests.

With continually expanding genetic testing capabilities that are becoming increasing available in the prenatal setting, diagnostic abilities are growing exponentially. However, the chance of detecting an unexpected (incidental) finding or a finding of uncertain clinical significance concurrently increase, and the potential anxiety or distress that may be invoked should be considered. Similarly, uncertainty and anxiety may arise when testing methods fail (such as when a low fetal fraction is detected with cfDNA), and even more traditional testing such as karyotype can detect unexpected genetic abnormalities. Anxiety may follow each decision incorporated into the branching logic of a cost-effectiveness analysis, or it can result from the uncertainty itself in making a decision. Estimates such as quality-adjusted life years (QALYs) are used to account for such effects on psychological, emotional, and physical well-being. Economic and psychological costs may ensue immediately through provision of prenatal genetic counseling and testing services, or can manifest in a delayed fashion if these services are delayed and a child is born with significant unanticipated morbidity.[27]

When a genetic abnormality is discovered or suspected, individuals are faced with the choice of what to do next. The first choice after screening is often whether or not to pursue diagnostic testing, and the risks and benefits of invasive procedures (risk of pregnancy loss, underlying genetic risk, accuracy of the test, etc.) must be weighed. Sometimes, additional

measures such as fetal imaging may provide further information to guide decision-making. If diagnostic testing is deferred, risks may or may not then exist to the fetus or child as a result of delayed diagnosis. The number of invasive procedures or pregnancy terminations performed or avoided as the result of a particular test may be estimated. Some individuals may terminate a pregnancy when faced with a particular genetic abnormality, and following this decision, there exists an element of risk for detrimental effects on quality of life. Other individuals would continue a pregnancy with the same genetic abnormality, in which case quality of life for both the parents and child must be considered, and may be negatively impacted by disabilities or major medical issues for the child. Detriments to quality of life are typically discounted over time, assuming that the negative impact of a decision or clinical outcome diminishes with time, but both short- and long-term outcomes for women and children are important to evaluate under all circumstances.

In terms of economic costs, there are a number of considerations for cost-effectiveness analyses of prenatal genetic testing. Cost and effectiveness must both be weighed. A test that costs slightly more, but that has a much greater positive predictive value for a particular genetic condition, is likely much more effective than its competitors. Utilization of particular tests is important to consider, paying attention to disparities that may exist across subgroups, although estimates of utilization are often challenging to find. Costs may be seen immediately, such as for direct payment of a specific test, or in the future, such as with costs incurred through treatment of a genetic condition leading to major morbidity. Both benefits and costs may apply to the individual, provider, third party payor, or society. Cost may also be hidden in the time required by health care providers to counsel prior to a test, counsel after receiving the results, and in the follow up evaluations that follow.

Development of a CROWN core outcome set may be an important strategy to identify the most important outcomes for cost-effectiveness analyses that evaluate prenatal genetic tests. The CROWN (Core Outcomes in Women's and Newborn Health) initiative was created in order to develop a set of core outcomes for different disorders in maternity care.[28] Given the long list of potentially important outcomes to consider for cost-effectiveness analyses of prenatal genetic testing, the application of this initiative could lead to identification of those on which future research efforts should focus.

Should professional societies consider cost and cost-effectiveness in creating guidelines?

Cost and cost-effectiveness are paramount for professional societies to consider as they create guidelines. Cost-effective allocation of resources is essential not only for the individual utilizing prenatal genetic tests, but also for the clinic or hospital through which she is receiving care and for society at large.[12] Examples of society recommendations for specific testing strategies are those in the Choosing Wisely publication from SMFM, which among other pathways for testing, advises that cfDNA testing should not be offered to low-risk patients and that irreversible decisions should not be pursued based on results of this screening test.[29]

Society recommendations behind a testing strategy should be evidence-based and supportive of tests that are truly indicated or necessary, not duplicative, and minimize harm. In creating these guidelines, important points for discussion include the available tests from which to

choose, the evidence from cost-effectiveness analyses behind recommending one testing strategy over another, and the clinical rationale for these recommendations. Societies should be responsible for reviewing the existing evidence behind genetic testing strategies, including where disparities might exist, and identifying which strategy or strategies minimize cost while optimizing health outcomes for a population. Societies also have a responsibility to make it abundantly clear that all individuals should have equal access to prenatal genetic tests that are standard of care, which means that insurance plans and hospital systems must take ownership of finding ways to absorb some of the costs of testing and counseling for those with public insurance coverage. In turn, this has the potential to decrease long-term costs associated with delayed diagnosis and work up for the child.

Society recommendations surrounding cost and cost-effectiveness should be publicized, and it is the responsibility of societies to shape conversations and explain the rationale behind their statements. This creates a system of accountability, and provides justification for clinician practice patterns as well as coverage afforded by third party payors. Finally, in the interest of transparency and clarity, societies have a duty to acknowledge when costs and cost-effectiveness are a driving force behind their recommendations.

How should disparities in health care and insurer coverage be considered in terms of prenatal genetic testing?

Prenatal genetic testing is a core element of obstetric care, and while individuals may forgo this testing if they wish based on personal or other beliefs, every pregnant woman should have access to the screening and diagnostic genetic tests that are standard of care. These tests include serum screening methods, ultrasound, diagnostic testing including karyotype and chromosomal microarray analysis (CMA), and carrier testing when appropriate. However, the decision about whether to proceed with prenatal genetic testing is personal, and influenced by individual desires, risk tolerance, cultural beliefs, and many other factors. Further, while all individuals should have access to the same set of choices in terms of prenatal genetic testing, financial constraints and insurance coverage may limit the available options.[30]

Individuals with public as compared to private insurance may face important limitations in the genetic testing options available to them.[31–35] Similarly, variation exists by insurance plan in terms of coverage for both screening and diagnostic tests, and these differences are often a driving factor in individual decisions about which testing strategy to pursue. For example, ACOG and SMFM have published clear guidelines regarding the indications for and advantages of CMA relative to traditional karyotype for diagnostic testing during pregnancy.[36] However, CMA is variably covered across insurance plans, and out of pocket costs ranging from hundreds to thousands of dollars may preclude some individuals from receiving this test. Some major insurance plans support the use of CMA for all patients undergoing invasive diagnostic testing during pregnancy, as well as those with fetal abnormalities characteristic of a genetic condition, stillbirth with anomalies, or individuals at increased risk of aneuploidy; others cover CMA only for situations in which a fetal anomaly is detected, karyotype results are normal, a stillbirth has occurred, or a stillbirth is associated with fetal anomalies.[31–35] While all individuals should have equal access to genetic tests that

are standard of care, disparities persist in access to insurance coverage and evidence-based tests.

In addition to economic disparities related to type of insurance coverage or lack thereof, racial/ethnic and other sociodemographic disparities remain prevalent. In a study investigating women's recall of discussions about prenatal genetic testing, significant sociodemographic differences emerged, with African American and Latina women understanding less clearly that screening tests were optional, and individuals with lower literacy being less likely to recall discussions of screening. In terms of diagnostic testing, several racial and ethnic minority groups were less likely to understand that diagnostic testing was optional, and younger women, parous women, and less educated women recalled discussions of diagnostic testing more poorly.[37] Numerous other factors are essential to consider with regard to disparities in genetic testing, including language barriers; health literacy; confidence established in both the test and the health care team; and religious, cultural, and personal belief systems.[38]

Also concerning is evidence that disparities may be furthered by the genetic counseling provided to individuals, such as if providers approach counseling in a more constrained manner when perceived patient viewpoints or economic limitations exist. One study found that CMA was offered more frequently to women who self-identified as White, spoke English, and did not receive care at a community health center.[39] Other studies have similarly uncovered sociodemographic disparities among women in being offered and utilizing screening, with a greater uptake of cfDNA among women with higher education as well as greater income and insurance coverage.[40,41] Another study found that women with public insurance are less likely than those with private insurance to undergo diagnostic testing as a follow up to a positive serum screen (odds ratio 0.26), which may stem from a variety of factors aside from economic limitations, such as inadequate genetic counseling and individual or cultural views toward genetic testing.[42]

Disparities in access to obstetric care also exist nationwide, including to prenatal genetic counseling services. This is largely the result of geographic location and lack of nearby obstetric services, and can be compounded by socioeconomic disparities. Individuals living in rural locations must travel longer distances to receive medical services, and are more likely to have limited economic means and to have limited or no health insurance.[43] As of 2010, nearly half of all counties in the United States did not have a practicing obstetrician-gynecologist.[44] Access to prenatal genetic counseling services may be even more limited in these areas. A shortage of certified genetic counselors currently exists to meet the needs of the population, and the National Society of Genetic Counselors and other bodies have commissioned a Genetic Counselor Workforce Working Group in order to evaluate and address the supply and demand of genetic counselors in the United States over the next decade.[45]

With the increasing number and complexity of genetic tests that have become available in the clinical setting, obstetrician-gynecologists and primary care physicians will need to become increasingly educated about the benefits, limitations, and risks of each genetic test. Mechanisms must exist in order to provide thorough pre- and post-test counseling, perform

indicated procedures such as amniocentesis, and refer patients who require counseling beyond the expertise of the provider. Without appropriate counseling, informed decision-making for individuals considering genetic testing suffers, and the risks of unexpected or misunderstood results increase substantially. Further, complete pre- and post-test counseling must include discussion of pregnancy termination. Not only do at least 87% of women in the United States lack access to abortion providers in their county, but access to these services is decreasing.[44,46]

As the availability and diagnostic potential of prenatal genetic tests continues to increase, there are tremendous opportunities for increasing the scope of prenatal diagnosis and for individualization of care.[47] However, there is a real risk of deepening the already present disparities that originate in sociodemographic factors, economic means, insurance status, racial/ethnic background, education history, language spoken, and many other factors. Important steps that can be taken to address these disparities are pursuing further research to better understand reasons for these disparities and identify possible solutions. Research should include adequate representation from all patient subgroups, and provider subgroups deserve evaluation as well. Disparities may originate at the level of the patient, provider, community, or larger society, and a thorough understanding of the underlying barriers and biases is essential. Women should be encouraged to invite those that are important stakeholders in their lives, such as family or religious advisers, to participate in decision-making. Efforts should be made to increase numbers of and access to providers who are qualified to counsel about prenatal genetic testing options, and pregnancy termination must become more available for women who receive results that lead them to a decision to terminate. Women's preferences vary in terms of prenatal genetic tests and outcomes, desire for follow up diagnostic testing, as well as inclination to terminate a pregnancy,[20,48] and population differences in testing uptake is acceptable only if based upon truly informed decision-making. Finally, more oversight will become necessary for states, not only to ensure equal access for all individuals, but also to regulate potential misuses such as application of cfDNA testing for the purpose of sex-based abortion.[49,50]

What is the role of commercial laboratories in introducing new prenatal tests?

Three major bodies in the United States play roles in regulating genetic tests that are marketed by commercial laboratories: the Food and Drug Administration (FDA), Federal Trade Commission (FTC), and Centers for Medicare and Medicaid Services (CMS). CMS regulates all clinical laboratories that perform genetic testing, and holds laboratories accountable to the Clinical Laboratory Improvement Amendments of 1988 (CLIA). CLIA ensures appropriate qualifications of laboratory technicians, verification of procedures, and quality of genetic tests. Although the FDA has the broadest authority in over-seeing genetic tests and medical devices, whether or not the FDA regulates a specific test depends on how that test is marketed. A critical point for providers and patients to understand is that the FDA practices "enforcement discretion" for laboratory-developed tests (LDT) and regulates only those marketed as commercial test kits, which are sold for use by multiple laboratories. cfDNA testing, for example, is not regulated by the FDA despite its widespread use.[51,52] Broadening the oversight of the FDA for LDTs has been a topic under consideration in recent years.[53,54]

Commercial laboratories are responsible for developing and implementing LDTs, and for reporting accurate and transparent data on their use. Under CLIA, commercial laboratories must establish preanalytic systems for a new test, meaning processes for receiving test requisitions, submitting and handling specimens, and referring specimens. Analytic systems must also be in place to ensure that tests are performed in accordance with manufacturer instructions, meet performance specifications (accuracy, precision, and analytical sensitivity and specificity), and are reviewed for accuracy and precision over time. Finally, post-analytic systems must exist to ensure accuracy of patient-specific reporting, maintenance of readily available test reports, and notification of errors.[55] National Institute of Health recommendations for parameters through which to evaluate a genetic test include analytical validity (reliability and accuracy), clinical validity (medical meaningfulness), and clinical utility (how the test improves health care).[51]

While commercial laboratories usually introduce new genetic tests and are responsible for reporting data on their validity and utility, they should not extend these responsibilities to recommending one test over another. They should also design marketing materials in ways that avoid advocating for particular actions based upon results, and should encourage values-based decision-making in conjunction with a qualified genetics professional. This becomes particularly applicable when considering direct to consumer genetic tests that have become available, such as carrier screening panels. The National Society of Genetic Counselors (NSGC) advises that companies offering direct to consumer testing should have mechanisms to offer referrals and easy access to genetics professionals, in order to assist with the interpretation and thorough understanding of information yielded by the test.[56]

The American College of Medical Genetics and Genomics (ACMG) has issued a number of guidelines for the minimum requirements of genetic tests that can reveal health-related information. These include accreditation by CLIA; inclusion of a knowledgeable health professional in ordering a genetic test, interpreting the test, and delivering the results; disclosure to the consumer about limitations of the test, as well as the potential for uncertain results, unexpected results, and implications for family members; and provision of the evidence behind validity and utility reports.[57] Commercial laboratories must also make it abundantly clear that genetic testing is only one component of genetic risk assessment and disease diagnosis and management. Further, commercial laboratories should offer the choice to deliver selected results based on individual wishes, and should only store patient samples or genetic data for the purposes of research with the explicit consent of the patient.

Ideally, international representatives of obstetric and genetics professional societies, in conjunction with major laboratories and consumer groups, should agree upon and publish minimum standards for health outcomes to report based on commercial genetic tests, research to prioritize, and education to provide for both providers and patients. A CROWN core outcome set, as discussed previously, could be created for new and existing genetic tests in order to outline essential health outcomes to report and define specific outcomes in need of research.[28]

What is the role of insurers in the introduction and use of new prenatal genetic tests?

Insurers are tasked with the responsibility of deciding which genetic tests to cover, and variability exists in coverage from one plan to another as well as by public versus private insurance.[31–35] Decisions made by insurers should ideally be based on existing evidence demonstrating the utility of genetic tests, with support from cost-effectiveness analyses. As discussed in the previous section, tests should be assessed in terms of analytical validity, clinical validity, and clinical utility. However, a high level of evidence is not always available, and there is a need for further research to clarify the validity and utilization of tests across sociodemographic subgroups, and better understand their cost-effectiveness. When sufficient evidence is lacking, decisions must be made based upon existing data and reasonable extrapolation. Statements issued by major medical societies provide valuable guidance about testing strategies that are standard to offer. A significant limitation of the fact that the FDA does not regulate many genetic tests is that FDA approval is not a driving force behind insurance coverage of these tests.

An essential principle, though, is that all individuals should have access to tests that are considered the standard of care. Insurers should not act as gatekeepers to tests; rather, they have a responsibility to provide consumers access to evidence-based testing that is at least the standard of care. There is no provision for excluding a service with adequate supporting evidence of medical necessity simply because it is too expensive. Similarly, because a test is much less costly is not a valid reason to cover its use, unless there are data to support its superior performance. When the validity and utility of two tests are similar based on adequate evidence, though, a reasonable choice would be to afford coverage to the less costly option. Decisions about insurance coverage become more complicated when tests have been less well researched, although an appropriate course of action would be to provide coverage for a test that is medically indicated, even if not yet considered standard of care. Beyond coverage of individual tests, insurers must also factor in coverage for referral services as indicated based on the results.

With the responsibility that insurers have in awarding coverage comes influence on the utilization of genetic tests. Downstream effects may result, such as changes in the uptake of specific tests, or of particular concern, worsening of socioeconomic and other disparities that already exist. The pace of genetic discovery and marketing is so fast that it may be outpacing the ability of insurance companies to keep up with technology assessments, but in-depth reviews of the existing evidence by insurance companies are essential for making informed and fair coverage decisions.

How should conflict of interest and commercial interests be considered and managed in introduction and use of tests?

Conflict of interest occurs when a relationship or set of circumstances lead to risk that a secondary interest improperly affects professional judgment. Conflict of interest may arise in many ways, such as when individuals with more limited access to health care turn to the counseling offered through genetic testing companies in order to make decisions about reproductive genetic testing. cfDNA was rapidly introduced into clinical practice before thorough data became available to understand its validity and limitations, and its drawbacks

of less clear utility for low-risk women and a low fetal fraction being associated with a greater risk of aneuploidy[58] are still less well understood and often not acknowledged commercially. Conflicts may also arise on the part of the health care provider, such as when genetics professionals are employed by clinics or hospitals in addition to genetic testing companies, imposing obvious bias. Additionally, professional societies may be at risk for conflicts of interest if their members have a secondary interest associated with commercial or personal gain.

It is imperative for patients and health care providers to understand situations that might constitute a conflict of interest, so they can assess effects on the counseling provided or decisions made. Full disclosure is the responsibility of all parties, and transparency is the best and safest approach when conflicts of interest are concerned. All efforts to acknowledge conflicts should be made by genetic testing companies, health care providers, and professional societies, to allow for unbiased decision-making by patients and providers.

What are the research priorities?

Genetic testing capabilities have grown exponentially over the past decade, and screening as well as diagnostic options during pregnancy have drastically expanded. With this expansion has come marked improvement in our ability to diagnose genetic conditions prenatally, counsel families about prognosis and recurrence risk, and anticipate neonatal needs. However, many additional uncertainties have been raised in conjunction with improved testing capabilities, and limitations exist in the current knowledge that guides our practice patterns for offering and counseling women about options for prenatal genetic testing.

As value-based health care becomes more of a focus, understanding patient-centered as well as systems-based outcomes relative to associated costs will become essential. Priorities for research include clarifying which short- and long-term health outcomes for mother and child are important in order to compare one testing strategy to another. The downstream effects of different prenatal genetic testing strategies will require further investigation, including the economic costs and quality of life impact associated with testing during pregnancy versus delaying the diagnosis and work up until after birth. Sources of disparities such as race/ethnicity and other sociodemographic factors, perception of risk, and personal and cultural beliefs should be examined to improve our understanding of how they affect individual decision-making, including ways in which these disparities can be minimized. The actual utilization of prenatal genetic tests is difficult to estimate based on currently available data, and further research is needed to understand how the uptake of testing strategies varies by sociodemographic subgroups, as well as the effects of factors such as personal belief systems and risk tolerance. Baseline rates of pregnancy termination, and termination rates in response to genetic testing results, are also challenging to understand based on currently available data.

To keep pace with expanding genetic tests moving forward, research efforts should also evaluate the utility of soft markers for aneuploidy as identified on ultrasound given the wide-spread use of cfDNA testing. Additional applications of cfDNA should be explored, such as the cost-effectiveness of its use for single gene disorders and in predicting preeclampsia, fetal growth restriction, and other adverse outcomes. The role of nuchal translucency should

be clarified in the context of different screening strategies, including the potential for delayed genetic diagnoses if not performed. Gene panels require some scrutiny to determine whether the trend toward a broad approach with inclusion of a multitude of genes makes sense, or whether a smaller set of more evidence-based genes is more cost-effective. The impact of whole exome sequencing and other emerging tests that are entering clinical practice will be important to assess, particularly with respect to effects on health outcomes, short- and long-term costs, and testing strategies. Only with a more informed understanding through these research efforts can further progress be made toward optimizing health outcomes for individuals, communities, and society, being mindful of associated costs.

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