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What Potent Blood: Non-Invasive Prenatal Genetic Diagnosis and the Transformation of Modern Prenatal Care

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What potent blood hath modest May,
What fiery force the earth renews,
The wealth of forms, the flush of hues . . . .

—Ralph Waldo Emerson[1]

I. INTRODUCTION

Someday soon, virtually any pregnant woman[2] will be able to learn — with 98-99% accuracy — whether her fetus has contracted a serious genetic disorder by undergoing nothing more than an inexpensive, non-invasive blood test. For years, scientists have sought a method of prenatal testing that could boast both high levels of accuracy and low levels of risk. The most promising solution lies in an exciting recent discovery: tiny quantities of fetal cells and DNA cross over into the mother's bloodstream during pregnancy.[3] If the fetal genetic material can be successfully isolated from the maternal blood, it can be used to diagnose a number of genetic disorders, such as Down Syndrome, cystic fibrosis, Tay-Sachs disease, and sickle cell anemia. Indeed, researchers have spent the last decade developing ways to accomplish this.

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[1] Ralph Waldo Emerson, May Day (1867).

[2] Hereinafter also referred to as "mothers."

[3] *See, e.g.*, Y. M. Lo et al., *Presence of Fetal DNA in Maternal Plasma and Serum*, 350 Lancet 485, 485-487 (1997); Lee P. Shulman, *Fetal Cells in Maternal Blood*, 3 Current Women's Health Reps. 47, 47 (2003).

These new blood tests promise significant advantages over present methods of prenatal testing. Unlike current prenatal screening tests, like ultrasound and chemical assays, this new technology could attain extremely high levels of accuracy and be performed as early as 6-10 weeks' gestation.[4] Unlike current prenatal diagnostic tests, like amniocentesis and chorionic villus sampling ("CVS"), the new genetic tests would be non-invasive; as such, they would pose no risk of miscarriage and could be offered to women of all ages and risk levels.[5]

This article introduces the emerging technology of non-invasive prenatal genetic diagnosis ("NPGD") and argues for its impending potential to revolutionize modern prenatal care. In particular, clinical implementation of NPGD — which is non-invasive, accurate, and inexpensive — could dramatically increase the availability of prenatal genetic testing to all pregnant women, change the standard of care, reduce the incidence of serious genetic disorders, and raise (with even greater force and urgency than past advancements in genetics) numerous ethical, legal, and social questions.

Part II offers a brief overview of the two modern methods of prenatal genetic diagnosis:[6] amniocentesis and CVS, both of which are considered "invasive" procedures and pose some risk to both the mother and the developing fetus. Part III explains the science behind two potential non-invasive alternatives for prenatal genetic testing, which I call "maternal serum fetal cell sorting" ("MSFCS") and "maternal plasma DNA recovery" ("MPFDR"). Although clinical implementation of these tests is still years away, scientists expect them to offer high levels of accuracy, early intervention options, and significantly lower prices and costs. Part IV proceeds from the assumption that researchers will successfully develop a highly accurate, clinical version of NPGD and attempts to explain some of the initial legal and social implications, including: NPGD's likely effect of dramatically increasing the number of pregnant women who utilize prenatal genetic testing, its capability of becoming the new standard of care, and its potential to garner both public and private funding through insurance. Finally, Part V discusses several long-term consequences of the likely widespread use of NPGD.

II. PRENATAL GENETIC DIAGNOSIS TODAY

Today, what is termed "prenatal testing" can involve both *screening* and *diagnostic* tests. Screening tests impose a lower threshold of accuracy and merely help identify an at-risk population for additional testing, while

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[4] Rossa W. K. Chiu & Y. M. Lo, *The Biology and Diagnostic Applications of Fetal DNA and RNA in Maternal Plasma*, 61 Current Topics in Developmental Biology 81, 84 (2004) (noting that fetal genetic material can be "reliably detected" as early as 5 weeks' gestation).

[5] Lynn B. Jorde et al., Medical Genetics 282 (2d ed. 1999).

[6] I use the terms "prenatal *genetic* diagnosis" and "prenatal *genetic* testing" to distinguish from other prenatal procedures that do not directly analyze the fetus's genetic material.

diagnostic tests are held to stringent accuracy standards (on the order of 98-99% accuracy) and result in a conclusion regarding the fetus's disease status.[7]

Many women who undergo prenatal genetic testing begin with a screening test. The most common screening tests include: (1) the maternal serum α-fetoprotein ("MSAFP") assay, a maternal blood test measuring levels of α-fetoprotein, which are considerably higher in cases of Down Syndrome;[8] (2) the "multiple-" or "triple-marker" screen, which measures maternal blood concentrations of α-fetoprotein, as well as two other chemicals associated with chromosomal abnormalities;[9] and (3) ultrasonography, which is used to screen for physical abnormalities (e.g. shortened or missing fetal limbs) and to assess the likelihood of chromosomal defects like Down Syndrome (e.g. by examining "nuchal lucency," the thickness of the skin at the back of the fetal neck).[10] It is important to note that such screening tests are non-invasive (i.e. do not involve entry into the mother's uterus) and do not actually sample fetal genetic material.

If a screening test suggests elevated risks — or for other women who are known to be at elevated risks because of their age or genetic history — a diagnostic test is used to determine with greater certainty whether the fetus has a genetic or chromosomal condition. The two principal diagnostic tests used are: (1) amniocentesis and (2) CVS.[11] Although these tests achieve a very high level of precision (about 99% diagnostic accuracy),[12] both have notable drawbacks. Amniocentesis and CVS are invasive procedures, entailing the use of a needle or catheter to enter the mother's uterus and obtain a sample of fetal tissue.[13] As a result, both tests also involve a small, but significant, risk to the mother and the fetus.

Amniocentesis, which is typically conducted at 15 to 17 weeks' gestation, recovers a sample of fluid from the amniotic sac by means of a needle inserted through the abdomen and guided by real-time ultrasound.[14] The resulting twenty to thirty milliliter sample of amniotic fluid will contain a notable concentration of living cells that have been sloughed off by the fetus.[15] Clinicians then analyze DNA recovered from these cells to diagnose particular genetic conditions. Test results may take up to three weeks to receive, depending upon the particular method used for DNA analysis.[16] The three

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[7] Jorde et al., *supra* note 5, at 275; Telephone Interview with Dr. Jane Chueh, Clinical Associate Professor, Obstetrics & Gynecology, Stanford Univ. Sch. of Med. (May 9, 2005).

[8] *See* Am. C. of Obstetricians & Gynecologists, ACOG Practice Bulletin No. 27: Prenatal Diagnosis of Fetal Chromosomal Abnormalities, at 2 (May 2001) [hereinafter ACOG Practice Bulletin No. 27].

[9] *See id.* at 2-3; U.S. Preventative Services Task Force, U.S. Dep't of Health and Human Services, Guide to Clinical Preventative Services, Section 1: Screening: Congenital Disorders: *Screening for Down Syndrome* (2d ed. 1996), *available at* http://www.ahrq.gov/clinic/2ndcps/downsyn.pdf.

[10] *See* ACOG Practice Bulletin No. 27, *supra* note 8, at 3-4 (describing ultrasound screening for anatomic indicators of aneuploidy, i.e. an abnormal number of chromosomes).

[11] Jorde et al., *supra* note 5, at 275.

[12] ACOG Practice Bulletin No. 27, *supra* note 8, at 5.

[13] *See* Jorde et al., *supra* note 5, at 275-78.

[14] *Id.* at 275-76.

[15] *Id.* at 276.

[16] *Id.* Karyotyping is especially time-intensive, taking as many as three weeks to complete. Thus, researchers are investigating a switch to molecular methods of analysis, like

primary methods are:[17] (1) karyotyping, which reveals chromosomal abnormalities;[18] (2) fluorescent in-situ hybridization ("FISH"), which is employed to diagnose both chromosomal and single-gene abnormalities;[19] and (3) polymerase chain reaction ("PCR"), which is usually used to diagnose single-gene disorders.[20] Because these methods are common to *all* types of fetal genetic diagnosis — whether the sample is obtained by amniocentesis, by CVS, or by non-invasive means — they are worth describing briefly here.

Karyotyping — a physical, as opposed to molecular, type of analysis — is the most commonly used method today.[21] It involves: (1) culturing ("feeding" and growing) the sample cells, (2) "arresting" cell division at the stage where chromosomes are most clearly visible, (3) staining and photographing the chromosomes, and (4) arranging the chromosomes in corresponding pairs according to function and size.[22] With a full "map" of genetic material, clinicians can determine whether the fetus's chromosomes exist in the correct number, shape, and size.[23] An abnormal number of certain chromosomes indicates a genetic disorder, such as Down Syndrome (3 copies of chromosome 21).[24] Karyotyping typically takes 10-12 days, but may take up to 3 weeks because of the extra time required to culture the cells from the sample.[25]

In contrast, FISH and PCR, the two "molecular" methods of analysis, take considerably less time (only about 2-3 days) to complete.[26] In FISH, a segment of DNA coding for a specific chromosome (usually X, Y, 13, 18, or 21)

FISH and PCR. *See* G.M. Grimshaw et al., Nat'l Coordinating Center for Health Tech. Assessment, U.K., Evaluation of Molecular Tests for Prenatal Diagnosis of Chromosome Abnormalities, at iii (2003), *available at* http://www.hta.nhsweb.nhs.uk/fullmono/mon710.pdf.

[17] *See* Sinuhe Hahn & Wolfgang Holzgreve, *Prenatal Diagnosis Using Fetal Cells and Cell-Free Fetal DNA in Maternal Blood: What is Currently Feasible?*, 45 Clinical Obstetrics & Gynecology 649, 649 (2002).

[18] *Karyotype Test* (May 26, 2005), http://my.webmd.com/hw/being_pregnant/hw6392.asp.

[19] *See Fluorescent IN SITU Hybridization (FISH)* (Aug. 21, 2004), http://members.aol.com/chrominfo/fishinfo.htm.

[20] Single-gene disorders are conditions arising from a mutation on a particular *gene* on one particular chromosome. They may be distinguished from chromosomal abnormalities, which arise when the fetus inherits too many or too few *full chromosomes*. Although amniocentesis and CVS are most frequently used to diagnose chromosomal abnormalities like trisomy-21 (Down Syndrome), trisomy-18, trisomy-13, Turner Syndrome (XO), and related conditions, they can be also used to detect a much wider array of conditions, for which scientists have developed relatively reliable genetic tests. Jorde et al., *supra* note 5, at 277. Examples include sickle cell disease, hemophilia, cystic fibrosis, and Tay-Sachs disease. *Id.*

[21] *See, e.g.*, Hahn & Holzgreve, *supra* note 16, at 652 ("[T]he metaphase karyotype has remained the gold standard for cytogenic analysis, which can of course be achieved only by the examination of a large number of rapidly dividing cells.").

[22] *See Lab VI Cytogenics: Human Karyotyping* (Sept. 25, 2001), http://academic.bowdoin.edu/courses/f01/bio212/dissemination/labIVkaryotyping.pdf; *Medical Encyclopedia: Karyotyping* (Jan. 11, 2007), http://www.nlm.nih.gov/medlineplus/ency/article/003935.htm.

[23] *See Karyotype Test*, *supra* note 18; *Lab VI Cytogenics: Human Karyotyping*, *supra* note 22.

[24] *See* Grimshaw et al., supra note 16, at 1.

[25] Jorde et al., *supra* note 7; Grimshaw et al., *supra* note 16, at iii.

[26] Grimshaw et al., *supra* note 16, at iii.

is labeled with fluorescent "probe" molecules,[27] so that it may then be used to detect the presence of the complementary DNA sequence in target cells to which it will pair itself.[28] If too many (or too few) copies of a given chromosome (or piece of a chromosome) appear colored within the same fetal cell, this indicates an abnormality.[29]

PCR, often used on a single fetal cell,[30] can replicate all or part of a cell's DNA in large quantities. Where a sample is small, PCR can increase the amount of genetic material to be analyzed.[31] PCR may also be used to amplify (i.e. make multiple copies of) a particular portion of DNA known to code for a certain genetic condition, in order to search for abnormalities in that locus.[32] This is typically done in bulk, on a sample of many cells, but may also be conducted on a single fetal cell, which increases reliability by reducing interference by non-fetal cells or DNA.[33]

Although "[t]he safety . . . of amniocentesis ha[s] been established by several large collaborative studies,"[34] the test is not without some risk to both the mother and the fetus. The procedure causes membrane rupture and fluid leakage in about 1-2% of pregnant women.[35] Mothers may also experience bleeding, infections, or early initiation of labor.[36] With respect to the fetus, amniocentesis increases the risk of miscarriage from about 1%[37] to about 1.5% — a 50% increase over the background rate of miscarriage during the second

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[27] Fluorescent probes specifically bind to target molecules and emit a bright, fluorescent glow under certain lighting and chemical conditions. *See generally* David M. Jameson, *Gregorio Weber, 1916–1997: A Fluorescent Lifetime* 75 Biophysical J. 419, 419 (1998), *available at* http://www.biophysj.org/cgi/reprint/75/1/419.pdf.

[28] *FISH Analysis—definition from Biology-Online.org* (Oct. 3, 2005), http://www.biology-online.org/dictionary/Fish_analysis; *see also* S. Hahn et al., Fetal *Cells in Maternal Blood: Current and Future Perspectives*, 4 Molecular Hum. Reproduction 515, 517-18 (1998); M. Roderiguez de Alba et al., *Prenatal Diagnosis on Fetal Cells Obtained from Maternal Peripheral Blood: Report of 66 Cases*, 19 Prenatal Diagnosis 934 (1999).

[29] *See, e.g.*, Vaidehi Jobanputra et al., *Prenatal Detection of Aneuploidies using Fluorescence In Situ Hybridization: A Preliminary Experience in an Indian Set Up*, 27 J. Biosciences 155, 159, 159 fig. 1(a) (2002), *available at* http://www.ias.ac.in/jbiosci/mar2002/155.pdf.

[30] *See, e.g.*, A. Sekizawa et al., *Prenatal Diagnosis of Duchenne Muscular Dystrophy Using a Single Fetal Nucleated Erythrocyte in Maternal Blood*, 46 Neurology 1350 (1996).

[31] *See* U.S. Patent 4,683,202, at [57] (filed Oct. 25, 1985).

[32] *See id.* at col.1, ll.23-32.

[33] *See, e.g.*, Hahn et al., *supra* note 28, at 518.

[34] Jorde et al., *supra* note 7, at 276.

[35] *Id.*; ACOG Practice Bulletin No. 27, *supra* note 10, at 5; Mark Deutchman & Ellen L. Sakornbut, *Diagnostic Ultrasound in Labor and Delivery*, 51 Am. Fam. Physician 145, 151 (1995).

[36] Deutchman & Sakornbut, *supra* note 35, at 151.

[37] Centers for Disease Control & Prevention, Draft Genetic Test Review: Cystic Fibrosis: Clinical Utility, at 4-26 (2002) [hereinafter Draft Genetic Test Review], *available at* http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFClilUti.pdf; *see also* Michel Sangalli et al., *Pregnancy Loss Rate Following Routine Genetic Amniocentesis at Wellington Hospital*, 117 N.Z. Med. J. U818 (Apr. 2, 2004), *available at* http://www.nzma.org.nz/journal/117-1191/818/ (citing earlier studies that demonstrated a background miscarriage rate of about 0.5-1.7%).

trimester.[38] In rare cases, it may also cause injury to the umbilical cord,[39] or fetal brain damage.[40]

CVS may be performed earlier than amniocentesis, at approximately 10 to 11 weeks' gestation.[41] In this test, a physician inserts a catheter into the uterus (either transcervically or through the abdominal wall) and takes a tissue sample from the chorionic villi, the finger-like projections that make up part of the placenta.[42] As with amniocentesis, fetal cells are isolated, and DNA analysis is conducted on the genetic material obtained from the cells' nuclei by means of karyotyping (most common), FISH, or PCR.[43]

The primary risk associated with CVS is an increased likelihood of miscarriage. CVS increases this risk from about 3%,[44] to about 4-4.5% (or 133-150% above the background rate at the end of the first trimester).[45] Thus, the miscarriage rate of CVS is higher than that of amniocentesis. Additionally, research suggests — and biology does not refute — that CVS may lead to an increased occurrence of birth defects, such as shortening of the limbs, fingers, or toes.[46]

Relatively few pregnant women undergo amniocentesis or CVS, in part because of the augmented risks and in part because of the costs. Because of the fetal and maternal hazards highlighted above, medical professionals recommend the procedures almost exclusively for women aged 35 and older,[47] unless the fetus is at particular risk for genetic disease or abnormality (e.g. because of a positive family history).[48] Another limiting factor is cost. Amniocentesis and CVS typically cost between $1100-$1200, but may range as high as $2000.[49] Insurance coverage of these procedures varies, but coverage is more likely for women over 35 whose screening tests returned positive results, and for others (like those with a family history for abnormalities) for whom the tests may be deemed a "medical necessity."[50] As a result of the foregoing factors, only about 88,000 women underwent

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[38] JORDE ET AL., *supra* note 7, at 276-77.

[39] Deutchman & Sakornbut, *supra* note 35, at 151.

[40] *See, e.g.*, M. Squier et al., *Five Cases of Brain Injury Following Amniocentesis in Mid-Term Pregnancy*, 42 DEVELOPMENTAL MED. & CHILD NEUROLOGY 554, 554 (2000).

[41] *See* Jorde et al., *supra* note 7, at 277.

[42] *See id.*; *Chorionic Villus Sampling*, http://www.healthatoz.com/healthatoz/Atoz/ency/chorionic_villus_sampling.jsp (Dec. 2002).

[43] *See, e.g.*, *id.*

[44] Eric Jauniaux, *Fetal Testing in the First Trimester of Pregnancy*, 22 THE FEMALE PATIENT 15 (1997) (listing a background miscarriage rate of 3% for weeks 9-12 of pregnancy), *available at* http://www.obgyn.net/femalepatient/default.asp?page=jauniaux.

[45] *See* JORDE ET AL., *supra* note 7, at 277.

[46] *Id.*; *see also* ACOG Practice Bulletin No. 27, *supra* note 10, at 6; Richard S. Olney et al., *Chorionic Villus Sampling and Amniocentesis: Recommendations for Prenatal Counseling*, 44 RECOMMENDATIONS AND REPS. 1 (Centers for Disease Control & Prevention, ed. 1995), *available at* http://www.cdc.gov/mmwr/PDF/RR/RR4409.pdf.

[47] It is generally acknowledged that when a woman reaches age 35, the risk of bearing a fetus with a chromosomal abnormality or other defect (which increases with age) outweighs the risk of miscarriage, thus warranting invasive prenatal genetic testing. *See* JORDE ET AL., *supra* note 7, at 276.

[48] *See id.* at 276-77.

[49] *See, e.g.*, Ryan A. Harris et al., *Cost Utility of Prenatal Diagnosis and the Risk-Based Threshold*, 363 LANCET 276, 278 tbl.1 (2004).

[50] *See* discussion *infra* Part IV.C.1.

amniocentesis in 2001;[51] 79,000 in 2002;[52] and 67,000 in 2003[53] (out of over 4,000,000 live births and about 5,000,000 pregnancies in each year).[54] The number of women undergoing CVS testing was likely even lower. In 2002, a study of genetic testing at the University of Connecticut Health Center recorded only 55 CVS referrals, as compared with 878 amniocentesis referrals — a rate of under 6% (of all prenatal genetic testing), which had remained relatively consistent in the years between 1991 and 2002.[55] The numbers were higher at the Stanford University Medical Center, but CVS nonetheless made up only 11% of the prenatal diagnostic procedures performed in 2004, and 12% of the procedures performed in 2005.[56] Thus, if an approximate rate of 10% is applied comparably across the nation, it would indicate a total of only about 8,800 CVS procedures in 2001; 7,900 in 2002; and 6,700 in 2003 (out of 5,000,000 pregnancies). In contrast, ultrasound, which is less precise than amniocentesis and CVS, was utilized in about 2,700,000 pregnancies in 2001-2003, most likely because it is a relatively inexpensive and generally non-invasive procedure.[57]

III. POTENTIAL NON-INVASIVE ALTERNATIVES FOR PRENATAL GENETIC DIAGNOSIS

Two alternative diagnostic tests are currently being developed that would enable doctors to obtain genetic material from the fetus without intruding into the uterine area. Thus, in contrast to the current invasive procedures, these methods pose virtually no risk of injury to the mother and eliminate the procedure-related risks to the fetus. Both of the new tests rely on the presence of minute quantities of fetal genetic material that cross the placenta and

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[51] Joyce A. Martin et al., *Births: Final Data for 2001*, 51 NAT'L. VITAL STATS. REPS. 70 (Centers for Disease Control & Prevention, Atlanta, GA), Dec. 18, 2002 [hereinafter Martin et al., *Births: 2001*].

[52] Joyce A. Martin et al., *Births: Final Data for 2002*, 52 NAT'L. VITAL STATS. REPS. 79 (Centers for Disease Control & Prevention, Atlanta, GA), Dec. 17, 2003 [hereinafter Martin et al., *Births: 2002*].

[53] Joyce A. Martin et al., *Births: Final Data for 2003*, 54 NAT'L. VITAL STATS. REPS. 79 (Centers for Disease Control & Prevention, Atlanta, GA), Sept. 8, 2005 [hereinafter Martin et al., *Births: 2003*].

[54] The 5,000,000 figure for annual pregnancies is derived from the CDC's most recent statistics on live births (indicating about 4,000,000 each year) and legal abortions [indicating a number between 854,000 (the CDC's 49-state survey—excluding Alaska, California, and New Hampshire) and 1,293,000 (the Alan Guttmacher Institute's estimate—based on interpolation from previous surveys) in 2002]. *See* NAT'L CENTER FOR HEALTH STATISTICS, CENTERS FOR DISEASE CONTROL & PREVENTION, HEALTH, UNITED STATES, 2005, at 149 (2005) [hereinafter HEALTH, UNITED STATES, 2005]. More generally, the CDC suggests a link between the decline in the number of amniocentesis procedures performed and the increased use of certain non-invasive screening measures like MSAFP testing and ultrasound. *See, e.g.*, Martin et al., *Births: 2003*, *supra* note 53, at 14. This is evidence of medical professionals' unwillingness to subject women to invasive testing (with its risks to fetal and maternal health) where other alternatives are available, and it illustrates the current push toward non-invasive testing.

[55] Peter A. Benn et al., *Changes in Utilization of Prenatal Diagnosis*, 103 OBSTETRICS & GYNECOLOGY 1255, 1257 (2004).

[56] Email from Louanne Hudgins, Director of Perinatal Genetics, Stanford Univ. Med. Center, to Henry T. Greely, Deane F. and Kate Edelman Johnson Professor of Law, Stanford Law Sch. (Feb. 22, 2006).

[57] *See* Martin et al., *supra* notes 51-53.

circulate in the mother's bloodstream during the pregnancy.[58] Each method merely requires a blood sample from the mother.[59] Section A describes the first method, maternal serum fetal cell sorting ("MSFCS"), which entails isolating *intact* fetal cells from maternal blood and analyzing the DNA within them.[60] Section B details the second method, maternal plasma fetal DNA recovery ("MPFDR"), which involves analyzing segments of *cell-free* fetal DNA found circulating in the mother's blood.[61] Neither procedure is ready for clinical use at present, yet each offers distinct possibilities and presents particular challenges.

A. Maternal Serum Fetal Cell Sorting

The presence of fetal cells in maternal circulation was first discovered in the late nineteenth century by German pathologist Christian Georg Schmorl.[62] Twentieth-century research has confirmed the existence of such fetal cells (as well as other types) in maternal blood,[63] but has also underscored their rarity. Although their relative concentration increases as the pregnancy progresses, fetal cells typically make up only about 1 in 1,000,000 to 1 in 10,000,000 cells in maternal blood serum.[64] One group estimated that there were only 19 fetal cells in a 16-milliliter blood sample.[65] As a result, isolating such cells for use in genetic testing has posed significant challenges. Since the 1980s, much of the research in MSFCS has focused on "enrichment" techniques, which aim to identify various types of fetal cells and recover them in increased quantities from maternal blood.[66]

The initial question is what *type* of fetal cell is easiest and most cost-effective to isolate. Researchers have experimented with three principal types: (1) trophoblasts (embryonic cells responsible for forming the placenta),[67] (2) leukocytes (white blood cells),[68] and (3) erythroblasts (nucleated red blood cells, or NRBCs).[69] Although trophoblasts were the first type to be detected and are easy to identify microscopically because of their unique shape, they also have a high rate of mosaicism ("mixing" with maternal tissue) that complicates analysis, and they are rapidly depleted from the mother's bloodstream, making them harder to locate.[70] Fetal leukocytes have been

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58 *See* Jorde et al., *supra* note 7, at 282.

59 *See infra* notes 83, 124 and accompanying text.

60 *See infra* note 83 and accompanying text.

61 Note that the terms and abbreviations for these procedures are my own. The scientific literature has not yet settled on a consistent term for either procedure.

62 Hahn & Holzgreve, *supra* note 32, at 649.

63 *Id.*

64 *Id.*

65 *See* Diana W. Bianchi et al., *PCR Quantification of Fetal Cells in Maternal Blood in Normal and Aneuploid Pregnancies*, 61 Am. J. Hum. Genetics 822 (1997).

66 *See, e.g.*, S. Hahn et al., *Fetal Cells in Maternal Blood: Current and Future Perspectives*, 4 Molecular Hum. Reprod. 515, 516 (1998).

67 *Id.*

68 *Id.*

69 *Id.*

70 *See id.* at 515; Lee P. Shulman, *Fetal Cells in Maternal Blood*, 3 Current Women's Health Rep. 47, 47 (2003).

successfully isolated by several research teams,[71] but pose difficulties because of the lack of specific antibody "markers" to separate them from maternal cells,[72] and because leukocytes from prior pregnancies may persist in maternal blood for many years following birth or spontaneous abortion.[73] Erythroblasts are the most attractive candidate for isolation because NRBCs are rare in adult blood, appear early in the pregnancy, are less likely to persist in maternal blood following pregnancy, and possess several potential antibodies for use in enrichment.[74] Even after enrichment, however, maternal cells still outnumber fetal erythroblasts, raising the possibility of accidental analysis of maternal (rather than fetal) genetic material.[75]

Several potential enrichment procedures have been tested in recent years. In fluorescence-activated cell sorting ("FACS"), target cells, such as NRBCs,[76] are "tagged" with a fluorescent antibody specific to such cells.[77] The tagged cells, with their bright labels, are identified using a "computer-assisted laser-guided device."[78] Magnetic-activated cell sorting ("MACS"), on the other hand, uses antibodies affixed to magnetic beads that "tag" the target cells.[79] When the combined cell mixture (tagged and untagged) is passed through a magnetic field, the desired fetal cells are retained, and the undesired cells flow through and are discarded.[80] MACS is often favored because it is relatively less expensive and does not require a high level of technical expertise.[81] Alternatively, some researchers have experimented with density gradients, which separate cell types based on differentials in relative mass.[82] Alone, or in conjunction with the above techniques, scientists may also employ "micromanipulation," in which a single fetal cell is identified by microscope and recovered for analysis.[83]

After enriching for fetal cells (or isolating a single fetal cell), scientists can then conduct genetic analysis on the fetal genetic material via karyotyping,

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[71] One seminal study involving leukocytes is L. A. Herzenberg et al., *Fetal Cells in the Blood of Pregnant Women: Detection and Enrichment by Fluorescence-Activated Cell Sorting*, 76 Proc. Nat'l. Acad. Sci. USA 1453 (1979).

[72] Shulman, *supra* note 70, at 48.

[73] *See, e.g.*, A. Ciaranfi et al., [*Post-Partum Survival of Fetal Lymphocytes in Maternal Blood*], 107 Schweiz Med. Wochenschr 134 (1977); J. Schroder et al., *Fetal Leukocytes in the Maternal Circulation After Delivery*, 17 Transplantation 346 (1974).

[74] *See* Hahn et al., *supra* note 66, at 516; Hahn & Holzgreve, *supra* note 32, at 650; Shulman, *supra* note 70, at 48.

[75] Hahn et al., *supra* note 66, at 516.

[76] *See, e.g.*, Diana W. Bianchi et al., *Isolation of Fetal DNA From Nucleated Erythrocytes in Maternal Blood*, 87 Proc. Nat'l Acad. Sci. 3279 (1990).

[77] Two typical markers that are utilized in both the FACS and MACS contexts are anti-CD71 (transferring receptor), *see e.g.*, *id.*, and anti-glycophorin-A (anti-GPA), which was preferred over anti-CD71 in C. Troeger et al., *A Comparison of Different Density Gradients and Antibodies for Enrichment of Fetal Erythroblasts by MACS*, 19 Prenatal Diagnosis 521, 523-24 (1999).

[78] Hahn & Holzgreve, *supra* note 32, at 650.

[79] *See id.*; Troeger et al., *A Comparison of Different Density Gradients and Antibodies for Enrichment of Fetal Erythroblasts by MACS*, 19 Prenatal Diagnosis 521, 522 (1999).

[80] *See* Shulman, *supra* note 70, at 49.

[81] *See* Hahn & Holzgreve, *supra* note 32, at 650.

[82] Hahn et al., *supra* note 66, at 516 (noting the pioneering research of Takayabashi et al., Development *of Non-Invasive Fetal DNA Diagnosis From Maternal Blood*, 15 Prenatal Diagnosis 74 (1995)).

[83] *See* Hahn et al., *supra* note 66, at 518.

FISH, or PCR.[84] These methods operate no differently for MSFCS than for the analysis of an amniocentesis or CVS sample.

Therefore, an ideal MSFCS procedure would proceed as follows: at approximately 8-12 weeks' gestation, a pregnant woman arrives at her doctor's office, where she gives a standard 10 milliliter (about 1/3 of an ounce) blood sample. The sample is then enriched for fetal erythroblasts by means of an efficient, automated process of cell sorting, with reliable, fetus-specific antibody markers. The enriched sample is then subjected to multicolored FISH (to search for more than one chromosomal condition at once) or PCR analysis of the DNA, where target abnormalities may be detected.[85] Results are obtained in less than a week.

The benefits of MSFCS are manifold. First and foremost, its non-invasive nature eliminates the risk of miscarriage and other dangers to the mother and the fetus. Moreover, because MSFCS could be used earlier in the pregnancy than amniocentesis (and about the same time as CVS), it would provide families with more time to make difficult decisions concerning the termination of an affected fetus, and allow for a safer and easier termination, if that is the ultimate choice. Moreover, following successful isolation of the fetal cell(s), medical professionals could diagnose virtually any genetic condition for which there are reliable genetic markers. MSFCS preserves the complete fetal genome and may be used to analyze any and all of it in searching for genetic abnormalities. So far, MSFCS has been successfully used to detect fetal gender,[86] muscular dystrophy,[87] Rh incompatibility,[88] and common chromosomal abnormalities like Down Syndrome.[89]

Despite its advantages, the MSFCS is not without challenges, which currently prevent the technology from being put to clinical use. First, there is still a large amount of "background noise,"[90] primarily from the vast quantity of maternal cells that remain in the blood sample following enrichment. "Even after enrichment, most cells are likely to be maternal," with "perhaps one [fetal cell] per 100 to 1000."[91] Part of the problem is the lack of sufficiently specific antibody markers. To increase yield, scientists continue to search for more reliable and fetus-specific antibodies, but such markers are still elusive.[92] The more reliable the markers, the more conducive the cell sorting process will be to *automation*, an ultimate goal of researchers.[93] Indeed, because the future utility of this procedure depends upon achieving a

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[84] *Id.*

[85] Note that MSFCS, like amniocentesis and CVS, would likely be used to target only the more common abnormalities in order to conserve medical resources and keep the price of the test down. Nevertheless, the technique may be used (likely manually, rather than in an automated manner) to diagnose less common conditions, for which the fetus is known to be at particular risk.

[86] *See, e.g.*, Y. M. Lo et al., *Prenatal Sex Determination by DNA Amplification from Maternal Peripheral Blood*, 334 LANCET 1363 (1989).

[87] *See, e.g.*, Sekizawa et al., *supra* note 30, at 1350.

[88] *See, e.g.*, Y. M. Lo et al., *Prenatal Diagnosis of Fetal RhD Status by Molecular Analysis of Maternal Plasma*, 339 NEW ENG. J. MED. 1734 (1998).

[89] *See, e.g.*, Roderiguez de Alba et al., *supra* note 28, at 936.

[90] Telephone Interview with Dr. Jane Chueh, *supra* note 7.

[91] Shulman, *supra* note 70, at 49.

[92] *Id.*

[93] *See* Hahn et al., *supra* note 66, at 517; Hahn & Holzgreve, *supra* note 32, at 651.

level of efficiency and cost-effectiveness that surpasses current invasive procedures like amniocentesis, automation of cell sorting is critical. Moreover, although it is currently easiest to test for only one disorder at a time, increased accuracy and reliability of multicolored FISH,[94] as well as better techniques for micromanipulation of a single fetal cell for PCR analysis, could allow scientists to efficiently screen for multiple abnormalities at once.

The most troubling problem, however, is the persistence of fetal cells from *prior* pregnancies (successful or unsuccessful) in maternal blood, which may confound enrichment and analysis of the *current* fetus's cells. Research studies have demonstrated the continued proliferation of fetal leukocytes in maternal blood 1 year post partum,[95] and 5 years postpartum.[96] One laboratory discovered male genetic material in one mother's blood a full 27 years following the birth of her last son.[97] There are few solutions to this dilemma, except perhaps to compare isolated fetal cells to the cells of a living child to determine whether the cells originated with the current fetus or the child (i.e. previous fetus). This method would not apply, however, where the fetal cells came from earlier *miscarriages* or *abortions*, where no basis for comparison exists. This issue would become especially problematic if chromosomally abnormal fetal cells remained in the mother's blood after the birth of an affected child or, more likely, after spontaneous abortion of an affected fetus.[98] The persistence of abnormal cells could lead to a false positive and possibly result in an unnecessary abortion.

All of the studies above, however, were performed on *white* blood cells and their precursors. In contrast, fetal erythrocytes ("NRBCs") have a lifespan of only about 90 days,[99] making them less likely to confuse prenatal genetic diagnosis via MSFCS. In fact, the authors of one study suggested, as a potential solution to the problem of fetal cell persistence, the use of a "highly differentiated fetal cell type that is unlikely to proliferate, like the fetal nucleated erythrocyte."[100] Indeed, targeting fetal NRBCs may largely solve the dilemma (except in the case of very recent pregnancies), *if* the NRBCs can be reliably isolated.

Nevertheless, the present-day accuracy and reliability of MSFCS reaches, at best, the level of a screening test.[101] With further research and refinement of procedures, it is possible that MSCFS may reach diagnostic-level precision.

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[94] For information on one lab's successful use of five-color FISH analysis, see F. Z. Bischoff et al., *Prenatal Diagnosis With Use of Fetal Cells Isolated From Maternal Blood: Five-Color FISH Analysis on Flow Sorted Cells for Chromosomes X, Y, 13, 18, and 21*, 179 Am. J. Obstetrics & Gynecology 203 (1998).

[95] *See* Schroder et al., *supra* note 73.

[96] *See* Ciaranfi et al., *supra* note 73.

[97] It is not known whether fetal cells can, in fact, persist in maternal blood for 27 years, as the 27-year figure noted above may have been the result of a failed male pregnancy that occurred subsequent to the birth of the woman's last child. Nevertheless, researchers have consistently demonstrated that certain types of fetal cells persist in maternal serum for many years after birth or pregnancy termination. *See, e.g.*, Diana W. Bianchi et al., *Male Fetal Progenitor Cells Persist in Maternal Blood for as Long as 27 Years Postpartum*, 93 Proc. Nat'l. Acad. Sci. USA 705 (1996); Ciaranfi et al., *supra* note 73.

[98] Shulman, *supra* note 70, at 50.

[99] Hahn & Holzgreve, *supra* note 32, at 650.

[100] Bianchi et al., *supra* note 97, at 707.

[101] Telephone interview with Dr. Jane Chueh, *supra* note 7.

B. Maternal Plasma Fetal DNA Recovery

Experimentation with cell-free fetal DNA in maternal blood is a much more recent phenomenon, but one that promises a number of advantages over intact cell isolation (as well as its own set of limitations). First discovered by Y. M. Dennis Lo et al. in 1997,[102] cell-free fetal DNA has been "reliably detected" in maternal serum as early as 5 weeks' gestation.[103] Such DNA exists in small fragments, and while its origin is presently unknown, researchers suspect that it results from the disintegration or death of intact fetal cells and subsequent passage through the placenta.[104] Significantly, cell-free fetal DNA has been shown to appear in maternal blood in greater quantities than intact fetal cells. According to one study, cell-free fetal DNA made up an average of 3.4% of all cell-free DNA in maternal plasma (0.13% in maternal serum) in early pregnancy, and an average of 6.2% of all cell-free DNA in maternal plasma (1.0% in maternal serum) in late pregnancy.[105] Thus, cell-free fetal DNA in maternal plasma may prove easier to enrich, if enrichment is necessary at all,[106] because of its already high relative presence.

Two principal enrichment techniques have been attempted. First, some researchers have found that treating maternal plasma with formaldehyde reduces breakage of maternal cells during analysis, thus minimizing "background" cell-free maternal DNA.[107] This, in turn, makes fetal DNA easier to recover and results in higher yields. Subsequent researchers, however, have failed to replicate these results, instead noting a "lack of dramatic enrichment of fetal DNA" after using formaldehyde.[108] The second technique is "size-fractionalization," which exploits the recently discovered discrepancy between the approximate size of cell-free fetal DNA and that of cell-free maternal DNA.[109] Because fetal DNA fragments are typically smaller (fewer than 300 base pairs [bp]) than maternal DNA fragments (greater than 500 bp), fetal DNA will travel farther when passed through a dense gel and may be extracted with little contamination by maternal genetic material.[110] This technique has thus far met with moderate success.

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[102] Y. M. Lo et al., *Presence of Fetal DNA in Maternal Plasma and Serum*, 350 Lancet 485 (1997).

[103] Rossa W. K. Chiu & Y. M. Lo, *The Biology and Diagnostic Applications of Fetal DNA and RNA in Maternal Plasma*, 61 Current Topics in Developmental Biology 81, 84 (2004).

[104] *Id.* at 86-87. *See also* Diana W. Bianchi, *Circulating Fetal DNA: Its Origin and Diagnostic Potential—A Review*, 18 Placenta S93, S94-S96 (2004).

[105] Y. M. Lo et al., *Quantitative Analysis of Fetal DNA in Maternal Plasma and Serum: Implications for Non-Invasive Prenatal Diagnosis*, 62 Am. Hum. Genetics 768 (1998).

[106] One pair of researchers notes that "[a]s a result of the relative abundance of fetal DNA in maternal plasma, its presence can be detected by a number of molecular techniques without special enrichment protocols." Chiu & Lo, *supra* note 103, at 99.

[107] *See, e.g.*, R. Dhallan et al., *Methods to Increase the Percentage of Free Fetal DNA Recovered From the Maternal Circulation*, 291 J. Am. Med. Ass'n 1114 (2004).

[108] Grace T. Y. Chung et al., *Lack of Dramatic Enrichment of Fetal DNA in Maternal Plasma by Formaldehyde Treatment*, 51 Clinical Chemistry 655, 655 (2005).

[109] *See, e.g.*, Ying Li et al., *Detection of Paternally Inherited Fetal Point Mutations for* β*-Thalassemia Using Size-Fractionated Cell-Free DNA in Maternal Plasma*, 293 J. Am. Med. Ass'n 843, 844 (2005).

[110] *See, e.g.*, *id.* *See also* K.C.A. Chan et al., *Size Distributions of Maternal and Fetal DNA in Maternal Plasma*, 50 J. Clinical Chemistry 88, 91 (2004) (reporting that 86% of cell-free fetal DNA fragments recovered contained fewer than 201 base pairs).

Following enrichment (or even without substantial enrichment), MPFDR may employ either FISH or PCR to analyze the fetal genetic material.[111] Karyotyping would not be possible for MPFDR, because cell-free fetal DNA exists in fragments, rather than in full chromosomes.[112] This fragmentary nature of fetal DNA should not pose any procedural problems, however, because FISH and PCR typically require cell and DNA breakage already.[113] For those reasons, running FISH or PCR analysis on a sample of "pre-segmented" cell-free fetal DNA produces similar results.

Thus, an ideal test for MPFDR would proceed much like the proposed MSFCS test. Because fetal DNA can be "reliably detected" in maternal blood as early as 5 weeks' gestation,[114] a mother could give a blood sample at perhaps 8-10 weeks' gestation. An enrichment step may be used to reduce (or, ideally, to eliminate) maternal cell-free DNA in the sample, and the fetal DNA would be extracted, optimally through an automated procedure.[115] Scientists would conduct FISH or PCR to analyze the fetal genetic material, and results would arrive within a week.

MPFDR offers several benefits over MSFCS. The higher ratio of fetal genetic material means that the enrichment-phase challenges are greatly reduced. Moreover, at least for certain types of diagnoses,[116] the enrichment step may be eliminated entirely, resulting in significant time and cost savings. Even more importantly, however, cell-free fetal DNA, unlike intact fetal cells, does not persist long in maternal blood following pregnancy.[117] Numerous studies have determined that fetal DNA is rapidly cleared from maternal circulation within days, or even *hours*, after birth.[118] As a result of the increase in correct fetal genetic material and the decrease in incorrect fetal genetic material, scientists have been able to reliably diagnose fetal Rhesus D status,[119] to avoid complications from Rh incompatibility.[120] In fact, Rhesus D

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[111] In addition, simple quantitative analysis of cell-free fetal DNA may be used as a non-invasive screening measure for chromosomal abnormalities, see Y. M. Lo et al., *Increased Fetal DNA Concentrations in the Plasma of Pregnant Women Carrying Fetuses With Trisomy-21*, 45 J. Clinical Chemistry 1747 (1999) (finding an average of twice as much fetal DNA in the blood of mothers carrying fetuses with Down Syndrome than in the blood of mothers carrying unaffected fetuses); and for pre-eclampsia, a condition of high blood pressure during pregnancy, see Bianchi, *supra* note 104, at S93, S98. The ultimate goal of MPFDR, however, is not to merely screen for, but accurately to diagnose, genetic conditions.

[112] *See, e.g.*, Chiu & Lo, *supra* note 4, at 86 (discussing the "size distribution of fetal DNA *fragments* in maternal plasma") (emphasis added).

[113] *Id.*

[114] Chiu & Lo, *supra* note 103, at 84.

[115] "[A]utomated platforms for fetal DNA extraction have been evaluated and adopted by some groups." *Id.* at 100 (citing J. M. Costa & P. Ernault, *Automated Assay for Fetal DNA Analysis in Maternal Serum*, 48 J. Clinical Chemistry 679 (2002) and R. Dee et al., *Validation of Automated Fetal DNA Extraction With the MagNA Pure for Large Scale RHD Typing on Maternal Plasma*, 49 J. Clinical Chemistry S11 (2003)).

[116] E.g, paternally inherited genetic mutations. *See* discussion *infra* p.22-23.

[117] *See, e.g.*, Y. M. Lo et al., *Rapid Clearance of Fetal DNA From Maternal Plasma*, 64 Am. J. Hum. Genetics 218 (1999).

[118] *See, e.g.*, *id.* (reporting that fetal DNA was undetectable in 7 out of 8 women just two hours postpartum).

[119] *See* Chiu & Lo, *supra* note 103, at 89.

[120] An individual's "Rhesus D status" refers to the presence or absence, in that individual's red blood cells, of Rhesus (Rh) factor, a protein substance that can cause a strong immune response. "Rh incompatibility" results when an Rh-negative mother (whose blood

genotyping has achieved such a "high sensitivity and specificity"[121] (90-100%)[122] that it has become part of "routine prenatal care in the United Kingdom, France, and the Netherlands,"[123] and researchers believe that the "United States should . . . bring this technology to patient care as soon as possible."[124] Recently, MPFDR has also been found to accurately diagnose for other genetic conditions, such as Huntington's disease and cystic fibrosis,[125] where the conditions are paternally inherited.

This research reveals a critical challenge with MPFDR: its use is currently limited to detecting *paternally* inherited genetic conditions. Because researchers cannot yet completely separate fetal DNA from the large amount of maternal DNA in every blood sample, MPFDR is currently only useful for analyzing fetal loci (chromosome locations) that are *not present* in the maternal genome, "such as Y-chromosome-specific sequences or the RhD gene in pregnant women who are Rh-negative."[126] Paternally inherited single-gene abnormalities may also be detected, but the resulting information cannot fully confirm the fetus's condition if the disorder is not dominant, but recessive (and thus requires two copies — one paternal, one maternal — to cause the disorder).[127] However, researchers are actively investigating promising solutions that will permit analysis of maternally inherited gene sequences.[128]

An additional drawback to MPFDR is that cell-free fetal DNA is present only in fragments — mere fractions of the complete fetal genome.[129] Upon aggregating all of the fragments in a 10 mL blood sample, however, it is likely that the entire fetal genome is represented many times over. Researchers have discovered an average of 25.4 genome equivalents per mL (or 254 genome equivalents per 10 mL) of cell-free fetal DNA in maternal plasma

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does not contain Rh factor) is carrying an Rh-positive fetus. In such situations, the presence of Rh-positive fetal cells in the mother's blood induces the formation of antibodies. These antibodies are usually harmless to the first fetus. However, a subsequent fetus is at serious risk if the mother's antibodies enter the later fetus's bloodstream and begin attacking and destroying fetal red blood cells. For this reason, it is important to learn the Rh D status of a fetus carried by an Rh-negative woman, particularly where the father is Rh-positive. *Rh Factor, Encyclopedia*, http://www.answers.com/Rh%20factor (last visited Jan. 21, 2007).

[121] Chiu & Lo, *supra* note 103, at 101.

[122] Diana W. Bianchi et al., *Noninvasive Prenatal Diagnosis of Fetal Rhesus D: Ready for Prime(r) Time*, 106 Obstetrics & Gynecology 841, 842 (2005).

[123] *Id.* at 841.

[124] *Id.*

[125] *See* Cristina González-González et al., *Application of Fetal DNA Detection in Maternal Plasma: A Prenatal Diagnosis Unit Experience*, 53 J. Histochemistry & Cytochemistry 307 (2005).

[126] Li et al., *supra* note 109, at 843.

[127] *See* Chiu & Lo, *supra* note 103, at 90.

[128] One possibility is the use of epigenetic markers, where each member of a pair of fetal chromosomes (called an "allele") differs, depending upon who supplied it. Using a particular locus where the maternally inherited allele is unmethylated and the paternally inherited allele is methylated, one group of scientists was able to amplify the maternally inherited fetal allele separately from the background maternal DNA. *Id.* (citing L. L. M. Poon et al., *Differential DNA Methylation Between Fetus and Mother as a Strategy for Detecting Fetal DNA in Maternal Plasma*, 48 Clinical Chemistry 35 (2002)). Another potential strategy employs messenger RNA molecules found only in the fetus and not in the mother. *See An Earlier Look at Baby's Genes*, Science, Sept. 2, 2005, at 1476, 1478.

[129] *See, e.g.*, Chiu & Lo, *supra* note 4, at 86 (discussing the "size distribution of fetal DNA *fragments* in maternal plasma") (emphasis added).

during early pregnancy — a number that increases significantly as the pregnancy progresses.[130] Moreover, scientists seem unconcerned with the possibility that the fragmentary nature of cell-free fetal DNA will produce "gaps" in the range of fetal genetic conditions that may be detected by this method.[131] Thus, MPFDR is a promising technology that appears to be garnering increased support in the medical community.[132] However, like MSFCS, further refinement of MPFDR is required before it will be ready for widespread clinical use.[133]

IV. CLINICAL USE OF MSFCS AND MPFDR: INITIAL LEGAL AND SOCIAL QUESTIONS

Despite the current limitations of MSFCS and MPFDR, this technology has the potential to dramatically impact worldwide use of prenatal genetic testing, if employed regularly in a clinical setting. Granted, the development of these procedures for cost-effective, efficient clinical use is still years (and perhaps decades) away. The lack of reliable fetus-specific markers for cell sorting and the restriction of MPFDR to paternally inherited gene sequences currently prevent the tests from rising above screening-level accuracy.[134] Nevertheless, scientists are making increasingly rapid strides toward improving the technology, and it is very possible that MSFCS or MPFDR will become a routine part of clinical prenatal care in the near future.[135]

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[130] Lo et al., *Quantitative Analysis*, *supra* note 105, at 768 (1998).

[131] *See, e.g.*, Chiu & Lo, *supra* note 103 (containing a detailed, 21-page summary of the current technology and its limitations, with no mention of potential "gaps" in the fetal genome).

[132] *See infra* note 135.

[133] Also note that scientists are currently investigating other, analogous prenatal diagnostics that are less invasive than amniocentesis and CVS, including recovery of fetal RNA from maternal plasma, see Chiu & Lo, *supra* note 103, at 92-94; and, most recently, isolation of intact fetal cells from cervical mucus, see Mandy G. Katz-Jaffe et al., *DNA Identification of Fetal Cells Isolated From Cervical Mucus: Potential for Early Non-Invasive Prenatal Diagnosis*, 112 British J. Obstetrics & Gynecology 595 (2005).

[134] Telephone Interview with Dr. Jane Chueh, *supra* note 7. However, the prospect of using MSFCS or MPFDR as a screening measure is significant in itself. Although they would not reach the level of accuracy required to positively diagnose the fetus's condition, these technologies could identify at-risk fetuses for further testing. Moreover, because MSFCS and MPFDR could identify virtually any genetic abnormality for which scientists have a reliable test, the screening would not be limited to detecting chromosomal and anatomical abnormalities, as current screening measures are. *See* description of current screening measures at *supra* Part II. A full discussion of the use of MSFCS or MPFDR as screening tests is beyond the scope of this Article.

[135] Particularly with respect to MPFDR, scientists are very optimistic. *See, e.g.*, Bianchi, *Circulating Fetal DNA*, *supra* note 104, at S99 ("With the microarray technology that is already available it is not difficult to imagine that amplified fetal nucleic acids will ultimately permit a non-invasive fetal genome scan as part of routine prenatal screening."); González-González et al., *supra* note 125, at 307 ("The detection of fetal DNA sequences is a reality and could reduce the risk of invasive techniques for certain fetal disorders in the near future."); *An Earlier Look at Baby's Genes*, *supra* note 128, at 1476 ("Ready or not, noninvasive fetal diagnosis is here. Tests based on fetal DNA circulating in a woman's blood are expected to replace invasive prenatal tests . . . ."). The technology is even beginning to receive mainstream hype, as evidenced by a recent "Today Show" story, which highlighted a Massachusetts company's introduction of the "Baby Gender Mentor," a $275 home test that apparently uses MPFDR to determine fetal sex from a maternal blood sample. *Id.* (citing *Today Show* (NBC television broadcast Jun. 17, 2005)).

This Part considers the legal and social issues arising from regular, clinical use of non-invasive prenatal genetic diagnosis ("NPGD"). Thus, this Part, as well as Part V (which discusses the long-term impact of widespread, non-invasive testing), assumes that scientists have successfully developed a diagnostically accurate (98-99%) and efficient (e.g. automated) procedure for evaluating a fetus's DNA by means of a simple maternal blood test. This prospect raises several critical questions. Section A discusses the effect that clinical use of MSFCS or MPFDR will likely have in drastically augmenting pregnant women's usage of prenatal genetic diagnosis, and it enumerates the reasons for such an increase. Section B discusses the development of "standard of care" as a legal concept tracking medical progress, ultimately contending that an accurate and efficient MSFCS or MPFDR procedure could quickly become standard of care for prenatal testing. Finally, in Section C, this article addresses a critical question that will inevitably impact the use of this new technology: who will pay for the procedures? Given the relatively large lifetime costs associated with caring for individuals with certain detectable genetic conditions — and the increased ability to "catch" and terminate affected fetuses through widespread prenatal testing — this article concludes that both private insurers and public insurers like Medicaid could benefit from covering the cost of MSFCS or MPFDR.

A. Effects of MSFCS or MPFDR on Women's Use of Prenatal Genetic Testing

If researchers can successfully develop an efficient and accurate MSFCS or MPFDR procedure for clinical use, the number of women who will obtain prenatal genetic testing will almost certainly increase by a significant amount.[136] While only about 150,000 pregnant women undergo amniocentesis or CVS each year in the U.S.[137] (out of about 5,000,000 pregnancies),[138] widespread clinical availability of NPGD could raise that number to at least 2,700,000. This is the approximate number of women in the U.S. who receive ultrasound screening each year.[139] Because prenatal ultrasonography is considered a routine part of prenatal care for most

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[136] While nationwide use of physical and chemical screening tests like ultrasound, MSAFP analysis, and the triple screen are already relatively high, current usage of *genetic* testing (i.e. through amniocentesis and CVS) is relatively low.

[137] The 150,000 figure is an estimate, which uses the most recent CDC figures and assumes that approximately equal numbers of amniocentesis and CVS procedures are performed each year. Martin et al., *supra* notes 51-53 (indicating about 78,000 amniocentesis procedures performed each year in 2001, 2002, and 2003). In reality, however, the number of CVS tests (which pose slightly more risk to the developing fetus) is likely much lower than the number of amniocentesis tests. *See* text at *supra* pp. 14-15; Benn et al., *supra* note 55. On the other hand, the CDC's amniocentesis statistics likely underestimate the number of tests performed each year, because they record such procedures based on the number of *live births* each year. Presumably, a number of women who receive a positive test result opt to terminate their pregnancies, and these uses would not be counted toward the CDC's total.

[138] As indicated earlier, this approximate number of pregnancies is derived from the CDC's most recent statistics on live births (about 4,000,000 each year) and abortions (between 854,000 and 1,293,000 in 2002). *See* Health, United States, 2005, *supra* note 54, at 149.

[139] *See* Martin et al., *supra* notes 51-53.

pregnant women,[140] the number of women undergoing this relatively non-invasive and inexpensive procedure is perhaps the best estimate of the number of expectant mothers who have regular access to prenatal care, and who, therefore, would be able to seek NPGD.

In fact, a number of factors support the conclusion that clinical use of MSFCS or MPFDR would result in significantly increased rates of prenatal genetic testing. These include: (1) elimination of risks for the developing fetus; (2) reduction of the pain, discomfort, and maternal complications currently associated with prenatal genetic testing; (3) increased accuracy, over currently available screening tests; (4) ability to undergo testing earlier in pregnancy; and (5) reduction of prices and costs, over current means of prenatal genetic diagnosis. Each of these benefits is discussed in further detail below.

1. No Risk of Miscarriage or Birth Defects

Researchers' most explicit and consistent goal in developing MSFCS and MPFDR has been to eliminate the risk of miscarriage and birth defects associated with current prenatal genetic testing. In their comprehensive article about MPFDR, Chiu and Lo explain that,

> As conventional methods for prenatal diagnosis, such as amniocentesis and chorionic villus sampling, are associated with a risk of fetal loss, the pursuit of safe noninvasive alternatives has been a long-sought goal in medicine. The discovery of . . . [fetal genetic material] in the maternal circulation has offered new avenues for the realization of this goal.[141]

Even ultrasonography, a screening measure, may cause some harm to the developing fetus, through exposure to ultrasound energy.[142] The clinical implementation of MSFCS and MPFDR, both "non-invasive" procedures,[143] would virtually eliminate the procedure-related dangers of miscarriage and birth defects. Indeed, "[t]he major advantage" of these tests is that they "require[] only a blood sample from the mother and thus pose[] no risk for the fetus."[144]

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[140] While not officially considered "standard of care," ultrasound is widely recommended by OB/GYNs, as evidenced by the fact that about 2/3 of all pregnancies in 2001, 2002, and 2003 were screened via ultrasound. *Id.* For a discussion of standard of care with respect to ultrasound and other procedures, see text at *infra* Part IV.B.3.

[141] Chiu & Lo, *supra* note 103, at 81.

[142] *See* Am. College of Obstetricians and Gynecologists, ACOG Practice Bulletin No. 58: Ultrasonography in Pregnancy, at 6 (December 2004) [hereinafter ACOG Practice Bulletin No. 58] (concluding that "ultrasound energy delivered to the fetus cannot be assumed to be completely innocuous" because it can "produce physical effects, such as mechanical vibrations . . . or an increase in tissue temperature" that may harm the fetus in unknown ways).

[143] As noted above, the term "non-invasive," as used in the context of prenatal genetic testing, means non-invasive to the *uterus*. Clearly, taking a blood sample involves puncturing the skin and is "invasive" to the pregnant woman in that sense. However, the invasiveness of concern to researchers is that which jeopardizes the integrity of the uterus.

[144] Jorde et al., *supra* note 7, at 282.

Because the introduction of diagnostic MSFCS or MPFDR would render prenatal genetic diagnosis essentially "risk-free,"[145] the new procedures would likely replace invasive protocols completely (or nearly so). Many women fear the risk of miscarriage associated with invasive genetic testing and would recognize MSFCS and MPFDR to be significantly safer. In fact, one study found that "[m]ost focus group participants perceived [genetic] carrier testing to be safe since it is 'just a blood test' similar to other routine blood tests during pregnancy."[146] MSFCS or MPFDR would likely be perceived in a similar manner.

Thus, women over the age of 35, for whom prenatal genetic diagnosis is most frequently recommended, will welcome the chance to undergo such testing without risking harm to the fetus. Even more importantly, women *under* 35, for whom prenatal genetic testing is now largely discouraged due to the risk of miscarriage, could readily obtain such tests as well. Clinical MSFCS or MPFDR would therefore open prenatal genetic testing to an entirely new group of expectant mothers — a group that represents the vast majority (over 85%)[147] of nationwide pregnancies each year. Of course, some women may refuse to undergo testing for religious or moral reasons; such abstention occurs under the present testing regime and is likewise inevitable with the advent of non-invasive procedures. However, unless the price of MSFCS and MPFDR greatly exceeds that of current genetic tests,[148] the vast majority of women who obtain prenatal care will make the obvious choice: undergo an accurate, non-invasive procedure that will provide important information about the health of their fetuses. Amniocentesis and CVS, already on the decline as a result of more accurate non-invasive screening tests, would almost certainly be abandoned.

2. Reduced Maternal Pain, Discomfort, and Complications

Although individual experiences vary, women undergoing amniocentesis or CVS may experience uncomfortable pressure, cramping, or pinching during the procedure,[149] and the tests may lead to bruising or several hours of pain following the test.[150] Moreover, most doctors recommend a period of rest

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[145] *Id.* at 524.

[146] Genetics & Pub. Pol'y Ctr., Reproductive Genetic Testing: What America Thinks 46 (2004), http://www.dnapolicy.org/images/reportpdfs/ReproGenTestAmericaThinks.pdf.

[147] *See, e.g.*, Martin et al., *Births: 2002*, *supra* note 52, at 31 (indicating that about 86.2% of live births in 2002 were women under the age of 35); Lilo T. Strauss et al., *Abortion Surveillance – United States, 2002*, 54 Morbidity & Mortality Weekly Rep., Nov. 25, 2005, at tbl.4, http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5407a1.htm (last visited Jan. 20, 2007) (indicating that, in 2002, about 87.7% of legal abortions in 46 states were obtained by women under the age of 35).

[148] An unlikely prospect, as explained at *infra* Part IV.A.5.

[149] Univ. of Penn. Health Sys., *Amniocentesis*, http://www.pennhealth.com/health_info/pregnancy/000207.htm (last visited Jan. 20, 2007); *What is Amniocentesis?*, http://www.babycenter.com/refcap/327.html (last visited Jan. 20, 2007).

[150] *See, e.g.*, *CVS Test*, Berkeley Parents Network, *CVS Test*, http://parents.berkeley.edu/advice/pregnancy/cvs.html (last visited Jan. 20, 2007); *Chorionic Villi Sampling (CVS)*, http://www.answers.com/topic/chorionic-villi-sampling-cvs (last visited Jan. 20, 2007).

following amniocentesis or CVS.[151] In contrast, clinical testing with MSFCS or MPFDR would involve no more pain than the prick of a blood-drawing needle — par for the course among pregnant women, who must undergo blood analysis many times during pregnancy. Indeed, because routine blood tests occur at various stages of prenatal care, this step of MSFCS or MPFDR could be combined with other tests (i.e. by obtaining enough blood for multiple analyses), thus reducing the number of uncomfortable procedures that each pregnant woman would have to endure. Furthermore, women could more quickly resume physical activity following a blood test, as opposed to more invasive mechanisms.

In addition, MSFCS and MPFDR would reduce the risk of maternal complications associated with amniocentesis and CVS. Current invasive procedures have been linked to problems of fluid leakage, excessive bleeding, infections, and premature inducement of labor.[152] Although a small risk of infection would persist with blood-drawing, most of the above complications would be eliminated with the implementation of MSFCS or MPFDR. As a result, women who would otherwise avoid such procedures for fear of pain, early labor, disruption of daily activity, etc., will be more likely to obtain prenatal genetic testing.

3. Increased Accuracy

Americans are uniformly concerned about ensuring accuracy in genetic testing. In fact, the subject was underscored in nearly every focus group conducted by the Genetics & Public Policy Center in 2004.[153] Most individuals consider "devastating" both the consequences of a "false negative" (leading to the birth of an affected child), and the consequences of a "false positive" (leading to the abortion of a healthy child).[154] As such, pregnant women are more likely to choose a test that is proven to be more accurate than other comparable alternatives.

If diagnostic-quality MSFCS or MPFDR can be developed, the accuracy of such tests would match that of amniocentesis and CVS, and would certainly surpass that of modern screening tests. MSFCS and MPFDR would be held to the 98-99% standard of accuracy characteristic of current invasive procedures, whereas the "triple screen" test (which detects levels of key proteins in maternal blood) can only identify 60% to 80% of fetuses with Down Syndrome.[155] Ultrasound screening is also less reliable. For example, when used to screen for Down Syndrome, ultrasound has been shown to vary greatly depending upon the technician's skill and the methods used, with

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[151] *See, e.g.*, St. John's Mercy Health Care, *Tests and Procedures: Chorionic Villus Sampling*, http://www.stjohnsmercy.org/healthinfo/test/gyn/TP108.asp (last visited Jan. 20, 2007) (instructing women to "rest at home and avoid strenuous activities for at least 24 hours"); Univ. of Penn. Health Sys., *Amniocentesis*, *supra* note 149 (noting that "most physicians recommend several hours of rest").

[152] Deutchman & Sakornbut, *supra* note 35, at 151.

[153] GENETICS & PUB. POL'Y CTR., *supra* note 146, at 45.

[154] *Id.*

[155] Christopher Cunniff, *Prenatal Screening and Diagnosis for Pediatricians*, 114 PEDIATRICS 889, 892 (Sept. 2004); *see also* ACOG PRACTICE BULLETIN No. 27, *supra* note 10, at 2 (estimating detection at approximately 60% for women under 35, and approximately 75% for women over 35).

detection rates ranging from 31% to 75% and false positive rates as high as 8.5% among high risk women.[156] Nevertheless, ultrasound is widely used to screen for hereditary and structural defects.

Thus, in light of the current popularity of ultrasound (about 2.7 million women each year), it is likely that even more women would embrace MSFCS and MPFDR, which are equally non-invasive, yet much more accurate. This is not to say that the new tests will completely replace ultrasound. The medical value (for discovering non-genetic structural abnormalities) and the popular appeal of obtaining a visual picture of the fetus are quite strong. It is, however, likely that most, if not all, women who currently obtain ultrasound would *also* seek MSFCS or MPFDR. When used in combination, parents will receive a more accurate picture of their fetus's health and will be better equipped to make difficult family-planning decisions.

4. Earlier Detection of Genetic Disorders

MSFCS or MPFDR would also allow clinicians to conduct prenatal genetic testing — and return test results — *earlier* in pregnancy than with many current methods of analysis. The ability to obtain results sooner is appealing for a variety of reasons. First, it reduces the duration of parental anxiety about the health of their future child. Second, in the event of bad news, earlier testing gives parents more time to contemplate the difficult decision of whether or not to terminate the pregnancy. Moreover, abortions in the second trimester are considerably harder — both physically and emotionally — than abortions in the first trimester. Early abortions are safer for the pregnant woman.[157] Additionally, several weeks into the second trimester, a woman may have already felt fetal movement, seen ultrasound "photos" of the fetus, or fantasized about the future child's gender or appearance,[158] thus establishing an emotional bond that is considerably more painful to break. As more time passes, the pregnancy also becomes more evident to others,[159] making the decision to abort more public, and potentially leading to embarrassment or harassment. Finally, current Supreme Court precedent makes it considerably easier for states to limit a woman's ability to obtain an abortion after the fetus becomes viable.[160] For these reasons, the value of a prenatal test depends greatly upon *how soon* a woman can undergo the procedure and obtain results.

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[156] U.S. Preventive Servs Task Force, U.S. Dep't of Health & Human Servs, Guide to Clinical Preventive Services, Section 1: Screening: Congenital Disorders: *Screening for Down Syndrome* (2d ed. 1996), http://odphp.osophs.dhhs.gov/pubs/guidecps/PDF/CH41.PDF (last visited Mar. 5. 2007). The variances also depended upon which fetal structures were examined (nuchal lucency, shortened femur length, etc.). More recent tests have found overall ultrasound sensitivities of about 80%, when screening for Down Syndrome. *See* Vintzelios et al., *Indication-Specific Accuracy of Second-Trimester Genetic Ultrasonography for the Detection of Trisomy-21*, 181 Am. J. Obstetrics & Gynecology 1045 (1999).

[157] Sonia Mateu Suter, *The Routinization of Prenatal Testing*, 28 Am. J. L. & Med. 233, 258 n.155 (2002).

[158] *Id.*

[159] *Id.*

[160] *See* Planned Parenthood of Southeastern Pa. v. Casey, 505 U.S. 833, 873 (1992).

Both MSFCS and MPFDR could be performed in the first trimester, and could therefore produce results earlier than such tests as: amniocentesis (conducted at 15-17 weeks' gestation), MSAFP screening (conducted around 15-20 weeks' gestation), the "triple screen" test (typically conducted in the second trimester), and ultrasonography to detect structural deformities (typically conducted in the second trimester).[161] In fact, fetal cells can be isolated from maternal blood as early as 6-8 weeks' gestation,[162] and "circulating fetal DNA can be reliably detected by the fifth week of gestation,"[163] making it possible to offer the new tests even prior to CVS (conducted around 10-11 weeks' gestation). However, MSFCS and MPFDR are likely easier (and more cost-effective) to perform after 8 weeks, when greater quantities of fetal cells and DNA exist in maternal blood and the process of isolating fetal genetic material is consequently less challenging. Therefore, it is probable that scientists would develop MSFCS or MPFDR for use at 8-12 weeks gestation, when the option of a first trimester abortion is still available. This is still earlier than amniocentesis and other second-trimester tests, attracting many women who would otherwise undergo similarly timed tests that are either invasive or less accurate.

Moreover, if MSFCS and MPFDR regularly employ molecular methods of genetic analysis (FISH or PCR), as opposed to manual karyotyping, the results may be obtained even sooner. Indeed, the literature suggests that MSFCS is ideally conducted in conjunction with FISH or PCR, and MPFDR *requires* molecular analysis, as karyotyping cannot be performed on mere segments of DNA. Thus, the new procedures will produce earlier — or, at least, equally timed — results, making MSFCS and MPFDR appealing alternatives to current invasive technologies and leading to increased use of prenatal genetic diagnosis.

5. Reduced Prices and Costs

The appeal of MSFCS and MPFDR will also be greatly affected by the tests' costs (to laboratories) and the tests' price (to consumers). Each procedure would require expenditures at three primary stages: (1) obtaining the maternal blood sample, (2) isolating the fetal cells or DNA, and (3) analyzing the genetic material by means of karyotyping, FISH, or PCR.

The blood-drawing stage would almost surely be inexpensive. If conducted in conjunction with another routine blood test, the costs would be only trivially higher than the present cost of testing at that stage. Even if blood-drawing for MSFCS or MPFDR is not combined with that of another

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[161] *See, e.g.*, Palo Alto Medical Foundation, *Your Second Trimester Testing and Exams*, http://www.pamf.org/pregnancy/second/prenatal.html (last visited Jan. 20, 2007) (noting that ultrasound is often used for a "routine anatomy scan of the fetus at 18 to 20 weeks"). The American College of Obstetricians and Gynecologists (ACOG) has recently issued a committee opinion noting that first trimester screening may be an option for some women, but only if strict criteria are met (such as maintaining high standards of ultrasound training and quality control, and ensuring availability of diagnostic tests following positive diagnoses). *See* News Release, ACOG, ACOG Issues Position on First Trimester Screening Methods (June 30, 2004), *available at* http://www.acog.org/from_home/publications/press_releases/nr06-30-04.cfm (last visited Jan. 20, 2007).

[162] *See* JORDE ET AL., *supra* note 7, at 282; Hahn et al., *supra* note 66, at 516.

[163] Chiu & Lo, *supra* note 103, at 84.

screening measure, however, the CDC has estimated that a reasonable laboratory cost for obtaining and shipping a blood sample is only about $10.[164] In contrast, the amniotic fluid-drawing stage of amniocentesis and the villi-sampling stage of CVS, which require the use of highly skilled technicians and expensive ultrasound equipment (for real-time guidance during sampling), cost considerably more, at about $250 to $400 per test.[165]

MSFCS and MPFDR would, however, add an extra step: isolation of fetal genetic material from maternal blood. If the isolation procedure can be automated, costs would still remain relatively low. Researchers believe that automated cell sorting is a real possibility.[166] Simplifying enrichment protocols or identifying reliable fetal markers for MSFCS could "permit the introduction of automated cell scanning devices."[167] If automation can be achieved, the cost of the isolation stage of MSFCS will depend largely upon (1) the one-time cost of acquiring the isolation machinery, and (2) the cost of each isolation procedure. A new and state-of-the-art FACS machine could cost as much as $180,000 to $220,000,[168] but MACS systems are much less expensive, running from about $500 to $1000 for the necessary magnet.[169] Moreover, once purchased, costs per isolation decline rapidly with each procedure performed, and no further expenditures are needed with respect to the physical machinery, other than, perhaps, periodic maintenance and software upgrades for computer programs. Individual isolations will require particular supplies (chemical markers, staining materials, magnetic beads, etc.), all of which may be purchased in bulk and are not particularly pricey. In addition, because an automated process greatly expedites the process,[170] and (possibly) obviates the need for continuous technician supervision, the cost of each isolation will probably be relatively low. One laboratory, which rents its

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[164] DRAFT GENETIC TEST REVIEW, *supra* note 37, at 4-38.

[165] *See id.* at 4-45 to 4-46 (listing several researchers' calculations of costs, including: $200 in 1994 dollars [or $255 in 2005 dollars], $315 in 1996 dollars [or $382 in 2005 dollars], and $332 in 1996 dollars [or $403 in 2005 dollars]).

[166] *See* Chiu & Lo, *supra* note 4, at 100 (noting and citing the research of scientists who have "evaluated and adopted" "automated platforms for fetal DNA extraction").

[167] Hahn & Holzgreve, *supra* note 17, at 651.

[168] *See, e.g.*, Grizzly Analytical Biotech Lab Equipment, *Used/reconditioned/rebuilt Biotech Lab Equipment*, Jan. 18, 2007, http://www.grizzlyanalytical.com/ (last visited Jan. 20, 2007) ($153,500 for a used 2001 FACSVantage™ system); Pacific Laboratory Medicine Services, *Clinical Immunology Fees Policy*, http://www.palmslab.com.au/research/flowcyto.pdf (about $180,000 U.S. dollars for a FACSVantage™ SE system, in 2000); *RE: FACScanto*, http://www.cyto.purdue.edu/hmarchiv/2004/1666.htm (last visited Jan. 20, 2007) (about $215,000 U.S. dollars for a FACSCanto™ system, one of BD Biosciences's most state-of-the art models).

[169] *See, e.g.*, BD Biosciences, *Magnetic Cell Separation*, http://www.bdbiosciences.com (listing the BD iMagnet™ at $495) (last visited Jan. 20, 2007). Compare this with the $50,000 to $200,000 outlay for clinic-quality ultrasound equipment currently used in prenatal testing. *See, e.g.*, Heidi Evans, *Doctors Who Perform Fetal Sonograms Often Lack Sufficient Training and Skill*, WALL ST. J., June 20, 1995, at B1 ("most sophisticated equipment" can cost up to $200,000); Prod. Eng'g – Med. Equip. Div., http://www.pemed.com/ultrasnd/ultrasnd.htm ("list" prices range from $38,000 to $165,000 for clinical ultrasound equipment) (last visited Jan. 20, 2007).

[170] The FACSCanto™ by BD Biosciences boasts speeds of up to 10,000 events per second. *See BD Biosciences Releases BD FACSCanto™ Flow Cytometry System for Clinical Diagnostics*, Sept. 21, 2004, http://www.bd.com/contentmanager/b_article.asp?Item_ID=21690&ContentType_ID=1&BusinessCode=20001&d=&s=&dTitle=&dc=&dcTitle= (last visited Jan. 20, 2007).

FACScan™ machine to local researchers, offered a price that, at a rate of one sample per minute, would cost less than $1.00 per sample.[171] The long-run cost with a previously purchased machine could be even lower.

MPFDR isolation procedures would be similarly inexpensive. Size-fractionalization to recover fetal DNA "is relatively simple and can be performed without the need for complex machinery, as it relies on technologies consistent with those currently used in many routine diagnostic and research labs."[172] Thus, sunk costs would be at a minimum, with low costs for bulk supplies, as with MSFCS.

Like the costs of isolation, the costs of genetic analysis with FISH or PCR will depend upon automation and the price of individual tests following the initial sunk costs of machinery. While so-called "budget" real-time PCR cyclers range in price from approximately $40,000 to $140,000,[173] many clinics and laboratories may already possess such machines, and the cost of chemical primers and other materials cost about $1 or less per sample.[174] Indeed, the CDC estimated that a reasonable laboratory cost for DNA analysis (in the context of cystic fibrosis mutations) is only $80 to $100 per sample, *without* automation.[175] And a group of researchers conducting MPFDR via size-fractionalization and PCR amplification "estimated that the cost of [a] single analysis may be as low as US $8" for the *entire process* (isolation + DNA analysis).[176] Thus, if, as is likely, MSFCS and MPFDR abandon time-consuming karyotyping in favor of automated PCR or FISH, costs could be lowered substantially.

Karyotyping, while more expensive, has the benefit of being more comprehensive, to some extent. While automated procedures may only be designed to diagnose a select set of genetic disorders (to save time and money), karyotyping offers a glimpse of *all* of the fetus's chromosomes. On the other hand, karyotyping can only detect major chromosomal problems — a relatively infrequent set of problems in successful pregnancies.[177] Karyotyping appears to add about $100 to $200 in costs to the lab and about $400-500 in price to consumers.[178]

Overall, consumer prices of MSFCS and MPFDR would likely range from $100-200 for standard automated procedures, and perhaps as much as $500 for individualized genetic tests or for testing with karyotyping (assuming

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[171] *See* University of Massachusetts, Amherst, *Introduction to the Flow Cytometry Facility: Cost & Availability*, http://www.bio.umass.edu/mcbfacs/intro.htm#cost (last visited Jan. 20, 2007).

[172] Li et al., *supra* note 109, at 849.

[173] *See* Bruno Verhasselt, *Comparison of the Different Real-Time PCR Machines* 1, 24, http://72.14.207.104/search?q=cache:UgO4UoIMzJQJ:www.cytometry.be/RTPCR2004/Verhasselt.pdf+cost+of+a+PCR+machine+Rotor+Gene&hl=en&start=10 (last visited Jan. 20, 2007) (showing prices from about 35,000 to about 120,000 Euros).

[174] *See Quantitative Real Time PCR: Blake's Cost Benefit Analysis*, http://www.uttyler.edu/biology/Bextine/bextineQRTPCR.htm (last updated Jun. 19, 2006).

[175] *See* Draft Genetic Test Review, *supra* note 37, at 4-39 ("This estimate includes the costs of reagents, supplies, licenses, royalties, technician time, administrative time and overhead. In the future, it is likely that automation and competition will reduce these costs.").

[176] Li et al., *supra* note 109, at 849.

[177] Most fetuses with major chromosomal abnormalities are spontaneously aborted.

[178] Draft Genetic Test Review, *supra* note 37, at 4-45 (estimating the lab costs of amniocentesis to be between $400 and $600, depending on whether karyotyping is performed).

automated isolation procedures). Given that most anomalies that can be detected by karyotyping, and those that are most common in the population can also be detected by FISH or PCR, a relatively small number of women will have to undergo a more individualized procedure, making overall costs closer to those for automation. Thus, the price of MSFCS and MPFDR would be substantially lower than that of amniocentesis and CVS ($1000-2000 each), and more on par with modern screening procedures like ultrasound (around $200-300 per procedure).[179] This reduction in price, coupled with the added benefits of non-invasiveness, increased accuracy, and earlier detection, will almost surely lead to an explosion of additional participants in prenatal genetic diagnosis.

B. Redefining the Standard of Care

The advent of a non-invasive, accurate, and low-priced genetic test will likely impact the prevailing standard of care for prenatal treatment. In order to determine how and to what extent, it is important to examine: (1) the legal/medical concept of "standard of care," (2) how such standards are developed, and (3) the prevailing standard of care for modern forms of prenatal testing, to which analogies may be drawn with the proposed MSFCS and MPFDR procedures.

1. Defining Standard of Care

The term "standard of care" has both legal significance (arising in the context of medical malpractice lawsuits) and medical significance (translating into particular protocols and conduct among medical professionals). Based upon a negligence theory of liability, medical malpractice claims require the plaintiff to prove that the defendant physician failed to exercise "due care" in a particular situation.[180] The due care standard for medical professionals "is not one of excellence or superior practice;" rather, it generally means conducting oneself as a "reasonable practitioner" (or a "reasonable specialist") would in similar circumstances.[181] Thus, in addition to proving that a physician failed to act with due care, a "med-mal" plaintiff must also establish an objective "standard of care" among similarly situated medical professionals. Standard of care is a question for the jury and is generally established through expert testimony.[182]

Courts are evolving in their view of what constitutes "similar circumstances" when delineating the standard of care among a particular group of physicians. Although historically most courts held physicians to the standards of the particular school to which the practitioner adhered (e.g.

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[179] *See, e.g.*, Bette Van Metter, *Ultrasound*, http://parenting.ivillage.com/pregnancy/psecondtri/0,,43hx-p,00.html (last visited Jan. 20, 2007) ($200 to $300); *Ultrasound for Screening During Pregnancy*, http://www.tennesseehealth.com/main-before-you-buy/MedicalTechnologies/Medical_Value_Index/ULTRASOUND_FOR_SCREENING_DURING_PREGNANCY.HTM (last visited Apr. 20, 2006) (average cost of $250.42, but range of $126 to $350).

[180] Marcia Mobilia Boumil et al., Medical Liability in a Nutshell 25 (2d ed. 2003).

[181] *Id.* at 25-26.

[182] Barry R. Furrow et al., Health Law 174 (4th ed. 2001).

osteopathic vs. allopathic),[183] or to the standards of the particular geographical location in which the physician practiced,[184] most modern courts regard such distinctions as obsolete. Today, the trend is toward recognizing a "national" or "nongeographic" standard of care, in light of "ubiquitous national communication networks both within and without the medical profession," the nationalization of modern medical education, and the free flow of scientific information through nationwide medical journals and continuing education programs.[185] Obstetricians and gynecologists, whose specialty boasts a vast network of professional organizations, publications, and guidelines-issuing entities, will almost certainly be held to a national standard of care, at least where they possess the necessary equipment.

2. Developing Standard of Care

The development of a standard of care within a particular field of medicine is complex and is not greatly influenced by government standards.[186] Instead, "[m]ost clinical policies develop from a flow of reports in the literature, at meetings, and in peer discussions."[187] In today's information age, this flow of medical information is enormous and occurs at lighting pace. Practitioners from widely disparate global regions can confer electronically regarding proper standards of treatment. In the field of obstetrics and gynecology, societies like the American College of Obstetricians and Gynecologists ("ACOG") and the Society for Maternal-Fetal Medicine create networks — in both physical space and cyberspace — for physicians to exchange views on standard treatments and protocols.[188] Moreover, clinical research studies from every part of the world are available in abundance over

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[183] *See, e.g.*, Cayton v. English, 23 F.2d 745, 748-49 (D.C. Cir. 1927) (noting that the lower court correctly instructed the jury that an osteopathic physician was to be held to the standard of an ordinary skillful practitioner of the osteopathic school); Force v. Gregory, 27 A. 1116, 1116-17 (Conn. 1893) (holding, in a malpractice action against a homeopathic physician, that defendant was to be judged by the tenets and practices of his own school).

[184] *See, e.g.*, SeaRiver Maritime, Inc. v. Indus. Med. Serv., Inc., 983 F. Supp. 1287, 1296 (N.D. Cal. 1997) ("physician must exercise the degree of skill or care possessed by doctors in good standing practicing in the same locality under similar circumstances"); Taylor v. Wilmington Med. Ctr., Inc., 577 F. Supp. 309 (D. Del. 1983) (neurosurgeon in Wilmington must conform to the standards of comparable specialists practicing in that city); Swan v. Lamb, 584 P.2d 814, 817 (Utah 1978) (professed expert surgeons in Salt Lake City should be held to the standard of care exercised by experts in the same field in cities of comparable size).

[185] Robbins v. Footer, 553 F.2d 123, 128-29 (D.C. Cir. 1977); *see also* Rojas-Ithier v. Sociedad Espanola de Auxilio Mutuo y Beneficiencia de Puerto Rico, 394 F.3d 40, 43 (1st Cir. 2005) ("Puerto Rico law holds physicians to a national standard of care."); Nalder v. West Park Hosp., 254 F.3d 1168, 1175-76 (10th Cir. 2001) (for purposes of medical malpractice claims, Wyoming requires nationally board certified physicians to conform to a standard of care adhered to by that national board, not a local standard of care).

[186] FURROW ET AL., *supra* note 182, at 266 ("Neither the Food and Drug Administration, the National Institutes of Health, the Department of Health and Human Services nor state licensing boards have had much to do with shaping medical practice.").

[187] *Id.*

[188] ACOG, for example, organizes conferences and seminars on important professional topics and sponsors "online discussions" from its website. *See* The American College of Obstetricians and Gynecologists, www.acog.org (last visited Jan. 20, 2007).

the Internet,[189] providing practitioners with up-to-date information about established or emerging technologies and treatments. In OB/GYN, much clinical research has been conducted, resulting in thousands of standards-guiding articles in dozens of practice-specific publications.[190] ACOG even publishes its own medical journal, *Obstetrics & Gynecology*, which is available online.[191] In addition, websites like the National Guideline Clearinghouse feature searchable databases of specialty-specific clinical practice guidelines.[192] Such practice guidelines include those issued by ACOG, which are derived from research studies and medical consensus.[193]

Indeed, the establishment of clinical practice guidelines has critically impacted standards of medical practice over the last several decades. These guidelines, prepared by specialty societies like ACOG or by individual hospitals, give suggestions for how to treat a particular condition or offer protocols regarding the "ideal sequence or timing of [particular] interventions . . ."[194] As defined by the Institute of Medicine, "[p]ractice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[195] Despite their avowed status as mere "guidelines," however, such statements can pose legal problems for physicians in malpractice suits if a plaintiff attempts to offer the guidelines as authoritative conclusions regarding the appropriate standard of care. Failure to act in accordance with a guideline could be treated as negligence per se, or as a rebuttable presumption of negligence.[196] In fact, a number of plaintiffs have successfully exploited practice guidelines, especially those of ACOG.[197]

Moreover, guidelines issued for legal, rather than medical, purposes can also contribute to the standard of care. For example, in 1985, ACOG's Department of Professional Liability issued an "Alert" regarding MSAFP

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[189] The number of "clinical research articles based on randomized clinical trials jumped from about 100 per year to 10,000 annually" between 1966 and 1995. FURROW ET AL., *supra* note 182, at 270.

[190] Some include the American Journal of Obstetrics and Gynecology; the British Journal of Obstetrics and Gynecology; Clinical Obstetrics and Gynecology; International Journal of Obstetric Anesthesia; Journal of Obstetric, Gynecologic, and Neonatal Nursing; Obstetrical and Gynecological Survey; Journal of Maternal-Fetal Investigation; and Maternal and Child Health Journal. Many OB/GYN articles are also published in general—rather than practice-specific—medical journals such as the Journal of the American Medical Association or The Lancet.

[191] The publication features "original articles and research studies on: scientific advances, new medical and surgical techniques, obstetric management, and clinical evaluation of drugs and instruments." *See* American College of Obstetricians and Gynecologists, http://www.acog.org/navbar/current/greenJournalLeader.cfm (last visited Jan. 20, 2007).

[192] *See* NGC - National Guideline Clearinghouse, www.guideline.gov (last visited Jan. 20, 2007).

[193] FURROW ET AL., *supra* note 182, at 267.

[194] *Id.* at 268.

[195] *See* INST. OF MED., CLINICAL GUIDELINES: DIRECTIONS FOR A NEW PROGRAM 38 (M. Field & K. Lohr, eds. 1990), *available at* http://books.nap.edu/books/0309043468/html/index.html

[196] FURROW ET AL., *supra* note 182, at 269.

[197] *See, e.g.*, Green v. Goldberg, 630 So.2d 606, 609 (Fla. Dist. Ct. App. 1993) (ACOG bulletin on breast cancer treatment could be used to cross-examine expert witness); Miles v. Edward O. Tabor, M.D., Inc., 443 N.E.2d 1302, 1303 (Mass. 1982) (obstetrician violated ACOG guidelines by failing to resuscitate infant immediately following delivery).

screening for pregnant women, at a time when routine MSAFP testing was still considered to be "of uncertain value."[198] Amidst an atmosphere of heavy malpractice litigation, the Alert announced that it was "imperative that every prenatal patient be advised of the availability of [MSAFP screening] and that member physicians' discussion about the test and the patient's decision with respect to the test be documented in the patient's chart."[199] As a result, MSAFP screening for Down Syndrome and neural tube defects quickly came to be regarded as standard of care,[200] in professional practice *and* in the context of malpractice lawsuits.[201] Thus, standard of care is influenced by many factors, including the threat of liability.

3. Delineating Standard of Care for Prenatal Testing & Analogizing to MSFCS and MPFDR

Gleaning from clinical practice guidelines and other indicators of practitioner consensus, several prenatal tests emerge as the current standard of care. These present standards inform the inquiry of whether and when MSFCS and MPFDR will similarly reach "standard of care" status.

First, as early as 1995, the CDC concluded that, "[i]n the United States, the current standard of care in obstetrical practice is to offer either CVS or amniocentesis to women who will be [greater than or equal to] 35 years of age when they give birth . . ."[202] This appears to be confirmed by a 2001 ACOG Practice Bulletin,[203] which recommends, on the basis of "consensus and expert opinion," that "[w]omen with singleton pregnancies who will be age 35 years or older at delivery should be offered prenatal diagnosis for fetal aneuploidy [i.e. abnormalities in chromosome number]."[204] While both sources note the high accuracy of such procedures (over 99%), the standard of care is merely to *offer* the tests — and only to women over a specified age — in light of the risk of miscarriage.

Second, most sources consider second-trimester maternal blood tests that screen for multiple protein markers — particularly, the "triple screen" — to be standard of care for women under 35 and others who do not undergo invasive diagnostic testing.[205] As described by the National Institutes of Health ("NIH"), "[s]econd-trimester screening is based on the current, standard-of-care, serum 'triple screen[]' . . . ."[206] ACOG, too, recognizes that the "triple

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198 Suter, *supra* note 157, at 252.

199 *Id.*; *see also* Basten v. United States, 848 F. Supp. 962, 967 (M.D. Ala. 1994).

200 Suter, *supra* note 157, at 252-53.

201 *See, e.g.*, Basten, 848 F. Supp. at 967-68.

202 Olney et al., *supra* note 46, at 2.

203 Such Practice Bulletins are considered "Clinical Management Guidelines for Obstetrician-Gynecologists," but, as with all recent ACOG recommendations, each bulletin is careful to include a disclaimer that "[t]hese guidelines should not be construed as dictating an exclusive course of treatment or procedure . . . ." *See, e.g.*, ACOG Practice Bulletin No. 27, *supra* note 10, at 1.

204 *Id.* at 8.

205 *See* citations at *infra* notes 206-07.

206 Nat'l Insts. of Health, Prenatal Diagnosis: First and Second Trimester Evaluation of Aneuploidy Risk (Faster), 43 (May 2004), *available at* http://www.nichd.nih.gov/ publications/pubs/upload/Council_MRDD_2001.pdf (describing a multi-center prospective study to compare first- and second-trimester noninvasive screening methods for fetal aneuploidy).

screen" "has been validated extensively and has become the preferred Down syndrome screening test for women younger than 35 years."[207] In fact, second-trimester serum screening has rapidly become standard practice, despite being relatively new (initially discovered in the mid-1980s,[208] whereas amniocentesis has been researched since the early twentieth century and used clinically since the 1960s).[209] The test has been shown to detect 60% to 75% of all Down Syndrome pregnancies.[210]

On the other hand, *first*-trimester maternal serum screening has not yet been demonstrated to be sufficiently accurate to be deemed standard of care. In 2001, ACOG noted that "preliminary data remain controversial and testing is not yet standard of care."[211] At that time, detection rates of certain analytes were low and appeared to be unhelpful for diagnosing Down Syndrome until 12 weeks.[212] By 2004, however, ACOG recognized the increased accuracy of combining first-trimester maternal serum screening with ultrasonography to measure nuchal lucency. In a Committee Opinion, ACOG noted that such a combination yielded detection rates for fetal aneuploidy that were comparable to those with the "triple" or "quadruple" screen in the second trimester.[213] Without endorsing the procedure as standard of care, the Opinion stated that "first-trimester screening for Down Syndrome and trisomy 18 is an option," which should be offered only if specific criteria are met.[214]

Like first-trimester serum screening, ultrasonography has not yet been recognized as standard of care in the U.S., despite its widespread use (by 67% of American women with live births in 2002)[215] and its standard-of-care status in other nations, such as England.[216] ACOG's Practice Bulletin of December

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[207] ACOG Practice Bulletin No. 27, *supra* note 10, at 2; *see also* Am. Coll. of Obstetricians & Gynecologists, ACOG Committee Opinion No. 296: First-Trimester Screening for Fetal Aneuploidy, 1 (July 2004) [hereinafter ACOG Committee Opinion No. 296] (second-trimester maternal serum screening is "commonly offered" to test for (fetal aneuploidy and) neural tube defects and other fetal malformations); Am. Acad. of Pediatrics & Am. Coll. of Obstetricians & Gynecologists, Guidelines for Perinatal Care 95 (5th ed. 2002) ("Women who are younger than 35 years as of the estimated delivery date should be offered multiple marker serum screening to assess the risk of trisomy 21, ideally between 16 and 18 weeks of gestation. . . . MSAFP testing also should be offered to all pregnant women not undergoing amniocentesis . . . ideally between 16 and 18 weeks of gestation.").

[208] ACOG Practice Bulletin No. 27, *supra* note 10, at 2.

[209] *See, e.g.*, Dr. Joseph Woo, *A Short History of Amniocentesis, Fetoscopy and Chorionic Villus Sampling*, *available at* http://www.ob-ultrasound.net/amniocentesis.html.

[210] ACOG Practice Bulletin No. 27, *supra* note 10, at 2; ACOG Committee Opinion No. 296, *supra* note 207, at 1.

[211] ACOG Practice Bulletin No. 27, *supra* note 10, at 4.

[212] *Id.*

[213] ACOG Committee Opinion No. 296, *supra* note 207, at 2.

[214] *Id.* at 2. The criteria included: appropriate ultrasound training and quality control, sufficient resources for comprehensive genetic counseling, and access to the appropriate diagnostic test in the event of a positive diagnosis. *Id.* at 2-3.

[215] Martin et al., *Births: 2002*, *supra* note 52, at 79.

[216] *See* James B. Rubenstein, *What is Ultrasound and How is it Used?*, N.Y. Daily News Health, Mar. 14, 2002, http://nydailynews.healthology.com/nydailynews/16236.htm (last visited Apr. 22, 2006). The National Collaborating Centre for Women's and Children's Health, based at the Royal College of Obstetricians and Gynecologists in the U.K., lists, as a "Class A" recommendation, that women should be offered an early ultrasound (prior to 12 weeks), and notes the routine offering of a later ultrasound (at 18-20 weeks) to test for structural abnormalities. Nat'l Collaborating Ctr. for Women's & Children's Health, Antenatal Care: Routine Care for the Healthy Pregnant Woman (2003), *available at*

2004 concluded that ultrasound is generally a safe and accurate procedure for determining gestational age, viability, and fetal number.[217] Yet the bulletin noted, "ultrasound energy delivered to the fetus cannot be assumed to be completely innocuous,"[218] and "casual" use of the test (e.g. to produce "keepsake" videos) should be avoided.[219]

In light of the current standards for prenatal testing, MSFCS and MPFDR, if successfully developed, will very likely become standard of care. The two most critical factors for achieving "standard of care" status appear to be: (1) accuracy and (2) safety. One multi-center study showed that MSFCS detected about "74% of Down Syndrome cases."[220] Moreover, Rodriguez de Alba et al. correctly diagnosed all six aneuploid fetuses among 66 random samples.[221] MPFDR has been shown to be even more accurate at detecting certain genes, like rhesus D — for which researchers observed "an accuracy of fetal genotyping in the 90-100% range" across thirteen large-scale, published studies.[222] Certainly, more clinical study and peer review is required to confirm these results and satisfy practice societies like ACOG as to the reliability of the procedures. Given that second-semester maternal serum screening (with its 60-75% accuracy) is currently standard of care, however, it is likely that MSFCS or MPFDR will reach sufficient levels of accuracy to support a "standard of care" designation. Thus, while much of this article assumes that diagnostic accuracy will eventually be achieved, it should be remembered that 98-99% accuracy levels are *not* required to become standard of care.

Whether or not MSFCS or MPFDR reach diagnostic-level accuracy, the procedures are likely to become standard of care because they are noninvasive and extremely safe. The significance of relative safety is apparent when considering current standards of care. ACOG's principal concern with ultrasonography, which is not yet standard of care, appears to be the potential for fetal harm from ultrasound energy. In contrast, the second-trimester "triple screen" — with accuracy rates similar to those of ultrasound — *is* considered standard of care, most likely because obtaining a maternal blood sample is essentially risk-free. Meanwhile, providing the option of amniocentesis or CVS is considered standard of care only for women at high risk for carrying affected fetuses, because otherwise, the dangers outweigh the concerns about genetic disorders. Because MSFCS and MPFDR are non-invasive procedures, they are most analogous to current second-trimester serum screens. Indeed, MSFCS and MPFDR are even better candidates than current "standard of care" procedures, because they could be conducted earlier in pregnancy than serum screening and amniocentesis, and because they will be considerably less expensive than amniocentesis or CVS. If MSFCS or MPFDR can attain diagnostic-level accuracy — thus making them more

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http://www.guideline.gov/summary/summary.aspx?doc_id=4808&nbr=3470&string=routine+AND+ultrasound.

[217] ACOG PRACTICE BULLETIN NO. 58, *supra* note 142, at 8-9.

[218] *Id.* at 6.

[219] *Id.* at 6, 9.

[220] *An Earlier Look at Baby's Genes*, *supra* note 128, at 1476 (citing U.S. National Institute of Child Health and Human Development Fetal Cell Study, or NIFTY trial).

[221] Rodriguez de Alba et al., *supra* note 28, at 937-40.

[222] Bianchi et al., *Noninvasive Prenatal Diagnosis*, *supra* note 122, at 842.

accurate than second-trimester serum screening — they will be a shoe-in for standard of care. Moreover, like the "triple screen," MSFCS and MPFDR could become the standard relatively rapidly after implementation — perhaps within ten to fifteen years — if demonstrably accurate for that period of time.

MSFCS or MPFDR may also become the standard of care in the context of medical malpractice litigation, or in response to fears about potential legal liability. The introduction of clinical MSFCS or MPFDR could induce a flurry of "wrongful birth" lawsuits (in which parents argue that a doctor's negligence deprived them of the right to prevent the birth of a sick child) or "wrongful life" lawsuits (in which an unhealthy child sues to recover for having been born).[223] Wrongful birth suits have been brought against physicians for failing to offer a diagnostic test that would have discovered fetal genetic defects,[224] or for failing to perform standard prenatal screening tests like the "triple screen" or MSAFP test.[225] The introduction of MSFCS or MPFDR — procedures that are safe, inexpensive, and relatively quick and easy to perform — will make it very difficult for physicians to defend such lawsuits, should they fail to inform their patients about these tests. Indeed, the mere anticipation of such suits may prompt ACOG to recommend that all doctors offer the tests to their patients (much like the MSAFP campaign referenced above), perhaps making MSFCS or MPFDR the *de facto* standard of care. Thus, although *medical* consensus would likely accept MSFCS or MPFDR as standard of care, *legal* influences may also hasten these tests toward "standard of care" status.

C. Covering the Costs of MSFCS or MPFDR

Because the ultimate value of the NPGD will depend upon its price, it is also critical to examine *who* will pay for MSFCS or MPFDR. Health insurance is a favorable choice, and, as argued below, it is likely that both private and public insurers would opt to cover clinical use of MSFCS or MPFDR. This would greatly increase access to prenatal genetic testing, allowing women of all socioeconomic backgrounds to obtain early information about their fetuses' health. In analyzing the likelihood of insurance coverage, this section examines: (1) the "medical necessity" standard, (2) the more straightforward issue of potential coverage under private health insurance, and (3) the thornier question of potential coverage under Medicaid.

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[223] Wrongful life lawsuits, which are more controversial than wrongful birth lawsuits, have nonetheless been recognized in several states. *See, e.g.*, Turpin v. Sortini, 643 P.2d 954 (Cal. 1982); Procanik v. Cillo, 478 A.2d 755 (N.J. 1984); Harbeson v. Parke-Davis, Inc., 656 P.2d 483 (Wash. 1983).

[224] *See, e.g.*, Phillips v. United States, 566 F.Supp. 1 (D.C.S.C. 1981) (failure to perform amniocentesis that would have diagnosed Down Syndrome in fetus); Berman v. Allan, 404 A.2d 8 (N.J. 1979) (failure to inform patient about availability of amniocentesis that would have disclosed Down Syndrome in fetus).

[225] *See, e.g.*, Smith v. Saraf, 148 F. Supp. 2d 504 (D.N.J. 2001.) (failure to perform either a "triple screen" or an alpha-fetoprotein test that would have revealed severe neural tube defects); Basten v. United States, 848 F. Supp. 962 (M.D. Ala. 1994) (failure to offer MSAFP screening that would have disclosed neural tube defects in fetus).

1. Insurance Coverage and "Medical Necessity"

Insurance coverage is principally determined by contract and "remains fundamentally a private agreement."[226] In response to the recent "proliferation of expensive and often unvalidated medical technology," many insurance companies have added contractual provisions to their policies that comprehensively exclude coverage for services deemed "experimental" or not "medically necessary" to treat an illness or condition.[227] While there is little consensus as to the meaning of "medical necessity,"[228] courts typically look to such factors as: "the terms of the policy, the nature of the treatment or equipment, and the circumstances under which it was rendered."[229] Policy terms, which range from the highly general[230] to the highly specific,[231] are usually construed in favor of the insured where ambiguity exists.[232] With respect to the "nature of treatment," an important consideration is whether the test or procedure is part of the "standard of care."[233] Moreover, judges frequently defer to medical opinion, and insurers "will often not prevail where an insured seeks payment for treatment judged necessary by the insured's physician . . . ."[234] No court has addressed the issue of whether prenatal genetic diagnosis is a medically necessary procedure. However, it is likely that there is *no true* "medical necessity" for amniocentesis or CVS,[235] or by analogy,

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[226] FURROW ET AL., *supra* note 182, at 466.

[227] *Id.* at 468.

[228] *See* Jeffrey R. Sang, *First-Party Insurance Coverage for Medically Necessary Treatment*, 15 AM. JUR. 3D *Proof of Facts* 355, § 2 (1991) ("definitions of medical necessity are almost as numerous and diverse as the cases in which they are found").

[229] 75 A.L.R. 4th 763 (1990 & Supp. 1998).

[230] E.g. medical necessity exists when, in the insurer's own "interpretation of accepted medical standards, it cannot be omitted without adversely affecting the patient's condition." Jacob v. Blue Cross & Blue Shield of Oregon, 758 P.2d 382, 383 (Or. Ct. App. 1988).

[231] E.g. medical necessity exists only if a procedure: (a) is ordered by one's physician and (b) is "commonly and customarily recognized throughout the doctor's profession as appropriate in the treatment of the sickness or injury and (c) is neither experimental nor educational and (d) "is not allocable to scholastic education or vocational training of the patient" in the case of hospital confinement." Dozsa v. Crum & Forster Ins. Co., 716 F. Supp. 131, 134 (D.N.J. 1989).

[232] *Id.*

[233] For a discussion of standard of care in prenatal genetic diagnosis, see text at *supra* Part IV.B.

[234] FURROW ET AL., *supra* note 182, at 470.

[235] Some states consider a viable fetus a "person" for the purposes of certain statutes. *See, e.g.*, Commonwealth v. Morris, 142 S.W.3d 654 (Ky. 2004) (unborn child is a "person" for purposes of homicide statute) and Whitner v. State, 492 S.E.2d 777 (S.C. 1997) (viable fetus is a "child" under child abuse and endangerment statute). However, it is unquestionable that a 15-17 week old fetus could not survive outside the womb, even with the most advanced technological assistance. *See* Pro-Life America, Facts of Fetal Development, http://www.prolife.com/FETALDEV.html (last visited May 5, 2006) (citing M. Allen et al., *The Limits of Viability*, 329 NEW ENG. J. MED. 1597 (1993)) (at 23 weeks, the fetus has a 15% chance of viability outside the womb; at 24 weeks, the chance rises to 56%). Even if the fetus could be considered a "person" requiring "treatment," however, medical necessity provisions likely apply only to the individual listed on the policy, not to any unborn children of the insured. And mere diagnosis of another "person's" health is unlikely to constitute "treatment," even if the natural and voluntary state of pregnancy could be considered a "condition" requiring such treatment.

for MSFCS or MPFDR, except in rare circumstances in which the mother's own health is endangered by carrying or delivering an affected fetus.[236]

Nevertheless, some insurance companies do provide coverage for amniocentesis or CVS, in limited circumstances that track the current standard of care. In other words, insurers are much more likely to cover testing for women aged 35 and older.[237] The Harvard Student Health Insurance Handbook, for example, notes that "Amniocentesis or Chorionic Villi Sampling ("CVS") for women under age 35 is not covered (unless medically necessary)."[238] This suggests that, if MSFCS or MPFDR attain "standard of care" status, insurance coverage would follow.

In addition, some insurance companies today deem prenatal genetic testing "medically necessary" in special circumstances, like having a positive family history or a positive carrier status for a particular condition. Aetna, one of the largest health insurers in the country, "considers genetic testing for fragile X syndrome medically necessary for" "[f]etuses of known carrier mothers."[239] Such limitations indicate a reason why insurers cover procedures, like amniocentesis, that may be technically "unnecessary" for medical treatment of illness or disease. Among women with family histories of certain conditions, there is a higher likelihood (relative to other pregnant women) of detecting incidents of genetic disease. Each accurate detection presents the possibility of aborting a very sick fetus, which, if born, could cost its parents (and its parents' insurer) large amounts of money. Thus, the medical necessity standard may be a moot point when it comes to coverage of NPGD. If the procedure is cost-effective, such that insurance companies will pay out less in benefits than the costs they will save by covering these tests, insurers (and, particularly, private insurers) will be willing to cover MSFCS or MPFDR — even for pregnant women under 35, among whom the majority of fetal defects occur.[240]

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[236] I am not aware of any such situations, as Rh incompatibility (discoverable by prenatal genetic testing) poses no risk to maternal health. Indeed, it is typically the *mother's* health conditions (i.e. diabetes, seizures, infections, asthma, or family history of genetic disease) that pose a risk for the developing fetus, not the other way around. However, I cannot rule such circumstances out completely. It is possible, for example, that certain genetic disorders of the fetus could increase the possibility of pre-eclampsia during delivery, thus endangering both mother and fetus.

[237] *See, e.g.*, U.S. Dep't of Health & Hum. Srvcs., Coverage and Reimbursement of Genetic Tests and Services: Report of the Secretary's Advisory Committee on Genetics, Health, and Society 17-18 (Feb. 2006) [hereinafter Coverage and Reimbursement of Genetic Tests], *available at* http://www4.od.nih.gov/oba/sacghs/reports/CR_report.pdf ("Of the few [private] coverage policies that are publicly available, most cover genetic testing for . . . prenatal and neonatal diagnosis . . . in certain situations (e.g. advanced maternal age, suspected fetal anomaly, or history of miscarriage or developmental problems in prior pregnancies)."); Univ. of California, San Francisco, Children's Hospital, *Prenatal Diagnosis: Amniocentesis*, http://www.ucsfhealth.org/childrens/medical_services/preg/prenatal/amniocentesis.html (last visited Jan. 20, 2007) ("Most insurance plans cover amniocentesis . . ., especially for women over 35 years of age").

[238] Harvard Univ. Health Srvc., Harvard Student Health Insurance Handbook 24 (2005-06).

[239] Aetna, Inc., Clinical Policy Bulletin No. 0140: Genetic Testing (reviewed Apr. 22, 2005), *available at* http://www.aetna.com/cpb/medical/data/100_199/0140.html.

[240] Around 80% of all babies with Down Syndrome are born to women under 35. *See* Nat'l Down Syndrome Soc'y, *Down Syndrome: Myths and Truths*, http://www.ndss.org/

2. Private Health Insurance Coverage: Costs to Be Saved by Abandoning Medical Necessity

Every year, insurance companies in the U.S. pay millions of dollars to families raising children with serious genetic conditions.[241] The average lifetime cost of caring for an individual with Down Syndrome, for example, is $612,000 (in 2005 dollars) above and beyond the cost of caring for a "normal" person.[242] Similarly, incremental lifetime costs of caring for an individual with cystic fibrosis can total $300,000 or more.[243] Many of these costs are health-related. With around 5,000 Down's-affected babies and around 2,500 babies with cystic fibrosis born each year in the U.S.,[244] it is clear that insurers stand to benefit greatly by helping to reduce the incidence of genetic disorders in the population. This could be accomplished by funding widespread prenatal testing, which would increase rates of detection — and, presumably, abortion — of sick fetuses.

Of course, an insurer's decision to cover the test will depend upon whether the cost of MSFCS and MPFDR will be sufficiently low, and the future cost savings sufficiently high, to justify insurance coverage. Each accurate detection and abortion ("catch")[245] will save the insurer a hypothetical lifetime of healthcare costs that would otherwise be incurred by an individual with a genetic disorder. Thus, by comparing the tests' cost with the present value of the per-person lifetime healthcare costs associated with a particular genetic condition, it is possible to determine how many "catches" are necessary to confirm the financial soundness of private insurance coverage.[246]

For instance, assuming that approximately 2.7 million American women would obtain MSFCS or MPFDR in a given year if the procedures were in regular clinical use,[247] and that the cost per test would be about $200, insurers would cover such tests if doing so would result in a present-value savings of at

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index.php?option=com_content&task=category&sectionid=23&id=58&Itemid=234 (last visited Jan. 20, 2007) [hereinafter *Down Syndrome: Myths and Truths*].

[241] *See* Tracy A. Lieu et al., *The Cost of Medical Care for Patients with Cystic Fibrosis in a Health Maintenance Organization*, 103 PEDIATRICS 72 (1999).

[242] *See* Tryfon Beazoglou et al., *Economic Evaluation of Prenatal Screening for Down Syndrome in the U.S.A.*, 18 PRENATAL DIAGNOSIS 1241, 1242 (1998) (estimating lifetime incremental costs of Down Syndrome, in 1996, to be about $504,000).

[243] *See* C. Krauth et al., *Cystic Fibrosis: Cost of Illness and Considerations for the Economic Evaluation of Potential Therapies*, 21 PHARMACOECONOMICS 1001 (2003) (estimating lifetime costs of CF, in 2003, to be $200,000 to $300,000). These numbers, however, may be much higher, depending upon the severity of the disease. One study estimated average annual costs of $13,300 for each CF patient, in 1996. With a 30-year lifespan, this results in over $399,000 in lifetime costs in 1996 dollars, or nearly $485,000 in 2005 dollars. *See* Lieu et al., *supra* note 241, at 72.

[244] *Down Syndrome: Myths and Truths*, *supra* note 240 ("Down syndrome occurs in 1 in 800 to 1,000 births."); ANTHONY J. F. GRIFFITHS ET AL., MODERN GENETIC ANALYSIS, at tbl.11-1 (7th ed. 1999) (citing CF incidence as "1/1600 Caucasians"); Martin et al., *Births: 2003*, *supra* note 53, at 37 (noting an estimated 2,300,000 yearly "non-Hispanic White" births); Part V at tbl.1.

[245] In this sub-section, the term "catch" refers to any fetus that is both positively diagnosed and aborted.

[246] Note that the following exercise is meant as a rudimentary estimation to illustrate a point. In reality, the calculations get trickier, because seriously disabled children become eligible for Medicaid rather quickly.

[247] This figure assumes that MSFCS and MPFDR are, or are beginning to become, the standard of care. Of course, this may not occur until several years after the tests' introduction.

least $540 million in that year (2,700,000 patients * $200 = $540,000,000). Down Syndrome, a condition that is readily diagnosed using a prenatal genetic test, has a birth incidence of 1 in 800 to 1 in 1,000, or 4,000 to 5,000 live births each year (I assume 4,500 in the calculations below).[248] The present value of incremental, direct medical costs for each individual with Down Syndrome is about $110,000.[249] As a result, in 2005, insurers would "break even" when the number of "catches," X, multiplied by $110,000, equaled $540 million. Thus, 4,909 "catches" are necessary in a given year to financially justify insurance coverage at $200 per test (X = 540,000,000/110,000 = 4909).

If 2.7 million out of approximately 4 million women (67.5%) obtain testing,[250] then only about 3,038 out of 4,500 (67.5%) possible Down's births could potentially be detected.[251] Assuming a 98% accuracy rate for the tests,[252] and an 85% termination rate upon positive diagnosis,[253] approximately 2,531 "catches" will be made (3,038 * 0.98 * 0.85 = 2,531). Thus, because the number of necessary "catches" (4,909) is greater than the number of possible "catches" (2,531), private insurance is *not* financially justified at a per-test cost of $200. On the other hand, with a per-test cost of $100 (and the same usage rate of 2.7 million out of 4 million women), insurance coverage would be justified with only 2,455 "catches" in a given year (270,000,000/110,000 = 2,455). Here, the number of necessary "catches" (2,455) is *lower* than the 2,531 "catches" that would be obtained by MSFCS/MPFDR testing. Thus, at a price of $100 per test, private insurance companies would likely cover MSFCS and MPFDR, since the potential savings exceed the costs.

It is important to note a couple of caveats, which further argue *in favor* of private insurance coverage for prenatal genetic diagnosis. First, Down Syndrome is not the only genetic condition that could be detected by MSFCS and MPFDR. In fact, scientists have developed reliable genetic tests for diagnosing a variety of serious disorders, including Turner Syndrome, Klinefelter Syndrome, sickle cell disease, hemophilia, Huntington's disease,

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[248] Nat'l Inst. of Health, Down Syndrome, Genetics Home Reference (Sept. 2005), http://ghr.nlm.nih.gov/condition=downsyndrome.

[249] *See* U.S. Envtl. Prot. Agency, The Cost of Illness Handbook, at III.8-8, tbl.III.8-2, (1991 & Supp. 2004), *available at* http://www.epa.gov/oppt/coi (assuming a 5% discount rate and converting from 1996 dollars to 2005 dollars by using an inflation calculator).

[250] Four million women is an estimate, based on the number of live births each year. However, a certain percentage of these births are multiple births, so the actual number of pregnant U.S. women each year is lower than 4 million. However, this merely makes my estimate more conservative.

[251] This assumes that there is no correlation between the status of carrying a fetus with Down Syndrome and a woman's desire or ability to obtain prenatal genetic testing.

[252] Note that this is a conservative figure. In fact, amniocentesis and CVS are both *at least* 99% accurate, according to ACOG. *See* ACOG Practice Bulletin No. 27, *supra* note 8, at 5.

[253] Note that this is a conservative figure, as studies show that termination rates range from 85-95% upon positive diagnosis. *See, e.g.*, Ralph L. Kramer et al., *Determinants of Parental Decisions After the Prenatal Diagnosis of Down Syndrome*, 79 Am. J. Med. Genetics 172, 172-73 (1998) (finding an elective termination rate of 86.9%, regardless of race, religion, or insurance); V.A. Vincent et al., *Pregnancy Termination Because of Chromosomal Abnormalities: A Study of 26,950 Amniocenteses in the Southeast*, 84 South Med. J. 1210 (1991) (finding termination rates of 92% to 95% for autosomal trisomies, at 14 centers in the southeastern U.S.).

cystic fibrosis, and Tay-Sachs disease. Therefore, a single blood test could help "catch" *many* types of affected fetuses, each with associated lifetime costs. When *all* potential savings are considered, it is quite probable that insurance coverage of MSFCS and MPFDR would be justified, even at a price of $200 or higher per test. Moreover, as noted above, insurers are more willing to cover treatments that are considered standard of care — a likely outcome for MSFCS and MPFRD. Therefore, if the price of the procedures remains relatively low, it is very likely that private insurers will cover MSFCS or MPFRD, given the potential costs to be saved in a regime of widespread NPGD.

3. Medicaid Coverage: A Good Investment Despite Political Concerns

Public funding for MSFCS or MPFDR is also an important consideration, given that Medicaid covers a staggering 37% of all U.S. births — over 1.5 million babies — each year.[254] Such coverage is critical if MSFCS or MPFDR are to truly "level the playing field" and provide prenatal genetic testing to all women across the nation. Like private health insurance coverage, Medicaid coverage of MSFCS or MPFDR is likely to be cost-effective in the long run. However, public funding of a procedure that could lead more women to abort affected fetuses will be considerably more controversial in certain states, where political forces may defeat efforts to provide public insurance coverage.

Medicaid is a cooperative federal-state program that provides health care to the poor.[255] Among those eligible for Medicaid services are: poor individuals who receive cash assistance; minimal-income individuals who are aged, disabled, blind, or dependent children; and, more recently, low-income children and pregnant women, even if ineligible for cash assistance.[256] Although jointly financed by both the state and federal governments, Medicaid is administered by the states. Federal statutes set basic conditions for eligibility, disbursement of funds, and benefits, but the states have great freedom to construct Medicaid programs (and disburse state Medicaid funds) as they see fit. This bifurcation results in wide variations in the way states operate their Medicaid programs.[257] Two examples of these differences are relevant to the potential controversy surrounding Medicaid coverage of MSFCS or MPFDR in certain states: (1) The Hyde Amendment and (2) Medicaid funding for genetic testing.

The Hyde Amendment is a federal statute designed to "prohibit the use of Federal funds to pay for abortions,"[258] except when "necessary to save the life of the mother or if the pregnancy is the result of an act of rape or incest."[259] Yet, the states' allocation of their own Medicaid funds varies greatly with

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[254] Nat'l Governors Ass'n, Ctr. for Best Practices, MCH Update: States Protect Health Care Coverage during Recent Fiscal Downturn, at tbl.1 (Aug. 11, 2005) (Draft), available at http://www.nga.org/Files/pdf/0508MCHUPDATE.PDF (noting that Medicaid births comprised 37.24% of nationwide births in 2001, and 36.07% of nationwide births in 2000).

[255] *See, e.g.*, 42 U.S.C. § 1396 (1984).

[256] *See* Furrow et al., *supra* note 182, at 728; 42 U.S.C. § 1396a(a)(10)(A)(i)(III-IV) (2005); 42 U.S.C. § 1396d(n) (2004).

[257] Furrow et al., *supra* note 182, at 586.

[258] 42 C.F.R. § 441.200 (1987).

[259] 42 U.S.C. § 1397ee(c)(1) (2003).

respect to abortion: some states have implemented statutes mirroring the Hyde Amendment; other states exceed federal requirements and fund all or most medically necessary abortions; while one state funds abortions only when necessary to protect the mother's life.[260] Similarly, federal law is silent on Medicaid funding for genetic testing. Yet states' coverage varies with respect to all types of genetic testing except newborn screening (for which *all* states provide Medicaid coverage). For example, while some states' Medicaid systems cover amniocentesis or chorionic villus sampling, others do not.[261]

These variations suggest the existence of a (relatively weak) *legal* obstacle and a (relatively strong) *political* obstacle to Medicaid coverage of NPGD in certain regions. Indeed, one could make the (somewhat attenuated) argument that public funding of prenatal genetic testing is equivalent to public funding of abortion (i.e. because it may lead to abortion in the case of a positive diagnosis), in violation of the Hyde Amendment and state analogs.[262] It is more likely, however, that *political* forces — in the form of moral opposition by a predominantly pro-life citizenry or statewide "public policies" of protecting life from conception,[263] would pose a more potent threat to Medicaid coverage of MSFCS and MPFDR in certain states.[264]

Nevertheless, rejection of Medicaid coverage for prenatal genetic testing will probably be limited to a mere handful of states. Of the 47 states that responded to the Kaiser Family Foundation's National Survey in 2000, 46 provided Medicaid coverage for amniocentesis, and 42 provided Medicaid coverage for CVS.[265] The coverage trends for MSFCS and MPFDR will likely

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[260] *See* Guttmacher Inst., *State Policies in Brief: State Funding of Abortion Under Medicaid*, 1-2 (March 1, 2007), *available at* http://www.guttmacher.org/statecenter/spibs/spib_SFAM.pdf.

[261] *See* Henry J. Kaiser Family Foundation, Medicaid Coverage of Perinatal Services: Results of a National Survey 14 & 16 tbl.II-5 (2001), *available at* http://www.kff.org/womenshealth/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=13738 [hereinafter Medicaid Coverage of Perinatal Services].

[262] Indeed, a plain language reading of the Hyde Amendment and state constitutional equivalents almost certainly precludes the argument that public funding of prenatal genetic testing constitutes public funding of abortion. The Arkansas Supreme Court faced this question when abortion rights opponents filed suit against the University of Arkansas School of Medical Science, alleging that the University's genetics program violated a state constitutional amendment. *See* Knowlton v. Ward, 889 S.W.2d 721 (Ark. 1994). A Hyde analog, the Arkansas amendment provided that "[n]o public funds will be used to pay for any abortion, except to save the mother's life." Ark. Const. amend. 68, § 1. Consistent with the language of the amendment, the Arkansas high court limited the funding ban to *actual payment for abortions*. *Knowlton*, 889 S.W.2d 721. It held that "the plain and unambiguous meaning of this provision does not prohibit the [genetic] testing, diagnosis, and counseling to families during the preconceptional, prenatal and postnatal periods that is performed at [the University]." *Id.* at 726.

[263] *See, e.g.*, Ark. Const. amend. 68, § 2 ("The policy of Arkansas is to protect the life of every unborn child from conception until birth, to the extent permitted by the Federal Constitution.").

[264] As noted by the Secretary of Health and Human Services' Advisory Committee on Genetics, Health, and Society, "Coverage decisions in some States also may be affected by the fact that genetic tests are used for reproductive decisionmaking or family planning, which are viewed by some as tests that can lead to pregnancy termination." Coverage and Reimbursement of Genetic Tests, *supra* note 237, at 32.

[265] Medicaid Coverage of Perinatal Services, *supra* note 261, at 14 & 16 tbl.II-5. This national survey, conducted in 2000, found that all states surveyed except one (Colorado) provided state Medicaid funding for amniocentesis, and all states surveyed except five

mirror this data, as amniocentesis and CVS are close equivalents of MSFCS and MPFDR.[266] In fact, diagnostic MSFCS and MPFDR would be even more persuasive as candidates for Medicaid funding, because they are non-invasive and much less expensive than amniocentesis and CVS. Moreover, an Advisory Committee of the Secretary of Health and Human Services recently recommended that "HHS should continue to encourage States to cover, adopt, and provide genetic tests and services with a sound evidence base."[267]

Even more importantly, states will likely find that it is in their best interest *financially* to provide Medicaid coverage for MSFCS or MPFDR. Medicaid currently covers low-income disabled individuals, including some with disabilities — like Down Syndrome and cystic fibrosis — that are readily identifiable through prenatal genetic diagnosis.[268] Thus, the cost-effectiveness logic described above (in the case of private insurance) applies with equal force in the realm of Medicaid. Every seriously sick fetus that is "caught" through MSFCS or MPFDR is one less seriously sick child for the state to support. So long as the price remains sufficiently low, public funding of MSFCS or MPFDR will lead to long-run cost savings for states.

Given that so many states already provide Medicaid coverage for prenatal genetic testing via invasive and expensive tests like amniocentesis, it is highly likely that most states would finance Medicaid coverage for non-invasive, inexpensive tests like MSFCS or MPFDR, especially with the significant cost savings to be had. With physicians, actuaries, and states on board, widespread funding — and widespread use — of NPGD is almost inevitable.

V. LONG-TERM CONSEQUENCES OF WIDESPREAD NON-INVASIVE PRENATAL GENETIC TESTING

Clearly, the clinical implementation of diagnostic MSFCS or MPFDR could dramatically increase the number of pregnant women who utilize prenatal genetic diagnosis each year. Undoubtedly, there will also be profound long-term consequences associated with such widespread use. Section A will discuss how this increased testing could significantly reduce the incidence — and ultimately, the total prevalence — of debilitating genetic disorders in the population. Section B previews the myriad ethical, legal, and social questions that will arise (and are already arising) in connection with such testing. Finally, Section C addresses the heightened need for high-quality genetic counseling services and clear procedural guidelines, to assist

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(California, Colorado, Missouri, Oklahoma, and West Virginia) provided state Medicaid funding for CVS. Mississippi, New Mexico, and Wyoming did not respond to the survey. *Id.* at 16 tbl.II-5. More recent information seems to confirm this trend. *See, e.g.*, Alabama Medicaid Agency, FY 2004 Annual Report 27, *available at* http://www.medicaid.alabama.gov/documents/Resources/4J-4_Annual%20Reports/4J-Medicaid.AR2004.pdf ("Medically indicated procedures such as ultrasound, non-stress tests, and amniocentesis are examples of other services covered by Medicaid.").

[266] They are equivalents in that genetic material is used to make diagnoses that could lead to abortion.

[267] Coverage and Reimbursement of Genetic Tests, *supra* note 237, at 5.

[268] Henry J. Kaiser Family Foundation, Medicaid Facts: Medicaid's Role for the Disabled Population Under Age 65, at 1-2 (Apr. 2001) ("Medicaid's disabled population has a wide range of physical and mental conditions including . . . cystic fibrosis, Downs Syndrome, mental retardation, autism, [and] spina bifida . . . .").

families with the difficult decisions that arise from the use of prenatal genetic diagnosis.

A. Reduced Incidence of Genetic Disorders

The most direct consequence of widespread prenatal genetic testing via MSFCS or MPFDR will be a decrease in the number of babies born with genetic diseases and chromosomal abnormalities each year.[269] Table 1 lists the approximate number of U.S. children born each year with various genetic disorders (i.e. the current "incidence" of such disorders). Each of the disorders listed is one for which researchers have developed a reliable genetic test, such that it could be detected via MSFCS or MPFDR analysis. In the final column of Table 1, I project the approximate decrease in the incidence of affected births in a future realm of widespread NPGD. These calculations assume a MSFCS/MPFDR usage rate of 67.5% (approximately equivalent to current ultrasound utilization) and a procedural accuracy rate of 98%.[270] The calculations also take into account disorder-specific pregnancy termination rates.[271] In addition, they assume that, where MSFCS or MPFDR is used, multiple genetic tests could be performed on a single blood sample, to detect more than one genetic condition.[272] Under such conditions, as illustrated in Table 1, widespread non-invasive prenatal genetic testing could cause a notable decrease in the incidence of many genetic diseases.

Furthermore, over time, such testing could also reduce the "prevalence" of genetic disorders (i.e. total frequency in the population). For disorders like

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[269] Calculations are based upon an estimated 4 million total live births and an estimated 49% female live births each year in the United States. *See, e.g.*, Martin et al., *Births: 2003*, *supra* note 53, at 8, 48. Incidence data is derived from the following sources: Anthony J. F. Griffiths et al., Modern Genetic Analysis, at tbl.11-1 (7th ed. 1999) (cystic fibrosis, Tay-Sachs disease, hemophilia, and sickle cell disease); Huntington's Disease Soc'y of America, *Fast Facts About HD*, (2006) http://huntingtondisease.tripod.com/usfhdcenterofexcellence/id14.html; Nat'l Inst. of Health, *supra* note 247; Nat'l Inst. of Health, *Turner Syndrome*, Genetics Home Reference, Sept. 2005, http://ghr.nlm.nih.gov/condition=turnersyndrome; *Statistics By Country for Klinefelter Syndrome,* http://www.wrongdiagnosis.com/k/klinefelter_syndrome/stats-country.htm (last visited Apr. 29, 2006).

[270] The basic formula is: Estimated Births if MSFCS/MPFDR Become Widespread = (Current Incidence) – [(Current Incidence) * 0.675 * 0.98 * (Disorder-Specific Rate of Pregnancy Termination)]. The estimates that I use are relatively conservative. I assume MSFCS/MPFDR usage by approximately 2,700,000 women out of 4,000,000 live births each year in the U.S. (67.5%), and an accuracy rate of only 98%. For simplicity's sake, I assume the full 2% of testing errors are false negatives, and thus, do not count toward the number of "catches." In addition, I include totals at both the lower and upper estimates for "approx. rate of pregnancy termination." Note also that while I use the same fractional approximation (67.5%) for sub-populations, it is likely that this is not fully accurate. For example, it is possible that, due to varying socioeconomic conditions, the Ashkenazi Jewish population would obtain prenatal genetic testing for Tay-Sachs at greater rates than 67.5%, and the African American population would obtain prenatal genetic testing for sickle cell disease at lower rates than 67.5%.

[271] Such rates will obviously vary region-by-region. The figures cited in Table 1 are estimates, based upon scientific studies that recorded rates of pregnancy termination. Where possible, I focused on U.S. studies.

[272] Multiple testing of this nature is currently too costly and time-consuming; thus, a fetus is usually tested only for conditions for it is at heightened risk. *See* Telephone Interview with Dr. Jane Chueh, *supra* note 7. However, the introduction of automation could make multiple testing a routine part of clinical practice.

cystic fibrosis, Tay-Sachs disease, and hemophilia — which are transmitted from parent to child via a mutated gene — a reduced incidence of the disease will ultimately lead to a reduced presence of the mutated gene in the population at large (fewer affected individuals and fewer carriers).

Table 1. Projected Incidence of Genetic Disorders with Widespread Prenatal Genetic Testing

	Genetic Disorder	Appx. No. of Affected Children Born Each Year in the U.S.	Appx. Rate of Pregnancy Termination Following Positive Diagnosis	Estimated Yearly U.S. Births if MSFCS or MPFDR Become Widespread
Chromosome Abnormalities	Down Syndrome (trisomy-21)	4000-5000 (1 in 800-1000)	85-95%[273]	1751-2189 (at 85%) 1486-1858 (at 95%)
	Turner Syndrome (XO)	800 (1 in 2500 females)	60-80%[274]	483 (at 60%) 377 (at 80%)
	Klinefelter Syndrome (XXY)	2040 (1 in 500 males)	40-60%[275]	1500 (at 40%) 1230 (at 60%)
Single-Gene Disorders	Sickle Cell Disease	1500+ (1 in 400 African Americans)[276]	40-60%[277]	1103 (at 40%) 905 (at 60%)

Table 1 continued on following page . . .

[273] *See, e.g.*, Ralph L. Kramer et al., *supra* note 253, at 172-173 (finding an elective termination rate of 86.9%, regardless of race, religion, or insurance); V.A. Vincent et al., *supra* note 253 (finding termination rates of 92% to 95% for autosomal trisomies, at 14 centers in the southeastern U.S.).

[274] *See, e.g.*, Tex. Dep't of State Health Srvcs., *Birth Defects Risk Factor Series: Turner Syndrome* (2002) http://www.dshs.state.tx.us/birthdefects/risk/risk25-turner.shtm (citing termination rates from 11 different studies in several nations, which range from 64% to 100%). As U.S. studies are scarce, my (conservative) estimate is at the lower end.

[275] *See* M. B. Forrester & Ruth D. Merz, *Pregnancy Outcome and Prenatal Diagnosis of Sex Chromosome Abnormalities in Hawaii, 1986-1999*, 119 Am J. Med. Genetics 305 (2003) (46% termination rate); *see also* Caroline Mansfield et al., *Termination Rates After Prenatal Diagnosis of Down Syndrome, Spina Bifida, Anencephaly, and Turner and Klinefelter Syndromes*, 19 Prenatal Diagnosis 808 (1999) (58% termination rate); Theresa M. Marteau et al., *Outcomes of Pregnancies Diagnosed with Klinefelter Syndrome: The Possible Influence of Health Professionals*, 22 Prenatal Diagnosis 562 (2002) (44% termination rate across 5 European nations and 11 years).

[276] This is based upon an estimated 600,000 yearly African American births. *See* Martin et al., *Births: 2003*, *supra* note 53, at 29.

[277] *See, e.g.*, X. Wang et al., *Experience With 500 Prenatal Diagnoses of Sickle Cell diseases: The Effect of Gestational Age on Affected Pregnancy Outcome*, 14 Prenatal Diagnosis 851 (1994) (finding, in New York, a 51% termination rate).

Table 1. – Continued . . .				
	Genetic Disorder	Appx. No. of Affected Children Born Each Year in the U.S.	Appx. Rate of Pregnancy Termination Following Positive Diagnosis	Estimated Yearly U.S. Births if MSFCS or MPFDR Become Widespread
Single-Gene Disorders	Hemophilia	204 (1 in 10,000 males)	15-20%[278]	184 (at 15%) 177 (at 20%)
	Huntington's Disease	400 (1 in 10,000)	25-40%[279]	334 (at 25%) 294 (at 40%)
	Cystic Fibrosis	1438 (1 in 1600 Caucasians)[280]	40-50%[281]	1057 (at 40%) 962 (at 50%)
Inborn Error of Metabolism	Tay-Sachs Disease	23 (1 in 3500 Ashkenazi Jews)	95-100%[282]	9 (at 95%) 8 (at 100%)

[278] Study results are based on questionnaire responses, rather than actual terminations. *See, e.g.*, M. Karimi et al., *Comparison of Attitudes Towards Prenatal Diagnosis and Termination of Pregnancy for Haemophilia in Iran and Italy*, 10 Haemophilia 367, 367 (2004) (16.7% of Italian respondents accepted pregnancy termination for hemophilia); E. M. Kraus & D. B. Brettler, *Assessment of Reproductive Risks and Intentions by Mothers of Children With Hemaphilia*, 31 Am. J. Med. Genetics 259 (1988) (17% would terminate); S. Ranta et al., *Hemophilia A: Experiences and Attitudes of Mothers, Sisters, and Daughters*, 11 J. Pediatric Hematology/Oncology 387 (1994) (16% of women would definitely terminate).

[279] M. Bloch et al., *Predictive Testing for Huntington Disease: Demographic Characteristics, Life-style Patterns, Attitudes, and Psychosocial Assessments of the First Fifty-One Test Candidates*, 32 Am. J. Med. Genetics 217 (1989) (29.4% would obtain prenatal testing and terminate a high-risk fetus); A. Maat-Kievit et al., *Experience in Prenatal Testing for Huntington's Disease in The Netherlands: Procedures, Results and Guidelines (1987-1997)*, 19 Prenatal Diagnosis 450, 450 & 452 (1999) (39% of fetuses at increased risk were terminated); D. S. Markel et al., *At-risk Persons' Attitudes Toward Presymptomatic and Prenatal Testing of Huntington Disease in Michigan*, 26 Am. J. Med. Genetics 295 (1987) (21% would undergo prenatal testing and terminate an affected fetus).

[280] This is based upon an estimated 2,300,000 yearly "non-Hispanic White" births. Martin et al., *Births: 2003*, *supra* note 53, at 37.

[281] U.S. studies are scarce. *But see, e.g.*, L. Henneman et al., *Attitudes Towards Reproductive Issues and Carrier Testing Among Adult Patients and Parents of Children With Cystic Fibrosis (CF)*, 21 Prenatal Diagnosis 1, 5 tbl.4 (2001) (45% of parents would abort); Neil Simpson et al., *The Cost-Effectiveness of Neonatal Screening for Cystic Fibrosis: An Analysis of Alternative Scenarios Using a Decision Model*, 3 Cost-Effectiveness & Resource Allocation 10 (2005), *available at* http://www.resource-allocation.com/content/pdf/1478-7547-3-8.pdf (surveys suggest about 50% of affected individuals and their family would terminate).

[282] This figure is estimated based upon Tay Sach's severity, its extremely shortened life span (affected children rarely live beyond age five), and its classification as a disease of the central nervous system. *See* Kenneth B. Schechtman et al., *Decision-Making for Termination of Pregnancies with Fetal Anomalies: Analysis of 53,000 Pregnancies*, 99 Obstetrics & Gynecology 216 (2002) (finding that termination rates are higher for diseases of greater severity, and in particular, for diseases of the central nervous system).

B. Ethical, Legal, and Social Implications

The prospect of widespread prenatal genetic testing raises a number of significant ethical, legal, and social concerns. In particular, it is necessary to consider the questions of pregnancy termination, informed consent, parental reproductive autonomy, costs of disability, society's interest in reducing genetic disorders, and implications for the disabled community. Although many of these issues apply even in today's regime of limited genetic testing, they will assume greater force and scope with the advent of an inexpensive, non-invasive, and accurate diagnostic test. The implications discussed in this section are — and will continue to be — the subject of intense debate. Accordingly, this article seeks merely to forecast, rather than to resolve, these concerns.

One clear ethical concern stems from the fact that widespread use of MSFCS or MPFDR will almost certainly increase the number of abortions performed each year,[283] an unsettling prospect for those who believe that life begins at conception. While some women may get tested merely to prepare themselves to raise a disabled child, many will undergo these procedures with the understanding that they will terminate the pregnancy if the fetus is affected — especially given that there is no cure or treatment for most of the disorders for which genetic testing is available.[284] Moreover, perhaps because of the incurable nature of such conditions or the general stigma associated with disability, many women may feel pressure (both overt and subtle) from family and friends to undergo testing or to abort an affected fetus.[285] Conversely, at-risk women in predominantly pro-life regions may feel pressured to avoid testing or to carry a known affected fetus to term.[286] Societal coercion on both sides could become increasingly intense as prenatal genetic testing becomes more common or attains standard-of-care status. Some even worry that states may legally *mandate* prenatal genetic testing for all pregnant women.[287]

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[283] *See* John Gillott, *Screening for Disability: A Eugenic Pursuit?*, 27 J. Med. Ethics ii21, ii22 (Supp. II 2001) ("We cannot avoid the fact that the primary choice offered by these services is the choice to avoid having a child with a genetic condition . . . .").

[284] Wendy E. Roop, *Not in My Womb: Compelled Prenatal Genetic Testing*, 27 Hastings Const. L.Q. 397, 409 (2000).

[285] *See, e.g.*, Lori B. Andrews, *Prenatal Screening and the Culture of Motherhood*, 47 Hastings L.J. 967, 981-82 (1996) ("Society may make women feel guilty for continuing the pregnancy of a fetus with even a slight disability.").

[286] Amy Harmon, *Burden of Knowledge: Tracking Prenatal Health; In New Tests for Fetal Defects, Agonizing Choices for Parents*, N.Y. Times, June 20, 2004, *available at* http://query.nytimes.com/gst/fullpage.html?sec=health&res=9402EED91539F933A15755C0A9629C8B63. This article mentions the pressure on many women in anti-abortion regions, quoting the manager of an Internet support group for people who have terminated pregnancies because of their fetus's health: "'I cannot turn on the computer any day without getting an e-mail from someone who needs help[.]' . . . 'But nobody's talking about it. Certainly not here in southeastern Virgina[.]'" *Id.* The decision can be even harder where, as in numerous cases, a woman's decision "contradict[s] [her] previously held beliefs." *Id.* ("'People will come into my office in tears and say they've been against abortion their whole lives,' [Dr. John Larsen] said, 'but they'll make an exception for themselves.'").

[287] *See, e.g.*, Andrews, *supra* note 285, at 972; Roop, *supra* note 284 (considering, but rejecting, the possibility that states could compel women to undergo prenatal genetic diagnosis).

Short of mandated testing, however, there may be consequences of the "routinization"[288] of prenatal genetic testing. As testing becomes more "routine," the informed consent process — whereby physicians must fully inform patients of the risks involved in accepting or refusing a particular test or treatment — could become "impoverished."[289] Faced with an increased threat of wrongful birth and wrongful life lawsuits, some doctors may push MSFCS or MPFDR on reticent or resistant patients, in order to "cover" themselves in the event of a malpractice action.[290] More subtly, though, physicians may de-emphasize the voluntary nature of the test, downplay or ignore the potential emotional consequences, or give misleading or incomplete information concerning the procedure and its results.[291] The latter of these concerns is perhaps the most dangerous, especially in a regime in which testing would be available to most pregnant women — including many who are poorly educated or do not speak English. Even well-meaning doctors may not explain the procedure and its consequences in a way that can be understood by patients, leading to confusion regarding critical facts. For example, women may not realize that testing could reveal genetic information about the *mother or father* as well as the fetus;[292] or they may not understand that the procedure does not actually treat the fetus (nor does it even offer that possibility where there is no cure for a particular disorder). This potential for misunderstanding underscores the need to prepare for NPGD by training doctors and genetic counselors and developing guidelines for offering and administering the new tests (see *infra* Part V.C).

On the positive side, widespread prenatal genetic testing will reinforce parental reproductive autonomy, a liberty recognized under the Supreme Court's constitutional law decisions,[293] and allow parents to gather important information before making difficult family-planning decisions. Although the

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[288] *See* Suter, *supra* note 157, at 233 (titling her article *The Routinization of Prenatal Testing*).

[289] *Id.* at 234.

[290] *Id.* at 253 (noting that, following California's legal mandate that healthcare providers offer MSAFP screening to all pregnant patients, some doctors "tried to make it difficult for women to refuse by telling them to take the test"). Indeed, such efforts may also have the consequence of bestowing de facto standard-of-care status on MSFCS or MPFDR before they have obtained the support of the medical community.

[291] *Id.* at 253-54 (describing how California's mandate to offer MSAFP screening to all pregnant women "profoundly influenced the way in which providers offered, described and discussed MSAFP screening," including: calling it a "simple blood test," spending no more than two minutes discussing the procedure, failing to explain that it was voluntary, or failing to explain the purpose of the test).

[292] For example, if a fetus is found to have a dominant genetic disease like Huntington's disease, for which the mother or father is known to be at risk (e.g. because one of their parents has the disorder), a positive diagnosis for the fetus is a positive diagnosis for the at-risk *parent* as well. *See* Andrews, *supra* note 285, at 976. Such revelations could also raise paternity issues if, for example, the fetus is found to have Huntington's disease, but neither the mother nor her husband are at risk of developing the disease; in that case, a positive diagnosis of the fetus means that the husband is not the fetus's true father.

[293] *See* Planned Parenthood of Southeastern Pa. v. Casey, 505 U.S. 833, 857 (1992) (noting that constitutional developments since *Roe v. Wade* have not disturbed or diminished "the recognized protection accorded to the liberty relating to intimate relationships, the family, and decisions about whether or not to beget or bear a child" and that *Roe* may also be seen as supporting "a rule . . . of personal autonomy and bodily integrity").

testing/decision process itself could cause stress for families,[294] it could also significantly alleviate anxiety. For parents who oppose abortion, learning about their fetus's condition could help them overcome their initial grief and guilt, prior to the birth, and allow them to better prepare to care for a child with special needs.[295] For parents who would consider abortion, prenatal genetic testing could also prevent considerable family and marital tension resulting from the increased costs — both financial and psychological — of raising a child with a severe disability.[296] Indeed, while parents of sick or disabled children acknowledge that their lives have been enriched, they may nonetheless experience considerable fear, anxiety, resentment, frustration, and pain — particularly when watching a child suffer and die from a condition like Tay-Sachs or cystic fibrosis.

Widespread prenatal genetic testing could also produce benefits for society at large. In reducing the incidence of genetic disease,[297] it could greatly alleviate the costs associated with raising children with serious genetic disorders. Some conditions may cost families — and, ultimately, all citizens (through taxes, insurance, etc.) — hundreds of thousands of dollars in incremental lifetime costs per child.[298] Moreover, costs *not* included in this calculus include: the value of family members' time spent providing care; the value of family members' time spent away from jobs, spouses, and other children; and the indirect costs (such as travel expenses) related to the provision of care.[299] With a prenatal test available to nearly all women at a low price, the savings could be enormous. Furthermore, many would argue that it is a worthwhile endeavor to rid the world of debilitating, life-shortening diseases — to improve the physical, psychological, and financial health of society. Widespread prenatal genetic testing, while unlikely to eliminate such disorders completely, could notably reduce their incidence.

The possibility of a marked decrease in the incidence of genetic disease raises additional questions about the impact of prenatal genetic testing on the disabled community. Some contend that prenatal genetic testing — with its implicit aim of preventing the birth of disabled babies — undermines the worth of individuals living with disabilities and "reinforces the medical model that disability itself, not societal discrimination against people with disabilities, is the problem to be solved."[300] Sanctioning widespread use of

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[294] I.e. through the initial anxiety of the test, the decision to terminate, or the additional genetic information obtained (e.g. a parent's diagnosis, a parent's carrier status, a husband's non-paternity).

[295] *See* Baptists for Life, Inc., *What About Prenatal Testing?*, http://www.bfl.org/Prenatal+Testing.aspx?Page=c0467858-5234-4ede-9c1b-952668abf113 (last visited Mar. 9, 2007). Indeed, a Harvard Medical School study found that mothers who received a diagnosis of Down Syndrome prenatally were "generally happier over the birth of their infant with DS than their counterparts who had received the diagnosis postnatally." Brian G. Skotko, *Prenatally Diagnosed Down Syndrome: Mothers Who Continued Their Pregnancies Evaluate Their Health Care Providers*, 192 AM. J. OBSTETRICS & GYNECOLOGY 670, 676 (2005).

[296] *See, e.g.*, Harmon, *supra* note 286 (citing the example of a woman who "knew her marriage would not survive having a severely ill child").

[297] *See* discussion at *supra* Part V.A.

[298] *See, e.g.*, Beazoglou et al., *supra* note 242.

[299] *Id.* at 1242.

[300] Adrienne Asch, *Disability Equality and Prenatal Testing: Contradictory or Compatible?*, 30 FLA. ST. U. L. REV. 315, 316 (2003).

such testing could mean that fewer and fewer disabled children are born each year. This raises questions about what these shifting demographics might mean for individuals with disorders like Down Syndrome, or for the families who love them. Might the dilution of the disabled population lead to diminished peer groups, support groups, and special education services; or to increased societal discrimination, intolerance, and misunderstanding? Of course, even if all women obtained NPGD and terminated affected pregnancies — a very unlikely possibility — a sizable number of disabled babies would still be born every year, as many birth defects are not genetic.[301] Nevertheless, some fear that offering more and more women the option of detecting and aborting fetuses that are not "normal" may foster the development of "a new, more subtle form of eugenics."[302]

C. Necessary Preparations

In light of the complex and challenging issues at stake, the increased use of NPGD will correspondingly require an increased number of well-trained technicians, genetic counselors, and healthcare providers, as well as an increased proliferation of guidelines and public education campaigns. It is imperative that the technicians who obtain and analyze maternal blood samples be highly skilled and well-supervised, in order to ensure high levels of diagnostic accuracy. Moreover, genetic counselors and physicians should be taught — in school or through continuing education programs — how to explain MSFCS or MPFDR in a manner that is thorough, understandable, and culturally as well as religiously sensitive. Such qualities are particularly necessary in a regime in which women of all ages, religions, races, ethnicities, and socioeconomic backgrounds will have access to prenatal genetic testing. In addition, counselors and doctors should approach the topic of testing in a non-directive fashion, leaving the ultimate decision to the parents themselves and thus preserving personal autonomy.

It is also important to develop clear and detailed guidelines, not only for how to effectively administer the test (e.g. isolation of fetal genetic material, PCR or FISH analysis, etc.), but also for how to offer the test, explain test results, and review possible consequences and alternatives with patients. Such guidelines, which could be promulgated by professional societies like ACOG or the National Society for Genetic Counselors, should stress the paramount interest in *providing information*. For example, in every case, counselors or physicians should explain, in plain language, all of the following: the types of tests available, the reliability of the tests, the risks of the tests (including psychological risks), the options (if any) for treatment, the alternatives in the absence of treatment, and the voluntary nature of such tests. Indeed, NPGD should be presented as "an alternative, not as a

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[301] *See* March of Dimes, *Quick References and Fact Sheets: Birth Defects*, http://www.marchofdimes.com/pnhec/4439_1206.asp (last visited Jan. 20, 2007). Birth defects may result from non-genetic factors, such as environmental factors (e.g. alcohol abuse, drug abuse, exposure to certain medications or chemicals) or infections (e.g. rubella, syphilis), or from a combination of genetic and other factors. Moreover, "the causes of about 70 percent of birth defects are unknown." *Id.*

[302] Suter, *supra* note 157, at 269. *But see* Gillott, *supra* note 283 (arguing against the notion that genetic screening programs or individual parents are pursuing "eugenics").

mandatory component of prenatal care."[303] Finally, efforts should be made to educate the public more generally about MSFCS/MPFDR, genetic disorders, and the reality of disability, in order to correct misconceptions and counteract the effects of regional disparities in the quality of counselor/physician training.[304]

VI. CONCLUSION

Throughout this article, I have argued that the impending development of NPGD — with its winning combination of high accuracy, low risk, and low cost — has genuine potential to attain researchers' long-sought goal: opening the option of prenatal genetic testing to most women, and ultimately reducing the incidence of devastating genetic disorders in the population. Indeed, so long as testing is voluntary and fully informed, NPGD can bring significant benefits to individual families, who must grapple with the prospect of raising a severely disabled child, as well as to society, which will experience enormous savings as a result of the decrease in severely ill babies.

Yet the spread of this technology may also precipitate the emergence of other, perhaps less "noble" objectives. Might NPGD be utilized to prevent the birth of children with less severe disorders (e.g. an extra finger, bowed legs, cleft palate)?[305] With merely the *potential* to develop a disorder (e.g. 40% chance of breast cancer, 60% chance of Alzheimer's disease)? With merely undesirable traits (e.g. propensity for obesity, poor eyesight)? With no "disorder" at all? What about parents interested in selecting the sex of their child?[306] Or parents with disorders such as dwarfism or deafness who want to abort a healthy fetus in favor of raising a child that is more like them? With clinical NPGD lurking just around the corner, the issue of the "slippery slope" will become especially pressing, necessitating a full and frank discussion — with representatives from all sides of the debate — of the many weighty issues at stake.

Undoubtedly, NPGD holds the promise of radically and rapidly transforming prenatal care. And it will require an equally radical and rapid collaboration of all interested individuals — physicians, geneticists, ethicists, lawyers, counselors, and parents — to determine the shape that it will ultimately take.

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[303] Roop, *supra* note 284, at 421.

[304] Moreover, to the extent that entrepreneurs may try to capitalize on this technology by offering commercial versions, the public should be encouraged to obtain tests from trained healthcare providers, who are held to far more stringent professional and institutional standards. *See* Diana W. Bianchi, *At-Home Fetal DNA Gender Testing: Caveat Emptor*, 107 Obstetrics & Gynecology 216 (2006) (warning about use of unregulated products like the "Baby Gender Mentor," see *Today Show*, *supra* note 135).

[305] *See* Harmon, *supra* note 286.

[306] *See id.*