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SYMPOSIUM:
WOMEN AND PRENATAL GENETIC TESTING IN THE 21ST CENTURY

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INTRODUCTION

With over four million women presenting for prenatal care in the
United States annually and current recommendations to offer aneuploidy
testing to all, there is no doubt that advances in prenatal genetic testing
will have an important impact on the health and well-being of women
and their children. Translational genomic research over the past decade
has vastly increased our knowledge of human health and disease,
bringing the promise of improving the lives of patients through new
medical technology. Initially used in adult testing indications, many of
these technologies are finding a place in obstetrics as pregnant women
and their partners now have access to a vast array of fetal testing
options that dramatically influence the delivery of prenatal care. With
the development of new molecular testing modalities, fetal cells can now
be analyzed for dozens of genetic mutations in a single pass and provide
rich genomic information that would be undetectable using conventional
testing methods.¹ The ability to conduct genetic tests on cell-free fetal

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1. See Lauren C. Sayres & Mildred K. Cho, Cell-Free Fetal Nucleic Acid
Testing: A Review of the Technology and Its Applications, 66
OBSTETRICAL & GYNECOLOGICAL SURV. 431, 438 (2011); see F. Lucy
Raymond et al., Molecular Prenatal Diagnosis: The Impact of Modern
Technologies, 30 PREGNATAL DIAGNOSIS 674, 674 (2010).
DNA in the maternal blood stream is paving the way for non-invasive diagnostic tests to become part of routine prenatal care. Direct-to-consumer test offerings have become increasingly visible and accessible in conjunction with these advances, expanding the avenues by which women can obtain information about their pregnancies. It is not just innovation in clinical genetics that has affected antenatal care. Parallel advances in the fields of maternal-fetal medicine and neonatology are also influencing how new genetic tests become incorporated into the care of the pregnant woman, establishing new boundaries for optimizing in utero health using genetic science.

The recent explosion of genetic science and technology has allowed innovative approaches for identifying and treating disease to become a clinical reality. While aimed at improving and preserving health, these advances produce some of the most profound ethical, legal, and social questions about how to integrate new technology into the healthcare and lives of patients. These questions are twofold, as they pertain not only to understanding the significance of personal genetic information but also to how such information can and should be used to guide fundamental choices about the self and family. Information about one’s genetic makeup leads to a host of interlaced ethical and pragmatic ramifications that spring from our limited understanding of how the presence of a mutation plays out over the course of one’s life. Despite a more sophisticated understanding of the human genome, it is striking that many of the ethical and practical challenges of genetic testing remain unresolved, such as the interpretation of personal risk from the identification of a genetic mutation, the privacy and confidentiality of genetic information, and the prediction of quality of life for those living with disease or disability.

These existing dilemmas have magnified implications in women’s reproductive health and prenatal genetic testing. While genomic research has opened up new possibilities to assess fetal health, the sheer volume of information generated by prenatal testing has amplified the fundamental ethical, legal, and social conundrums that already exist for genetic testing in other areas of medicine. In the context of pregnancy, decisions regarding genetic testing of the developing fetus involve a complex calculus based largely on conjecture and uncertainty. As in the case of genetic testing for adults, it is necessary for the pregnant woman to weigh the benefits of accessing genetic information about the fetus against the disadvantages and limitations of that information. She must consider the well-being of the unborn child and, as such, must integrate a host of unknowns about disease severity, progression, and quality of

life for her future child. Given the rapid advance of medical technology, she is also faced with considering what therapies or other resources that do not exist in the present may be available in the future that could alleviate any pain or suffering resulting from a genetic condition. It is based on these considerations that she must make the critical decision to continue a pregnancy while planning for the birth of a child with a genetic condition, to take part in an experimental procedure that may influence neonatal outcomes, or to end the pregnancy.

Because of the special maternal-fetal dyad of pregnancy, women are uniquely affected by fetal genetic information and the decisions this information invites. Choices about prenatal genetic testing are often a collaborative effort between expecting parents. Yet, due to the biology of reproduction and pregnancy, women have a distinct role and a specific interest in the integration of these tests into clinical practice. Although prenatal genetic tests are conducted to assess the health of the fetus, they are performed on the pregnant woman and, as a result, have direct implications for her health and well-being. It is critical to recognize that these implications extend far beyond collecting a maternal blood sample or fetal cells through an invasive *in utero* procedure. The decision to proceed with testing has the potential to produce a cascade of downstream tests and procedures during the pregnancy to further evaluate or manage fetal genetic findings. Additionally, as the fields of perinatology and neonatology are advancing in conjunction with genetic science, the decision to undergo testing may also affect intrapartum management in the delivery suite. Finally, genetic information or procedures conducted in response to that information may also influence future reproductive decision-making.

Women are uniquely affected by advances in prenatal genetic tests in another significant way. The decision to proceed with or to decline testing is a very personal choice that weaves a woman’s most personal values and beliefs about self, pregnancy, and parenthood into her healthcare choices. However, these individualized choices about the pregnancy are often influenced by factors external to her. Many of a woman’s reproductive decisions are bound by laws, policies, clinical practice guidelines, and public opinion about what a pregnant woman should and can do during the pregnancy. Given the ramifications of all of these issues, it is critical to understand how advances in genetic technologies affect the health and lives of women.

I. THE EVOLUTION OF GENETIC TECHNOLOGIES

To understand the evolution and salience of these issues, it is important to first understand how genetic technologies have evolved over the past fifty years. One category of prenatal genetic testing that has undergone important changes is the screening test. Screening tests provide information about the chance that a fetus has Down syndrome or other related chromosomal abnormalities. The advantage of screening tests is that they are performed by drawing a sample of blood from the mother without the use of more invasive procedures; thus, the pregnant woman can bypass the uncommon but real risks associated with chorionic villus sampling (CVS) and amniocentesis. When used as a triage mechanism, screening tests help to determine which women might benefit from definitive diagnostic testing, thus reducing the potential number of iatrogenic losses of chromosomally normal fetuses that could occur with generalized use of these procedures. Screening tests also have limitations. One limitation is the ability of the screen to detect all fetuses with an abnormal compliment of chromosomes, so that there is a chance of a screen-negative result in the context of an affected fetus. There is also the possibility of a false positive result, in which case the screen would indicate an increased risk of a chromosomal abnormality when the fetus has, in fact, a normal complement of chromosomes. Thus, this information can only be used to inform decisions about further testing.

The first screening tests were developed in the late 1980s and 1990s. Initially, it was determined that the combination of three maternal serum chemicals (human chorionic gonadotropin, unconjugated estriol, and alpha-fetoprotein) conferred information about possible abnormalities caused by extra or missing chromosomes (referred to as “aneuploidy”). This test analyzing these three chemicals was known as the Triple Screen. In the years following, the Quadruple Screen was developed to increase detection rates with the addition of another maternal serum marker called inhibin A. Since that time, there has been a move towards earlier screening modalities. While the Triple and Quadruple Screens provided fetal risk information, they could not be


performed until after the fifteenth week of pregnancy. Thus, choices about the pregnancy following confirmatory diagnostic testing could not be made until well into the second trimester, a time when the choice to continue or terminate the pregnancy may have very different ramifications for the woman than if the decision had been made earlier in the pregnancy. First trimester aneuploidy screening is a new screening approach consisting of assessment of maternal serum markers in conjunction with sonographic measurement of the back of the fetal neck (also known as nuchal translucency).7 This new tool confers similar fetal genetic risk information regarding Down syndrome as the Triple and Quadruple Screen but can be performed as early as eleven weeks into gestation.8 Timed one month earlier than its second trimester counterparts, this new screening modality gives patients a wider range of options over the course of their prenatal care, including immediate diagnostic procedures in the initial weeks of pregnancy.

Important advances have also taken place in another category: diagnostic testing. The procedures of CVS and amniocentesis were developed in the latter half of the twentieth century as ways to directly test fetal cells to confirm the presence or absence of a genetic condition. Both procedures involve inserting a needle into the pregnant woman’s uterus to access fetal or placental cells for testing. While amniocentesis cannot be performed until the second trimester of pregnancy, CVS can be performed in the first trimester.

The procedures of CVS and amniocentesis have changed little over the decades since their development. What has changed, however, is the number of testing applications that can be performed using these procedural platforms. Initially, these diagnostic procedures were used to conduct analysis for a single genetic mutation (e.g., cystic fibrosis) or chromosomal abnormality (e.g., Down syndrome) at a time. The development of multiplex testing techniques then allowed assessment for multiple different single Mendelian mutations or fetal characteristics (e.g., gender) simultaneously.9 Further advances in genetic science have changed the basic paradigms of genetic conditions and shifted our perception of diseases away from the concept of their being monogenic in origin towards the idea that they often involve multiple genes in concert.


As a result, there has been a move towards incorporating microarrays into prenatal care, allowing analysis to identify from tens to thousands of variants during a single testing process. Prenatal microarray testing is able to generate detailed genetic information that could not be detected using standard cytogenetic techniques.

Until recently, diagnostic information about the fetus could only be obtained through invasive procedures such as CVS and amniocentesis. Now, non-invasive prenatal genetic diagnosis is changing conventional paradigms about accessing and using fetal genetic information to guide antepartum care. Performed by drawing a blood sample from the pregnant woman, it is anticipated that non-invasive prenatal genetic diagnosis will ultimately provide the same degree of diagnostic information as more invasive procedures while bypassing the physical risks to mother and fetus. The clinical potential for non-invasive prenatal genetic diagnosis is great. Studies show that pregnant women are very interested in using this new approach to prenatal genetic testing. Preliminary studies also show that including the option of non-invasive prenatal genetic diagnosis increases women’s interest in and willingness to undergo prenatal genetic testing for a number of different conditions and also alters core beliefs about genetic testing in pregnancy. Access to genetic information via a sample of maternal blood is also likely to encourage the already growing direct-to-consumer movement of genetic testing, which may further complicate legal, ethical, and social ramifications. As the development of genetic, genomic, and molecular technologies concurrently accelerates, the scope of possible in utero investigations will drastically expand.

II. THE IMPACT OF ADVANCING GENOMIC TECHNOLOGIES ON INFORMED DECISION-MAKING BY PREGNANT WOMEN

While research in the field of genetics has opened up new possibilities to assess fetal health, the sheer volume of information generated by prenatal testing generates a host of dilemmas, challenges, and questions. To date, many of these discussions have focused on the

10. Ronald J. Wapner et al., Integration of Microarray Technology into Prenatal Diagnosis: Counselling Issues Generated During the NICHD Clinical Trial, 32 Prenatal Diagnosis 396, 399 (2012).


health and well-being of the expectant child and, by so doing, have displaced considerations about the pregnant woman. Yet it is paramount that discussions address the impact of these technologies on women’s lives both during and after the pregnancy. This includes a discussion not only of the scientific and medical aspects of the newest technologies but also the expectations, moral obligations, values, and preferences surrounding genetic testing, motherhood, and family that are placed on women. Some of the issues are novel; they present women, healthcare providers, scientists, and policy makers with nuanced questions about the meaning, significance, and implications of acquiring detailed fetal genetic information during pregnancy. In some cases, these issues can be foreseen and, with adequate preparation, negative sequelae can be mitigated before the technology is broadly implemented. In other cases, the full ramifications of a new genetic technology do not become evident until that technology has been widely integrated into patient care. What is remarkable, however, is that still other issues have been lingering unresolved since the earliest stages of prenatal genetic testing. Of greatest concern, these pre-existing issues may be exacerbated by the introduction of new tests that provide more detailed information about the fetus.

One set of issues pertains to a woman’s ability to make informed choices about her prenatal genetic testing options. With an expanding array of testing options, a pregnant woman must have the resources to make informed, value-reflective choices about her prenatal testing options. Without a mechanism to support her access, understanding, and considerations of this information, she is at risk for going down two equally negative paths. In one scenario, she may proceed with a prenatal genetic test without an adequate understanding of its indications, limitations, and implications, leaving her grossly underprepared to consider the outcomes of either ending the pregnancy or planning for the birth of a child with a genetic condition. In the other case, she may decline a test that might have otherwise been wanted because she did not understand how genetic information can potentially optimize outcomes for the expected child. Both scenarios can lead to weighty and significant implications for the health and well-being of the woman in the context of both the current pregnancy and future family building plans.

Since the initial days of prenatal genetic testing, studies have shown that pregnant women have struggled to make informed, value-reflective decisions about their prenatal genetic testing choices. This trend has been evident for both screening and diagnostic tests. What is significant is that many of the same barriers to women’s education and decision-making continue to persist even with ongoing advancement in prenatal applications of genetics. A core issue has been women’s ability to access patient-centered information about genetic diseases and the approaches
to identifying them. The priority for this kind of information is high because decisions to undergo or decline prenatal genetic testing are an individualized calculus requiring knowledge of the fetal genetic condition in question, approaches to identify it, and post-test choices for the pregnancy. In addition, these considerations must also incorporate personal values about disability and illness, parenthood, and quality of life. However, there are significant problems to the informed decision-making process related to pregnant women’s knowledge of prenatal genetic testing, as the fundamental concepts associated with screening and diagnostic testing remain elusive to many. Barriers associated with a lack of health literacy and a limited understanding of the concepts of risk and probability also have a notable effect on minorities and women from lower educational and socioeconomic groups.

Contemporary studies provide important insight into how these pre-existing barriers will pose even greater challenges for innovative ways to assess fetal health assessments. Using the first trimester aneuploidy screen as a litmus test for the readiness of the healthcare field to support women’s decision-making, it is evident that the same underlying problems that arose with the introduction of the Triple and Quadruple Screens continue to exist. For pregnant women, this manifests as deficits in understanding (1) the purpose of this new test, (2) the ways in which it differs from conventional tests, and (3) possible ways to navigate the expanded decision tree of post-test options for the pregnancy. For clinicians, there continue to be challenges in mobilizing adequate resources to support the decision-making process for new tests. The ongoing challenge for the healthcare provider to acquire and maintain knowledge of clinical genetics is another contemporary problem. These underlying problems stem not only from limitations of time and clinical resources to support patient education but also from the reality that it has become difficult for medical education to keep pace with advances in


genetic science. In addition, although some degree of uncertainty has been a long-standing component in choices about prenatal genetic tests, such as questions about subsequent disease severity and impact on quality of life, microarray testing has made uncertainty a much stronger presence in the decision-making process. With the ability to identify thousands of genetic variants, some with as-yet-unknown relevance for health, women struggle to reconcile the meaning of an abnormal result with choices about the pregnancy. Because the core leading medical, ethical, and personal implications of accessing fetal genetic information remain constant with all forms of prenatal genetic testing, these issues must be addressed both for already established forms of testing as well those innovative approaches positioned to be broadly integrated into prenatal care. Without the recognition of these issues and mobilization of resources to address them, pregnant women will be vulnerable to the hazards of uninformed decision-making.

III. The Voluntary Nature of Decisions about Prenatal Genetic Testing

Access to accurate, patient-centered information is only one component of a pregnant woman’s preparedness to make informed choices about prenatal genetic testing. Equally important is her ability to make voluntary decisions about whether to proceed or decline forms of testing. Discussions early in the development of prenatal genetic testing brought attention to the voluntary nature of decision-making and the need to ensure that women were positioned to make autonomous choices about their testing options. Leading scholars paved the way to examining the meanings and implications of the “good mother,” including the expectations and obligations for or against testing placed on her during pregnancy by healthcare professionals, society, and

17. Sandy Suther & Patricia Goodson, Barriers to the Provision of Genetic Services by Primary Care Physicians: A Systematic Review of the Literature, 5 GENETICS MEDICINE 70, 75-76 (2003); see Susan B. Trinidad et al., Educational Needs in Genetic Medicine: Primary Care Perspectives, 11 COMMUNITY GENETICS 160, 160 (2008); Charles J. Macri et al., Implementation and Evaluation of a Genetics Curriculum to Improve Obstetrician-gynecologist Residents’ Knowledge and Skills in Genetic Diagnosis and Counseling, 193 AM. J. OBSTETRICS & GYNECOLOGY 1794, 1797 (2005); see Caulfield & McGuire, supra note 2, at 25.

family. On the one hand, there were cautions for utilizing genetic tests, raising the specter of eugenics and devaluing those individuals living with illness and disease. On the other, there were warnings against restricting a woman’s autonomy and autonomous decision-making. Concepts of coercion and non-directive counseling are at the heart of these discussions. While coercion is often conceptualized as overtly directed counseling, it can also be more subtle in nature, such as when information is withheld or biased. As decisions regarding testing during pregnancy align closely with a woman’s personal beliefs, these discussions also brought to light that the voluntary nature of decisions can be eroded by healthcare providers who may not be aware of her individual and cultural preferences about pregnancy, motherhood, disability, and illness.

Over the past several decades, there has been a move not only to develop tests that can generate a vast amount of genetic information about the pregnancy but also to provide these data with the lowest risk possible to the fetus. In response, new approaches to prenatal genetic testing are being developed to fulfill these criteria. This new cohort of tests reawakens interest in voluntariness in prenatal genetic testing and provokes foundational discussions addressing women’s abilities to make unhindered choices about their use. For many women, the iatrogenic risks of CVS and amniocentesis served as a barrier to accessing fetal genetic information. Now, the real possibility of gaining diagnostic level information through a maternal blood draw stands to fundamentally change the risk-benefit calculus that women undertake when considering testing as an option. At the present, non-invasive diagnosis is emerging as a tool to assess fetal risk for chromosomal abnormalities. However, its potential for expanded genomic testing is great and, in the coming years, it is expected that its techniques can be applied to search for a number of different genetic variants simultaneously. In removing the medical risks of diagnostic testing, it is important to safeguard the protections of


informed consent, including the voluntary aspects of a woman’s choice to proceed with or decline testing.

Because the leading medical, ethical, and personal implications of accessing fetal genetic information remain the same for all forms of diagnostic testing (whether invasive or non-invasive), an important part of the translational process will be to ensure every pregnant woman has the resources to make informed, value-reflective choices about her prenatal testing options. Thus, there is a need for contemporary discussions to revisit the issues of voluntariness, to recognize issues pertinent to women’s autonomous decision-making within the current context of prenatal genetics, and to construct mechanisms to ensure that pregnant women are not coerced with regards to genetic testing.

IV. MATERNAL-FETAL SURGERY AND THE CHANGING CALCULUS OF PRENATAL GENETIC TESTING

The evolution of prenatal genetic testing technology is not taking place in a vacuum. Contemporary discussions must also consider the discipline of obstetrics and how changes in this field have an undeniable impact on how the ethical, legal, and social implications of prenatal genetic tests take shape. The great majority of these procedures remain experimental, and many more studies must be performed before they become part of standard practice. However, the possibility and availability of interventions to ameliorate the sequelae of a genetic condition in utero will begin to shift how the benefits and limitations of the available prenatal genetic tests are framed by patients and their healthcare providers.

It is important to recognize the discordance between what can be diagnosed in utero using genetic tests and what can be done to prevent or mitigate the illness associated with a genetic mutation. Despite advances in genetic science, procedures to effectively alter DNA-level mutations to prevent disease or, in many cases, control the effects of a genetic variant on an individual’s phenotype have yet to be developed. Because of these limitations, pregnant women have customarily been given two options following in utero diagnosis of a genetic condition. One option was pregnancy termination, most often performed in the second trimester of pregnancy after the testing process was completed. For women who did not elect for or were unable to access abortion services, another option was to continue the pregnancy and plan for the birth of a child with a genetic condition.

For many women, the potential of being put in the position of having to decide between these dichotomous outcomes was a key reason for declining testing. Yet advances in the field of high-risk obstetrics and fetal intervention have begun to alter the choices presented to pregnant women. Together with the efforts to advance clinical genetics, there has been a growing interest in interventions during pregnancy to improve fetal and neonatal outcomes. Maternal-fetal surgeries entail conducting surgery on the pregnant woman, procedures which entail making an
incision in the woman’s abdomen and uterus to access the fetus. While the risks of these procedures to fetus and mother are clearly identifiable, their benefits overall remain unclear. Recent data about a procedure to correct neural tube defects in utero may mark a pivotal point in how prenatal genetic testing is presented to women. One of the functions of screening tests is to identify the risk of neural tube defects, which are errors in how the early nervous system takes shape. The primary approach to management of pregnancies included heightened antepartum surveillance and plans for intervention after birth. A recent study shows that surgical management of a specific type of neural tube defect (myelomeningocele) in utero may lead to improve outcomes for some children, though more research must be conducted. However, this procedure comes at a cost, as it presents serious medical risks to the pregnant woman. Yet the mere availability of this option for those women whose pregnancies have been diagnosed with a neural tube defect fundamentally changes how the utility of prenatal genetic testing will be framed.

This maternal-fetal surgery addresses just one of the thousands of genetic conditions that can now be diagnosed in utero. The reality is that, while the past decade has witnessed the growth of prenatal genetic testing technology, there has not been parallel expansion of pregnant patients’ post-testing options. As a result, pregnant women continue to grapple with the dilemmas that come with the many ways to diagnose a multitude of different genetic conditions while having very few proven therapeutic options either during pregnancy or after birth. Thus, an important part of discussions about the impact of new prenatal genetic tests is recognizing that an expanding discordance is developing between what can be identified in utero and current options to change outcomes for the child. The result is a new and nuanced set of ethical, legal, and social dilemmas for women as they face their prenatal genetic testing options.

**Conclusion**

Some of the most profound, difficult, and controversial questions regarding women, motherhood, family, children, and disability exist at the intersection of obstetric and clinical genetics. Advances in molecular genetics intensify our uncertainties and, in some cases, our discomfort with the ability of genetic technology to affect our lives and the world in which we live. The quickly changing and increasing analytical capabilities of genomic applications in the prenatal clinical context invoke the need to evaluate the ethical, legal, and social implications of

these issues for those pregnant women in the position of considering prenatal testing.

In 1991, the National Institutes of Health sponsored a workshop entitled “Reproductive Genetic Testing: Impact upon Women” to begin to address some of these core issues. Led by Elizabeth Thomson and Karen Rothenberg, the workshop’s mission was to examine the impact of prenatal genetic testing on the lives of women and to identify a set of themes to guide the development and use of these technologies. This meeting was a landmark event because it was the first of its kind to bring together a multidisciplinary panel of experts to examine advances in prenatal genetic testing within the context of women’s lives.

A host of events have taken place in the past twenty years that have changed the landscape of prenatal genetic testing and the care of women during pregnancy. As discussed here, these events have taken place not only in genetic science and the practice of obstetrics but also in discussions and policies about the delivery of prenatal care, women’s reproductive rights, informed decision-making, and disability. Some of these advances provoke new and unexplored questions about how to integrate advances in clinical genetics into the care of pregnant women. At the same time, other cornerstone issues associated with genetic testing, such as defining and identifying illness and disease in addition to the implications of fetal genetic information, remain unchanged and as provocative today as they were twenty years ago. Given the accelerating trajectory of clinical genetics, medical science, and surgical innovation, it is critical to revisit how the lives of women are uniquely affected by the newest approaches to prenatal care.

In response to this need, the Case Western Reserve University School of Law hosted a symposium entitled, “New Technologies, New Challenges: Women and Prenatal Genetic Testing in the 21st Century.” The aim of the symposium was to bring together a group of leading experts from the disciplines of bioethics, social science, clinical medicine, law, and genetic science to identify those challenges and critically examine how the health and lives of women are affected by the advances taking place in the care of pregnant women. Scholars who participated in the original 1991 conference joined in collaborative dialogue with new leaders in the field, generating a solid foundation for understanding the breadth and depth of these issues as they have evolved over the past twenty years. Over the course of a day and a half, important strides were made toward understanding the unique ways in which women’s lives are affected by advances in genetic technology and the carryover of these effects for children, families, and the practice of medicine. As the emergence of new genetic technologies accelerates in the months and years to come, it will be vital that multidisciplinary experts continue to engage in examining the challenges associated with prenatal genetic tests and forming ethical guidelines for their translation into patient care.