



Reproductive Genetic Testing: **Issues and Options for Policymakers**



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Preface

We are currently in the midst of a genetic revolution in medicine. Advances in science, especially the completion of the human genome sequence, have led to greater understanding of the role of genes in health and disease. Genetic tests for diseases and disease risks are available currently and new medicines and preventive strategies are on the horizon.

Many people first encounter genetic testing when having a baby. Reproductive genetic testing – carrier testing, prenatal genetic testing, preimplantation genetic diagnosis – combines the newest advances in genetics with the most profound human activity of creating life. Reproductive genetic testing provides information: information about the risk of parents passing a genetic mutation to their children; information about the genetic characteristics of embryos produced through in vitro fertilization; information about the genome of a fetus in utero. This information can provide reassurance to prospective parents, or be the basis for important decisions: to attempt a pregnancy or not; to transfer an embryo to the uterus or not; to continue a pregnancy or not. The growing availability and use of reproductive genetic testing presents a host of complicated ethical, legal and social issues.

New genetic technologies will touch the lives of millions of Americans. Yet, there is relatively little oversight of reproductive genetic testing. As the number and type of genetic tests grows and their use becomes more widespread, the time has come to seriously consider how these new technologies will affect individuals and shape society, and whether changes in oversight are needed. Some believe that the decision to use reproductive genetic testing should be left up to individual parents in consultation with their doctors. Others believe that reproductive genetic tests for certain uses are ethically inappropriate and that the tests should be either controlled stringently or banned entirely. The challenge is to consider the scientific, ethical, social and political issues these technologies raise in formulating policies that also reflect the public's values and enhance the public good.

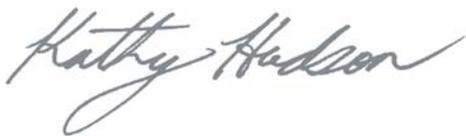
This report, *Reproductive Genetic Testing: Issues and Options for Policymakers*, aims to help focus and facilitate the discussion about reproductive genetic testing by outlining key scientific and medical facts, considering ethical and social implications, and assessing both current and potential oversight for the development and use of reproductive genetic tests. It presents a range of policy options supported by expert analysis that consider the potential effects, positive and negative, of distinctly different policy directions. Our goal at the Genetics and Public Policy Center is not to advocate for or against any technology or policy outcome but to make sure that policy decisions, including the decision to maintain the status quo, are undertaken with a clear-eyed understanding of their potential impact.

The growing debate about the use and oversight of reproductive genetic testing has been largely framed by two opposing views: those who see reproductive genetic testing as an opportunity to prevent suffering and who oppose limitations on research, technological advance and reproductive choice; and those who believe that reproductive genetic testing will have adverse ethical and social impacts and who support restrictions on its development and use. The views of most Americans, however, are more nuanced and elastic, reflecting the tensions among hopes, values and personal experience.

The Center has undertaken an in-depth effort to assess public attitudes toward genetic technologies – with public opinion surveys, town halls, focus groups, and online group discussions – as a means of making the discussion about genetics and public policy more democratic and less divisive and the province of special interests. The goal is not to encourage policy making by public referendum, but to give everyone involved a clearer sense of the diversity of opinion surrounding these issues.

In 2004, we organized public meetings around the country and invited those whose voices are not typically heard by policy makers; we held meetings with stakeholders to gather their input on policy options; we held interactive forums online that allowed individuals to register their opinions; we conducted the largest ever survey of the American public about their opinions of reproductive genetic testing and technologies. The accompanying report, *Reproductive Genetic Testing: What America Thinks*, presents the results of our research on the public's attitudes about reproductive genetic testing and possible approaches to its oversight.

We hope that together these two reports will be useful tools for enhancing public discussion of reproductive technologies and assisting decision makers in both the private and public sectors as they consider policies to govern the development and use of reproductive genetic testing.

A handwritten signature in cursive script that reads "Kathy Hudson". The signature is written in black ink and is positioned above the printed name and title.

Kathy Hudson
Director, Genetics & Public Policy Center

Introduction

Genetic testing is undergoing tremendous changes. Scientists are identifying disease-causing mutations in human genes at a rapid pace and developing tests to detect them. In addition, new laboratory technologies will allow many genetic tests to be performed at once on a single sample of DNA. These developments are part of an ongoing “genetic revolution” in medicine and biotechnology. Tests to detect the presence of a genetic mutation or abnormal chromosomes can help diagnose an existing disease or can be used to predict either the certainty or probability that a disease will develop in the future.

Many people first encounter genetic testing in the reproductive context as genetic testing has become an integral component of reproductive health care. Reproductive genetic testing refers to those genetic tests and procedures that are used to provide prospective parents with information about their chances of having a child with a specific genetic disorder or characteristic in a current or future pregnancy. These include: (1) carrier testing, which is done to determine whether an individual carries one copy of an altered gene for a particular recessive condition; (2) prenatal genetic testing, in which the cells of a developing fetus obtained through procedures such as amniocentesis and chorionic villus sampling (CVS) are genetically tested; and (3) preimplantation genetic diagnosis (PGD), in which embryos produced through in vitro fertilization (IVF) are genetically tested to select which embryos to transfer to a woman’s uterus.

For many, reproductive genetic tests ultimately provide extremely valuable and reassuring information. But the experience of reproductive genetic testing is often not easy. Women sometimes report feeling they have boarded a roller coaster ride of choices that may include discovering their child has an increased risk of genetic disease, undertaking invasive genetic testing procedures, making decisions regarding termination or bearing a child with a potentially serious condition and assessing whether and how to approach future pregnancies.

There are many alternative policies—some complementary, some conflicting — that could guide the development and use of reproductive genetic testing. Currently, prospective parents decide whether to seek reproductive genetic testing to detect a particular condition or trait. Providers and clinical laboratories, in turn, make the decisions about what genetic tests they will offer. Some individual clinics and providers may refuse to perform testing for certain reasons, such as sex selection. A “status quo” policy approach would leave the current system in place, avoiding government interference in personal reproductive choices and the practice of medicine. It would also allow scientific and medical advances to move forward unimpeded by government restraints. Some observers are content with this level of oversight.

Others believe that decisions about technologies so profound that they could shape future generations should not be left entirely to the discretion of individual parents and

Reproductive genetic testing refers to those tests and procedures that are used to provide prospective parents with information about their chances of having a child with a specific genetic disorder or characteristic in a current or future pregnancy.

providers. They raise concerns about the inappropriate use of reproductive genetic tests and believe that broader societal consensus and input are needed. Some believe scientific and technologic capability itself will drive practice to move forward, regardless of what society may believe is ethical. Others question how safe, accurate, effective and beneficial these technologies are, and whether as a society we have allowed them to become commonplace without fully considering their implications. Some worry that any benefits from these technologies will be inequitably distributed because of their high cost.

Many observers believe new policies — governmental or private — are needed to keep pace with the rapid changes in reproductive genetic testing. Oversight can spur good development and uses of new or existing tests and avoid inappropriate uses or outcomes.

Some people want to limit or ban reproductive genetic testing. An outright ban of all testing is unlikely, as some forms of genetic testing have already become a routine part of reproductive health care, one that prospective parents know about and expect to be offered whether or not they choose to pursue these tests. Even so, some countries,

including the United Kingdom, France, Germany and India have enacted laws setting limits on the use of prenatal genetic testing. The emergence of PGD has been sufficiently troubling to some that its use has been prohibited in some countries such as Germany and Switzerland.

Ultimately, policymakers face the challenge of balancing personal values of liberty and choice with more community-based values such as ensuring that society is the kind of place that individuals want to live.

This report, *Reproductive Genetic Testing: Issues and Options for Policymakers*, addresses the scientific, legal, regulatory, ethical, moral and societal issues raised by carrier testing, prenatal screening and testing and PGD. It also lays out an array of possible policy options to guide the development and use of reproductive genetic testing.

The options presented here seek to explore the full measure of possible policy approaches, including federal, state and non-governmental strategies to address the issues surrounding reproductive genetic testing. Each option includes a brief overview of its purpose and potential implications, and explains some of the arguments that could be made in support or opposition.

Ultimately, one's policy preferences are likely to be influenced by a range of factors, including perceptions of existing and likely future applications of reproductive genetic testing and one's view of the proper balance between governmental involvement

and individual liberty. These preferences also frequently turn on core beliefs about the moral and ethical acceptability of genetic testing, abortion and destruction of human embryos. One's perspective may also include assumptions about the expected costs and benefits of various applications of these technologies and how they will be distributed in society.

Reproductive Genetic Testing:

A Scientific and Medical Overview

Genes and Inheritance

Advances in reproductive genetic testing have emerged from our growing knowledge of how an individual's genetic blueprint is linked to inherited characteristics such as risk of disease. To understand what is behind this technology, it is worth reviewing some fundamental facts of human biology and genetics.

Every person is born with a genetic code that is made up of DNA. DNA is composed of four chemical subunits, or nucleotides, abbreviated as A, T, C and G. These subunits come together as pairs; an A always pairs with a T and a C always pairs with a G, to form the rungs of a twisting ladder called the DNA double helix.

The sequence of these base pairs along the double helix represents a code or set of instructions. A length of DNA encoding an instruction, such as for the manufacture of a certain protein, is called a gene. It is estimated that humans have 20,000 to 25,000 genes.

The DNA in each human cell is packaged into 23 pairs of chromosomes within the cell's nucleus. Our chromosomes and the genes they carry are inherited from our parents. During fertilization, half of the nuclear DNA, or 23 chromosomes, comes from the mother's egg. The other half comes from the father's sperm. These chromosomes contain all the genetic instructions necessary to create new life. As an embryo develops and cells divide, the complete DNA blueprint is copied over and over

into each new cell. A small amount of DNA also is contained in cellular structures called the mitochondria, which are inherited only from the mother.

Genes and their Role in Disease

We all carry alterations, or variations, in our genetic code. The DNA from any two people is 99.9 percent identical. But one-tenth of one percent is different between any two individuals and this difference is part of what makes a person unique. Many of these variations in the DNA code have no harmful effect. Other variations can cause disease

or increase the risk of disease. Sometimes, a change in only one or a few letters in a gene can cause a gene to malfunction, e.g. produce a non-functioning protein or fail to produce a protein at all. Variations with deleterious consequences are generally referred to as genetic "mutations." An inherited disease or condition, such as Huntington disease, cystic fibrosis or sickle cell anemia, can be caused by one or more mutations in a single gene.

We all have two copies of each gene on our "autosomal" chromosomes, meaning those other than the X and Y chromosomes



DNA double helix shows pairing of A to T and C to G. The order of the base pairs in a gene provides the instructions to make a protein. A variation occurs in one gene. The gene on one chromosome contains a T-A and the other a G-C.

that determine sex. Sometimes both copies of a gene must have a mutation to cause disease. Such mutations are called “recessive.” A person who carries only one copy of a recessive gene mutation is called a “carrier.” Carriers are usually healthy but if two carriers have a child, then there is a 25 percent chance that their child will receive two copies of the mutation, one from each parent, and be affected by the disease.

Some genes are on the X or Y chromosome. Such genes are termed “X- or Y- linked.” The impact of an X-linked recessive mutation will be different in males, who have one X and one Y chromosome, and females, who have two X chromosomes. For example, the recessive mutation that causes Duchenne muscular dystrophy is on the X chromosome. A female who has one copy of the mutation will be a carrier, since she will have a normal copy of the gene on her other X chromosome. A male who has the mutation on his X chromosome, however, will have the disease, since he has only one X chromosome. Thus, each male child of a mother who is a carrier has a 50 percent risk of inheriting the mutation and developing Duchenne muscular dystrophy. Each female child has a 50 percent chance of being a carrier like her mother.

Sometimes, a mutation in only one copy of a gene can cause disease. Such mutations are called “dominant.” If one member of a couple has a dominant mutation then there is a 50 percent chance that each child will inherit the dominant mutation and also be affected.

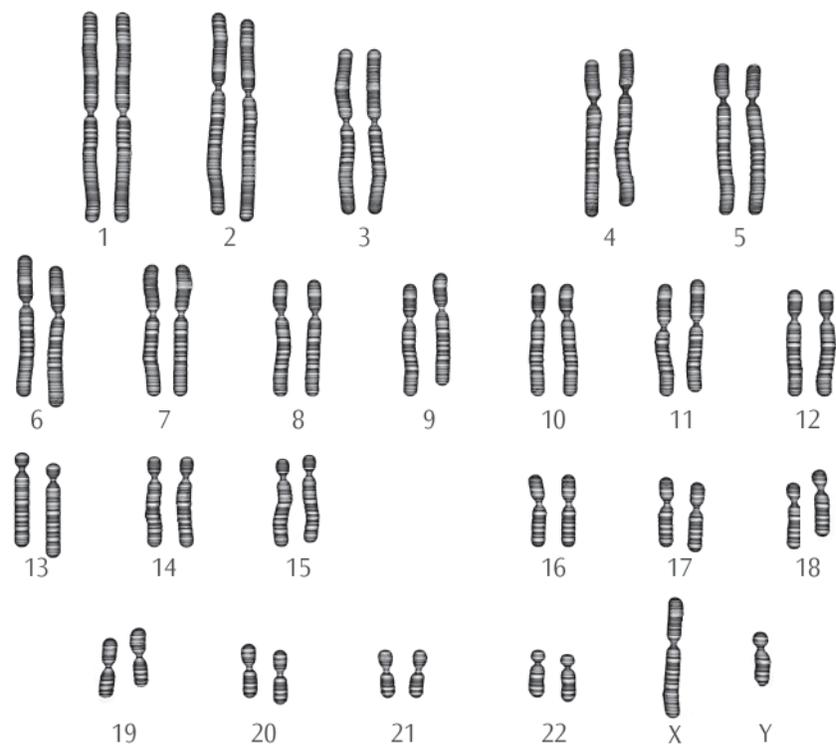
Sometimes genetic diseases are the result of chromosomal abnormalities. A person may have too many or too few copies of a particular chromosome, or have a missing or extra region of a chromosome. For example, Down syndrome is caused by the presence of an extra copy of chromosome 21. Many chromosomal abnormalities are incompatible with life and result in pregnancy loss or stillbirth whereas others can cause birth defects, developmental delays or mental retardation.

The Limits of Genetics

Many health conditions are not caused by mutations in a single gene but rather involve multiple

genes and their interaction with the environment. A major focus of modern biomedical research is to identify those genes that contribute to common disorders such as heart disease, diabetes, asthma and most cancers. These conditions are frequently termed “polygenic disorders” (meaning many genes) or “multifactorial diseases” (meaning caused by a combination of genetic and environmental factors).

In addition, some mutations are linked only to a heightened risk, not a certainty, of disease. For example, women who carry a mutation in the BRCA1 or BRCA2 gene have a more than 80 percent increased risk of developing breast cancer by age 70, as well as an increased risk for



Normal Male Chromosomes

Types and Purposes of Reproductive Testing

| Reproductive Genetic Testing | Test performed on | Indications | Uses |
|-----------------------------------|-------------------|--|--|
| Carrier Testing | Adults | Family history or high incidence of disease in relevant population | Inform reproductive decision making, including whether to use PGD or prenatal genetic testing |
| Prenatal Genetic Testing | Fetuses in utero | Increased risk identified from carrier testing, family history, advanced maternal age, screening tests results | Give parents information, allowing them to prepare for birth of affected child, consider treatment options after birth, consider termination |
| Preimplantation Genetic Diagnosis | Embryos in vitro | Increased risk identified from carrier testing, family history, advanced maternal age | Select embryos for transfer to avoid known risks, select particular trait, or increase success of IVF |

ovarian cancer. But it is not certain that they will develop any cancer. Men with a mutation in one of these genes are at increased risk for breast, prostate and other cancers.

Furthermore, a genetic mutation does not necessarily predict the severity of a disease if it does occur. Two people with the same disease-causing mutation can have widely differing prognoses. Additionally, even when there is a complete correlation between having a mutation and developing a disease, such as in the case of the mutation linked to Huntington disease, the genetic test cannot predict when in the person's life the disease will manifest itself.

These inherent limitations mean that although genetic testing provides additional precision to modern medical diagnosis it also introduces new uncertainties. Although a test can determine the presence of a mutation with certainty it cannot with certainty predict the outcome of having that mutation. Genetic disease risks are frequently

stated in terms of probabilities, and that can lead to the need to make difficult health care choices in the absence of definitive information.

The Technology of Testing

The number of conditions for which genetic testing can be done is rapidly increasing at the same time that the technology has become ever more powerful. Historically, certain genetic diseases have been diagnosed through the use of biochemical tests. For example, before the advent of a DNA-based test for Tay Sachs disease, both disease and carrier status could be identified through a biochemical test, which revealed the level of the Tay Sachs-related protein. Reduced level of the protein allowed the inference that there was a mutation in the gene sequence coding for that protein.

DNA-based (molecular genetic) tests have largely replaced biochemical tests for a number of reasons. For one, DNA is more readily available and is stable. A DNA-based test can be done on

virtually any cell in the body. DNA-based tests are often easier, less expensive, more accurate and faster than biochemical tests, allowing for more rapid results at a lower cost to the patient.

Molecular tests to examine an individual gene require either probing for a particular mutation or variant or comparing the DNA sequence in a patient's gene to that in a normal version. Tests can detect very small changes in the DNA, as small as a single DNA base pair. There are genetic tests available or in development for over 1000 diseases. Currently, not all genetic tests are generally offered in the reproductive context. But there is no technological barrier to introducing them as part of reproductive genetic testing.

Cytogenetics (chromosome analysis) assesses the number or structure of chromosomes present in the cells. Fluorescently labeled, chromosome-specific probes are used to visualize spots representing each copy of that chromosome. Too

few or too many spots can indicate abnormalities.

Instead of looking for one DNA variation at a time, new “gene chip” technology can test for hundreds, even thousands, of possible DNA variations simultaneously. In addition to detecting specific DNA mutations, gene chip technology is used to detect chromosome abnormalities or to measure the “expression” of genes, that is, which genes are turned on and off and to what extent they are functioning.

Carrier testing is typically performed on adults, either before they conceive or after conception, to see if they risk passing a mutation to their child. All that is required is a small sample of DNA, which is typically obtained from a blood sample or a swab taken from inside the cheek.

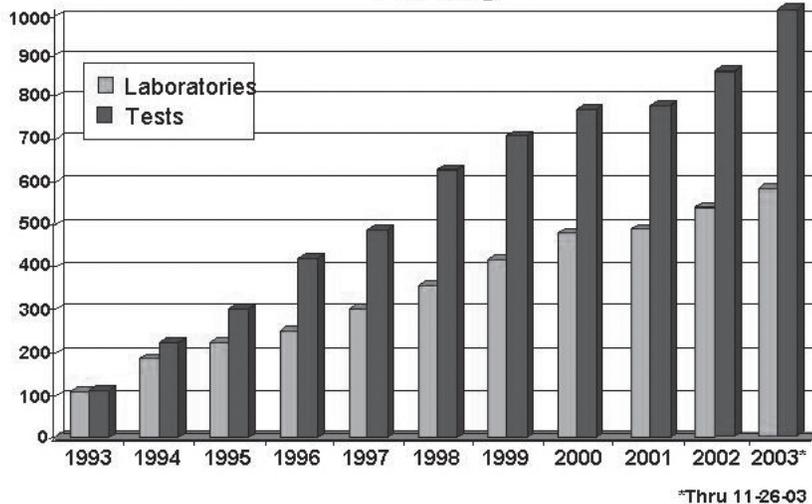
Genetic testing is laboratory analysis of DNA, RNA, or chromosomes. Testing can also involve analysis of proteins or metabolites that are the products of genes. Genetic testing is done to predict risk of disease, screen newborns for disease, identify carriers of genetic disease, establish prenatal or clinical diagnoses or prognoses and direct clinical care. Testing can be done using many different biological samples, including blood, amniotic fluid (from which fetal cells are obtained) or individual embryonic cells. *Cytogenetic analysis* is used to detect abnormalities in chromosomal number and/or structure, such as those that might indicate Down syndrome. *Molecular genetic testing* examines individual genes.

Prenatal genetic testing is done during pregnancy. Most often, this involves conducting tests on fetal cells obtained from fluid surrounding the fetus (amniocentesis) or from fetal cells removed from the placenta (CVS).

with the desired characteristics are then transferred to a woman’s uterus.

PGD is done on embryos that are created outside the womb through in vitro fertilization. One or two cells are removed from the embryo and tested for the presence of a particular genetic trait or condition. Embryos

Growth of Genetic Testing



Data source: GeneTests database (2003)
www.genetests.org

Genetic Testing and Issues for Society

Reproductive genetic testing offers prospective parents information about their risk of having a child with a genetic disease. This information can be used to help parents make profound decisions such as whether to pursue pregnancy at all; use donated eggs, sperm or embryos; seek additional testing; select specific embryos for transfer into the woman's uterus; or decide whether to continue or end a pregnancy. Reproductive genetic testing raises ethical, social and legal issues that cannot be resolved by science and technology alone.

Reproductive genetic testing may help relieve anxiety by reassuring prospective parents that their risk is low for having a baby with a particular genetic disease or diseases. However, reproductive testing also may cause tremendous worry for some patients and family members. Patients sometimes do not fully understand what the tests mean and what decisions they will need to make based on the results. Some observers worry about how the information obtained from testing will be used, particularly whether it will lead prospective parents to have an abortion or to selectively destroy embryos. Others worry about the effect of genetic testing on the way we view each other and our children. And many ask who will have access to reproductive genetic testing, who pays for it and whether widespread reproductive genetic testing is an effective use of limited health care resources.

Given these concerns, people differ about whether there should be limits on reproductive genetic

testing, what those limits should be and who should set them.

Perceiving Genes As Destiny

In the public's mind, genetic testing is often viewed differently from other diagnostic tests and medical treatments. Genetic tests, while not necessarily more informative than other medical tests, are often perceived as such. Genetic information carries with it an aura of immutability that other medical data do not. Genetic testing gives people information — albeit sometimes uncertain information—about themselves or their family members. While these conditions may be treatable or manageable, the DNA itself cannot be altered, and genetic test results are therefore perceived as presenting a fixed destiny. As a result, many have raised concerns about the potential stigma of genetic information if it is used to a person's disadvantage, for example by employers or insurers.

Genetic test results also may affect other family members and family relationships in a way other medical information does not. Prospective parents may learn that they have a genetic mutation and have to decide whether to inform other family members who may also have the mutation.

The Social Meaning of Genetic Difference

A genetic test can only identify a particular DNA sequence or chromosomal abnormality. It cannot ascribe social significance to that finding; only individuals and society can do that.

Many Americans believe that certain diseases caused by genetic mutations, such as those that lead to suffering and death in early childhood, are serious enough to justify testing and preventing the birth of an affected child. However, the distinction between what is a “normal” genetic variation and what constitutes a “disease” is often not clear or agreed upon by society.

“I think if we as a society determine that we want to screen out disability and use genetic testing for that, we will have lost a great deal in terms of the amazing contributions people who are labeled disabled can make. . . . as well as to have really misunderstood what it means to be human.”

*Sharon Terry, Genetic Alliance **

Some fear that the availability of more genetic tests, combined with greater technological ease in performing them, will lead to people viewing genetic variation as either “diseased” or “desirable.” As more people use genetic information to make reproductive choices, the tendency may be to classify mild disorders or natural variations as abnormal, leading to societal stigma and decreased tolerance and appreciation for human difference.

Specific concerns also have been raised about the societal impact of using prenatal testing or PGD

* Quotations used in this report are from Chosen Children: Issues in Reproductive Testing (video), on file with Genetics and Public Policy Center

to select traits viewed by some as more desirable. For example, some oppose the use of prenatal testing or PGD to select sex when the purpose is to satisfy parental preferences and not to avoid X- or Y- linked disease. Historically, in many societies females have been subjected to discrimination based purely on gender. In some parts of the world, there are cultures that still openly prefer male children to female. In those cultures, some parents terminate a pregnancy if the fetus is known to be female. Given this history of discrimination and existing cultural preferences for boys, some observers see using PGD for sex selection as having the potential to devalue women. However, others argue that in many countries, including the U.S., one sex is not currently preferred over the other and sex selection has been used to select boys and girls equally.

“Children are not like a recipe, where you pick different things and you mix it up in a petri dish and you come out with a child that you expect on the other end.”

*Paul Miller, former
Commissioner, Equal
Employment Opportunity
Commission*

Impact on Parents and Children

Some fear that as testing becomes available for an increasing array of inherited diseases and conditions,

couples will face growing medical and societal pressure to avoid the birth of a child that has not “passed” all the requisite genetic tests. These parents may feel they have no choice but to undergo invasive prenatal testing, taking unwanted risks with a wanted pregnancy. Others envision that the spread of carrier tests will create a climate in which those with “bad” genes will be discouraged from biological reproduction, or feel pressure to use PGD or prenatal diagnosis to avoid having a child with a genetic disease. The question remains whether the availability of reproductive genetic testing might lead to a decrease in resources and support for those living with disabilities, less money for treatments and cures for genetic diseases and a more negative societal attitude towards people with disabilities generally.

On the other hand, some have argued that the more widespread genetic testing becomes, and the more each individual knows about his or her genetic makeup and risk for particular diseases, the more society will tolerate human differences. Rather than expecting each fetus to meet some definition of genetically “normal,” the knowledge that no individual is a “perfect specimen” will lead to less pressure to use all available technology to have a “perfect” child.

Some also fear that reproductive genetic testing will change the way we view children. In the future, it is possible that parents could choose to transfer only those embryos possessing particular characteristics not related to health but viewed as socially advantageous, such as

appearance. These observers say it is a natural, but troubling, human impulse to try to have a “perfect” child — whatever one defines “perfect” to be. The argument is that if parents have the power to accept or reject an embryo or fetus based on its genetic characteristics, children will no longer be viewed predominantly as precious gifts to be loved unconditionally but as carefully selected collections of attributes chosen from conception to meet a parent’s expectations.

“When you begin to do genetic testing . . . at the early stages, you are also on the way to saying that children have to . . . be able to climb over a certain genetic bar to be able to be entitled to get into the world and entitled to parental acceptance.”
Leon Kass, American Enterprise Institute

Even now, with the reproductive testing already being done, there is concern that the large number of parents who terminate a pregnancy after learning the fetus has Down syndrome will make the condition so rare that children will be viewed as avoidable “mistakes” and their parents as irresponsible.

On the other hand, others argue that a positive impact of testing will be to reduce the number of children with disabilities being born into families who are unable or unwilling to love them and care for them.

Some also point out that testing for Down syndrome has been available for decades and that during that time, society's acceptance of people with disabilities has not decreased.

“Over the past 20 or 30 years there have been opportunities to terminate fetuses with Down syndrome and that has been going on for a generation and yet I don't believe that individuals with mental retardation or with Down syndrome are any more or less excluded or that parents have the sense or society has the sense that this is a child that could have been or should have been prevented.”

*Paul Miller, former
Commissioner, Equal
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Commission*

The development of tests for genetic diseases or predispositions to genetic disease has far outpaced the development of methods to prevent or cure these conditions. That leads some, particularly pro-life individuals, to wonder whether it is a net benefit or harm to know that one carries a particular disease-causing genetic mutation when there is no viable treatment and where the “treatment” is to eliminate the “patient.”

In addition, there is debate about whether it is appropriate to test fetuses or embryos for disorders, such as Huntington disease, that would not affect them for many years, during which time a treatment may be discovered. Debate also exists about the use of reproductive genetic tests that identify predisposition to, or increased risk of, developing a disease such as breast cancer, particularly when the disease itself is potentially treatable and even curable. At issue is how a life is determined “not worth living,” and the level of risk parents are willing to take.

The Changing Experience of Pregnancy

The proliferation of genetic testing before and during pregnancy has had a significant effect on how women

and their partners experience having children. From the beginning, a woman considering pregnancy or a newly pregnant woman may be told that genetic testing is needed to determine whether she is at risk for carrying a fetus affected by a genetic disease. Many of the early pregnancy visits to a provider may be spent in part discussing the choices of prenatal screening tests or more invasive testing. Then, weeks may go by when the woman is already pregnant and awaiting the results of testing. Testing may lead to more testing, to decisions whether or not to terminate a fetus and to an overall heightened sense of anxiety. While many individuals and couples appreciate the information and reassurance that testing can provide, some experience the process, if not the result, as too much information and too many choices.

The Role of Genetic Counseling in Testing

Many providers recommend genetic counseling prior to testing. Genetic counseling may be done by certified genetic counselors or geneticists or by other providers with appropriate expertise. Ideally, after reviewing medical and family histories, a genetic counselor or other provider assesses the specific genetic risks to a pregnancy and helps the patient through the decision-making process about whether or not to undergo testing based on the parent's own values and beliefs.

In the context of reproductive genetic testing, the options for the family will be specific to the type of testing (whether carrier, prenatal or preimplantation), what is being tested for and whether treatment is available. Genetic counseling gives prospective parents the information necessary to make an informed decision. However, decisions made about whether to have genetic testing and what to do with the results should be determined solely by the parents-to-be.

Referrals for genetic counseling are increasing. However not all genetic counseling services are available in all areas and many questions exist about whether and when these services are reimbursed by insurers.

Some observers note that even once pregnant, mothers-to-be may avoid feeling connected to the fetus and the pregnancy until they receive a “clean bill of health” from prenatal testing.

Access to Care and Insurance

It is not certain whether and to what extent insurers cover carrier testing, prenatal screening and genetic testing, PGD and the genetic counseling that goes with testing. There is significant variation in both the specific tests plans cover and the detail available to enrollees about what is covered.

In general, the longer a medical test or procedure has been in use the more likely it is to be covered. Older technologies such as amniocentesis and CVS tend to be covered, while the newer technologies, such as first-trimester screening, may not be covered because the insurer sees them as unproven and unnecessary.

It is not clear how coverage of testing will be affected by the advent of gene chips and other high-throughput “microarray” technology that can quickly detect a number of genetic variations in one test. While such methods could make testing cheaper overall, initially insurance companies are likely to be skeptical of paying for an unproven, cutting-edge technology. The issue of what tests should be bundled together could be difficult to resolve.

Bundles that include a wide range of known genetic indicators mean that insurance companies may have access to an increasing amount of information about an individual’s

genetic makeup potentially even before birth. Such information may include mutations indicating an increased likelihood (rather than a certainty) of developing a disease either in childhood or in adulthood. Many observers have raised concerns about discrimination on the basis of a person’s genetic makeup by insurers and employers, and these concerns could create a barrier to testing for patients.

The Moral Standing of Embryos and Fetuses

Reproductive genetic testing is inextricably bound to the intense and often divisive discussion within our society about the status and respect that should be afforded to human life at different stages of development, and when, if ever, having an abortion or destroying or discarding an embryo should be considered justified or acceptable. Americans have deeply held—yet not necessarily rigid—views about the moral standing of both the human fetus and the embryo. Reproductive genetic testing invariably taps into other, sometimes conflicting values and beliefs. And those beliefs influence perspectives about various forms of reproductive genetic tests. But with a wide range of ethical complexities and choices, the issues raised by reproductive technologies are sometimes colored in shades of gray rather than black and white.

The Role of Religion

Many prospective parents turn to their religious tradition or individual clergy for guidance in decisions about the use of reproductive genetic technologies. However,

many religions are just beginning to grapple with these issues. For some religions, acceptability depends on the specific technology and how the information it provides will be used. For example, some religions find that prenatal testing that ends in abortion or testing of human embryos goes against their faith but that carrier testing to consider one’s risk of having offspring with a genetic disease is acceptable. Other religions rely on case-by-case determinations that consider the circumstances and personal beliefs of the couple and the potential impact on the family of having a child with a serious disease. Not surprisingly, there is a rich diversity of religious perspectives on reproductive genetic testing.

Carrier Testing:

What it is and how it works

Carrier testing is performed because an individual's family history or racial or ethnic background indicate heightened risk of carrying a mutation for a particular autosomal recessive (non sex-linked) disorder. In autosomal recessive disorders, a person must have two copies of the mutation to be affected. Individuals who carry one copy of the alteration are carriers and typically show no signs of the disease. When both parents are carriers, there is a one in four, or 25 percent, risk for each child to inherit the mutation from both parents and be affected.

Carrier testing is genetic testing to determine whether an individual carries one copy of an altered gene for a particular recessive condition.

Examples of disorders for which carrier testing can be done in specific populations include cystic fibrosis (CF) in Caucasians, sickle cell disease in African Americans, thalassemia in Asians and individuals of Mediterranean descent and Tay Sachs and Canavan disease in Ashkenazi Jews.

One important limitation of some carrier tests is that it may not detect every disease-causing mutation in a gene. For example, more than 1000 mutations that can cause cystic fibrosis have been identified. The recommended carrier test panel for cystic fibrosis is pan-ethnic and includes 23 of the most common mutations and four reflex tests that are used to clarify or elaborate initial test results. In addition, since the frequency of different mutations

varies among population groups, the detection rate of the test panel will vary by group. But those who carry a rare mutation will not be identified using the standard test.

Carrier testing may be used in several ways by prospective parents to make decisions about whether and how to have children. Depending on the condition in question, at-risk couples may choose not to risk having a child born with a particular disorder and may adopt or use donated eggs, sperm or embryos. Some may go through in vitro fertilization and test the embryos using PGD to select unaffected embryos for transfer into the woman's uterus. Others may decide to become pregnant and to pursue the earliest available prenatal testing. Some parents may use carrier testing to learn about their risks before they become pregnant but not pursue prenatal testing.

In addition to the carrier testing discussed above, it has become more common for adults to be tested for mutations linked to late onset disorders and those that indicate increased risk, not certainty, of developing disease. Thus more adults have undergone testing either for their own health or for reproductive planning, providing information about genetic risks that can be passed along. Indeed, we can expect that in the future, young people entering reproductive age will know quite a bit about their genomes before even considering having a family.

Current Issues in Carrier Testing

The identification of genetic mutations with higher prevalence in certain racial or ethnic groups has led to targeted, population-based carrier testing programs in the United States with widely varying results. These experiences provide important lessons for the design of future genetic testing policies and programs.

Lessons from the Past

Tay Sachs: An Effective Use of Carrier Testing

Tay Sachs is an autosomal recessive disorder caused by a mutation in the gene that makes hexosaminidase A (hex A), a protein that is necessary to break down fatty substances in brain and nerve cells. Children who receive two copies of a mutation in the hex A gene deteriorate mentally and physically, eventually suffering blindness, deafness and paralysis. There is no treatment available and the condition typically leads to death by age five.

Tay Sachs disease occurs most frequently in descendants of Central and Eastern European (Ashkenazi) Jews. About one out of every 30 American Jews is a carrier. The mutation is also more common in some non-Jewish individuals of French-Canadian ancestry (from the East St. Lawrence River Valley of Quebec), and members of the Cajun population in Louisiana.

Early carrier testing programs measured the amount of the hex A protein in the blood. Since the

Carrier Frequency in Different Populations for Selected Single Gene Disorders

| Condition | Frequency in U.S. Population | | | | |
|--|------------------------------|--------------------------------|-------------------------------------|-------------------------|----------------|
| | All | Caucasian | Hispanic | African American | Asian American |
| Cystic fibrosis | 1/31 | 1/29 | 1/46 | 1/65 | 1/90 |
| Sickle cell | | | ~1/17 | 1/12 | |
| Tay Sachs | All | Ashkenazi Jewish | Sephardic Jewish | French Canadian / Cajun | |
| | 1/250 | 1/27 | 1/250 | ~1/30 | |
| Thalassemia ¹ | All | Mediterranean / Middle Eastern | SE Asian / Pacific Rim ² | | |
| | ~1/5,000 | ~1/20 | ~1/10 | | |
| ¹ includes both β -thalassemia and α -thalassemia ² this population is mostly affected by α -type thalassemia | | | | | |

gene was identified in the late 1980s, however, genetic testing has largely replaced the biochemical tests. The DNA-based test is also used for prenatal genetic diagnosis after amniocentesis or CVS and for PGD.

Testing programs for Tay Sachs within the Ashkenazi Jewish population were first established in the United States in 1971 and within five years had extended to 52 American cities and Canada. Testing programs took place in a variety of settings, including synagogues, high schools and Jewish community centers. They were characterized by a high degree of collaboration between clinical researchers and community leaders. At the same time, a voluntary quality assurance program was instituted

for laboratories performing testing, under the auspices of the National Tay Sachs Association.

Tay Sachs carrier testing programs in the Ashkenazi Jewish community have been cited as an example of a successful testing effort because they led to a dramatic decrease in the incidence of Tay Sachs in that population and because they were viewed positively by those targeted for testing. There has been little controversy within the community about the appropriateness of testing for the disease, in part because Tay Sachs is fatal in early childhood.

Jews differ in their views about abortion. For example, Orthodox Judaism prohibits abortion under most circumstances, making

preconception, and even premarital, testing preferable to prenatal testing. One voluntary, anonymous premarital testing program is run by an organization called Dor Yeshorim, which primarily targets certain Orthodox communities where many marriages are arranged and where abortion is rarely permitted. Many individuals are tested while in school, and men and women who test positive as Tay Sachs carriers are not introduced to each other as potential mates. If a couple submits for testing after they have begun dating, and they are both found to be carriers, they are counseled not to marry.

Sickle Cell: Carrier Testing Causes Concerns

In contrast to the success of the Tay Sachs testing program, the establishment of testing programs for sickle cell anemia in the 1970s was marred by lack of collaboration between the community and those establishing the testing programs, and discrimination and misunderstanding regarding the health consequences of being a carrier.

Sickle cell anemia is an autosomal recessive disease caused by mutations in the beta hemoglobin gene that result in the malformation of red blood cells. People with mutations in both copies of the beta hemoglobin gene experience symptoms including anemia, recurrent infections, pain and vascular complications that can lead to strokes and other serious medical problems. However, the severity of the disease is variable. Treatments exist to prevent and mitigate some of these symptoms, and have led to increased life expectancy. Many people with sickle cell disease live into their 40s and beyond. Carriers of sickle cell anemia — those who have only one copy of the mutation — experience no symptoms of the disease under most conditions.

In the United States, most cases of sickle cell disease occur among African Americans and Hispanics of Caribbean ancestry. About one in every 500 African Americans has sickle cell disease and one in twelve is a carrier.

Technical capacity for sickle cell carrier testing and interest in

developing programs to identify carriers of the disease developed in the 1970s. Medical geneticists saw testing for sickle cell carriers as providing benefits similar to those gained from Tay Sachs testing: identification of carriers of a serious genetic disorder in a defined population to allow for informed reproductive decision making.

Between 1971 and 1973, legislation related to sickle cell carrier testing was passed in 17 states and the District of Columbia. In some states, carrier testing was mandated by law, rather than voluntary, and was generally targeted at African Americans. Some states made testing a requirement for school entrance, giving the false impression that carrier status had a bearing on a child's health. Some employers used sickle cell testing to exclude carriers from certain jobs, and insurers used it as a basis to deny coverage. On the federal level, Congress passed the National Sickle Cell Anemia Control Act in 1972, which provided funding for research, testing, counseling, education and treatment, and predicated such funding on voluntary testing programs.

Sickle cell carrier testing came to be viewed by many in the African American community as an effort by the white power structure to impose a stigmatizing genetic testing program on a minority population. Testing programs were usually administered by health departments composed of predominantly white medical personnel, contributing to the impression that testing was being imposed on the black community.

The programs also were instituted against a backdrop of historical discrimination, eugenics and unfounded claims of black biological inferiority. Confusion between sickle cell disease and carrier status (which was historically called sickle cell “trait”) among physicians, the public and policymakers created a false perception that being a carrier was a health risk.

“Until we are able to give everyone access to do something about a problem, those people who have historically been disadvantaged in our society . . . either as a result of minority status or because of socio-economic conditions are certainly going to be disadvantaged and undoubtedly look with skepticism [on these technologies].”

Patricia King, Georgetown University Law Center

Currently, sickle cell carrier testing programs in the United States exist on a voluntary basis, and testing is recommended by the American College of Obstetricians and Gynecologists (ACOG) for all couples at increased risk for having children with sickle cell anemia. High-risk groups include people of African American, Southeast Asian or Mediterranean ancestry.

Sickle cell carrier testing continues to take place; however, some data indicate that relatively few at-risk couples choose prenatal diagnosis to detect the disease in a fetus. Similarly, relatively few couples choose to terminate a pregnancy if the fetus is found to have the disease. The reasons for these choices are many. Some couples lack access to early prenatal care and thus may miss the opportunity for prenatal testing. Others may choose not to test because the disease is treatable and has a variable and unpredictable severity. Individual and cultural attitudes about children and abortion more generally also may play a role.

Cystic Fibrosis: The Push for Broad Testing

Cystic fibrosis carrier testing is the most recent and most far-reaching carrier testing program in the United States. In contrast to Tay Sachs and sickle cell anemia, the decision to offer population-based testing was preceded by more than a decade of discussion and consensus-building within the genetics community and professional organizations. While it is too soon to tell how this testing effort will fare, certain concerns already have appeared.

Cystic fibrosis is an autosomal recessive disorder that affects the respiratory, digestive and reproductive systems. It is one of the most common genetic diseases among people of northern European descent. The carrier frequency in white Americans is 1 in 29. In contrast, carrier frequency in African Americans is 1 in 65, and in Asian Americans it is 1 in 90. While

The Preconception Care Challenge

Many women are unaware of the genetic tests available to them or of the implications of test results to their reproductive decision making. Providers typically do not discuss reproductive genetic risk factors until after a woman is already pregnant. But testing before pregnancy begins increases a woman's reproductive options. Providers need to assess reproductive risks based on age, family history and ethnic background during routine visits and to discuss appropriate testing options with patients and patients, in turn, need to know to ask their providers about their reproductive risks on routine visits. Private and public payors need to recognize the value of covering genetic counseling and testing services prior to pregnancy. A public information or consumer campaign would help individual patients know what to ask their providers before initiating a pregnancy.

historically CF almost invariably led to death from pulmonary disease in early childhood, advances in treatment over the last 30 years have led to improvements in life expectancy. Median survival is now 33.4 years. The course of the disease is variable, with some individuals suffering significant morbidity such as frequent lung infections and difficulty breathing, and others having more mild symptoms.

Identification of the most common mutation causing CF in 1989 led to interest in population-based carrier testing. But, as more mutations were identified — to date over 1000 have been identified — scientists realized that carrier testing would be complicated.

In 1997, the National Institutes of Health convened a panel to consider CF carrier testing. The panel, which included scientists, physicians, bioethicists and economists, recommended that CF carrier testing be offered to all individuals with a family history of CF and their partners, as well as to anyone pregnant or planning

a pregnancy, particularly those in high-risk populations. In 2001, ACOG and the American College of Medical Genetics (ACMG) issued recommendations that CF carrier testing be “offered” to non-Jewish Caucasians and Ashkenazi Jews, and “made available” to other ethnic and racial groups. These guidelines, however, did not clarify the operational distinction between “offering” a test and “making it available” in clinical practice.

There have been anecdotal reports relating to incorrect performance and reporting of test results by laboratories not following the ACOG/ACMG guidelines, incorrect interpretation of results by providers and failure to get informed consent. Some evidence suggests that unnecessary amniocenteses may have been performed as a result and there have been unconfirmed reports that some women may have terminated pregnancies based on the false belief that their child would have CF.

Clearly, implementation of widespread carrier testing

recommendations, such as those for cystic fibrosis, can be challenging. For a variety of reasons, providers are often slow to follow new guidelines in practice.

These three historic examples merit careful evaluation and are instructive for future carrier testing efforts. Four lessons in particular stand out: (1) the importance of scientific and community consensus regarding the development and use of a test; (2) the value of community participation in determining the context of testing; (3) the need for ongoing monitoring and evaluation of test implementation; and (4) the importance of responding to new developments as testing evolves.

Timing of Carrier Testing

Professional guidelines generally recommend that, when possible, carrier testing should take place before pregnancy occurs. Testing before pregnancy provides prospective parents with information about their risks of having a child with a genetic disease, allowing them to consider reproductive alternatives.

But there is evidence to suggest that, in practice, carrier testing is in most cases offered to women or their partners after a pregnancy begins. For example, according to a study published in 2004 by ACOG, almost one-half of obstetrician-gynecologists do not ask non-pregnant patients about their family history of cystic fibrosis, provide them with information about cystic fibrosis carrier testing or routinely offer carrier testing to patients who are not yet pregnant. Many providers view genetic tests for

patients who are not pregnant as less urgent and something that also would add time and paperwork to the patient encounter. Patients may also not be interested in carrier testing until they are pregnant. Finally, providers and patients are often unsure whether and under what circumstances insurers will reimburse for carrier testing prior to pregnancy. Insurers are inconsistent in this area, even though guidelines clearly recommend that testing be offered.

Other factors could prevent a couple from obtaining carrier testing prior to pregnancy. Some research has showed that as many as one-third to one-half of pregnancies are unplanned. In addition, many women considering getting pregnant may not discuss their plans with their health care provider. Some women, particularly those who do not have health insurance or who have limited access to care, do not see a provider until the second-trimester of pregnancy or later, further limiting their options.

There are opportunities for offering carrier testing to women of reproductive age during a routine visit. For example, according to the Centers for Disease Control and Prevention (CDC), over 95 percent of women between 18 and 39 have had a pap smear in the past three years. Therefore, there is an opportunity in place for providers to discuss carrier testing during these visits.

Finally, a number of issues related to communication of information affect carrier testing. For example, carrier testing often is presented

as routine, but sometimes patients are unsure what tests they are receiving. Often, testing laboratories group tests for mutations in several different genes in a “panel” for efficiency, but the provider may not explain every test to the patient. In addition, providers may not know how to interpret or communicate the results of a carrier test even if they know when to offer it. This may be because of the way test results are communicated by some laboratories or because of providers’ limited training in genetics or genetic counseling.

Prenatal Testing

What it is and how it works

Prenatal testing includes prenatal screening to identify fetuses at higher risk for genetic or other abnormalities and prenatal genetic testing to diagnose genetic abnormalities in utero. Test results may be used to help parents prepare for the birth of that child or make a decision about terminating the pregnancy. This section will focus on the use of these tests and procedures and the issues raised by their use.

Prenatal Screening

Prenatal screening includes a variety of technologies that identify those fetuses that have an increased likelihood of having genetic or other abnormalities.

Ultrasound uses high frequency sound waves to obtain an image of the fetus in utero. It is routinely used to determine fetal viability, the number of fetuses present and the position of the fetus and to estimate fetal age. Sex may also be determined depending on the age and position of the fetus. Some fetal malformations can be detected by ultrasound in utero, such as neural tube defects and some heart malformations.

Maternal serum screening measures levels of fetal proteins circulating in the mother's blood. Physicians now commonly screen for three or four proteins in the mother's blood (called either a triple screen or a quadruple screen) to screen for birth defects such as neural tube defects or certain chromosomal abnormalities such as Down syndrome and trisomy 18. Typically, maternal serum screening is done around 15 to 20 weeks gestation, in

Prenatal screening includes those tests and procedures used to assess fetal risk for an abnormality, including genetic disorders. It does not provide a definitive diagnosis of a genetic abnormality.

Prenatal genetic testing (or prenatal genetic diagnosis) is genetic testing of fetal cells obtained through procedures such as amniocentesis and CVS.

the second-trimester of pregnancy. If screening results indicate abnormal protein levels, counseling about prenatal diagnosis is recommended.

About 75 percent of pregnancies in which the baby has Down syndrome can be detected with the second-trimester screening. Maternal serum screening detects 80 to 85 percent of babies with spina bifida and essentially all babies with anencephaly. However, there are significant false positive and false negative rates.

First-trimester screening is a new option that is increasingly used but is not yet widely available in the United States. It uses the combination of a first-trimester ultrasound and serum screening to assess fetal risk of Down syndrome or other chromosomal abnormalities. A specially trained physician or sonographer performs an ultrasound at approximately 11-13 weeks of pregnancy to measure the nuchal fold translucency, which refers to the thickness of the fluid-filled space at the back of the fetus' neck. Increased thickness indicates a heightened risk of chromosomal disorders including Down syndrome or trisomy 18. In addition, the woman's blood is tested for two pregnancy-related proteins, whose presence in abnormal levels can also indicate heightened risk for these disorders. The laboratory results, the ultrasound measurements and the

woman's age are used to calculate her risk.

In the case of Down syndrome, researchers have reported that first-trimester screening can identify more than 80 percent of affected fetuses. In addition to some affected fetuses not being detected with first-trimester screening (false negatives), there is a five percent false positive rate (meaning that an unaffected fetus is identified as affected).

The advantage of first-trimester screening is that a normal result provides earlier reassurance and an abnormal result allows the option of early diagnostic tests.

Diagnostic tests and procedures

Prenatal genetic testing of a fetus requires two steps: an invasive procedure (amniocentesis or CVS) to obtain fetal genetic material and an analysis of the material to identify genetic abnormalities or characteristics. Fetuses may be at increased risk for genetic abnormalities because of the mother's age (35 or greater at delivery), because the parents already have a child or other family member with a genetic condition, because one parent has a balanced chromosome rearrangement or because prenatal screening or carrier testing indicates an increased risk.

Amniocentesis is usually performed in the second-trimester of pregnancy, at approximately 15-20 weeks gestation. A thin needle removes a small quantity of amniotic fluid from the sac that holds the developing fetus. The fluid contains fetal cells that provide the material for genetic analysis.

“Many couples at high risk for a child with a disease will choose to have the testing done to prepare themselves . . . we ought to separate in our minds genetic testing and what to do about [the information].”

Francis Collins, National Human Genome Research Institute

Amniocentesis is generally considered a relatively simple and safe procedure when performed by an experienced physician. Although miscarriage after amniocentesis is infrequent (one in 200-400 cases), it is a major reason the procedure is not routinely offered to all women. Infection and leakage of amniotic fluid are other possible complications of amniocentesis.

Amniocentesis is not usually performed until the second-trimester because most providers consider performing the procedure earlier too risky. Thus, one drawback of amniocentesis is that by the time results are available the pregnancy may have progressed 16 weeks or more.

Chorionic villus sampling is an alternative to amniocentesis, and can be performed during the first-trimester of pregnancy. Fetal cells are obtained through biopsy of the chorionic villi — the cells that will become the placenta. CVS is generally done at 10-13 weeks gestation. Fewer physicians do CVS than amniocentesis, and as a result, it is not available in all areas. The risk of miscarriage after CVS is approximately 1 in 100, as compared with the 1/200-400 risk following amniocentesis.

CVS can be used to determine all disorders that can be diagnosed by amniocentesis except the presence of neural tube defects, since CVS does not include analysis of amniotic fluid alpha-fetoprotein.

Current Issues in Prenatal Screening and Testing

The Experience of Testing

Many factors go into an individual's decision to obtain prenatal screening or prenatal genetic testing. Screening and testing provide information; they do not dictate a course of action. Prospective parents can use this information to guide decisions about additional testing, prepare for the birth of a child with a genetic disease or as a basis to end the pregnancy.

People differ in their desire to obtain information about the future — some may find it reassuring, while others consider it unnecessary or simply nerve-wracking.

For some, the actions they will or will not take based on the

information dictate whether to test at all. Some people who would not terminate a pregnancy irrespective of the test results decline testing on that basis. Others may decline testing because they prefer to welcome the child first, and then address any health problems the child may have. For them, prenatal testing may seem intrusive and unnecessarily worrisome.

Others may want to know test results, even if they would not terminate. For them, the information allows them to prepare emotionally, medically and economically, and allows for appropriate medical support at the time of the birth. For these people, knowing as much as possible about the health of the fetus, as early in the pregnancy as possible, is of primary interest.

“I think there is a popular myth that information is value neutral and that . . . more information is necessarily a good thing. But with information comes responsibility.”

C. Ben Mitchell, Trinity Evangelical Divinity School

For couples who would consider abortion in case of a serious genetic disease, information about the disease and the prognosis helps them make the decision whether or not to terminate the pregnancy. Most would prefer that decision be made as early in the pregnancy as possible.

Some people make their decisions about prenatal testing based on their perceptions of the risk of having an affected child, views about how difficult it would be to raise a child with a disability, or previous experience with the disorder. Family size, financial circumstances and basic access to health care also may play a role in decision making, as may perception of the accuracy of test results and fear that the information learned could be used to discriminate against them. Some may also worry about the small but real risk of miscarriage from amniocentesis or CVS.

There are probably as many reasons to undergo prenatal testing — or to refuse it — as there are parents. Yet whether someone will ultimately accept or decline testing, and what course of action they will take based on the information testing provides, is impossible to predict.

“There are a lot of children who are born who, you can’t say it in polite company, but silently, people say, ‘if only these people had done what they were supposed to do, these children wouldn’t be here.’”

Leon Kass, American Enterprise Institute

Sometimes women do not have the chance to consider prenatal testing. They may not see a health care provider until the pregnancy

is too far along for some forms of prenatal screening and testing. Some women do not know they are pregnant — or do not want to be and therefore do not seek early prenatal care, even if they ultimately carry the pregnancy to term. Some lack insurance or the means to get to a provider or clinic that they can afford.

Some observers have raised questions about the impact of prenatal genetic testing on society and whether society should try to control its use. Some believe it should always be an individual parent’s choice about whether to seek screening and testing. By contrast, others argue that the individual choice argument fails to give adequate weight to how prenatal screening and testing may be profoundly changing the way we, as a society, view procreation and children.

Furthermore, as screening and testing become easier, earlier, cheaper and capable of detecting a broader range of conditions, the concern is that society will see reproductive testing as the “right” thing to do. Therefore, the failure to test will be viewed as unacceptable. People who do not test — and perhaps even those who do but do not have an abortion when a test shows a genetic problem — could be stigmatized as irresponsible, and children born with genetic diseases could be seen as avoidable mistakes.

How Tests And Results Are Provided

Some observers are concerned about how information about

prenatal genetic screening and testing is delivered to patients. This information is conveyed in a variety of settings and contexts. Sometimes it is a physician who discusses prenatal testing with the patient, sometimes a nurse or midwife and sometimes a patient is referred to a genetic counselor. Providers have varying levels of knowledge and comfort discussing these issues, and often very little time in which to cover all of the information adequately. In some settings, a patient may be given an informational pamphlet about the most common forms of prenatal testing, such as maternal serum screening, and offered the opportunity to ask questions, while in other settings a dialogue between health care professional and patient takes place. But in the course of most medical examinations, only a few minutes are spent discussing genetic testing. Thus, patients may end up making decisions based on incomplete or inaccurate information. Some may proceed with testing without fully considering the decisions they may have to make depending on the results of the tests.

Patients sometimes report feeling pressured by health care providers to agree to testing. Health care providers may present these tests as routine, just like all the other tests one gets during pregnancy. For example, little time may be devoted to discussing what a woman would actually do if told her maternal serum screening test came back abnormal, and thus she may suddenly find herself facing difficult decisions about more invasive testing.

Another issue is whether there are economic, cultural, language or other factors that influence who is offered or receives testing. Differences in access to testing may reflect troubling underlying societal problems, such as inequitable distribution of health care resources, counseling that is not sensitive to cultural differences or mistrust based on historical experiences of discrimination.

Additional concerns have been raised about how test results are conveyed and how providers influence decision making once the parents have learned that a fetus is affected by genetic disease. Some disability advocates have claimed that providers who discuss prenatal screening and testing describe conditions in the most extreme clinical terms and assume that parents will want to terminate an affected fetus. These critics say that providers are predisposed to counsel in favor of that decision, without giving sufficient context to the prospective parents about what it would actually be like to raise a child with the particular disorder. Indeed, those affected with a particular genetic disorder sometimes view it as far less disabling than unaffected people.

Preimplantation Genetic Diagnosis

What it is and how it works

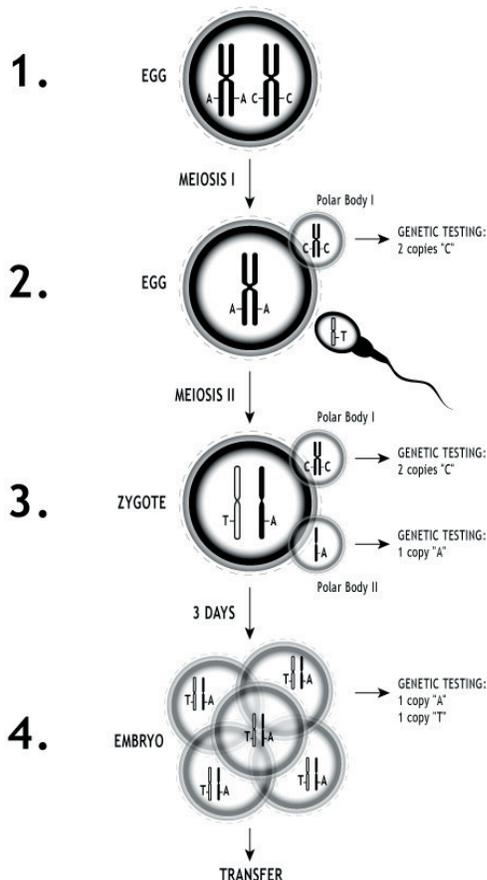
Preimplantation genetic diagnosis (PGD) is a process in which embryos developed outside the womb are tested for particular genetic characteristics, usually genetic abnormalities that cause serious disease, before being transferred to a woman's uterus. Whereas prenatal diagnosis can detect genetic abnormalities in a human fetus in utero, PGD offers genetic testing before pregnancy begins.

PGD has emerged from a convergence of two technologies — in vitro fertilization (IVF) and genetic testing. As genetic research

has progressed, so too has work on IVF. In 1978, scientists achieved the first viable human pregnancy from an egg fertilized outside the womb in a petri dish, or in vitro. Eventually, scientists developed methods to perform genetic tests on single cells taken from an early embryo.

This new area of reproductive genetics, PGD, permits doctors and prospective parents to select embryos for transfer to the womb that do not have a genetic abnormality associated with a specific disease or, alternatively, that possess a genetic characteristic deemed desirable.

In the more than ten years since PGD was first made available to facilitate embryo selection, over 1,000 babies have been born worldwide following a preimplantation genetic test. Inherited chromosome abnormalities and single gene disorders including cystic fibrosis, Tay Sachs disease, muscular dystrophy, sickle cell anemia and many others have been detected with PGD. In theory, any of the hundreds of genetic tests now commercially available, and the many more in development, could be used to test embryos.



Genetic testing in PGD can be done by testing one or both polar body cells (2 & 3) that are cast off from the egg as it matures and is fertilized, or by testing cells from the embryo (4).

1. Genetic testing in PGD starts with knowing the genetic makeup of one or both parents (only the egg is shown in 1).

2. Genetic testing of Polar Body I allows inference about the genetic composition of the egg. In this example, two copies of "C" are detected in the polar body inferring that the egg carries two copies of "A". If "A" was the desired copy of the gene, this egg could be used for fertilization. If not, it would be discarded.

3. Testing Polar Bodies I and II simultaneously after fertilization is another approach to polar body testing. In this example, two copies of "C" are detected in Polar Body I and one copy of "A" in Polar Body II, inferring that the fertilized egg contains one copy of "A".

4. More typically, PGD involves testing one or two cells of the embryo removed 2-3 days after fertilization when 5-8 cells are present. This permits direct analysis of the embryo's genes. In this example, "A" and "T" are detected in the cell.

Compared to carrier testing and prenatal screening and testing, PGD is much newer and much less common. Nevertheless, PGD is becoming much more widely known and used, with some predicting that every couple using IVF will someday be offered PGD in order to boost their success rates. PGD sounds futuristic, but it is here and now, in use and subject to animated discussions both in favor and against. Thus in a sense, PGD shines a bright light on how society reacts to and deals with new reproductive genetic technologies.

The Mechanics of PGD

PGD is a multi-step process involving egg extraction, in vitro fertilization, cell biopsy, genetic analysis and embryo transfer. First, as in all in vitro fertilization processes, eggs removed from the mother after she has been given drugs to stimulate egg production are fertilized in the laboratory. The genetic material for testing can be obtained in two ways. The most common method is to use one or two cells taken from an embryo two to four days after fertilization. Alternatively, genetic tests can be performed on cells (called polar body cells) that are cast off by the egg as it matures and is fertilized. The results of the genetic tests on the polar bodies are used to infer the genetic makeup of the fertilized egg.

Two techniques are used to analyze the genetic material from single cells: chromosomal analysis to assess the number or structure of chromosomes and DNA analysis to detect specific gene mutations. For chromosomal analysis, fluorescently

labeled, chromosome-specific probes are used to visualize spots representing each copy of that chromosome present in the cell. Too few or too many spots can indicate abnormalities. For direct DNA analysis, a technique known as a polymerase chain reaction (PCR) is used to make many copies of the targeted gene, which are then examined for evidence of a specific DNA sequence.

Regardless of the methods, the results of preimplantation genetic diagnosis are used to inform the selection of embryos for transfer to a woman's uterus.

What PGD is Not

PGD should not be confused with gene therapy or any other efforts to alter an embryo or a person's genetic makeup. PGD as currently practiced can reveal a considerable amount of information about an embryo's genetic makeup, but it is not possible today to correct or alter an embryo's genes.

Current Issues In PGD

PGD was initially developed to identify and avoid specific disease-causing mutations prior to pregnancy. More recently it has also been used as an adjunct to standard IVF to detect chromosomal abnormalities, called aneuploidy, arising during egg or embryo development. There is some evidence that transferring only chromosomally normal embryos can boost the success rate of IVF procedures. Some providers

recommend PGD for all IVF patients over 35 or those with repeated IVF failure. Aneuploidy screening already accounts for the majority of PGD procedures and since one percent of all births in the United States are babies born as a result of IVF, there is the potential for continued steep growth in the use of PGD.

“Children have a right to be born as healthy as we can make them. We can't guarantee that they will be healthy, even if we do all things possible, but we should try to avoid those things that might cause them to be unhealthy.”

Robert Murray, Howard University

Other current applications of the technology that have generated controversy include using PGD (1) to select an embryo that is an immunological match to a sick sibling so the resulting child can be a stem cell donor, (2) to select the sex of an embryo purely for gender preference — that is, in the absence of a sex-linked disease risk — and (3) to test embryos for gene mutations associated with adult onset diseases such as Alzheimer disease or mutations that indicate a heightened but uncertain risk of developing a particular disease, such as hereditary breast cancer.

There are alternatives to PGD. Prospective parents at risk of

passing a genetic condition to their offspring can choose to avoid pregnancy, conceive using donor egg or sperm from an individual who does not carry the mutation in question, proceed with a pregnancy but undergo a prenatal diagnostic test and possibly terminate the pregnancy if it reveals a genetic abnormality or accept the possibility that their child could be born with a genetic abnormality.

PGD is a powerful tool that may allow parents to identify and select only those embryos that possess the genetic characteristics they desire in their children. PGD cannot, however, create new genetic characteristics that neither parent possesses. PGD can allow parents to select only among the genetic combinations present in the embryos they have produced.

“I believe that when it comes to the application of a genetic test in the embryo selection arena, that widespread use of that for sex selection is a boundary that we should not cross. I think that is stretching to the breaking point the reasons why we are in the genetic technology business in the first place.”

Francis Collins, National Human Genome Research Institute

Since PGD requires IVF, it is mainly used today by parents who are willing to undergo IVF to avoid a known serious or fatal genetic condition or who are unable to get pregnant without IVF because of infertility problems. For the moment, one would expect very few people who otherwise have no problems achieving a healthy pregnancy to utilize PGD. Nonetheless, that could change as IVF techniques improve and the number of genetic tests that can be employed successfully in PGD increases.

For families at high risk of a genetic disorder, PGD may increase their chance to bear a healthy child. Similarly, for parents with a child who suffers from a disease treatable with donor tissue, the use of PGD to produce a genetically-matched sibling may be the only way to save their child’s life. And, for women with repeated miscarriages and IVF failures, PGD may be their best hope for a successful pregnancy.

Some see ethical issues arising from the use of PGD to test embryos for aneuploidy in order to improve IVF success rates. Parents who have enough embryos that are considered genetically good candidates for transfer may be asked whether they want a boy or girl, or — possibly in the future — a child who is tall or short, blond or brunette. By giving prospective parents the opportunity to choose among embryos, PGD is arguably the form of reproductive genetic testing that gives parents the greatest power to predetermine the genetic characteristics of children.

For those who categorically oppose manipulation or destruction

of human embryos, PGD is never appropriate because it necessarily involves one or both. Some in this group would favor a ban on the technology, while others would not support a policy that would prevent others from using the technology, even if they would not use it themselves.

Many people, including some who are troubled by the manipulation or destruction of embryos may nevertheless support PGD when it is used to detect certain serious medical conditions but have reservations about its use for other purposes.

For others, concerns arise not from the status of the embryo but from the potential safety of the procedure for women and the resulting children. There are many unanswered questions about the long-term consequences of PGD and IVF.

Some observers view PGD, or any technology that allows parents the ability to choose their children’s characteristics, as potentially altering the way we view human reproduction and our offspring in a fundamental way. They worry that human reproduction could come to be seen as within the realm of technology and children the end result of a series of meticulous, technology-driven choices.

Others argue that widespread use of PGD could exacerbate existing societal inequalities if some have the means to select their children for a range of “desirable” traits while others do not. For some, the genetic conditions that PGD can now detect,

such as hereditary deafness, are merely human variations that do not prevent an individual from leading a useful and satisfying life. Some say that the use of PGD could make society less tolerant of people with disabilities. Specific concerns have also been raised about using PGD for sex selection, given the history of discrimination against women and preference for male children that has existed — and continues to exist — in some cultures.

Finally, some worry that PGD will alter parental expectations of those children who have been carefully selected to possess certain attributes and cause tension between siblings who are the result of PGD and those who are not.

The Future of Reproductive Genetic Testing

The technology for genetic testing is changing rapidly in all areas, including reproductive genetic testing. As was noted previously, new technologies such as gene chips, or “microarrays”, could soon allow individuals to learn about numerous gene mutations or variants by ordering a single test. The advent of testing that can quickly reveal an abundance of genetic information — from the conclusive to the murky, from the serious to the trivial — will amplify the promise and pitfalls that now exist with genetic testing.

Some argue that the more we know about our genetic makeup and that of our children, the better we and our doctors can manage our family’s health. However, not all genetic information may be equally informative, desirable or beneficial.

Helping patients make choices about testing will present new challenges for health care providers and genetic counselors. Providers may feel pressure to seek as much information as genetic testing can provide — more than the patient wants or needs. Economic efficiencies may drive the decision by commercial laboratories to test for everything at once, even if the patient and provider are interested in only a small subset of the test results.

As more tests become available, patients may have to pay a premium for a test that is more accurate and reveals more information, which could have an effect on who has access to the best care. Insurance companies usually take a cautious approach in considering whether to cover new, cutting-edge technologies

and their coverage policies could limit the dissemination of new tests.

Furthermore, as new testing comes on the market, it is not clear who will set the standards that will be used to gauge their accuracy or establish the guidelines for proper use and interpretation of the results. Such standards and guidelines already are lacking for much of what is currently available.

“We may be facing a paradigm shift, in that in the future there will be a vast distinction between well-planned and medically calibrated children and the accidental children of the poor.”

Amy Laura Hall, Duke Divinity School

Genetic counseling as a field also will be challenged to keep pace with the ramifications of the technological changes. And health care providers likely will struggle to provide high quality care especially as a greater amount of time is needed to help each patient sift through the growing list of testing options.

Testing Before Pregnancy

The number of carrier tests available and the number of people offered these tests will grow. Some speculate that carrier testing will increase to a point where tests will be available for all recessive

genetic disorders that cause serious childhood disease or death. Others believe this use is not cost effective or appropriate and is unlikely to occur.

As testing becomes part of adult medicine, there is the prospect that people will know a great deal about their own genetic makeup as young adults and will come to marriage and childbearing with that knowledge. Of particular relevance will be the increase in predictive or predisposition testing. A test undertaken to inform an adult about risk of cancer, diabetes or heart disease and perhaps to guide preventive care will also mean that parents will know that any child they have may inherit these same risks.

Prenatal Genetic Testing

There are a number of trends in prenatal screening and diagnostic genetic tests, all of which suggest that the prevalence of these tests and procedures will grow considerably in the years to come.

Developments like first-trimester maternal serum and nuchal fold translucency screening allow earlier non-invasive screening tests. Many more prospective parents are likely to avail themselves of the information — and reassurance — to be gained from prenatal screening if the procedure carries no risk to the pregnancy and can occur weeks before anyone need know the woman is pregnant. In addition, while the overall risks to women of death from induced abortion are low, the risk increases significantly as pregnancy progresses, thus early

screening can protect the lives of women who subsequently choose termination based on the test results.

New techniques are being developed to collect fetal cells or DNA samples through non-invasive procedures to minimize the risk to fetus and mother. Studies are underway to determine how to best obtain and concentrate fetal cells or free DNA that normally circulate in maternal blood during pregnancy so that chromosome, biochemical and DNA analyses can be performed using those cells.

The recommendations for who should be offered amniocentesis and CVS are also changing. Screening tests are offered to many patients, but current guidelines dictate that diagnostic tests — tests that pinpoint the actual genetic mutation or chromosome abnormality — be reserved for those who have specific risk factors. However, some studies have challenged this standard and suggest that diagnostic prenatal genetic testing may be offered differently in the future. There is a developing recognition that some women without known risk factors may nevertheless want to pursue amniocentesis and CVS. Because patients have varying tolerances for risk, some women might prefer to accept the small risk of miscarrying a healthy fetus in order to avoid even a remote risk of having a child with a genetic disease. Others, who may know they are high risk, may nevertheless choose to forgo testing altogether for fear of losing a wanted pregnancy. Recent studies in the *Lancet* and *Genetic Testing*, among others, have suggested that it may be preferable and cost-effective for all or

nearly all prospective parents to be offered prenatal diagnostic genetic testing and permitted to make the decision for themselves.

“After all, if parents are going through the trouble to have in vitro fertilization and then preimplantation genetic diagnosis to make sure the child is healthy, it’s but a short step for them to say, ‘well, why shouldn’t we get the best of all possible babies out of this process?’ Assuming that they have some idea of what that best will be.”

Leon Kass, American Enterprise Institute

There are those who argue that testing for more diseases in a broader patient population will greatly increase the overall number of pregnancy terminations. Furthermore, they worry that more and more genetic variations will come to be considered serious defects for which termination is sought. The future promises prenatal genetic testing characterized by more choices than ever, as well as more confusion.

Preimplantation Genetic Diagnosis

Any genetic test that can be used to test an adult may also be used to test an embryo. There are no limits

to the types of genetic tests that may be performed on an embryo. Thus, in the future PGD may be used to test an embryo for any genetic disease-causing mutation or trait that may be identified. And as more couples use PGD as an add-on to IVF, PGD could allow parents to choose among embryos based on a range of genetic characteristics. PGD has already been used to detect — and select embryos free from — a mutation associated with a high risk of developing Alzheimer disease as an adult. In the future, parents may use PGD to attempt to have children free of genetic risk factors for heart disease or any disease with a known genetic component. And if it becomes possible to test for a gene associated with intelligence, height, athleticism or other “traits,” PGD could be used for that purpose as well.

Bundles, Panels and Chips

Uncertainties abound about how tests should be bundled and how much control patients will have over the information they receive. For example, in the future standard prenatal genetic testing could conceivably test for every known disease-causing mutation. As an alternative, the number of tests could be limited but it is not at all clear how the limits should be drawn. Another possibility would be to allow prospective parents to opt-out of certain diagnostics; for example, if the “bundle” includes testing for susceptibility to adult-onset diseases such as Huntington or Alzheimer diseases but that information is not wanted, they could decline that information.

Some disease-causing mutations will be present at varying frequencies in different populations. In the case of CF, this has resulted in test panels for the most prevalent mutations. In the case of sickle cell disease and Tay Sachs, screening programs have targeted particular populations. While limited panels and targeted screening are cost effective with today's technologies and health care delivery systems, this approach also may mean that tests may not be developed for mutations that cause significant disease in small population groups, particularly those groups with less economic power. In addition, testing may not be made available to lower risk populations. For example, as a result of the Tay Sachs screening programs predominantly in the Jewish community, the number of Tay Sachs births is now actually higher among non-Jews than among Jews (although still very rare). Looking to the future it is possible that high throughput testing platforms such as gene chips will bring costs down such that universal testing, even for rare mutations, can be offered.

The Current Legal and Regulatory Landscape

Government Oversight of Reproductive Genetic Tests

Federal

The federal government does not typically directly regulate the practice of medicine, leaving such oversight to the states. The federal government does, however, have authority to regulate certain aspects of genetic testing. As discussed in detail below, some federal agencies exert limited oversight of genetic tests and the facilities that perform them.

Some have argued that government oversight of genetic testing has fallen between several regulatory cracks and that government involvement in this area is inadequate given the growing importance of genetic testing in medical care and in reproduction. But before any new regulatory actions are considered, it is important to understand the existing authorities that are now in play.

FDA

The Food and Drug Administration (FDA) has limited regulatory authority over some aspects of genetic testing. FDA regulates diagnostic test kits, such as those used to diagnose HIV or to detect pregnancy, as “in vitro diagnostic devices” (IVDs). A small number of genetic tests are sold as freestanding “kits” or IVDs. IVDs are subject to premarket approval or clearance requirements, which may require the submission of clinical data showing the device is safe and effective.

FDA has approved a few molecular genetic tests for marketing as IVDs. One, approved in 2001, is a test for the overexpression of the HER2 gene in breast cancer patients. The other two tests, approved in 2003, detect Factor V Leiden and Factor II, genetic abnormalities which are linked to blood clotting disorders. None of these FDA-regulated tests are used, at least currently, in reproductive genetic testing. Moreover, considering that genetic tests for over 700 diseases are available clinically, those approved by FDA represent a negligible fraction of genetic tests.

However, most genetic tests are not regulated as IVDs because they are not sold as kits. Rather, a laboratory offers them as a medical service. These tests, developed in-house by a laboratory, are called “home-brew” tests. Because these tests are not sold as products, FDA does not regulate them or the clinical laboratories that use them.

FDA does, however, regulate certain components used in developing home-brew genetic tests. FDA regulates “analyte specific reagents” (ASRs), the active ingredients of home-brew tests. Like other medical devices, FDA classifies ASRs according to their level of risk. Class I is the lowest risk and Class III the highest. FDA has the authority to impose additional requirements to assure the safety and effectiveness of Class II or Class III ASRs. However, FDA has classified ASRs for genetic testing as Class I ASRs and thus they are not subject to heightened regulation.

Two recent FDA actions suggest the agency may be laying the groundwork for more extensive regulation of new gene chip-based genetic tests as medical devices. In April 2003 FDA prepared a “draft guidance” to help companies understand what they will need to submit to the agency in order to get the approval required to make the tests commercially available. FDA noted that its goal was “to establish a set of recommendations that will both define the levels of data needed to establish a reasonable assurance of safety and effectiveness of a device, and suggest the least burdensome path to market for manufacturers of multiplex and array devices.” Also in 2003, FDA notified the manufacturer of a gene array chip that it could not sell the chip for diagnostic use without additional agency review and that the chip could not be classified as an ASR. However, it is not clear what degree of review FDA intends to apply to this technology and what the specific requirements will be.

With regard to PGD, FDA involvement to date has been limited. FDA generally has not sought to regulate assisted reproduction directly, although it does regulate the drugs and devices used as a part of fertility treatments. FDA also regulates human tissues, including reproductive tissue, used for transplantation, but such oversight is limited to preventing disease transmission and ensuring tissue integrity by requiring procedures for tissue testing, storage, and record keeping. FDA does not generally review the safety and effectiveness of fertility treatments, such as PGD, that use reproductive

tissue; it is unclear whether FDA has the authority to do so. It is possible that FDA could seek to regulate the embryo resulting from IVF and PGD as a “biological product,” and require premarket approval on that basis, but there has been no serious consideration of such an approach to date. While FDA has at times been willing to extend existing authority to cover new technologies, these decisions are generally made because of a perception that the technologies at issue pose serious public health threats. For example, in 2001, FDA asserted authority over ooplasm transfer, an experimental fertility procedure, stating that it could be performed only as part of an FDA-authorized research protocol.

Even if FDA were to attempt to increase regulation of genetic testing including reproductive genetic testing, there are still limits on its authority that could affect its ability to dictate safeguards for patients. Although FDA regulates the claims a manufacturer may make about an approved product, it does not have authority to regulate how a doctor uses or administers it. Such decisions are considered part of medical practice. An analogous situation is frequently seen with FDA-approved drugs. The drug may be approved for specific indications, but once approved, doctors are free to use their judgment to prescribe the drug for other conditions. Thus, even if FDA found a way to require premarket approval for genetic tests, the agency could not restrict how health care providers decide to use the tests. The role of professional societies in establishing guidelines for how providers use tests and procedures will be discussed below.

CLIA

One of the key issues in the regulation of genetic testing is whether or not there is adequate oversight of the laboratories that perform the genetic analysis. Most genetic testing is considered a commercial service that is provided through clinical laboratories and is subject to regulation by the Centers for Medicare and Medicaid Services (CMS) through a law known as the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

In enacting CLIA, Congress directed the Secretary of the Department of Health and Human Services (HHS) to issue standards for the certification of laboratories in order “to assure that such laboratories will consistently perform tests in a valid and reliable manner.” CMS is responsible for developing and enforcing these standards, which apply to all clinical laboratories regardless of whether or not they service Medicaid and Medicare beneficiaries.

CLIA defines a “clinical laboratory” as a laboratory that examines materials “derived from the human body” in order to provide “information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.” CLIA requirements include laboratory personnel qualifications, documentation and validation of tests and procedures and quality control standards. These general requirements apply to laboratories performing genetic tests when the results of those tests are used as part of health care decision making. It is

unclear whether so-called “research” laboratories that develop new genetic tests for rare genetic disorders are always CLIA certified. Physicians ordering genetic tests from these laboratories may not be aware that such laboratories are not permitted to report the results of their tests back to the patient or physician unless they are CLIA certified.

The stringency of CLIA regulation depends on the complexity of the test that the laboratory performs. “High complexity” tests are generally grouped according to “specialty areas” and are subject to specified additional requirements, including proficiency testing requirements. Proficiency testing is a means by which a laboratory demonstrates its ability to accurately perform certain tests. However, while genetic tests are considered high complexity, there is no specialty area for molecular genetic tests and no specified proficiency tests for them. Laboratories must therefore determine for themselves how to demonstrate their proficiency in performing most genetic testing. Some do so by using proficiency testing programs established by professional organizations; however, use of these programs is not required under CLIA. Cytogenetics (chromosome analysis), in contrast, is recognized as a specialty area and some cytogenetic-specific standards are required under CLIA.

The absence of a molecular genetic testing specialty area under CLIA, and in particular of uniform prescribed proficiency testing requirements for genetic testing, makes it difficult to evaluate the

accuracy of laboratory performance of genetic tests.

While laboratories performing prenatal and carrier testing fall under CLIA jurisdiction, its applicability to laboratories that perform genetic testing for PGD is less certain. The outstanding question is whether the genetic tests performed in PGD laboratories provide information that will be used to diagnose, treat or prevent disease or to assess human health. Some within the agency worry that including PGD within the definition would require CMS to take the position that an embryo meets the legal definition of a human being. It is unclear whether this concern is well-founded since neither the agency nor any court has had occasion to formally address it. Some PGD providers argue that their activities constitute the practice of medicine and are not within the scope of CLIA.

Even if CLIA reached all reproductive genetic testing, many observers believe that CLIA's requirements are inadequate. The relatively restricted scope of CLIA ultimately limits its power to deal with many of the issues raised by genetic testing. The focus of the statute is the environment in which tests are performed and the processes involved in performing them.

In addition, although CLIA does address some aspects of analytic validity — whether the lab can perform the test accurately — it does not address clinical validity, i.e. the accuracy with which the test will predict a clinical outcome, or clinical utility, i.e. whether the test is useful

analytic validity refers to the ability of a laboratory test to identify the targeted characteristic (e.g., a DNA sequence variant).

clinical validity refers to a test's ability to predict a particular clinical outcome.

clinical utility refers to a test's ability to provide information that leads to an improved health outcome.

for health and treatment decision making. Each laboratory director makes these determinations and decides whether to offer a genetic test, without any oversight from CLIA.

CDC

The Centers for Disease Control and Prevention's activities include monitoring, detection and surveillance of health and disease, as well as data collection and analysis. CDC differs from FDA and CMS in that it does not have specific statutory authority to regulate a particular industry (e.g., medical device manufacturers, clinical laboratories). Nevertheless, CDC engages in activities related to some aspects of reproductive genetics.

CDC advises CMS concerning the implementation of CLIA through the Clinical Laboratory Improvement Advisory Committee (CLIAC). In 1997, CLIAC formed a Genetic Testing Working Group, whose purpose was to define CLIA's applicability and scope with respect to all phases of genetic testing. CLIAC has made several

recommendations concerning genetic testing, including the development of proficiency testing standards for clinical laboratories engaged in molecular genetic testing. In 2000, CDC announced its intention to revise CLIA regulations applicable to laboratories performing human genetic testing by creating a new specialty area that would address all phases of genetic testing. To date, no proposed regulations have been issued.

CLIAC also has made recommendations concerning regulation of laboratories engaged in in vitro fertilization. In 1998, CLIAC recommended that embryo laboratory procedures be under the purview of CLIA. This recommendation has not been adopted by CMS.

Through the Pregnancy Risk Assessment Monitoring System (PRAMS), CDC also collects data related to maternal attitudes and experiences prior to, during and immediately following pregnancy. Questions include whether a woman had health insurance coverage before and during pregnancy, when she began receiving prenatal care, whether she encountered difficulties in accessing prenatal care, the content of discussions between the pregnant woman and her health care provider and early infant development and health status.

In the current PRAMS questionnaire (2004-2007), among more than 50 questions asked in every state, there is only one question related to reproductive genetic testing. One subpart of one question asks whether during a prenatal care

visit, a health care provider discussed “doing tests to screen for birth defects or diseases that run in my family.” No questions ask whether the woman actually used the tests. There are additional questions that states may choose to add to the questionnaire administered in the state. Among these questions are two on whether the mother used assisted reproductive technologies, although there is no mention of PGD.

CDC implements the 1992 Fertility Clinic Success Rate and Certification Act (FCSRA). This law requires clinics that provide IVF services to report pregnancy rates annually to the federal government. The FCSRA requires clinics to report data concerning the type of assisted reproduction procedure used, the medical diagnosis leading to IVF treatment, the number of cycles of IVF attempted, whether fresh or frozen embryos were used, the number of embryos transferred in each cycle, the number of pregnancies achieved and the number of live births. The statute does not require clinics to report the health status of babies born as a result of the procedure or the use of diagnostic tests such as PGD. CDC analyzes the data and makes its findings available to the public, including via the Internet.

In 2001, the most recent year for which data are available, 384 clinics reported data. The law requires CDC to list on its web site the names of clinics that do not report at all or that fail to verify the accuracy of the data. Thirty-seven clinics known to be in operation throughout 2001 that did not report data are listed as non-

reporters. Other than being listed by CDC, there are no penalties for failure to report.

Federal Oversight of Research

Federal regulations require all institutions receiving federal funds to follow rules aimed at protecting human participants in medical research. Requirements include review of research protocols by an institutional review board (IRB), informed consent of the research subject and periodic reporting obligations. Special protections are in place for pregnant women and in utero fetuses in order to minimize the risk of harm. Research that will be used to support an application for approval of a product by FDA is also subject to these human subject protection regulations.

If a federally-funded research institution were to conduct research on reproductive genetic technologies with human participants, such research would be subject to these requirements. In practice, however, some reproductive genetics research, and in particular research on PGD, is precluded from receiving federal funds. This is because of a 1996 Congressional ban on federal funding of any research in which an embryo is created, destroyed or subjected to more risk than is permitted for an in utero fetus. As a result, embryo-related research is most often conducted with private funds.

Federal funding may, however, be used for research involving fetuses under certain circumstances. Such research would be covered by the federal human subject protections.

In the absence of federal funding for research and FDA premarket review of genetic tests, research to develop these tests is not subject to federal human subject regulation.

Government Advisory Committees on Genetic Testing: Unheeded Advice

Several government advisory bodies have reviewed the oversight of genetic testing in the United States and made recommendations for improvement. While these bodies did not consider reproductive genetics specifically, the concerns they identified are relevant to the oversight of reproductive genetic testing. However, very few of their recommendations for enhanced oversight have been adopted.

In 2001, President Bush established the President’s Council on Bioethics (PCB) to advise him on emerging bioethical issues. Although the PCB charter does not specifically refer to reproductive genetic testing, the Council addressed several issues related to assisted reproduction, including PGD, in a March 2004 report, *Reproduction and Responsibility: The Regulation of New Biotechnologies*. The PCB’s recommendations included undertaking a federally funded study into the health and well-being outcomes of children born using assisted reproductive technologies including PGD, expanding the data collected by the FCSRA to include data about use of PGD, and Congressional prohibition of certain reproductive techniques such as the creation of animal-human hybrid embryos. (Several of these topics will be discussed later in

| Government Advisory Committee on Genetic Testing | | | |
|--|--|---|--|
| NAME | PURPOSE | RECOMMENDATIONS | OUTCOME |
| 1995: National Institutes of Health-Department of Energy Task Force on Genetic Testing | Address concerns that: <ul style="list-style-type: none"> • genetic tests introduced clinically before safety, effectiveness and utility demonstrated; • clinical laboratories not meeting standards; • patients and providers lack sufficient information to understand the tests | <ul style="list-style-type: none"> • All genetic testing research should be approved by an IRB; • Federal agencies should facilitate research into safety and effectiveness; • Specified data should be collected prior to commercial availability of test; • Clinical validity should be established before commercial availability; • CDC should implement proficiency standards for laboratories conducting genetic tests as part of a national accreditation program for genetic testing laboratories. | <p>Report issued in 1997. None of the recommendations adopted.</p> <p>Report led to establishment of Secretary’s Advisory Committee on Genetic Testing.</p> |
| 1998: Secretary’s Advisory Committee on Genetic Testing (SACGT), Department of Health and Human Services (HHS) | Implement Task Force Recommendations. SACGT was asked to frame its recommendations around five issues: <ul style="list-style-type: none"> • criteria that should be used to assess benefits and risks of genetic tests; • tailoring criteria to different categories of tests; • process that should be used to collect, evaluate and disseminate data on tests in these categories; • options for oversight of genetic tests; • appropriate level of oversight for each category of test. | <ul style="list-style-type: none"> • Analytic and clinical validity, clinical utility, and social consequences should be major criteria used to assess benefits and risks of genetic tests; • Tests should be classified into “scrutiny level.” Review should be based on factors including use of test, type of mutation being detected, treatment availability, potential for stigma based on test results and ease of interpretation of results; • FDA should be responsible for review, approval and labeling of all new genetic tests,. • CLIA regulations should be augmented to ensure quality of laboratories conducting genetic tests; • IRB review should be conducted of all research protocols for genetic tests in which individually identifiable human subjects or samples used; • Tests already on market should be reviewed for clinical efficacy by a multidisciplinary group, which should develop guidelines for their appropriate use. | <p>Report issued in 2000.</p> <p>In 2001, then Secretary Donna Shalala stated that HHS would implement the committee’s recommendations.</p> <p>Thereafter, committee retracted its proposed criteria for determining level of scrutiny, stating that, “in the final analysis, SACGT came to question the feasibility and utility of such a methodology.”</p> <p>SACGT’s charter expired in 2002. None of its recommendations has been implemented.</p> |
| 2002: Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) | Serve as a public forum for deliberations on broad range of human health and societal issues raised by genetic technologies and advise the Secretary on these issues. | <ul style="list-style-type: none"> • Sent letters to Secretary of HHS in support of genetic discrimination legislation. | Has heard testimony and engaged in discussion on health care professional education, reimbursement for genetic technologies, genetic discrimination and direct-to-consumer marketing of genetic testing. |

this report). Thus far, no actions have been taken by the Administration or Congress to respond to these recommendations.

States

States traditionally have had primary authority to pass laws and develop regulations protecting the health, safety and welfare of their citizens. States fulfill this oversight role in a variety of ways.

States license physicians and other healthcare providers. However, they do not license physicians to perform specific procedures or impose specific limits on their practice. Rather, board certification by various specialty organizations defines competence to practice a specialty or subspecialty, although there are few regulations prohibiting physicians from practicing outside their area of specialty.

There are a variety of other health professionals relevant to reproductive genetic testing, including nurses and genetic counselors. Nurses are licensed by state licensing boards. Only a few states license genetic counselors, who are certified by the American Board of Genetic Counseling.

Some states regulate medical laboratories, including placing limits on who may order a test from a laboratory. Some states categorically prohibit direct patient access to clinical laboratory testing, while others allow some clinical laboratory tests such as cholesterol or pregnancy tests to be ordered by patients without a prescription from a health care provider. And

still other state laws are silent on the issue, which leaves the determination of whether to offer direct access testing up to individual laboratories. While there has been an increasing trend toward direct marketing of some genetic tests over the Internet, it appears that most genetic testing in the reproductive context is obtained through medical professionals. This is particularly true in the case of PGD and prenatal testing, because the skills of a health care professional are required to obtain the DNA sample needed for testing. However, direct testing may be more feasible in the area of carrier testing, since an individual can easily provide a sample of his or her own tissue — usually a simple blood test — to a laboratory.

For the most part, state agencies implement the CLIA program but do not add to it, although some states have enacted more stringent requirements. New York and Washington states are exempt from CLIA because their own regulatory framework has been deemed by the federal government to be sufficiently rigorous. Most states have not included laboratories that conduct IVF or PGD in their laboratory oversight duties. However, New York's standards for laboratories do include oversight of the genetic tests associated with PGD by the state Department of Health. Laboratories must demonstrate their ability to detect in an embryo each mutation for which they offer testing.

Under the FCSRA, CDC developed a model state program for certifying laboratories that work with human embryos. It includes standards for procedures, record

keeping and laboratory personnel and criteria for inspection and certification. According to CDC, no state has formally adopted the model program.

States have jurisdiction over insurance benefits included in health insurance plans sold within their borders. Some states mandate that providers offer prenatal testing. For example, a law in Washington state requires that insurers providing pregnancy or childbirth benefits must also include benefits covering tests and procedures relating to genetic diagnosis of the fetus. Washington also requires health care providers to inform pregnant women about the availability of prenatal tests. A state-administered program in California requires providers to offer serum screening blood tests to all women who begin prenatal care before the 20th week of pregnancy. Testing is subsidized and insurance companies are required to pay for the test. Subsidized follow-up services, including genetic counseling, ultrasound and amniocentesis, are available at state-approved Prenatal Diagnosis Centers.

Fifteen states have enacted laws mandating that insurers offer or provide some degree of coverage for infertility treatments, which may or may not include IVF services, but no state currently requires insurance coverage for genetic testing of embryos.

A state's ability to influence health care policy by mandating certain types of insurance coverage is limited by a federal law (the Employee Retirement Income Security Act or ERISA) that exempts employers who

assume the risk for their employees' health care costs from state insurance mandates. The practical effect is that nationwide about half of the 131 million Americans who get health insurance through their jobs may not be receiving the benefits required by state laws.

Some states have used their authority over medical practices to pass laws related to assisted reproductive technology (ART). These laws are mainly concerned with defining parentage, ensuring that the transfer or donation of embryos is done with informed consent or ensuring insurance coverage for fertility treatment. Some states prohibit the use of embryos for research purposes and one state, Louisiana, prohibits the intentional destruction of embryos created via IVF. For the most part though, states have not assumed oversight responsibilities for fertility clinics.

Self-Regulation and the Role of Professional Organizations

Medical and scientific professional organizations are a source of oversight of reproductive genetic testing. These groups, which generally comprise members of a particular occupation or specialty, serve a variety of oversight or self-regulation functions. They educate members about advances in the field and develop guidelines addressing appropriate conduct or practices such as indications for particular treatments. They may require compliance as a condition of membership. Professional guidelines and standards vary widely in their scope and level of specificity. In the case of genetic testing, guidelines

may describe the indications for a particular test, give specific technical instructions for how the laboratory should perform the test or provide information on how providers should interpret results.

For the most part, professional guidelines and standards are voluntary. Professional organizations typically do not have authority to sanction members for noncompliance. Unless the organization is specifically authorized to act on the government's behalf in administering and enforcing government standards, actions of the professional organization do not have the force of law.

Therefore, professional guidelines often play an exhortative role, setting a standard for the best possible conduct by providers. They also may have a legal impact. Courts may use clinical practice guidelines to help determine whether a provider met the "standard of care" in treating a patient. The standard of care is the minimum level of non-negligent healthcare that a provider must give, and is generally defined as reasonable and customary treatment provided by a competent medical practitioner. If guidelines are used as evidence of the standard of care by a court, then a provider who deviates from them could face liability if a patient is harmed as a result. Conversely, guidelines may also function as a 'safe-harbor' for medical practitioners who would not be liable for any claims arising from treatment in compliance with guidelines.

However, courts differ regarding the evidentiary value of guidelines in establishing the standard of care. Courts generally weigh heavily the quality of the guideline and its general acceptance within the relevant medical specialty. Some guidelines are not comprehensive, do not represent professional consensus, are supported by poor research and data or were promulgated by an entity with a potential conflict of interest, such as an insurer or HMO. Such guidelines are less likely to be persuasive to a court determining the standard of care. In contrast, guidelines supported by evidence and reflecting consensus within the medical community are more likely to be persuasive to a court. While disseminating guidelines and persuading providers to adhere to them is often challenging, their potential legal impact can create a strong impetus for their adoption.

Some observers have raised the concern that guidelines reflect not how the practice of medicine should be performed but how it is already done. Often guidelines are not developed until a test or procedure is already commonplace, when practice patterns have already been established. This may reflect the many challenges of creating new guidelines as well as the reluctance of the profession to develop guidelines with incomplete information about a new test or procedure.

Professional societies such as ACOG and ACMG have each published guidelines regarding carrier and/or prenatal genetic testing. But the guidelines that exist cover only a fraction of the genetic tests that can be performed.

ACOG publishes both professional guidelines and opinions. ACOG has addressed specific tests such as Tay Sachs, Canavan disease and cystic fibrosis, and ethical issues such as sex selection and embryo research. There are also a few Practice Bulletins on topics related to reproductive genetics such as *Prenatal Diagnosis of Fetal Chromosomal Abnormalities*. Overall, the intent of all of these documents is to be educational rather than directive. Following the standards is voluntary. ACOG has avoided regarding these statements as defining the standard of care, although these documents may be viewed as performing that function.

The American College of Medical Genetics has also issued policy statements and guidelines for some areas of carrier and prenatal genetic testing. ACMG has developed guidelines for carrier testing for cystic fibrosis and Canavan disease, and prenatal testing for open neural-tube defects. ACMG also has published more general statements on genetic testing for a specific disease such as Huntington disease, that also include discussion of prenatal testing.

In 2001, the American Society for Reproductive Medicine (ASRM) issued a practice committee opinion addressing PGD, stating that PGD “appears to be a viable alternative to post-conception diagnosis and pregnancy termination.” It further states that while it is important for patients be aware of “potential diagnostic errors and the possibility of currently unknown long-term consequences on the fetus” from the biopsy procedure, “PGD should be

regarded as an established technique with specific and expanding applications for standard clinical practice.” ASRM also has issued an ethics committee opinion cautioning against the use of PGD for sex selection in the absence of a serious sex-linked disease. However, there are ASRM members who offer and advertise sex selection services for non-disease related reasons such as “family balancing.”

The PGD International Society (PGDIS), was created in 2002 to promote PGD and to organize and coordinate research, education and training in PGD among providers working in the field. In 2004, PGDIS developed and published *Guidelines for Good Practice In PGD* outlining topics such as setting up a PGD program, patient management, IVF and PGD protocols, diagnostic techniques, embryo transfer, spare embryos, follow-up of pregnancy and quality control and assurance.

The European Society for Human Reproduction and Embryology (ESHRE) tracks PGD outcomes on a voluntary basis, but captures primarily European data. In May 2004, ESHRE’s PGD consortium released “Best Practice Guidelines” for PGD testing. ESHRE’s guidelines are currently under review by ESHRE membership.

It is interesting to note that the ESHRE guidelines begin with an explanation of why guidelines are important. According to ESHRE, genetic testing of embryos for single-gene disorders (referred to as PGD) and to screen for chromosomal abnormalities (referred to as PGS) “are treatment options that are

relatively unregulated and lack standardization compared to other diagnostic testing.” According to the guidelines, this is “ironic considering the comparative difficulty in achieving the highest levels of accuracy and reliability with single cells as part of PGD/PGS versus more routine genetic testing.” They recommend that one step towards higher quality overall and standardization for PGD is to “build consensus opinion on best practices within the PGD/PGS community.”

The College of American Pathologists (CAP) runs voluntary programs certifying clinical laboratories including those performing genetic testing. In conjunction with ACMG, CAP operates proficiency testing programs for a variety of genetic testing, including the molecular genetics and cytogenetics that are part of carrier and prenatal testing. CAP also has programs in some areas specific to reproductive genetic testing, such as maternal serum screening and prenatal genetic testing. They also certify laboratories in embryology, including the techniques and procedures necessary for IVF, although the certification does not include standards for PGD. In addition, CAP has been empowered by the federal government to inspect laboratories seeking certification under CLIA.

Oversight by Court Action

Courts play an important role in overseeing health care, including reproductive genetic testing. The possibility of malpractice liability provides a strong incentive for health care providers to conform to the

standard of care, which may require adopting new medical technologies.

Lawsuits claiming medical malpractice following the birth of a child with an abnormality preceded the advent of reproductive genetic testing, and gave rise to legal theories, such as “wrongful birth” and “wrongful life,” that are potentially applicable to the genetic testing context. For example, a parent who gives birth to a child with a genetic abnormality and either was not offered a genetic test or believes the test was improperly interpreted may sue the provider who failed to order or properly interpret a test or the laboratory that improperly performed a test or incorrectly reported the results. The parent may allege that, but for the provider’s negligent actions, the parent would not have chosen to become pregnant or continue a pregnancy. These cases have been called “wrongful birth” suits. The parent may also argue on behalf of the child that, but for the provider’s negligent action or failure to act, the child would not be alive—so called “wrongful life” suits. Courts differ on the extent to which they recognize these arguments or would permit damages to be awarded.

These legal theories have, in a few cases, been applied to PGD. In one case, the parents of a child born with cystic fibrosis following PGD, as well as the child, sued those involved with the embryo screening for failing to detect the condition. The parents made the claim of “loss of consortium,” meaning the loss of the companionship they would otherwise have had with a child not affected by cystic fibrosis. The court rejected this claim, finding that it was

too speculative. Also, it ruled that the defendants could not be held legally responsible for causing the child to suffer from a genetic disease.

“In the case where a mother might terminate a pregnancy based on a mutation, one has to be very sure that one knows that mutation correlates to that disease.”

Sharon Terry, Genetic Alliance

The child made the claim of “wrongful life,” alleging that the defendants’ negligent failure to detect cystic fibrosis denied his parents an opportunity not to give birth to him. The court rejected this claim as well. Indeed, most courts have rejected wrongful life claims in other circumstances, such as those arising from a flawed prenatal test, in part because doing so would require accepting the general argument that there can be instances in which an impaired life is worse than no life at all.

The proliferation of genetic testing and the ability to perform increasing numbers of tests prior to birth is likely to create more opportunities for such cases to be brought. For example, if a provider performs carrier testing on a prospective parent and learns that the parent is a carrier at heightened risk for passing on a particular disease, what obligation, if any, does the provider have to disclose this information to other family members potentially at risk — including any subsequent

children? While there have been a few court cases addressing this issue, court rulings have been inconsistent, leaving providers without clear guidance on how to proceed.

In determining a provider’s responsibility and liability for a bad outcome, the court asks whether the provider followed the standard of care. Answering this question may, in turn, be informed by whether specific practice guidelines or recommendations from a relevant professional society exist and are generally followed by others in the provider’s specialty.

Policy Options

Reproductive genetic testing provides tremendous benefits to prospective parents seeking information about their risk for having a child with a genetic disease. Yet for many observers these tests raise questions about whether there is sufficient oversight of these technologies. Some ask whether clear oversight rules are needed to ensure the **ethical use** of reproductive genetic testing. Others focus on how to improve **clinical delivery** of tests to patients, ensuring that the right test is offered to the right person at the right time. Many want increased oversight of the **accuracy and safety** of reproductive genetic tests. And some ask about **access**, whether the cost of reproductive genetic testing means it will be available only to a privileged few.

“These are not decisions that should be made by some political elite; they are not decisions that should be made by religious elite. These are decisions that we all have a stake in because we all share a common heredity.”

*C. Ben Mitchell, Trinity
Evangelical Divinity School*

There are a variety of intelligent public policy approaches that could address these concerns. In this section we suggest an array of policy options to respond to different points of view. Each option also includes arguments for and

against, exploring the strengths and weaknesses in each approach.

Ethical Use of Reproductive Genetic Testing

Concerns about the ethical use of reproductive genetic testing take a variety of forms. Some observers emphasize that the growth of reproductive genetic testing over time will mean the destruction of many more embryos and fetuses and a decrease in the value placed on human life. These concerns are most often raised about prenatal testing or PGD. Fewer concerns have been raised about the use of carrier testing before pregnancy because such tests can inform decision making before conception and thus do not directly result in the discarding of embryos or termination of pregnancy.

Many concerns relate to why testing is used, whether parents are attempting to prevent a life-threatening disease or whether they are pursuing testing for a disorder that is amenable to treatment or an inherited characteristic with no health impact. Of course, most people acknowledge that the line between these two kinds of use is sometimes difficult to draw.

Advances in testing technology will soon make it possible — and perhaps more tempting — for parents to test for many things at once and to go beyond the conditions that now are the focus of prenatal genetic tests. For example, an add-on to amniocentesis or CVS for maternal age might be to test for genetic predisposition to adult-onset diseases. Some are troubled by the impact of such decisions on the

relationships between parents and children.

Some who have concerns about the ethics of reproductive genetic testing would like to see targeted restrictions to moderate the impact on individuals, families and society. Others would ideally want prenatal testing and PGD banned completely, although most acknowledge that it would be difficult to accomplish this. A variety of approaches to limit the uses of reproductive genetic testing and/or the impact of these tests follows.

Option: Establish federal or state rules for ethical uses of reproductive genetic testing.

Current oversight of reproductive genetic testing is highly fragmented, but where it does occur it is aimed primarily at accuracy and safety issues. Government could also play a role by setting ethical limits on the uses of reproductive genetic testing.

Congress, federal agencies or state governments could create and enforce prohibitions of prenatal testing or PGD for uses determined to be unacceptable (e.g. sex selection for reasons not related to health). Federal or state agencies could also license and inspect facilities that perform or process reproductive genetic testing to ensure compliance with prohibitions.

Government bodies could also collect data on which tests are performed and how information is used for reproductive decision making to help inform policymaking.

In addition to setting and enforcing limits and collecting data, government could play a more significant role in overseeing the accuracy and safety of reproductive genetic testing.

Arguments for:

- Clear government-mandated restrictions will create certainty about what is and is not permissible, providing legally enforceable rules based on shared societal values.
- The process of creating federal or state rules will stimulate a productive public discussion about how to effectively oversee genetic testing and what limits are appropriate.
- Limits on the use of testing will result in fewer abortions of fetuses and fewer embryos discarded or destroyed on genetic grounds.

Arguments against:

- This approach constitutes a significant intrusion into private medical practice. These decisions are best left to patients and providers.
- Any limits on decision making in human reproduction raises concerns about reproductive choice and could be subject to a Constitutional challenge.
- There is no societal consensus on appropriate uses. It will be difficult for any entity to draw lines between acceptable and unacceptable uses.
- Enforcement of such policies requires devising systems to determine why testing, or subsequent abortion, was performed.
- Setting limits nevertheless gives explicit government approval to practices that many people reject outright.
- Increased oversight will affect ease of access. In general, more scrutiny will mean restricted or delayed availability and increased costs.

GOVERNMENTAL**Ethical Use****Option: Federal or state ban of PGD.**

Unlike carrier testing and prenatal testing, PGD is not a common part of reproductive health care. Already banned or restricted in some countries, PGD is the form of reproductive genetic testing most likely to be targeted for a ban. PGD requires the creation and sometimes leads to the destruction of embryos. Some who believe a human embryo has the moral status of a live born child believe that PGD should be banned because of the loss of embryos involved.

There are others who do not hold such a firm position on the moral status of the early human embryo but who nonetheless oppose PGD because they view it as unnatural and as violating the natural process of procreation. Also, some argue that PGD should be avoided even if it is not inherently wrong or offensive because it places society atop a slippery slope that will lead to genetic enhancement and human control of evolution.

Congress or state legislatures could decide that PGD is sufficiently problematic to justify banning the procedure entirely.

Arguments for:

- Any use of PGD is unacceptable because it results in human embryos being destroyed.
- Any use of PGD, no matter how sympathetic the reason, is an unwarranted intrusion into the natural process of procreation.
- PGD should be banned because it is discriminatory and is a form of eugenics.
- New technologies should not be allowed without limits. PGD should be banned, at least until its implications are more clearly understood.
- A ban will contribute to the common good.
- A ban provides a bright-line rule and clarity about what is and is not permitted.

Arguments against:

- This approach is too blunt an instrument because it does not allow exceptions even under the most sympathetic circumstances.
- This approach is inconsistent from a policy perspective. There are no restrictions on the genetic tests that can be performed on a fetus or on the reasons for which a woman may terminate a pregnancy.
- Prospective parents may go to “underground” providers, or, for those who can afford it, to another country where PGD is legal.
- Banning PGD imposes a single moral or ethical perspective on those who may have different views.
- Any limit on decision making in human reproduction raises concerns about reproductive choice and could be subject to a Constitutional challenge.
- Bans on a medical procedure will be difficult to enact and enforce.
- Bans at the state level can lead to inconsistencies in access to PGD.

Option: Develop professional guidelines for ethical uses of reproductive genetic testing.

A number of relevant medical professional societies have some reproductive genetic testing guidelines, including when a test should and should not be offered. But the number of guidelines relative to the number of tests is small. As more tests become available, professional guidelines will become an important source of guidance for providers as to what testing is appropriate. For example, guidelines may be needed on whether reproductive genetic testing of embryos and fetuses for sex selection, or predisposition to an adult-onset disease, is appropriate. Guidelines will likely guide insurers' reimbursement decisions for genetic tests.

Federal funding should be available to professional societies to support this work.

Federal funding would help professional groups devote adequate resources to this process, particularly as many more tests become available.

The federal health agencies fund extensive research that underlies the development of new genetic tests and have a responsibility to aid in the translation of these fruits of research into quality health care.

Arguments for:

- Professional guidelines setting limits on reproductive genetic testing will provide guidance to providers and patients alike on the ethical use of these tests.
- Professional guidelines allow those with the most knowledge of testing to develop the framework for appropriate use.
- Professional guidelines are more easily developed and more easily revised in response to new scientific developments than legislation or regulation by agencies.
- By clearly delineating indications for testing, clear guidelines prevent over-testing by providers concerned about liability.
- Guidelines can be used by insurance companies to determine coverage, further limiting use.
- Federal funding will help professional societies keep pace as many more tests become available.

Arguments against:

- Guidelines are voluntary. Providers are not compelled to comply.
- Providers may not have the appropriate expertise to establish guidelines based on morality or value judgments.
- Consensus on ethical uses is difficult. Guidelines may be in conflict with the moral views of providers.
- Providers benefit financially from testing so there is inherent conflict of interest when professional societies consider limit-setting.
- It is difficult for professional groups to devote adequate resources to this process, particularly as many more tests become available.
- Guidelines may limit individual reproductive choices.
- Decisions about ethical uses should not be left entirely to the discretion of professional groups. Broader societal consensus and input are needed.

Option: Limit uses of reproductive genetic testing through insurance coverage decisions.

Insurers could pay only for reproductive genetic testing done for reasons they deem acceptable and refuse to pay for reproductive genetic testing for reasons they determine to be unacceptable. Insurers would need to list and define prohibited uses for enrollees.

Arguments for:

- Insurance companies' coverage policies can operate as effective de facto enforcement, requiring prospective parents to follow guidelines for appropriate use in order to be reimbursed.
- Insurers have mechanisms in place for determining when a test or procedure is "medically necessary."

Arguments against:

- It will be difficult for any entity, including insurers, to draw lines between acceptable and unacceptable reasons for testing.
- Enforcement of such policies will be difficult, requiring insurance companies to determine the reason testing is performed.
- People able to pay out-of-pocket for reproductive genetic testing will be able to use it for any reason.

Clinical Delivery of Reproductive Genetic Testing Services

Reproductive genetic tests can provide valuable information to patients, but many believe changes are needed to improve the quality and experience of genetic testing and related services. The quality of patient care would be enhanced if (1) health care providers were more knowledgeable about testing, (2) testing were offered when prospective parents could make the best use of the information, and (3) prospective parents were provided all of the information and counseling needed to understand the choices that they are making about testing and the implications of those choices.

Most experts agree that genetic risk information and reproductive genetic testing options should be discussed with prospective parents before pregnancy. The health care provider should take a family history and assess genetic risk based on family history, maternal age and ethnic background and discuss carrier testing options. Carrier testing done before pregnancy provides prospective parents additional information about potential risks.

Patient experiences with counseling about reproductive genetic testing vary greatly. Although some patients find the counseling they receive adequate and appropriate, others report feeling not fully informed of the purpose of a test or what information the test will provide. Prospective parents need to understand what testing is

appropriate for their situation, the risks and benefits of the testing and the implication of having a child with the condition being tested for. They also need to have an opportunity to consider whether they want to pursue testing and what they might do with the information obtained from testing.

Some observers have suggested that counseling include access to information from people living with genetic diseases and their families so that prospective parents may better understand the reality of having a child with the disease. Some believe that more widespread reproductive genetic testing means people with disabilities will be looked at as mistakes that could have been prevented through testing and society will reduce resources available for treatments, cures and support services.

Prenatal genetic screening and testing can occur as early as the first-trimester. Improving access to early prenatal care and encouraging women to pursue that care would increase the number of women who could consider earlier testing.

Option: Develop professional guidelines for appropriate delivery of reproductive genetic testing. Federal funding should be made available to professional societies to support this work.

Professional societies should develop comprehensive laboratory and clinical guidelines for the appropriate delivery of carrier testing, prenatal testing and PGD. Guidelines should be reviewed and updated regularly.

Guidelines should encourage providers to inform people about their risks and available testing including carrier testing **before** pregnancy, and encourage early prenatal care. Clear guidelines about appropriate indications for testing will not only help guide providers, it will help insurers make decisions about coverage.

Federal funding should be made available to professional societies to support this work.

Federal funding would help professional groups devote adequate resources to this process, particularly as many more tests become available. The federal health agencies fund extensive research that underlies the development of new genetic tests and have a responsibility to aid in the translation of these fruits of research into quality health care.

Arguments for:

- Professional guidelines that ensure the right patients are offered the right test at the right time with the right information will improve the quality of care that is delivered.
- Guidelines will help ensure that tests are offered appropriately and interpreted accurately.
- Professional guidelines can be revised in response to new scientific developments.
- Professional societies usually have regular communication with providers, optimizing chances for education and implementation among providers.
- Federal funding will help professional societies keep pace as many more tests become available.
- Clear guidelines will help prevent over-testing by providers who are concerned about liability and under-testing by providers who do not know about, or do not personally approve of, testing.

Arguments against:

- Guidelines are difficult, expensive and time-consuming to develop.
- Providers may disagree about appropriate testing guidelines, frustrating consensus.
- Given the many types of providers who may deliver this care, (obstetrician-gynecologists, family practice physicians, internists, nurse-midwives, nurse practitioners, geneticists and genetic counselors), individual professional societies may not be broadly-based enough to reach all those concerned.
- Providers benefit financially from testing so there is inherent conflict of interest when professional societies consider limit-setting.
- Guidelines alone will not result in a change in provider behavior. Providers must also accept the guidelines, be educated and trained in their use and use them consistently.
- Guidelines are voluntary. Providers are not compelled to comply.
- Guidelines may have the effect of limiting individuals' choices.
- Guidelines that recommend offering reproductive genetic testing for specific diseases may be perceived as making a value judgment about whether and what diseases should be avoided.
- Guidelines that recommend offering tests and counseling about reproductive genetic testing may be in conflict with the moral views of providers.

PRIVATE**Clinical Delivery****Option: Improve healthcare provider education about reproductive genetic testing.**

Providers, including obstetrician-gynecologists, family practice physicians, internists, nurse-midwives and nurse practitioners should be knowledgeable about reproductive genetic testing in order to counsel patients about the risks, benefits and implications of testing, and refer for genetic counseling when appropriate. This would ensure voluntary reproductive genetic testing with appropriate consent.

Arguments for:

- This approach will result in health care providers being better prepared to obtain a family history, assess risk and discuss reproductive genetic testing and reproductive options with patients before pregnancy.
- Better informed providers will lead to better-informed patients.
- An increase in genetic “literacy” among providers will lead to appropriate referrals to genetic counseling when necessary.

Arguments against:

- There are limited resources for genetic literacy training and maintaining up-to-date educational materials and guidelines.
- Given growing economic pressures, health care providers may simply not have adequate time to assess genetic risks and discuss reproductive genetic testing including carrier testing with their patients.
- Guidelines offering tests and counseling about reproductive genetic testing may be in conflict with the moral views of providers.

PRIVATE**Clinical Delivery****Option: Educate patients, especially those of reproductive age, about reproductive genetic testing.**

Professional societies, consumer and patient groups, government agencies and/or schools and universities could undertake a public education campaign to emphasize the benefit of pre-conception care that includes a family history, risk assessment, genetic counseling and offering carrier testing. In addition, every individual should know about the benefits of receiving the earliest possible prenatal care, which allows patients the most choices about early prenatal genetic screening and testing.

Arguments for:

- Giving information directly to consumers will increase number of people knowledgeable about reproductive genetic testing and allow them to make more educated choices.
- Better-informed consumers will create a demand for providers to provide quality counseling and care.
- This option is in keeping with trends towards patient self-education and autonomy in health care decision making.

Arguments against:

- Patient demand for counseling and testing may be so high as to strain the ability of providers to meet demand.
- Patient education alone is not enough. Providers must also be prepared to discuss, order and interpret genetic tests.
- Creating patient demand for carrier and early prenatal testing may lead to inappropriate testing and over-testing.

Option: Increase genetic counseling services and information before and during pregnancy.

Reproductive genetic tests provide information that is the basis for profound decisions. Yet patients often receive little guidance when deciding whether or not to pursue testing and are overwhelmed trying to make decisions based on test results once they are received.

Patients should have access to providers, including genetic counselors, who are trained to help people understand the tests and confront the decisions that could come from test results. Patients should also have information about the condition the test is for and what it means for affected individuals and their families medically, emotionally and financially. Improved insurance coverage of counseling services would also allow providers to ensure that patients understand the decisions they are making.

Some disability advocates believe that demand for prenatal testing and PGD would be reduced if prospective parents had more balanced information about the condition for which testing is being sought and the reality of caring for a child with the condition. Some have suggested that prospective parents should have the opportunity to meet with those living with the particular condition and their families. Patient advocacy organizations working on behalf of people with the condition could work with providers to facilitate such interactions.

Arguments for:

- Access to quality counseling will mean patients are better able to make fully informed decisions about carrier tests as well as prenatal screening and diagnostic tests.
- As more choices in genetic testing become available, more counseling is necessary to help patients understand the scope of choices before them and manage the anxiety that may come from “too much information.”
- Non-directive counseling by trained genetic counselors may alleviate the concerns that some patients have raised about feeling pressured either to agree to testing or to refuse it.
- Covering genetic counseling services will increase access to counseling from providers with the necessary training and expertise.
- More information about the condition being tested for could reassure parents, reducing the number of prospective parents seeking prenatal genetic testing, abortions and PGD.

Arguments against:

- Additional funding and other resources would be necessary to adequately train providers to do genetic counseling or to increase the number of certified genetic counselors.
- As more tests become available to more people for many more diseases, it may be impossible to adequately counsel every patient about every test being offered.
- If done incorrectly, counseling may be perceived as pressure to agree to testing.
- “Non-directive” genetic counseling may be problematic because it does not prevent patients from making decisions that may be viewed as unethical by some.

Accuracy and Safety of Reproductive Genetic Testing

The accuracy and safety of reproductive genetic testing is of the utmost importance. The information tests provide is the basis for profound decisions about when, whether and how to bear children.

As is the case with most medical tests and procedures, no reproductive genetic test or procedure can be

100 percent accurate. There will always be some false positive and false negative results, whether due to inherent problems with the test, errors in the performance of the test or problems in interpretation. False positive results can lead to significant anxiety for the patient, the need for more testing and potentially the termination of healthy pregnancies. False negative results can result in the unexpected birth of affected children.

Government oversight in this area is limited and fragmented. There is no government review of the analytic or clinical validity, or clinical utility, of a genetic test before it is marketed. FDA has a small role, as does CMS through CLIA. Without any central and comprehensive oversight, many if not most aspects of genetic testing occur without any government monitoring.

| GOVERNMENTAL | Accuracy & Safety | |
|--|--|---|
| <p>Option: Increase federal oversight of genetic testing.</p> <p>FDA, CMS (through CLIA) and/or CDC should ensure that tests are approved before becoming available, laboratories performing reproductive genetic testing are certified and competent to perform the tests at issue, procedures related to testing are competently performed and data are collected to assess how well these tests and procedures are performed.</p> <p>These agencies have played a limited role in the past. They may have the authority currently to expand their role. In addition, Congress could pass legislation delegating to these federal agencies the authority to:</p> <ul style="list-style-type: none"> • License and inspect facilities involved with genetic testing including laboratories and clinics providing PGD and IVF. • Establish analytic and clinical validity and possibly clinical utility before tests get to market. • Regulate and monitor how test results are reported to providers and patients. • Collect data on test performance, accuracy and reliability of testing, safety of prenatal procedures (amniocentesis, CVS), and health outcomes of children born following PGD. • Ensure patients are giving informed consent. <p>These agencies could also take on the role of overseeing the ethical use of reproductive genetic testing.</p> | <p>Arguments for:</p> <ul style="list-style-type: none"> • Federal agencies have expertise in oversight and could significantly improve the accuracy and safety of reproductive genetic testing. • This approach gives clear authority for the federal government to take the lead. • Federal oversight will create greater confidence in genetic testing. • The legislative process to extend federal oversight will stimulate a productive public discussion about how to effectively oversee genetic testing. • This approach will allow monitoring of the impact of genetic testing on individuals, families and society. • The data collected by the government will inform future policymaking. | <p>Arguments against:</p> <ul style="list-style-type: none"> • It may be difficult to create the political will or consensus to increase oversight of the accuracy and safety of genetic testing. • It is difficult to create stable, effective and non-partisan oversight. For example, if testing cannot occur without licensing or approval by a single government authority, lawmakers who disagree with an agency's decisions could effectively halt agency actions by denying the agency funding. • Increased oversight will affect access. In general, more scrutiny will mean restricted or delayed availability and increased costs. • Authorizing a federal agency to determine clinical utility will be controversial, as the determination of whether a test provides useful information depends on an individual's situation, perspective and values. These decisions should be left to providers and patients. • Federal oversight will give explicit government approval to practices that many people reject. |

Option: Increase role of state governments

The activities, authority and responsibilities of state entities such as public health agencies vary from state to state. In general, all endeavor to influence public health policy and practice. They promote health by tracking and monitoring disease, promoting disease prevention, screening newborns, regulating laboratories, licensing health care providers and delivering basic health services.

It is difficult to create a uniform policy approach for state public health agencies because, statutorily and bureaucratically, they take so many different forms. Nonetheless, each state could take its basic charge to protect the public health and apply it to improving the safety and accuracy of reproductive genetic testing.

Some states already have programs in place that oversee reproductive genetic testing. For example:

- Washington and New York states certify laboratories performing testing and the oversight is extensive enough that laboratories passing the state requirements are deemed CLIA compliant.
- In New York state, the oversight of the tests is analyte and test specific, making for more robust oversight.
- California oversees the state maternal serum screening program. Women who are at high risk based on the screening test results are offered follow-up services including genetic counseling, ultrasound and amniocentesis. Participation in the screening, testing and follow-up services is voluntary. State approval is needed for a laboratory or diagnostic center to participate in this program. Nearly every laboratory or center in the state meets the state standards, and the overall quality of care in the state has improved as a result.

Arguments for:

- State initiatives may be more politically feasible when a national approach proves too difficult.
- A state-by-state approach allows additional flexibility depending on the needs and resources of the state.
- State approaches are often testing grounds for systems that may later be adopted nationally.

Arguments against:

- A state-by-state approach means that safety and accuracy may vary depending solely on where the patient lives.
- State public health agencies already are stretched thin and would be hard pressed to find additional resources and develop new expertise to address new fields.

PRIVATE**Accuracy & Safety****Option: Develop professional guidelines to improve accuracy and safety of reproductive genetic testing.**

Professional societies could develop guidelines for laboratories and health care providers addressing the performance of reproductive genetic testing and the delivery of test results. Guidance could include information about how, when and for whom to order specific tests and how to interpret results. Guidelines for laboratory directors and technicians could address best laboratory practices.

Federal funding should support guideline development in order to help professional societies keep pace as many more tests become available.

Arguments for:

- Guidelines help ensure that patients are appropriately informed, tests are administered and interpreted accurately and the test results are useful.
- Professional guidelines are more easily developed and more easily revised in response to new scientific developments than legislation or regulation by agencies.
- Federal funding will provide the resources necessary for this process, particularly as many more tests become available.
- Clear guidelines provide the guidance needed to prevent over-testing by providers concerned about liability.

Arguments against:

- Providers may disagree about testing guidelines, frustrating consensus.
- Providers benefit financially from testing so there is inherent conflict of interest when professional societies consider limit-setting.
- Guidelines alone will not result in a change in behavior. Laboratories and providers must also accept the guidelines, be educated and trained in their use and use them consistently.
- Guidelines are voluntary. Providers and laboratories are not compelled to comply.
- It is difficult for professional groups to devote adequate resources to this process, particularly as many more tests become available.
- Guidelines that recommend offering tests and counseling may be in conflict with moral views of providers.

Option: Establish professional certification programs for proficiency in reproductive genetic testing.

In addition to creating voluntary guidelines for reproductive genetic testing, professional organizations could establish certification programs for providers and others involved in reproductive genetic testing (physicians, geneticists, counselors, embryologists, technicians) similar to the specialty boards that currently certify physicians in different practice areas.

Although such certification may be voluntary, once established it often becomes self-enforcing: in many cases insurers will not reimburse for services provided by non-certified providers or laboratories, and patients know to look for certified care. In addition, state licensing boards may use such certification in their own licensing or approval determinations.

There are a number of entities whose expertise could contribute to a professional certification system for reproductive genetic testing. The American Board of Medical Genetics (ABMG), the American Board of Obstetrics and Gynecology (ABOG), and the American Board of Genetic Counselors (ABGC) are among those whose certification encompasses specialists most likely to be involved with reproductive genetic testing. Other medical and nursing boards could also contribute.

Other programs certify laboratory personnel. The American Association of Bioanalysts (AAB) maintains a Board of Registry, the primary purpose of which is to identify laboratory specialists who meet minimum standards. The American College of Medical Genetics (ACMG) in conjunction with the College of American Pathologists (CAP) runs voluntary programs certifying laboratories in a range of areas, and has developed some standards and guidelines for clinical genetics laboratories working in reproductive genetics, although no guidelines bear specifically on PGD.

Individual organizations could develop their own certification programs or several could collaborate in a comprehensive certification system that draws on several areas of expertise.

Arguments for:

- Certification of personnel will improve the quality of services by establishing training criteria and requiring a demonstration of competency.
- Certification developed jointly by relevant organizations will have the benefit of combining multiple areas of expertise to set high standards for clinical and laboratory services.
- Certification developed and implemented through professional organizations will be especially responsive to developments in science and technology.

Arguments against:

- Because there are many kinds of providers and laboratory personnel involved in reproductive genetic testing, developing a comprehensive certification system that draws on the expertise of several professional organizations will be challenging.
- Certification requirements have often functioned to limit competition, suppress innovation and increase costs.
- Private sector certification will be used as an argument to delay or eliminate federal oversight.

Access to Reproductive Genetic Testing

For many people, the cost of reproductive genetic testing and the uncertainty of insurance coverage means they are not offered reproductive genetic testing or do not receive testing services at the appropriate time. In addition, some people refuse reproductive genetic testing because they fear the consequences of insurers having information about their child's genetic makeup before birth.

It is difficult to determine, based on available information, whether and to what extent insurers cover genetic counseling, carrier testing, prenatal screening and testing and PGD. In general, most insurers cover testing they consider "medically necessary," a concept that some plans define clearly and others do not. There is a strong element of subjectivity to the determination of medical necessity. Insurers generally prefer to wait for strong evidence of clinical validity, utility and cost-effectiveness.

A complicated regulatory scheme limits the impact of state and federal insurance laws on insurance coverage of specific services. Governmental mandates are typically needed to reach all insured individuals. But, under federal law (ERISA), employee health benefit packages in which the employer bears some or all of the risks of paying for the costs of care are exempt from state insurance mandates. Thus, even if a state law required coverage of reproductive genetic testing, people in employer-sponsored plans would not be guaranteed this particular benefit. Approximately 61 million Americans are in employer-sponsored plans that

are exempt from state mandates.

There could be pressure on insurers not to pay for some forms of reproductive genetic testing given the moral issues involved. And from a health policy standpoint, there could be an argument made that there are many other health care needs that should be covered first before the newest reproductive genetic test.

Medicaid

Medicaid pays for medical assistance for individuals and families with low incomes. It is jointly funded by the federal government and state governments. Federal law determines the minimum standards that state Medicaid programs must meet to receive federal funds. Beyond that, each state determines the benefits included in its program.

Because Medicaid benefits vary by state (within certain federal guidelines), it is difficult to know how many states cover reproductive genetic services. In the 1990s, several surveys found that amniocentesis was widely covered.

Medicaid eligibility rules may present a barrier to coverage of reproductive genetic testing. While the program is designed to provide services to low-income pregnant women, children and families, in many cases, a woman is not eligible for Medicaid until she is pregnant. Thus, Medicaid coverage may not be available for her to obtain counseling or carrier testing pre-pregnancy. Eligibility rules may also affect access to prenatal testing. Because most women are not eligible for Medicaid before pregnancy, if a woman does not know she is pregnant, or does not apply for Medicaid until she is

well into her pregnancy, she will miss the opportunity to have some of the earlier prenatal tests.

Medicaid Managed Care, which enrolls Medicaid recipients in managed care plans, also plays a role in how care is delivered to the Medicaid population. While it is difficult to know for sure, Medicaid Managed Care probably provides greater coverage for carrier testing and prenatal testing when they are covered in the general Managed Care plan (Medicaid and non-Medicaid). A survey of state Medicaid directors would be needed to know the extent of Medicaid and Medicaid Managed Care coverage of reproductive genetic testing.

Medicaid's policy towards abortion is restrictive. Federal Medicaid funds may not be used to pay for abortions except those necessary to save the life of the mother or in cases of rape and incest. Some states provide state funds to pay for abortions for Medicaid recipients.

A related federal program is State Children's Health Insurance Program (SCHIP). This program allows states to offer health insurance for children, up to age 19, who are not already insured. SCHIP is a state administered program and each state sets its own guidelines regarding eligibility and services within certain federal restrictions.

Medicare is commonly known as the national health insurance program for people over 65 years of age, but it also provides coverage for some people under 65 with disabilities. SCHIP and Medicare each reach some women who are of reproductive age or already pregnant.

Option: Enact federal and/or state laws to prohibit genetic discrimination.

Legislation to prevent the misuse of genetic information by employers and insurers would reassure parents who turn down testing, because they fear that the information from testing will be used against their child in the future.

Arguments for:

- Laws against genetic discrimination will ease prospective parents' fears that reproductive genetic test results will be used against them or their child in insurance or employment decisions.
- Such laws will eliminate one barrier to accessing reproductive genetic testing.

Arguments against:

- There is little documented evidence that insurers or employers are using genetic information in a discriminatory manner.
- Legislation in this area will create burdens for insurers and employers and increase costs.
- Genetic information should not be treated differently from other medical information.
- Creating legislative protections specifically for genetic information will increase the stigma associated with genetic testing.

Option: Require private insurance coverage of reproductive genetic testing consistent with recommendations by qualified professional groups.

Federal and/or state legislation could mandate coverage of reproductive genetic testing by private insurers. There is precedent for such an approach in federal and state laws requiring coverage of particular benefits. By following professional societies' guidelines on genetic counseling, carrier testing, prenatal screening and testing and PGD, insurers will make coverage decisions consistent with quality health care.

Arguments for:

- Increasing access to reproductive genetic testing makes good public health sense, giving people information about their risk of having a child with a genetic disease.
- Insurance companies typically weigh professional guidelines heavily in determining coverage of testing. This option would create additional stimulus to adopt coverage policies consistent with guidelines.

Arguments against:

- Expanded coverage could raise premiums for everyone as a result.
- There are a lack of sufficient data on cost-effectiveness of testing to conclude that insurance companies should cover such testing.
- This approach may create new problems. Insurance companies could use the results of testing individuals to discriminate, raising premiums or denying coverage to individuals based on their genes, unless laws are enacted to prevent access to and use of this information.
- Professional guidelines are often slow in development and address only a small subset of the tests available. In practice, this approach may mean that insurance companies will cover only a few tests, reducing access to those tests less commonly used or recommended.
- People object to some testing, particularly prenatal testing and diagnosis and PGD, on a range of ethical grounds. Mandating coverage treats them as universally accepted.

GOVERNMENTAL

Access

Option: Require public programs to cover reproductive genetic testing consistent with recommendations of qualified professional groups.

Congress could require Medicaid (as well as SCHIP and Medicare, where applicable) to cover testing recommended by professional groups' guidelines. Medicaid is discussed in more detail below. There is precedent for such an approach in federal laws requiring public payors' coverage of particular benefits. By following professional societies' guidelines on genetic counseling, carrier testing, prenatal screening and testing, and PGD, these programs will provide quality care to enrollees.

In addition, the federal government, the nation's largest employer, has significant direct regulatory control over the Federal Employee Health Benefit Plan (FEHBP). FEHBP provides health insurance to more than eight million federal enrollees and their dependents, including approximately 1.2 million women of childbearing age. Congress could require FEHBP plans to cover testing recommended by professional groups' guidelines.

Public programs often drive private insurance generally, and could lead to reforms throughout the private insurance market.

Arguments for:

- Increasing access to reproductive genetic testing makes good public health sense, giving people information about their risk of having a child with a genetic disease.
- Insurance companies and other payors typically weigh professional guidelines heavily in determining coverage of testing. This option would formalize that process for public programs.
- This approach provides a strong incentive for insurers and providers to work together to improve the proper use of reproductive genetic testing.

Arguments against:

- People object to some testing, particularly prenatal screening and testing and PGD, on a range of ethical grounds. Mandating coverage and using federal funds to pay for tests treats them as universally accepted.
- Such a mandate may raise the cost of public programs to taxpayers. There are a lack of sufficient data on cost-effectiveness of testing to know the financial impact of mandating test coverage.
- Professional guidelines are often slow in development and address only a small sample of the tests available. In practice, this approach may mean that federal programs will cover only a few tests, reducing access to those tests that are less commonly used or recommended.

Option: Expand Medicaid eligibility and outreach to give low-income women better access to reproductive genetic testing.

Many women are not eligible for Medicaid until after they become pregnant. As a result, many low-income women do not have access to pre-conception genetic counseling and carrier screening to inform reproductive decision making. In addition, many may not receive early prenatal care including genetic counseling and prenatal screening and testing because they do not know that they are eligible for Medicaid until after the pregnancy is well underway.

Expanding Medicaid to allow access to pre-conception counseling and carrier testing and better patient education about reproductive genetic testing would give low-income women better information about their level of risk, their pregnancies and their testing options. With additional resources, federal and state governments could also make PGD available to Medicaid recipients.

Arguments for:

- Allowing low-income women the opportunity to make fully informed reproductive decisions with better access to reproductive genetic testing makes good public health sense, giving people information about their risk of having a child with a genetic disease.
- Genetic counseling and carrier testing before pregnancy allows better prenatal care by alerting providers and patients to the possibility of a high-risk pregnancy that may be better monitored and followed.
- PGD services provide an important benefit for Medicaid recipients by increasing their chance of having healthy children free of genetic disease.

Arguments against:

- Expanding Medicaid eligibility will increase costs, requiring additional state and/or federal funding.
- People object to prenatal screening and testing on a range of ethical grounds. Mandating coverage and using federal funds to pay for tests treats them as universally accepted.
- Such changes may raise the costs of public programs to taxpayers. There are a lack of sufficient data on cost-effectiveness of testing to know the financial impact of covering these tests.
- Medicaid reform should focus on providing basic preventive care, diagnosis and treatment to patients, not on providing every possible technology, especially when it is relatively untested and very expensive.
- Few Medicaid patients will pursue PGD. Creating a mandate is thus a solution without a problem.

PRIVATE**Access****Option: Use employer purchasing power.**

Employers could ensure access to reproductive genetic testing by making sure those benefits are included in their employee benefit plans.

Large employers spend significant money on purchasing health care for their employees. Smaller employers often work through purchasing coalitions, which are groups of employers who use their collective leverage in purchasing health care for their employees. Together, these employers determine the health benefits that will be made available to the millions of Americans who depend upon their employer for health insurance, and influence the benefits insurers offer more generally.

Employers make purchasing decisions based primarily on an analysis of what benefits they think will result in a more productive workforce (e.g., fewer sick days, greater efficiency at work). If reproductive genetic testing is shown to increase productivity, the end result would be cost savings to employers.

Arguments for:

- This non-governmental solution avoids the challenge of passing new laws for insurance mandates.
- This approach allows employers to determine what is best for a specific workforce population.

Arguments against:

- Most employers do not have enough purchasing power to make tailored purchasing decisions. They make decisions based on what the market offers them, which may or may not conform to their notion of what benefits are best for their employees.
- It is difficult to quantify the costs and benefits of reproductive genetic testing in the short term, which is the time frame that employers must consider given the short time most people stay in a job.

PRIVATE**Access****Option: Coordinate and improve insurers' research into coverage decisions.**

Insurers and other payors typically rely on a range of information including technology assessments and cost-benefit analyses to make decisions about coverage of new technologies such as reproductive genetic testing.

Insurers could coordinate this research by creating a task force or other independent entity to look at these issues. This approach could create more consistency and predictability in coverage of genetic counseling, carrier testing, prenatal genetic screening and diagnosis and PGD.

Arguments for:

- Coordination among payors will allow companies to share information about cost-effectiveness and health impacts of various coverage decisions.
- More consistent policies create predictability and less anxiety for patients wondering if their insurance will cover a particular test or procedure.

Arguments against:

- Most payors are for-profit entities competing with each other. They will be reluctant to collaborate with their competitors in such research.
- Often coverage policies are made in response to individual cases, making industry-wide consistency difficult.

Option: Provide financial assistance for PGD through IVF clinics.

IVF clinics and PGD providers and laboratories could offer financial assistance directly to prospective parents seeking PGD.

Due to the high cost associated with assisted reproductive technologies, some IVF programs offer IVF on a “shared-risk,” “warranty,” “refund” or “outcome” basis. Shared-risk plans operate by refunding a portion of the fee paid for one or more IVF cycles in the event that they do not result in a pregnancy or live birth of a child. Typically, shared-risk patients pay a higher fee than other IVF patients and, in return, receive a refund of 70 to 100 percent of this fee if treatment fails. Accordingly, someone who succeeds in having a baby may pay more under the shared-risk plan than she would have under a traditional fee-for-service plan. However, this option helps ensure that unsuccessful couples will have the financial resources to pursue other options for starting a family.

In addition, many fertility clinics offer IVF at a reduced price to patients who provide their eggs to other patients, although some critics say this practice is coercive and creates psychological issues for some patients.

Clinics or laboratories could also offer discounts or payment plans for families who could not otherwise afford PGD. For example, a clinic could offer discounted IVF services if PGD is included.

Arguments for:

- Discounts and shared costs will give people access to PGD and IVF services that otherwise would be out of reach.

Arguments against:

- Because the market for PGD is significantly smaller than the IVF market, and will continue to be for some time, clinics may not want to offer discounts on PGD services.
- Critics find some financial assistance programs coercive because they create strong incentives for patients to donate eggs or embryos.

What More do We Need to Know?

While it is sometimes fashionable in science and policy to opine that “more research is needed,” in the case of reproductive genetic testing, critical data are truly needed to develop effective, appropriately tailored and evidence-based policy.

One key question for each technology we have discussed is how many people are currently using it or are likely to adopt it in the future. Defining the size of the likely population of users is critical because it informs the type of policy approach to apply.

Another important data question is how these technologies are being delivered to patients and what barriers to access are encountered by those for whom they might be beneficial. These questions include (1) how many people are being offered testing, how many accept or reject it and the reasons for their decisions, (2) whether carrier testing is offered preconception or post-conception and what factors influence the timing of testing, (3) whether pregnant patients receive information about options for prenatal screening and testing early enough in the pregnancy to make fully informed choices, (4) whether and under what circumstances these technologies are covered by insurance and how that influences access, and (5) for what purposes these technologies are being offered and used.

Also of great importance is obtaining more information about the safety and accuracy of these technologies. This information is particularly difficult to obtain, since these technologies are regulated

in a piecemeal and decentralized way. Tests and procedures are typically delivered as part of the practice of medicine, rather than in a research context. Nevertheless, effective policymaking requires accurate information concerning the outcomes of using these technologies. For example, how often do genetic tests lead to false negative or false positive results? How often are results of these tests misreported, and what is the result of such inaccurate information being transmitted? What is the benefit of using certain tests and is such benefit adequately considered before they are introduced clinically?

PGD, the newest technology, raises some specific questions. There are incomplete and conflicting data on the long-term health effects of IVF for women and children and no systematic studies on the health and developmental outcomes for children born following PGD. Does the embryo biopsy process damage embryos in a way that decreases their viability or injures the resulting child? How often does PGD fail to detect a genetic mutation? Does aneuploidy screening improve IVF results?

Many questions have been raised about the potential societal impact of reproductive genetic testing, but little information exists in this area. In particular, what impact does increased testing have on family relationships, particularly between parents and children? In addition, disability advocates have raised questions about whether, in a society where genetic diseases can be avoided, resources will be provided to those already living

with disabilities, including both support services and funding for research to develop treatments. Some also question whether society’s perception of people with disabilities will become more negative.

Many questions exist about the extent to which insurance companies cover reproductive genetic testing. It would also be useful to know how state Medicaid directors have handled new reproductive genetic technologies and how Medicaid Managed Care may have affected access by Medicaid recipients.

Any proposal for research begs the question of who will do it and who will fund it. In order to collect such a vast array of data, a number of different reporting mechanisms may need to be established.

As we have described in earlier chapters, some reporting systems, such as the FCSRA-mandated IVF reporting requirements and the PRAMS program, are already in place. Current IVF reporting to the CDC mandated by FCSRA does not include data on whether PGD was used, but this information could be added. PRAMS collects state-specific, population-based data on maternal attitudes and experiences prior to, during and immediately following pregnancy. Currently, almost no information gathered relates to carrier testing, prenatal screening or prenatal testing. These questions could easily be added to the questionnaire.

Establishing a patient registry would allow data collection on the long-term health of children born after PGD. ESHRE, a PGD

professional society based in Europe, has established such a registry. In the U.S., longitudinal studies of women who have undergone IVF and children born following IVF and PGD would provide valuable information about the safety and risks of IVF and embryo biopsy.

Although it is challenging to study the societal impact of reproductive genetic testing, research could track changes in resources available for the disabled and in societal perceptions over time. In addition, a survey of private and public insurers would provide additional insight into the access questions raised in this report.

For laboratory and clinical research that involves embryos, funding from the federal government is restricted by the 1996 Congressional ban that prohibits federal funding of research in which human embryos are created, or subjected to greater risk than that permitted for a fetus in utero. However, notwithstanding the ban, research to answer many questions concerning reproductive genetic testing would not involve the creation, destruction or harm of embryos and thus would not be subject to the federal ban. In addition, the federal ban in no way restricts the private sector, including both industry and non-profit foundations and advocacy groups, from funding research involving human embryos that could help assess and improve techniques. Research sponsors, either individually or collaboratively, could establish a common set of research priorities, ethical standards for research and data collection and distribution requirements.

Finally, we note that constructing policy that is responsive to and reflective of the public's mores and preferences requires a more detailed understanding of informed public attitudes toward this new technology. One option is to use public or private resources to increase societal discussion about reproductive genetic testing. In particular, increasing the input of key stakeholders, including patients who have chosen to use or reject reproductive genetic testing, providers and advocates, could provide valuable perspective to any entity or individual considering limits on reproductive genetic testing.

Table of Abbreviations

ACMG

American College of Medical Genetics

ACOG

American College of Obstetricians and Gynecologists

ART

assisted reproductive technology

ASR

analyte specific reagent

ASRM

American Society for Reproductive Medicine

CAP

College of American Pathologists

CDC

Centers for Disease Control and Prevention

CF

cystic fibrosis

CLIA

Clinical Laboratory Improvement Amendments

CLIAC

Clinical Laboratory Improvement Advisory Committee

CMS

Centers for Medicare and Medicaid Services

CVS

chorionic villus sampling

DOE

Department of Energy

DNA

deoxyribonucleic acid

ERISA

Employee Retirement Income Security Act

ESHRE

European Society for Human Reproduction and Embryology

FCSRA

Fertility Clinic Success Rate and Certification Act

FDA

Food and Drug Administration

FD&C Act

Federal Food, Drug and Cosmetic Act

FEHBP

Federal Employee Health Benefit Plan

HHS

Department of Health and Human Services

HMO

health maintenance organization

IRB

institutional review board

IVD

in vitro diagnostic device

IVF

in vitro fertilization

NIH

National Institutes of Health

PCB

President's Council on Bioethics

PCR

polymerase chain reaction

PGD

prenatal genetic diagnosis

PGDIS

Prenatal Genetic Diagnosis International Society

PRAMS

Pregnancy Risk Assessment Monitoring System

RNA

ribonucleic acid

SACGHS

Secretary's Advisory Committee on Genetics, Health, and Society

SACGT

Secretary's Advisory Committee on Genetic Testing

SART

Society for Assisted Reproductive Technologies