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## Genetic Services Policy Project Final Report

### Chapter 1: Introduction

The following report and recommendations reflect a body of work performed from 2004-2008 as part of the **Genetic Services Policy Project (GSPP)**, funded by the Health Resources and Services Administration, Maternal and Child Health Bureau, Genetic Services Branch.

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This work was initiated recognizing the rapid growth in the availability of medical genetic technologies that can identify persons at increased risk for acute and chronic diseases, countered by the slow pace of public policy development to guide appropriate adoption and use of these technologies. In addition, the work was guided by the understanding that diffusion of new

knowledge about human health into practice is complex, often very slow, and influenced by economic, legal, and cultural factors. The emergence of these genetic discoveries serves to add to the existing burden on health care professionals providing genetic services, who increasingly find it difficult to be reimbursed for their services and are experiencing growing demand for their expertise. The issues addressed by the project are multifaceted: how and how well does the current genetic service delivery model work? Are there alternative models that would work better? How can research relevant to genetic services be best translated into practice? And, what public policy changes do we need to get us from here to there?

To understand and describe the existing genetics health care delivery system, the GSPP investigators used existing data, compiled new data, and utilized the expertise and wisdom of many varied stakeholders to inform this work. Chapter 2 depicts the genetics health care delivery system as it exists today. While this information is useful in understanding the system across the United States, for comparison, the reader may also want to review the State Genetic Profiles that describe the genetics health care system from a state perspective rather than national perspective (<http://depts.washington.edu/genpol/GSPPproducts/stgenprofindex.htm>).

In addition, GSPP investigators and advisors considered the family experience in accessing services. This was done to better highlight potential service delivery gaps or issues as well as to consider alternative models for services. To do so, several case studies were created to give more in-depth consideration to the impact of cultural, legal, ethical, and past policy issues. For each condition for which a case study was prepared, a vignette was developed to create a context around how one might enter the medical genetics pathway for a given condition and what a family might encounter along the way. These case studies and vignettes are found in Chapter 3, and include several of the thoughtful questions raised during discussion.

In Chapter 4, we explore economic issues. First we performed a critical review of all published cost benefit or cost effectiveness papers that dealt with genetic services. We also conducted our own cost effectiveness study looking specifically at a genetic test marketed to clinicians, primarily pediatricians, that can identify individuals at risk of hearing loss if exposed to certain medications. This proved to be enlightening work not only in its conclusion but also because it demonstrated that there are, in fact, times when genetic testing may be detrimental to the health care of an individual if it causes a clinician to alter the treatment plan by using substandard treatment methods based on genetic test results.

In thinking about genetic services, it is also important to consider public perception. This work, articulated in Chapter 5, began by trying to understand how the media presents genetics information (e.g., in a positive or negative context, accurately or inaccurately) because this is where many Americans receive information about emerging technologies.

Having a grounded sense of what the existing genetics health care delivery system looks like and why, the GSPP investigators then focused on what is influencing the future and how genetic services might be provided in an alternative model of health care (Chapter 6). We reviewed which genetic services are available directly to consumers and whether they are portrayed as a clinical service. We also describe how new tests are brought to market and the factors that influence this developmental process.

Finally, Chapter 7 articulates how medical services are already being reshaped in their delivery as a direct result of globalization and other forces. Likewise, there is no reason why genetic services will or could not be provided in alternative ways given the increased use of the internet and telehealth options.

The GSPP concludes this report (Chapter 8) by offering, in a prioritized fashion, specific recommendations that are intended to increase equitable access to cost effective, appropriate genetic services for all who need them. These recommendations were developed in concert with and vetted by our GSPP Advisory Committee; however, the GSPP investigators selected and prioritized those we felt were most feasible and/or likely to result in the desired outcome.

Several additional documents are included as appendices, including a complete list of dissemination activities, an analysis of the Genetic Information Nondiscrimination Act through the advocacy coalition framework, a case study on how one system is integrating genetic services into its health care services and insurance coverage, and the changing landscape of genetic services in clinical settings.

For ease in reviewing, each Chapter is posted individually and can serve as a stand alone document, or the report can be downloaded in its entirety. It is important for readers to recognize that information presented here reflects the most accurate and current information available at the time the work was being conducted; they are encouraged to note the date stamp for each section. We sincerely hope that this collective body of work will enlighten readers and stimulate much discussion.

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## Genetic Services Policy Project Final Report

### Chapter 2: The Delivery of Genetic Services in the United States

#### **A. What are genetic services?**

The Genetic Services Policy Project defines genetic services as genetic testing, diagnosis of genetic conditions, genetic counseling, and treatments for individuals with genetic disorders. Genetic services occur across the lifecycle, and they affect behavior, disease monitoring, and treatment for those individuals being tested and their families.

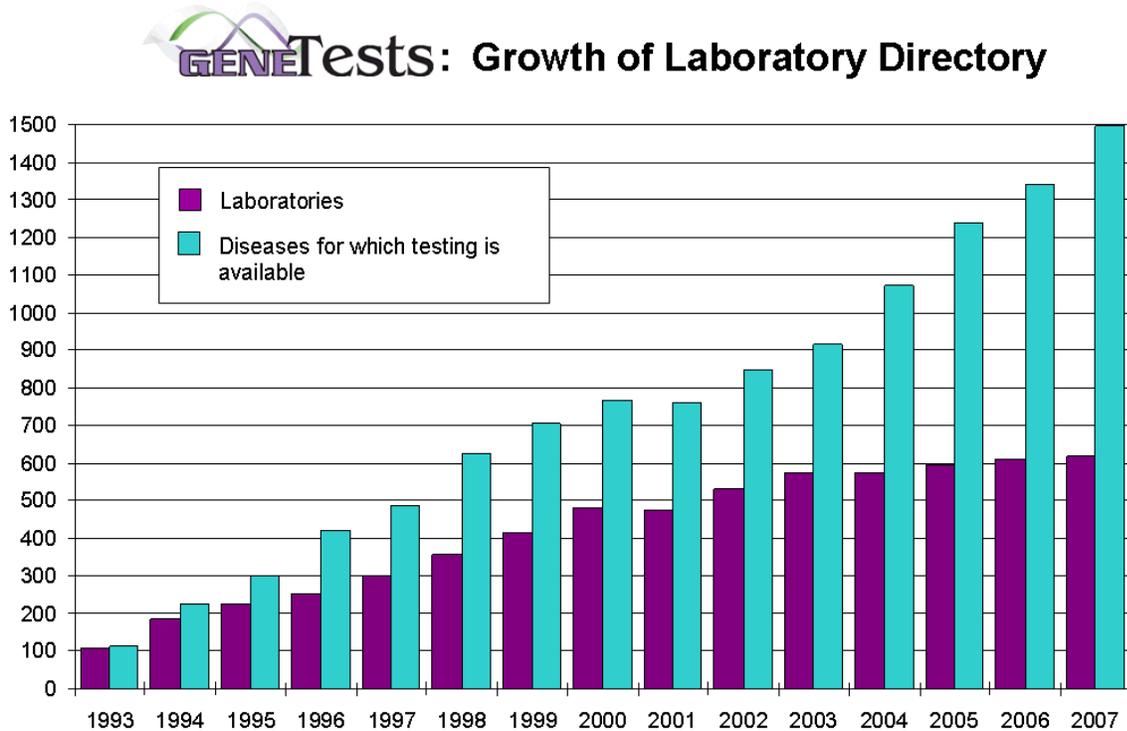
**Genetic testing** is defined as the laboratory analysis for DNA, RNA, chromosomes, or gene products (GeneTests: Educational: Fact Sheet). The most common types of genetic tests include:

- *Diagnostic testing*, to confirm or rule out known or suspected genetic disorders in symptomatic individuals (Jansson, 2007);
- *Screening* of a population, to identify an increased risk of illness or abnormality;
- *Predictive testing*, to identify future health risks in asymptomatic individuals with a family history of a genetic disorder (Jansson, 2007);
- *Pharmacogenetic testing*, to predict an individual's response to one or more drugs;
- *Carrier testing*, to determine whether an individual carries a mutation associated with a recessive disease;
- *Prenatal testing*, during pregnancy to provide information about genetic conditions or birth defects, using methods such as ultrasound, chorionic villus sampling, amniocentesis, and DNA studies of the fetus; and
- *Preimplantation genetic diagnosis*, to test embryos for known or suspected genetic conditions prior to implantation in the uterus.

**Diagnosis and treatment** of genetic disorders involves:

- *Genetics examination*: either a complete physical examination primarily to identify dysmorphism or a directed genetic examination to find evidence of a specific genetic condition;
- *Genetic counseling*, to help people understand the medical, personal, and family implications of genetic contributions to the disease. The process includes:
  - collection and interpretation of family and medical histories to assess the chance of disease occurrence or recurrence;
  - education about inheritance, testing, management, prevention, resources and research; and
  - counseling to promote informed choices and adaptations to the risk or condition (Resta et al., 2006).
- *Genetic therapies* or other clinical interventions arising from genetic research and investigation, including pharmaceuticals, diets, enzyme replacement, gene therapy; and,
- *Pharmacogenomics*, the use of genomic concepts in the development and clinical application of pharmaceuticals to improve drug treatment by decreasing adverse drug reactions and increasing drug effectiveness.

Genetics services are expanding rapidly. Since 1993, the number of diseases for which genetic testing is available has grown from slightly more than 100 to over 1500 as of March 2008 (GeneTests: Growth).



Data source: GeneTests database (2007) / www.genetests.org

In addition, technological advances are allowing increasingly larger numbers of conditions to be tested rapidly via a single test, e.g., microarray-based comparative genomic hybridization (CGH) analysis (Bejjani et al., 2005). Ancillary genetic services, such as parentage testing and DNA banking for future testing, are also growing service areas.

### B. Who receives services?

Traditionally genetic services have focused on individuals and families with, or at risk for, rare single gene disorders or chromosomal abnormalities. This focus is now shifting as genetic testing and other services are being incorporated into diverse areas of medical practice. For example, genetic testing for the Her2 gene is now recommended in the clinical care of all patients with invasive breast cancer to determine the appropriate course of therapy. Positive Her2 status, which is present in approximately 20 percent of invasive breast cancer cases, has been shown to predict beneficial response and improve survival with the drug trastuzumab (Herceptin) (Carlson et al., 2006). In addition to new applications for specific diseases, efforts are underway to incorporate genetic information into the provision of routine clinical care, including preventive care. The Department of Veterans Affairs is implementing a VA Genomic Medicine Program that will link the individual genetic information of volunteers in the system to their electronic health records. These data will “eventually enable VA healthcare providers to

consider patients' genetic profiles when prescribing treatments or recommending preventive measures" (U.S. Department of Veterans Affairs, 2006). Duke University has launched an innovative "Prospective Medicine" initiative that includes plans to integrate biomarkers and genomic information, as they become available, with other clinical information into individualized risk assessment, health planning and coaching (Snyderman and Williams, 2003).

To date, the provision of genetic services has been closely associated with the life cycle and occurs across five broad stages: preconception, prenatal, newborn, pediatric, and adult. The following table shows which genetic services are provided during different life stages and the questions they address.

<p><b>Preconception:</b> <i>What is "our" risk of having an affected child? Should I get pregnant?</i></p> <ul style="list-style-type: none"> <li>• Genetic counseling</li> <li>• Carrier test</li> <li>• Predisposition / susceptibility test</li> <li>• Diagnostic test</li> </ul>	<p><b>Prenatal:</b> <i>How will I manage my pregnancy?</i></p> <ul style="list-style-type: none"> <li>• Genetic counseling</li> <li>• Carrier test</li> <li>• Predisposition / susceptibility test</li> <li>• Diagnostic test</li> <li>• Preimplantation genetic diagnosis</li> <li>• Prenatal testing</li> </ul>	<p><b>Newborn, Pediatric, and Adult:</b> <i>How might my genetics affect my health?</i></p> <ul style="list-style-type: none"> <li>• Genetic counseling</li> <li>• Carrier test</li> <li>• Predisposition / susceptibility test</li> <li>• Diagnostic test</li> <li>• Genetic evaluation</li> <li>• Pharmacogenetics</li> <li>• Gene therapy</li> </ul>
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The following list includes a number of common reasons why individuals and families are referred to, or seek, genetic services (GeneTests: Educational: About Genetic Services).

- *Preconception/prenatal:*
  - Mother will be 35 years or older at delivery. Note: Maternal age of 35 years has historically been used as a decision point for referral to genetic services, particularly evaluation for Down syndrome. New guidelines suggest all pregnant women regardless of age should be screened and/or offered diagnostic testing for Down syndrome. (American College of Obstetrics and Gynecology, 2007)
  - Abnormal results from a multiple marker maternal serum screen or fetal ultrasound
  - Personal or family history of a known or suspected genetic disorder, birth defect, or chromosomal abnormality
  - Exposure to a known or suspected teratogen
  - Mother has a medical condition known or suspected to affect fetal development
  - Two or more pregnancy losses
  - Close biological relationship of parents
  - Increased risk of certain genetic disorders associated with ethnicity.
- *Pediatric:*
  - Abnormal newborn screening results
  - One or more major malformations in any organ system

- Abnormalities in growth
- Mental retardation or developmental delay
- Blindness or deafness
- Presence of a known or suspected genetic disorder or chromosomal abnormality
- Family history of a known or suspected genetic disorder, birth defect, or chromosomal abnormality
- *Adult:*
  - Mental retardation
  - Personal or family history of hereditary cancers
  - Personal or family history of a known suspected genetic condition or chromosomal abnormality
  - Development of a degenerative disease including blindness or deafness
  - Risk assessment for pregnancy planning
  - Infertility including multiple pregnancy losses

Unfortunately, data about who actually utilizes genetic services are extremely limited. In other clinical areas, billing information can provide valuable data about utilization. Prior to 2007, genetic evaluation and/or genetic counseling services were billed using evaluation and management codes (e.g., “consultation” or “office visit”), the same codes used by all sub-specialists. As a result, data on their utilization are incomplete and unreliable. As of January 1, 2007, medical genetic services and genetic counseling are specifically included in the Current Procedural Terminology (CPT) codes that describe health services for billing and reimbursement purposes (McDermott, 2007). It is hoped that the new CPT code, 96040, will improve data collection specifically about these services and the individuals who utilize them.

In the meantime, by recognizing the distribution of genetic services across the life cycle, it is possible to make inferences about the people using them. For example, nearly all of the 4.1 million babies born in the United States every year are screened for several genetic and metabolic disorders (National Newborn Screening and Genetics Resource Center website). Fourteen percent of women giving birth are 35 years and older (U.S. Centers for Disease Control and Prevention: Births, 2006), the age at which they would be offered amniocentesis. Increasingly, younger pregnant women are undergoing screening. Therefore, it is likely that at least 600,000 U.S. women are offered some type of genetic screening during pregnancy in each year (Rabin, 2007). Recent guidelines from the American College of Obstetrics and Gynecology (2007) recommend that all pregnant women be offered multiple marker screening for neural tube defects and chromosomal abnormalities. The results of these screening tests could lead to invasive diagnostic testing such as chorionic villus sampling or amniocentesis (American College of Obstetrics and Gynecology, 2007). The impact of this change on genetic service utilization is not yet known. In addition, ACOG recommends that information about cystic fibrosis carrier screening be provided to all couples and, at a minimum, screening should be offered to all couples where both partners are Caucasian, European or Ashkenazi Jewish prior to conception or in early pregnancy (American College of Obstetrics and Gynecology, 2005).

A 2003 survey of medical geneticists describes children (birth through adolescence) as the major client group for services, accounting for 76 percent of all new patients, with reproductive genetics patients accounting for 11 percent of those who use services, and “other adults” totaling

13 percent (Cooksey, 2005). A 2006 National Society of Genetic Counselors (NSGC) study found that, from 2000-2002, respondents shifted specialty areas away from prenatal (59 to 56 percent) and toward adult (26 to 28 percent) and cancer genetics (34 to 42 percent).

The GSPP analyzed utilization trends at nine regional genetics clinics in Washington State from 1995-2004 and found that the number of visits grew by an average of 8 percent a year, a rate surpassing that of other health care providers (Wang and Watts, 2007). The analysis did not include visits for prenatal services. The analysis revealed changes in the patient mix. The share of female and urban clients increased, as did the share of adults 35 years and older. The study found that in 2000, the number of adults visiting the clinics surpassed the number of children, and the trend has continued since then. Adults 20 years and older comprised 40 percent of all visits in 2004, compared with 29 percent in 1995.

Distribution of genetic services, and therefore access to these services, is dependent on broad issues of resources and public awareness, which are strongly influenced by the activities of the advocacy groups organized around specific genetic conditions or diseases. These groups play important roles in mobilizing public support for research and application of new technologies, shaping public policies, and providing clinical services directly. The number of these groups has grown significantly with the work of the Human Genome Project. More than 3,000 support groups, networks, and informational web sites are listed under Google's directory of genetics-associated diseases and conditions, including 148 groups associated with cystic fibrosis, 111 for Down Syndrome, 30 for Huntington's Disease, and 19 for sickle cell disease (Google Directory).

Most of the advocacy groups were established by parents of children with genetic-related disabilities and the organizations that work with them. The Washington, D.C.-based Genetic Alliance, formed in 1985, identifies itself as a coalition of "millions of individuals" and more than 600 organizations, from the Aarskog Syndrome Parents Support Group to the Y-ME National Breast Cancer Organization (Genetic Alliance website).

In common with most of the largest genetics-related advocacy groups, the Genetic Alliance raises both public and private resources—the alliance is partly supported by funding from the federal Health Resources and Services Administration (HRSA) and the Centers for Disease Control and Prevention (CDC). Many of the groups advocate for specific public policies. The March of Dimes, for example, has become strongly supportive of legislative efforts to mandate a broad, consistent panel of conditions for newborn screening by the states (March of Dimes website). The reach and influence of the advocacy groups is not proportionate with the prevalence or public health impact of the specific conditions that are their focus. For example, the Cystic Fibrosis Foundation annually raises more than 30 times the resources raised by the Sickle Cell Disease Association of America, despite the fact that sickle cell disease's national prevalence is more than twice that of cystic fibrosis (80,000 v. 30,000). The inequity, which reflects the ethnicity and socio-demographics of the individuals and families affected, has led to significant gaps in federally sponsored research and in application of gains in clinical care (Smith et al., 2006). However, recent data indicate that the National Institutes of Health (NIH) funding for cystic fibrosis research has been reduced from \$117 million in 2003 to \$85 million in 2006, which is less than 2006 funding for sickle cell disease at \$91 million (National Institutes of Health, 2007).

### C. Who provides genetic services?

The genetic services workforce consists primarily of health professionals providing diagnosis, counseling, testing, and test interpretation. Nearly all licenses and credentials to perform genetics services are conferred by private organizations and trade associations.

Providers fall into two general categories: those who are specifically trained to provide genetic services and are certified by professional organizations, and those who perform genetic services but are licensed in another discipline and have received little or no formal training or certification *specifically in genetics*.

In the first category—those with formal training—are four types of providers that are essential to genetic services delivery. These professionals provide direct patient care, as well as work to educate the public and their colleagues, participate in research, and administer public and private programs.

These four provider types are:

- **Medical geneticists**, all of whom have medical or doctorate degrees, who provide counseling about the risk for genetic disorders as well as diagnosis, management, and treatment. The American Board of Medical Genetics (ABMG) certifies five categories of practice: PhD medical genetics (for which the certification exam has been dropped in 2007), clinical genetics, clinical cytogenetics, clinical biochemical genetics, and clinical molecular genetics. Certification requires at least 48 months of full-time training in addition to MD, DO, or doctoral degrees. Patients often see medical geneticists when a screening test comes back positive and they are seeking confirmation or interpretation of test results and a diagnosis. Most medical geneticists work in academic medical centers (see page 8), and may also direct laboratories, research, and genetics-related organizations. Approximately 2,300 individuals have received certification in one or more of the ABMG categories of practice since 1982, with 166 individuals becoming certified in 2007 (American Board of Medical Genetics website).
- **Genetic counselors**, who must complete master's level training at an American Board of Genetic Counseling (ABGC)-certified program. Instruction includes principles of human genetics, applicability of related sciences to the practice of clinical and medical genetics, psychosocial issues, and the ethical, legal, and social issues associated with genetic services delivery. According to the NSGC, these providers “identify families at risk, investigate the problem present in the family, interpret information about the disorder, analyze inheritance patterns and risks of recurrence and review options with the family. [They] also provide supportive counseling to families, serve as patient advocates and refer individuals and families to community or state support services.” (National Society of Genetic Counselors: FAQs) Since 1993, 2,035 genetic counselors have been certified by the ABGC, with about 400 new counselors certified nationwide every two years (American Board of Genetic Counseling website). Primary sub-specialties are prenatal, pediatric, adult, cancer, specialty disease, and molecular/cytogenetic testing (NSGC Professional Status Survey, 2006).

- **Genetic nurses**, who are trained to assess and discuss genetic disease risk with patients and families. The Genetic Nursing Credentialing Commission oversees two types of credentials for genetic nursing: Advanced Practice Nurse in Genetics (APNG), which requires a master's in nursing, and Clinical Genetic Nurse (CGN), for baccalaureate degree nurses. Credentialing, which has been available only since 2001 for APNG and 2002 for CGN also requires a practice portfolio indicating a 50 percent or greater genetic practice component. As yet, no states require licensure and certification for genetic nurses, beyond standard nursing requirements (Greco and Mahon, 2003; Lea et al., 2006).
- **Genetic technologists**, who work in laboratories and generally do not interact with patients. The National Credentialing Agency for Laboratory Personnel offers certification for cytogenetic technologists and molecular technologists, who must have bachelor's degrees in a scientific discipline or medical technology and at least 6 months to one year of laboratory experience in their discipline (National Credentialing Agency for Laboratory Personnel website). They must also meet competencies in areas such as specimen collection, handling, processing, and the use of general laboratory skills.

The second category of genetic services providers—those without formal training or certification specifically in genetics—consists of:

- **Physicians**, particularly those in primary care and in specialties in which they see high numbers of patients who are undergoing some type of genetic testing. These specialties include, but are not limited to, oncology, neurology, obstetrics-gynecology, psychology, and endocrinology (Washington State Department of Health, 2006). All physicians receive some basic genetics training in medical school with the specific curriculum dependent on the particular school. Residency programs may also offer genetics rotations to non-geneticist trainees. Physicians in practice qualify for continuing medical education credits for courses related to genetics and also may receive genetics training from their professional associations.
- **Other clinicians**, including nurse practitioners, midwives, physician assistants, and social workers. Genetics-related competencies have been developed in some of these areas (e.g., social work), but they are unevenly implemented across the country.

The genetic services workforce is growing. Genetic counselors serve more than 1.2 million clients each year, and the number of clinical patients they see has been increasing by 5 percent each year since 2000 (NSGC Professional Status Survey, 2004). But in some areas, the workforce is not growing at a rate consistent with expansion of knowledge and clinical applications. Medical geneticists, in particular, do not appear to be entering the field in numbers that would keep pace with population needs, and they are distributed unevenly across the country (Cooksey et al., 2005). For example, Georgia has been providing genetic services via telemedicine for several years. Several other states are beginning to explore this venue as well, including three western states, Hawaii, Oregon, and Washington, who have piloted programs in “telegenetics,” which provide opportunities for genetic consultations in real-time, interactive video (Western States Genetic Services Collaborative website). Such programs can help overcome problems of access to genetic services caused by poor representation of providers in

rural areas and geographic barriers, and have received funding from the federally supported Region 7 Genetics Collaborative. In the Midwest, the Region 4 Genetics Collaborative is also exploring telemedicine as a vehicle for genetic services delivery as part of an overall goal to facilitate access to genetics expertise for underserved populations (Region 4 Genetics Collaborative website). Within the region, in Wisconsin, the Marshfield Clinic began offering telemedicine for genetics in November 2006.

<b>Provider type</b>	<b>Number</b>
Medical geneticists	2,342 (American Board of Medical Genetics: Numbers)
Genetic counselors	2,035 (American Board of Genetic Counseling: Fact Sheet)
Genetic nurses	27 with Advanced Practice Nurse in Genetics credential; 9 with the Clinical Genetic Nurse credential (Genetic Nursing Credentialing Commission)
Genetic technologists	1,200* (Association of Genetic Technologists)

\*Note: There are 1,200 members of the Association of Genetic Technologists; the absolute number of genetic technologists (including those who are not members) could not be found.

**State governments** play several important roles in delivering genetic services for life stages from prenatal to adult.

In California, the Genetic Disease Branch of the state health department administers the Expanded AFP (XAFP) Screening Program to assure that all pregnant women are offered prenatal screening and follow-up for certain birth defects and conditions, including open neural tube defects, Down syndrome and Trisomy 18. Participation in the program is voluntary and fee-based. California insurance providers are required to cover this service (California Genetic Disease Branch website).

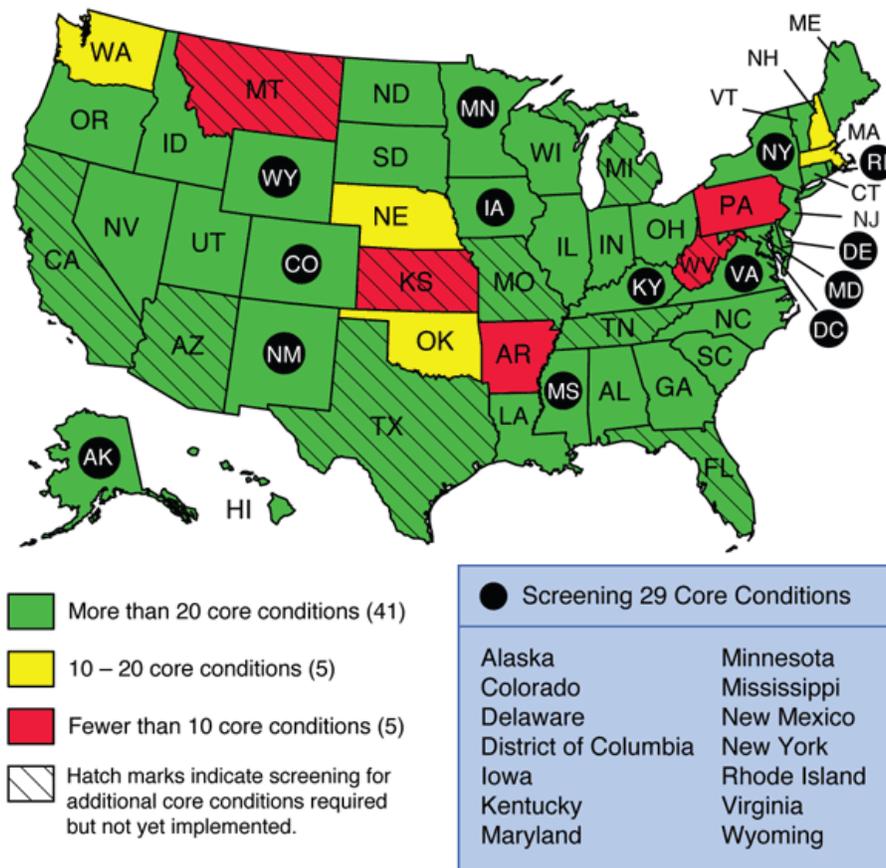
Newborn screening is a major prevention-based, public health program for every state, usually performed to detect genetic and metabolic disorders. Maryland is the only state requiring parental consent to screen newborns, though most states have provisions for parents to opt out of screening for religious or other reasons (Therrell et al., 2006). Typically, blood samples are collected at birth and processed in state, regional, or contracted private laboratories. All states perform newborn screening for 5 to 50+ genetic and metabolic disorders, including disorders that cause mental retardation, disability, and premature death (National Newborn Screening and Genetics Resource Center website).

States differ considerably in the numbers of disorders on their screening panels, as well as how they count the number of tests they conduct; for example, Washington state counts hemoglobinopathy screening as one test while other states may count the same testing as 4 or more, including SS, SC, beta-thalassemia, and alpha thalassemia. In 2005, the American College of Medical Genetics recommended mandated screening for 29 disorders, including certain metabolic conditions and hearing loss (American College of Medical Genetics, 2006). But as of June 2006, only five states (Iowa, Maryland, Mississippi, New Jersey, and Virginia) and the District of Columbia required screening for all these conditions. At the same time, 31 states,

representing 64 percent of newborns, reported screening for more than 20 conditions. Most states have significantly expanded their newborn screening panels in recent years (March of Dimes website).

The following map shows how the state newborn screening panels compare as of 2007 (McDowell, 2007):

### Newborn Screening Tests by State, 2007



Source: March of Dimes

The decision regarding which conditions to include in the panels involves complex social, ethical, and political issues. Especially since the late 1990s, with the availability of technology that allows laboratories to test for many disorders with a single blood sample, the technical capabilities of newborn screening have outpaced public health policy in this area. Advocacy groups for children’s health and those organized around genetic conditions, as well as many professional groups and researchers, have encouraged expansion of the newborn screening panels in recent years. One example is the Save Babies Through Screening Foundation. During 2006, the U.S. Senate considered legislation that would have established a standard slate of conditions subject to newborn screening and required states to contribute to a national database on screening results (S.3743). The companion bill was not introduced in the House.

At the same time, some health policy makers in the genetics field have proposed that the issue be addressed more consistently in the context of evidence-based public health, which requires

consideration of the balance of benefits, risks, and costs—including opportunity costs—of using public resources to screen newborns, particularly for rare conditions (Grosse et al., 2006). In this “new paradigm,” the panels would also address potential harm to children and families, including the parental stress and expense caused by ambiguous test results, false positives, false negatives, labeling of children with mild or benign conditions, and unnecessary or otherwise misapplied therapies.

Another issue associated with expansion of the newborn screening panels is the availability of follow-up services for infants receiving abnormal test results. Families who, under these circumstances, are advised to seek genetic counseling may not possess the stable health insurance coverage needed to facilitate access to services. An analysis of 2001 data collected for the National Survey of Children with Special Health Care Needs (CSHCN) showed that 19 percent of families of CSHCN who needed genetic counseling—123,117 CSHCN families—did not receive it. CSHCN with interrupted insurance coverage and those without insurance were significantly less likely to receive needed genetic counseling services (Wang and Watts, 2007).

Few states employ genetic services providers. As of 2002, 21.6 percent (11) of the state genetics coordinators were certified by either ABMG or ABGC, but the majority did not have formal training in genetics (Coalition of State Genetics Coordinators, 2002).

Eighteen states have developed genetics plans or needs assessments, some with the support of federal funds from HRSA (National Newborn Screening and Genetics Resource Center: State Genetics Plans). These plans identify broad areas of genetics activities: newborn metabolic and hearing screening, clinical genetic services including testing and counseling across the lifespan; programs providing treatments and support to individuals and families with genetic disorders; educational activities; birth defects or other genetics related surveillance programs; policy development (e.g., genetic legislation, privacy and discrimination); and public health genetics research/evaluation activities. Some plans also aim to create Integrated Child Health Information Systems, an effort to improve health outcomes for children by increasing data sharing efficiencies and program coordination. Most state activities are directed by state genetics units, newborn screening programs, or federally supported CSHCN units.

States do coordinate initial screening and confirmation testing of infants identified through the newborn screening programs (both mandated and non-mandated) as well as follow-up activities when infants are diagnosed with a condition. Some states only do so through the primary care provider being notified to refer the infant for further testing and others oversee care coordination. In some states (e.g., Washington, Idaho, Alaska), state-sponsored genetics outreach clinics offer general testing, evaluation, and counseling services to individuals and families in geographic areas that would not normally have access to genetic services providers. Some states also provide treatment and direct care programs for individuals diagnosed with genetic conditions. In particular, many states provide and coordinate direct care for children and adults with genetic disorders such as sickle cell disease and hemophilia.

States also conduct a wide variety of activities that focus on surveillance for genetics related conditions. Forty-two states either have or are developing birth defects surveillance programs, financed primarily by federal grants, service-related fees and private sources (Wang et al., 2005).

In addition to these direct effects, states also have indirect influence on genetic services through their purchasing power. States are purchasers of genetic services for their employees, and they help shape public coverage of services through their work with their legislatures, insurers in their state, and state Medicaid programs.

**D. Where are services provided?**

Genetic services are provided across both clinical and laboratory settings. Clinical settings include private and group practices, hospitals, community health centers, specialty programs, state programs, and hospitals. Laboratory providers work in public (including state) laboratories and commercial labs. The following table shows different provider types and the settings in which they most often work.

<b>Provider type</b>	<b>Practice settings</b>
Medical geneticists	Academic medical centers (62%), hospitals (9%), commercial labs (9%), medical practices (9%), other settings (10%) (Cooksey et al., 2005)
Genetic counselors	Academic medical centers (41%), private hospitals or medical facilities (21%), public hospitals or medical facilities (11%), diagnostic laboratories (7%), HMOs (4%), physician’s private practice (4%), and other (4%) (NSGC Professional Status Survey, 2004)
Genetic nurses	Specialty genetics clinics, primary health settings, cancer centers, prenatal and reproductive centers, research centers, industrial health, school health, biotech and insurance industries
Genetic technologists	State public health labs, commercial laboratories, biotech industry

The GeneTests Laboratory Directory website, a voluntary listing of molecular genetic testing offered by laboratories, indicates that, as of March 2008, 608 U.S. laboratories offer genetic testing and 1,144 clinics offer one or more of the following services:

- Adult genetics
- Pediatric genetics
- Prenatal diagnosis
- Cancer genetic counseling and risk assessment
- Telemedicine
- Preimplantation genetic diagnosis

In general, genetic services and consultations are more readily available in urban areas (such as those with academic medical centers) as opposed to rural areas (Acheson et al., 2005).

Advances in genomics as well as technological and cultural shifts toward the use of Internet-based services have contributed to the booming direct-to-consumer commerce in genetic tests. These retail tests bypass the traditional role of the health care provider to recommend genetic testing and interpret results. More than three dozen companies already offer such services online, ranging in cost from \$200 to \$3,456 (Google.com, 4/19/07). The new e-commerce is raising many consumer protection issues. While at least one online company offers genetic

counseling over the phone, most do not. Consumers who lack genetics knowledge and are unable to gauge tests' analytic or clinical validity may be vulnerable to inflated promises from advertisements. They may lack the knowledge to interpret test results and thus risk making ill-advised, even harmful health care decisions (Gollust et al., 2002). Direct-to-consumer tests have provoked a range of regulatory questions, as the federal government does not currently regulate the safety of most genetic tests (Genetics & Public Policy Center: FDA Regulation, 2006). In July 2006, the Federal Trade Commission issued an alert warning consumers to be skeptical about "at-home genetic tests" and to consult with their doctors or health care practitioners prior to purchasing or undertaking any tests and to discuss test results with a doctor or a genetic counselor (U.S. Federal Trade Commission, 2006). On the other hand, there are several potential benefits to online testing services, including increased uptake by the public of valuable services if people perceive greater privacy, and decreased concerns about insurance discrimination, especially if services are paid out-of-pocket.

#### **E. Who pays for services?**

As new genetic tests and services continually become available, consumers, providers, and payers must develop mechanisms to pay for them. Several factors present barriers to the integration of genetic services in the U.S. health care system and its current methods of financing, particularly reimbursement by third-party payers (Secretary's Advisory Committee on Genetics, Health and Society, 2006). These factors include the use of multiple providers (medical geneticists, genetic counselors, laboratory technicians, and others), uncertainty concerning the role of genetic factors in the actual onset of disease, complex issues of ethics, privacy and confidentiality, historical experience, and continuing issues of insurance coverage and reimbursement. In addition, many payers require providers to be licensed, and only six states require licensing of genetic counselors (National Conference of State Legislatures: Genetic Counselor Licensing).

Medicare reimbursement for genetic services is complicated by a longstanding U.S. Centers for Medicare and Medicaid Services (CMS) policy to exclude coverage of predictive and pre-symptomatic tests and services (Secretary's Advisory Committee on Genetics, Health and Society, 2006). Private health plans often follow CMS policies. Not all genetic services providers may bill Medicare directly; those who are statutorily eligible to bill directly for their services are physicians, nurse practitioners, physician assistants, certified nurse specialists, certified nurse midwives, clinical psychologists, and clinical social workers. Other non-physician providers must bill "incident to a physician," often using CPT codes that do not cover the full time required to provide care (Secretary's Advisory Committee on Genetics, Health and Society, 2006). Experience with the new CPT code for medical genetic services and genetic counseling, described earlier in this paper, is too limited at this time to determine the impact on billing and reimbursement; however, CMS Medicare has already decided it will not cover this code (McDermott, 2007).

Medicaid coverage is subject to state variation, but most state programs reimburse for "medically necessary" genetic services, including tests such as amniocentesis, maternal-serum screening for neural tube defects and Down syndrome, and chromosomal analysis from amniotic fluid (Secretary's Advisory Committee on Genetics, Health and Society, 2006).

**Private health insurance plans** are financing a significant share of genetic services—in general, covered services are those related directly to an enrollee’s health, not those suggested by a disease or condition of a family member. Once again, the inconsistent methods of billing and reimbursement make it difficult to know which payers are financing which services. A 2004 survey of genetic counselors revealed that 57 percent report billing under their supervising physician’s name, 9 percent bill under their own name and the supervising physician, and 14 percent do not bill for services at all (NSGC Professional Status Survey, 2004).

Established services, such as amniocentesis for pregnant women older than 35, are the most likely to be covered. Generally, private insurance plans cover genetic testing for chromosomal abnormalities, prenatal and neonatal diagnosis, and some pre-implantation genetic diagnosis services. Coverage decisions are often based on what competing plans are doing and which services are moving from experimental to standard practice. Many specifically exclude certain types of genetic testing, such as tests for Alzheimer’s disease, which are considered experimental. This exclusion creates a particular problem with rare diseases, whose low prevalence presents difficulty in establishing clinical validity. Other considerations in coverage decisions include whether a technology has received FDA approval, if clinical trials demonstrate medical effectiveness, and whether practice guidelines exist to justify its use, as well as costs and projected cost savings (Secretary’s Advisory Committee on Genetics, Health and Society, 2006). The 1996 Health Insurance Portability and Accountability Act (HIPAA) prohibits group health insurers from denying coverage based on genetic information.

Federal genetics-related expenditures—primarily for research through agencies within the U.S. Department of Health and Human Services—amount to about 15 percent of HRSA spending and 10 percent of Centers for Disease Control and Prevention (CDC) spending projected for 2007. The National Institutes of Health will spend more than \$1.06 billion on the Human Genome Project in 2007 and nearly \$4.8 billion on other genetics-related activities, including \$355 million on gene therapy, \$32 million on gene therapy clinical trials, \$417 million on genetic testing, and \$103 million on “conditions affecting unborn children” (National Institutes of Health, 2007).

States finance their genetic services activities through an array of public and private funding sources, including newborn screening fees (ranging from \$0 to \$139 with a mean of \$54) (National Newborn Screening and Genetics Resource Center: Summation, 2008), state general funds, federal Maternal and Child Health Block Grant resources, CDC grants, and private grants. States receive reimbursement for the direct services they provide through private insurers, Medicaid, State Children’s Health Insurance Plans (SCHIP), CSHCN programs, and consumers’ out-of-pocket payments. States, for the most part, have published little expenditure data about the costs and reimbursement for the genetic services they provide (Wang, 2006).

## **F. How are genetic services regulated?**

Regulation of genetic services includes government oversight of genetic testing, licensing of laboratories and their personnel, and quality assurance and control. This regulatory environment is changing rapidly and incorporates federal agencies, state initiatives, and professional organizations.

At the **federal level**, the Clinical Laboratory Improvement Act (CLIA), the Food, Drug, and Cosmetic Act, and the Federal Policy for the Protection of Human Subjects regulate both the development and application of genetic tests (Genetics & Public Policy Center: Who Regulates, 2006). But CLIA, which has general regulatory authority for all laboratory testing, has not yet implemented genetic-specific regulations, except for the cytogenetics specialty. As a result, genetic tests are not subject to uniform quality control and proficiency testing requirements—no single government agency has these responsibilities. It is often unclear to health care providers which laboratories are qualified to perform genetic testing. CMS is responsible for implementing CLIA and its standards, and the agency has come under growing pressure in recent years from health care provider and consumer groups advocating that it implement a genetic testing specialty (Javitt and Hudson, 2006). In 2006, the Government Accountability Office exposed the uneven oversight of genetic tests sold over the Internet and highlighted potential harms to consumers who may be misled by the information received from this testing, such as recommendations for nutritional supplements that are not only expensive but unnecessary or even contraindicated (U.S. Government Accountability Office, 2006).

The Food and Drug Administration (FDA) regulates genetic tests that are sold to laboratories. These “test kits” are considered diagnostic devices and are subject to agency approval for their safety and efficiency. But the test kits are available for only a small share of genetic tests compared with the far greater number of “homebrew” tests that are developed in-house and are marketed as clinical laboratory services. The agency has implemented regulations for some of the active ingredients in the homebrew tests (analyte specific reagents), and in recent years, it has suggested that it will reconsider additional controls. But it has resisted more stringent regulation so as not to discourage innovation, a situation that puts developers of the test kits at a competitive disadvantage to homebrew makers in the rapidly expanding market.

CDC collaborates with other public agencies and private-sector groups to develop both regulatory and voluntary laboratory standards and to promote integration of validated genetic tests into clinical and public health practice. The Office of Genomics and Disease Prevention at CDC (now the National Office of Public Health Genomics) has initiated two projects: the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) and an evaluation of the analytic validity, clinical validity, clinical utility, and associated ethical, legal and social implications (ACCE) of genomic test data. These projects support the first phases of a coordinated process for evaluating genetic tests that are in transition from research to clinical and public health practice (U.S. Centers for Disease Control: Genetic Testing). The CDC National Center for Environmental Health offers, in partnership with the Association of Public Health Laboratories, a Newborn Screening Quality Assurance Program to help state agencies and laboratories improve the quality of test results.

Congress is increasingly addressing legislation to regulate the protection and use of genetic information. Since 1995, healthy individuals with a genetic predisposition to certain disabling diseases fall within the scope of the Americans with Disabilities Act’s nondiscrimination rules (Americans with Disabilities Act Compliance Manual, 1995). As mentioned previously, the 1996 HIPAA legislation (HIPAA Title I) prevents insurers from discriminating against individuals in enrollment and eligibility for benefits in group health plans, based on health status including genetic information (McAndrew, 2007). In addition, group insurers must not increase

premiums or use genetic information in the absence of a diagnosis as the basis for a “pre-existing condition.” For a number of federal legislative sessions, Congress has debated various bills focused on discriminatory practices against people without symptoms of illness but who possess a known genetic mutation for illness. In 2005, the Genetic Information Nondiscrimination Act of 2003 passed the Senate, but was stalled in the House. A new bill, the Genetic Information Nondiscrimination Act of 2007 was introduced in January 2007. The bill passed the House on April 25, 2007 and passed the Senate unopposed on April 24, 2008. It was signed into law on May 21, 2008 and became Public Law No: 110-233 (S.358, 2007; H.R.493, 2007).

In 2006, Sen. Barack Obama (D-IL) introduced the Genomics and Personalized Medicine Act, which would promote research and application of new genetic technologies by improving access and utilization of “valid, reliable and accurate molecular genetic tests by all populations, thus helping to secure the promise of personalized medicine for all Americans” (S.3822, 2006). The measure would expand research programs in genetics and personalized medicine (“new methods of molecular analysis to better manage a patient’s disease or predisposition towards a disease”) (Personalized Medicine Coalition), promote translation of research findings into clinical and public health applications, and require more extensive federal review of the safety and efficacy of genetic tests. It would also convene stakeholders in a “Personalized Medicine Interagency Working Group” including the National Institutes of Health, CDC, FDA, CMS, HRSA, and the Department of Energy. Sen. Obama reintroduced the bill in 2007 (S.976, 2007).

An important section of the Obama bill—one that was also addressed by Sen. Edward M. Kennedy (D-MA)—was clarification of the FDA’s authority to regulate homebrew tests. The Obama measure would have required developers of homebrew tests to submit to the FDA evidence to support their tests’ analytical and clinical validity for inclusion in a public database. Although new homebrew tests could be marketed without FDA clearance, labeling would indicate whether the tests were FDA-cleared or -approved.

**States** conduct various levels of genetic services regulation (National Conference of State Legislatures: Genetic Technologies Project), including:

- *Mandated screening of all newborns.* State legislatures appropriate funds or authorize fees for newborn screening programs. State statutes may address newborn screening panels, privacy and confidentiality issues, and laboratory standards.
- *Licensing of genetic counselors.* Only six states (California, Illinois, Massachusetts, Oklahoma, Tennessee and Utah) require licenses and define minimum qualifications for licensure, as of January 2008 (National Conference of State Legislatures: Genetic Counselor Licensing).
- *Use of genetic information in health insurance.* Most states (44) have enacted legislation prohibiting insurance companies from using genetic information for decisions on eligibility for policies; 41 states prohibit use of genetic information for risk selection or risk classification; and 27 states prohibit insurance companies from disclosing information without informed consent.

- *Protection of genetic privacy.* Most states have imposed rules requiring more rigorous protection of genetic information than other types of health information. Twenty-seven states require consent to disclose genetic information, and 17 have laws requiring informed consent for a third party to perform a genetic test or obtain genetic information. Washington State alone treats genetic information the same as other health information under its state health privacy protections.
- *Laboratory practice standards.* New York is the only state that has implemented specific laboratory practice standards for several genetic specialties. New York and Washington State conduct their own laboratory inspections because they have more stringent standards than CLIA.
- *Regulation of embryonic and fetal research.* State laws may promote or prohibit stem cell research, and they may restrict funding for this purpose. About half of all states have implemented laws that, in various ways, restrict research on aborted fetuses and embryos.
- *Genetic nondiscrimination in employment.* Thirty-four states have implemented laws prohibiting discrimination in employment decisions of hiring, promotion and/or termination based on the results of genetic tests. Most states also restrict employer access to genetic information.

In the **private sector**, professional societies and other organizations are involved in developing guidelines for genetic tests. These organizations include the Association of Public Health Laboratories, the American College of Medical Genetics, the College of American Pathologists, the National Committee on Clinical Laboratory Standards, and the Commission on Office Laboratory Accreditation.

In addition, the federal Agency for Healthcare Research and Quality (AHRQ) supports the development and use of evidence-based quality measures in health care practice, including genetics related measures (Agency for Healthcare Research and Quality website). Professional organizations, such as the American Medical Association Physician Consortium for Performance Improvement, are engaged in performance improvement initiatives that include the use of quality measures (American Medical Association). Though limited in number, examples of genetics related measures include percentage of prenatal patients aged 35 years and older at the time of expected delivery who are offered amniocentesis or chorionic villus sampling and percentage of prenatal patients less than 35 years who are offered multiple marker testing for congenital anomalies (National Quality Measures Clearinghouse).

## **G. The Future of Genetic Services**

The science behind genetic services is expanding rapidly. New services, particularly new genetic tests, follow closely on the heels of scientific discovery. Thus, public policy must address not only issues arising from the delivery of current services but also translational issues such as when genetic tests are ready for clinical application. What level of evidence, and what kind of evidence, is sufficient before a test reaches the marketplace? Who should provide the evidence? Who should pay for its development? When the test is marketed, what standards of

practice should apply to its use? Who should pay for the test? Who should provide it? These questions are among the translational policy issues we address in the remainder of this report.

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## Genetic Services Policy Project Final Report

### Genetic Technologies in the Management of Breast Cancer: A Policy Brief

#### Overview

- Genetic technology has an increasing role in the diagnosis and treatment of disease. Breast cancer serves as a valuable model to explore emerging service delivery and policy issues related to integration of new genetic technologies.

#### Who is affected?

- A woman's chance of developing breast cancer in her lifetime is approximately 1 in 8 (12.7 % of women). (National Cancer Institute, 2007)
- An estimated 178,480 new cases of invasive breast cancer will be diagnosed in the United States in 2007.
- Breast cancer is the second leading cause of cancer death in women, sixth leading cause of death overall. An anticipated 40,460 women and 450 men will die of breast cancer in 2007.
- Currently, there are an estimated two million breast cancer survivors in U.S.

#### What is the role of genetic technology in breast cancer treatment?

- When diagnosed with breast cancer, individuals are faced with a “baffling” array of choices, including surgery, radiation, chemotherapy, and hormonal treatment with tamoxifen or other agents. (Griffin, 2006)
- Until the last few years, breast cancer treatment has been guided by broad clinical characteristics (age, menopausal status) and pathologic features of the tumor (grade, stage, estrogen and progesterone receptor status). Unfortunately, outcomes have been highly variable and it has been difficult to determine how any one tumor or person will respond to a given treatment.
- Genetic technologies are now emerging that have the potential to optimize treatment decisions based on unique tumor and patient characteristics. These technologies may play a role in determining prognosis, targeting treatment, and avoiding adverse effects of therapy. (Thurston, 2006)

#### Prognosis: Gene expression profiling

- Gene expression profiles examine the activity of various genes within biological tumor specimens using microarray and other DNA based technologies. Patterns of gene activity may be associated with tumor behavior and clinical outcomes, e.g., recurrence, distant metastasis, and response to chemotherapy.
- Examples of current gene expression profiling tests include:
  - Oncotype DX®
    - Developed and marketed by Genomic Health, Inc. in California. The test is performed at a central CLIA-approved laboratory, but the “home brew” test is not subject to FDA approval.

- Company data indicate that over 6,000 physicians have ordered more than 33,000 tests since launching in 2004. (Genomic Health, 2007)
- The test is currently indicated for the evaluation of estrogen receptor positive, node negative, stage I or II breast cancer in women who will be treated with tamoxifen. The test is being evaluated in other groups (e.g., node positive) as well.
- The test uses reverse transcriptase-polymerase chain reaction (RT-PCR) technology to quantify expression of 21 genes within paraffin fixed breast tumor tissue. A complex algorithm is then applied to create a “Recurrence Score”®. Possible scores are low, intermediate, or high. Individuals with a low Recurrence Score® may potentially avoid chemotherapy, and its associated costs and complications. (Paik, Tang et al. 2006) High scores suggest the need for chemotherapy. Management of intermediate scores is less clear.
- The test has been validated in a large number of stored specimens with known outcomes (Cronin, Sangl et al. 2007) (Paik, Shak et al. 2004), but there have been no randomized controlled studies to determine clinical utility. (McNamara, 2007)
- Patients are currently being enrolled in a large multi-center trial (Trial Assigning Individualized Options for Treatment (Rx), or TAILORx) to evaluate benefit of chemotherapy in individuals with intermediate Recurrence Score®. (NCI, 2006)
- The test may help health care providers and patients select the best course of therapy, but some question its readiness for clinical use given the lack of clinical studies. (Ioannidis, 2007)
- Ready or not, the test is increasingly being used in clinical care. In one recent study, the results of the test changed 32 percent of clinical treatment decisions, and increased patient and provider confidence in the treatment decisions (Lo, Norton et al. 2007)
- Oncotype DX® currently costs \$3,500. As evidence has emerged regarding the potential to avoid chemotherapy in patients who might otherwise be treated unnecessarily, numerous large private payers and Medicare have issued positive coverage statements and developed reimbursement agreements with Genomic Health, Inc.
- The National Comprehensive Cancer Network (NCCN), a leader in the development of cancer guidelines and standards, has commented on the possible benefits of gene expression profiling including Oncotype DX®, but has not issued a recommendation pending additional clinical evidence. (NCCN, 2007)
- MammaPrint® (also known as the Amsterdam 70-gene breast cancer gene signature)
  - Developed by researchers in the Netherlands and marketed by Agendia.
  - The test uses DNA microarray technology to determine the likelihood of cancer recurrence in the next 5-10 years. The test assesses expression of 70 genes in breast tumor specimens. An algorithm is applied and the tumor is then designated as low risk for spread or high risk for spread.
  - The test is the first multivariate assay to be approved by FDA (February 2007), but is not widely available in the US. The test requires fresh tumor tissue, as opposed to Oncotype DX®, which uses paraffin fixed samples. (Glas 2006)
  - MammaPrint® costs the same as Oncotype DX® (\$3,500), although most US payers have not opted to cover the test at this time. The test has been reviewed in

technology assessments in the US, but currently lacks evidence to meet criteria for a medically necessary service.

- A large multi-center trial to assess the clinical efficacy of the test has begun enrolling subjects in Europe. (EORTC, 2007)
- eXagenBC®:
  - New test undergoing FDA review. To be distributed by Exagen Diagnostics, Inc. (Exagen, 2007)
  - Uses fluorescence *in situ* hybridization (FISH) technology to evaluate for 3-5 genes associated with prognosis in both hormone receptor positive and negative breast cancers.
  - Anticipated benefits of the test are the ability to perform the test in any lab with FISH technology and the relatively low cost (estimated at \$700).
  - The genetic markers have been validated in studies using stored samples, but as with other gene expression techniques, clinical experience is lacking. (Davis, Harris, et al. 2007)
- The FDA has recently issued a voluntary industry guidance document on gene expression profiling. (May 2007)

### **Targeted treatment: HER2/Herceptin™ experience**

- A significant amount of cancer research activity is currently focused on identifying genetic and other molecular markers that can be used as highly specific targets for treatment. The HER2/Herceptin™ experience is widely touted as evidence for the benefits of this approach. Biotechnology and pharmaceutical companies are turning their focus to paired diagnostic and treatment combinations largely based on the success of HER2 testing and Herceptin™ therapy. (Phillips, 2006)
- The Her2/neu gene on chromosome 17 codes for the human epidermal growth factor receptor 2 protein, a protein that plays a role in regulating cell growth. Breast cancer tumors (and other cancers) that have increased expression of the Her2/neu gene (HER2+) tend to be aggressive and resistant to traditional therapies. Approximately 20 percent of breast cancers are HER2+.
- A gene-based test for HER2 expression became commercially available in early 1998. Several different HER2 testing products are now available. Testing involves either immunohistochemistry or FISH analysis (or a combination of methods). Reliability of testing methods has been an area of some concern.
- The benefits of HER2 testing were unclear, until Genentech, a large biotech/pharmaceutical company, launched trastuzumab (Herceptin™), a monoclonal antibody directed at the HER2 protein.
- Herceptin™ showed promise in two clinical studies in the mid-1990s, so it was fast tracked for FDA approval. Approval was given in late 1998 with requirements for ongoing study and monitoring of potentially serious cardiac effects.
- Since that time, additional studies have provided evidence for Herceptin™'s benefit, including one study that showed a 52 percent reduction in breast cancer recurrence in HER2+, node positive breast cancers.
- The National Comprehensive Cancer Network now recommends testing all invasive cancers for HER2 status and supports the use of Herceptin™ in appropriate candidates. (Carlson et al, 2006)

- One of the biggest challenges with Herceptin™ has been cost. A course of Herceptin™ adjuvant therapy runs approximately \$60,000.
- Despite the high cost, recent economic analyses indicate Herceptin™ treatment is cost-effective for early HER+ breast cancer. (Garrison et al., 2007) (Kurian et al., 2007) Garrison estimated that life expectancy improves three years on average through decreased recurrence. The cost effectiveness ratio was \$26,417/QALY.
- Until recently, there have been no other products that specifically target HER2+ cancers. Given the evidence of benefits and the lack of competition, U.S. sales for Herceptin™ have risen astronomically, reaching \$1.2 billion in 2006. (Global Insight Report 2007)
- The impact of new products on pricing policies is unclear. The FDA approved Tykerb™, a new drug developed by GlaxoSmithKline, in March 2007. Currently Tykerb™, in conjunction with the chemotherapy drug capecitabine, is indicated as a treatment for those who have previously failed treatment with Herceptin™, rather than first line treatment. Pricing is expected to be similar to Herceptin™.

### **Optimizing treatment: CYP2D6 and tamoxifen**

- Cytochrome P450 genotyping for tamoxifen treatment is an example of the use of genetic technology for optimizing treatment.
- Tamoxifen, a mainstay of breast cancer treatment, is metabolized to its active form, endoxifen, by cytochrome P450 enzymes. The CYP2D6 enzyme is a key enzyme in this process. Numerous studies have demonstrated that individual genetic variations (polymorphisms) in the CYP2D6 enzyme are associated with variation in plasma levels of endoxifen as well as in efficacy of tamoxifen treatment. (Goetz et al., 2005) (Goetz et al., 2007) (Borges et al., 2006) Poor metabolizers have decreased levels of endoxifen and worse clinical outcomes (more frequent relapse and worse survival) than extensive metabolizers. Approximately 7-10% of the population has a genotype associated with poor metabolizer status.
- Genotyping for CYP2D6 is now commercially available.
  - The AmpliChip® CYP450 test by Roche was the first FDA approved product for this indication. (Roche 2007) The test evaluates for common polymorphisms in CYP2D6 and CYP2C19, another p450 enzyme. The test costs \$500. (Lynch et al. 2007)
  - DNA Direct, a web-based virtual genetics clinic, is also offering “Tamoxifen 2D6” testing for \$300. (DNA Direct, 2007)
- In October 2006, a panel advising the FDA recommended relabeling tamoxifen to indicate the potential for decreased effectiveness in some patients and the availability of genetic testing. (Kaiser Network, 2006)
- Despite the potential value of genotyping, there are no studies to determine the impact of testing on clinical outcomes. In addition, the lack of effective alternatives to tamoxifen in some groups (e.g., pre-menopausal women) raises the question of whether it is ethical to offer testing in these groups. (Hartman, Helft, 2006)
- Given the large number of medications that are metabolized through the cytochrome P450 system, including many commonly used depression medications, genetic technology in this area has the potential to have a significant impact on clinical practice. However, clinical studies and guidelines are needed to assure appropriate use.

## **What policy issues are associated with genetic technologies in breast cancer treatment?**

### **What are the implications for broader genetic services policy?**

- Advances in genetics and genomics are driving the rapid development of tests and services, but evidence base for clinical utility lags behind. Even while the jury is out on one product, additional similar products are entering the market, leading to a confusing array of options for health care providers, consumers, and payers. This highlights the critical need for information, education and guidelines that can keep pace with the science and the market.
- The rapid pace of commercialization of tests and treatments presents a challenge for payers in the development of coverage and reimbursement policies. Payers typically rely on systematic technology assessment and review of other payer policies to make decisions regarding coverage. Tests and treatments may show promise, but may not meet technology assessment criteria for coverage. In addition, tests or treatments may show benefits in the long run (e.g., reductions in mortality with Herceptin™), but with many consumers changing health plans on a regular basis, payers may not reap the cost-savings and benefits. (Carlson 2005)
- Private payers often follow the lead of public payers, especially Medicare. Experience with Oncotype DX® is somewhat unique in that Medicare issued a positive coverage decision despite lack of randomized clinical trials. It is not clear whether this reflects a shift in Medicare philosophy or is an isolated occurrence. However, Medicare's move to create a coverage category for tests and treatments with limited evidence, referred to as "coverage with evidence development," demonstrates recognition of the need to create incentives for innovation while supporting evidence-based coverage policy. (Tunis, Pearson, 2006)
- Consumer demand for technologies may play a significant role in the integration of these technologies into practice, particularly in high profile conditions such as breast cancer. Review of breast cancer consumer and advocacy websites suggests a strong interest in technologies that can optimize treatment. (National Breast Cancer Coalition, 2007) Policy makers must balance consumer demands with the need to ensure safe, effective services and contain costs.
- Industry policies related to pricing new technologies will have an impact on the integration of technologies into practice. These policies also raise ethical concerns. In a recent editorial, Hillner and Smith (2007) pose the following questions: Even if Herceptin™ is cost-effective, are costs justified? Does industry have a moral obligation to ensure access to effective treatments and services? They point out that if we (as a society) continue to pay for Herceptin™ and other products at current prices, we will not be able to pay for other needed services unless we raise taxes, significantly increase patient co-pays, or limit access.

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Purpose	TEST	Type of Test	Current Indications (2007)	Implications	Impact on Care	Cost of test	POLICY ISSUES
Risk of disease	BRCA1/2 <sup>1</sup>	Single genes Mutation analysis	Family Hx Ethnicity	60-80% lifetime risk of breast/ovarian cancer	↑ monitoring (early mamm/ MRI)  Prophylactic surgery (breast/ovary)  Prophylactic tamoxifen	~\$300-3,000 (depending on full sequence analysis or single mutation analysis)	Patenting of genetic tests  Clinical guidelines for testing and breast cancer screening
Response to treatment	Her2/neu oncogene <sup>2</sup> (IHC or FISH)	Test for tumor gene amplification/overproduction HER2 protein	Invasive breast cancer	50% reduction in recurrence in Her 2+ tumors treated with trastuzumab  Improved outcomes with chemo regimens (anthracyclines)	Treatment with Herceptin <sup>TM3</sup> (trastuzumab) + paclitaxel  (Impending competition: FDA has recently approved Tykerb <sup>TM4</sup> for HER2+ advanced breast cancer)	Test - ~\$150  Treatment - \$60,000/pt/yr	Standard of care (NCCN guidelines)  Cost-effectiveness of testing methods  Accuracy of Her 2 tests
Risk of adverse drug reaction/poor response to treatment	CYP2D6 <sup>5</sup>	Test for variants in a gene for cytochrome P450 drug metabolizing enzyme	Tamoxifen treatment in post-menopausal women	Poor metabolizers have ↓ effect of tamoxifen/ may develop toxic levels	Selection of alternate hormone therapies (e.g., aromatase inhibitors)	Test - \$300 (from DNA Direct)	Clinical utility  Lack of prospective studies
Risk of recurrence	Oncotype DX <sup>TM6</sup>	Gene expression profile (21 oncogenes), algorithm assigns Recurrence Score® (RS)	Stage I/II ER+, node -	Low RS → opt for no chemotherapy High RS → chemo Intermediate RS → ???	Decisions re: addition of chemotherapy	\$3,200-3,500	Clinical utility  Use in node + cancer  No FDA approval
Risk of distant metastasis	MammaPrint <sup>TM7</sup>	Gene expression microarray assay (70 genes), "Good" or "poor" prognosis	Stage I ER + or ER-  Stage II ER+ or ER - and node -	May help guide follow-up care	Unclear. May impact decisions re: treatment or monitoring	Similar to Oncotype	Clinical utility  FDA approved, not widely available in US

<sup>1</sup> Myriad Genetics

<sup>2</sup> Multiple FDA approved tests (IHC-HercepTest®, Pathway; FISH-PathVysion, Her2 FISH pharmDX)

<sup>3</sup> Genentech: Herceptin<sup>TM</sup> (trastuzumab) is a therapeutic antibody targeted at the Her 2 receptor, a component of the tumor-stimulating signal pathway.

<sup>4</sup> Glaxo Smith Kline, approved March 2007

<sup>5</sup> Approved tests include: AmpliChip® by Roche

<sup>6</sup> Genomic Health, Inc, Redwood City, CA (CLIA approved lab, not FDA approved)

<sup>7</sup> Agendia

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## Genetic Services Policy Project Final Report

### **Cystic Fibrosis: A Policy Brief**

#### **What is Cystic Fibrosis (CF)?**

- CF is an autosomal recessive genetic condition with multi-system effects.
- Clinical course is highly variable, though early mortality is a common feature.
- It is often described as the most common fatal genetic disease in Caucasians.

#### **Who is affected by CF?**

- CF affects approximately 30,000 children and adults in the U.S. and occurs in approximately 1 in 3,500 live births.
- CF most often affects people of European descent, though may be found in all racial and ethnic groups.
- 80% of patients with CF are diagnosed by age three; only 10% of patients are diagnosed after age 18. The age at diagnosis is decreasing due to increased utilization of prenatal diagnosis and newborn screening.

#### **What are the genetic and non-genetic contributions to CF?**

- CF results when an individual inherits two abnormal copies of the CFTR gene on chromosome 7, one copy from each parent. Individuals who carry one abnormal gene (CF carriers) are typically unaffected.
- The estimated carrier frequency for a CF mutation is between 1 in 25 and 1 in 29 among European-Americans.
- The  $\Delta F508$  mutation, the most common gene variant, accounts for about 70% of CF carriers.
- Since the initial discovery of the CFTR gene in 1989, researchers have identified over 1,000 mutations of the gene. Severity of illness may be related to particular mutations.
- Non-genetic modifiers, such as environmental tobacco smoke, respiratory pathogens, and socioeconomic status (SES), may affect health outcomes.

#### **What are the clinical features of CF?**

- Patients with CF produce mucus that clogs the lungs and results in lung infections and eventual pulmonary failure.
- Patients with CF have difficulty in absorbing nutrients from food because the mucus keeps digestive enzymes from reaching the intestines.
- Liver damage and hepatic failure may result from blocked bile ducts.
- Pancreatic damage may lead to diabetes.
- Median life expectancy for individuals with CF is 33.4 years (CFF, 2006 data).

#### **What are the psychosocial impacts of CF?**

- As with other chronic illnesses, CF may have significant psychosocial impacts on affected individuals and families.

- Adolescents may be at particular risk for emotional and behavioral difficulties and poor adherence to complex treatment regimens.
- Stressors may include missed school and work, financial difficulties, and challenges associated with planning for the future (e.g., vocation, intimate relationships, and family).
- Better lung function and strong social support are associated with improved psychological status in adults with CF.

### **Who provides care for CF? In what setting?**

- Multiple providers are typically involved in the identification and care of individuals with CF, including prenatal care and primary care providers, pulmonology and gastrointestinal specialists, geneticists and genetic counselors, respiratory therapists, nutritionists, social workers, and nurses.
- Given the multi-system nature of the disease, comprehensive coordinated care is recommended and has been shown to improve health outcomes.
- The Cystic Fibrosis Foundation (CFF), the leading advocacy group for CF, accredits 115 comprehensive care centers nationwide (including 94 adult programs) and is affiliated with an additional 54 programs. (CFF, 2007)

### **What are standard treatments and therapies for CF?**

- Treatment depends on the stage of disease and the organs involved. Regimens often involve multiple medications and treatment modalities, and may include investigational therapies.
- Particular treatments include:
  - Chest physical therapy (PT) or percussion, which involves clapping on the back and chest to dislodge mucus. Studies suggest high frequency oscillating therapy vests may improve compliance and outcomes over manual chest PT.
  - Antibiotic treatments like TOBI® (tobramycin) aerosolized antibiotic to help address lung infections. Azithromycin is another antibiotic used for patients who are chronically infected with *Pseudomonas aeruginosa* bacteria.
  - Mucus-thinning therapies such as Pulmozyme® (rhDNase, dornase alfa) and hypertonic saline to improve lung function
  - Enzyme replacement for pancreatic insufficiency
  - Nutritional supplements to combat nutritional deficiencies
  - Lung transplantation and lifetime use of anti-rejection medication and immunosuppressant therapies to treat patients with end-stage CF
  - Psychosocial support
- Numerous new products and services, including gene-based therapies, are in the development pipeline or in clinical trial stages.
- Treatment outcomes are monitored in a national CF registry supported by CFF.

### **What costs are associated with CF?**

- Lifetime direct costs of CF are estimated at \$200,000 to \$300,000 (1996 values, 5% discount rate).
- Annual cost of medical care in 1996 averaged \$13,300 per patient, ranging from \$6,200 among patients with mild disease to \$43,300 among patients with severe disease.
- Of total costs, 47% were from hospitalization, 18% were from DNase (Pulmozyme®), 12% were from clinic visits, and 10% were from outpatient antibiotics.

## What is the role of genetic services in CF?

- Overview
  - The primary role of genetic services in CF is in the identification of carriers and affected individuals, as well as counseling for reproductive decision-making. Genetic research plays an important role in the development of new therapies.
- Carrier screening and prenatal diagnosis:
  - Expert opinion has recommended carrier screening for CF mutations for adults with a positive family history, partners of people with CF, couples planning a pregnancy, and couples seeking prenatal care. (ACOG/ACMG, 2001)
  - Mutation panels used in carrier screening identify the most common mutations, but may miss rare mutations. Specific mutations may vary between different racial/ethnic groups (e.g., African Americans, Hispanics).
  - Prenatal diagnosis for CF (i.e., amniocentesis and DNA testing of the fetus) is offered when both the mother and father are carriers, or if the mother is a carrier and the father's status is unknown. Prenatal diagnosis may offer reassurance if the fetus is unaffected or give the couple the options of preparing for the birth of an affected child or terminating the pregnancy.
  - CF carrier screening and prenatal diagnosis costs are approximately \$150-200 per person for carrier testing, and \$1,500-2,000 for amniocentesis. Prenatal carrier screening and subsequent prenatal diagnosis for CF is cost effective assuming affected pregnancies are terminated.
  - Pre-implantation genetic diagnosis (PGD) and selection of unaffected embryos may be used by carrier couples who choose to undergo *in vitro* fertilization (IVF); however, this option is expensive (average cost \$12,400 for IVF plus an additional \$3,000 for PGD) and not widely utilized.
- Newborn screening
  - The Centers for Disease Control and Prevention has suggested and endorsed the inclusion of CF on newborn screening panels because of potential benefits from early nutritional treatment, such as improved growth, as well as potential cost savings from reduced use of health care services.
  - Guidelines for implementing CF newborn screening programs have been developed to address concerns that adequate treatment, counseling and support services are in place prior to initiation of universal screening programs. (CFF, 2007)
  - Several different protocols using combinations of immunoreactive trypsinogen (IRT), DNA analysis, and sweat testing have been developed.
  - As of September 2007, 31 states have implemented CF newborn screening programs and an additional 12 states offer optional/selective testing or are planning to implement mandatory programs. (NNSGRC, 2007)
- Diagnosis
  - Diagnostic testing to confirm an abnormal newborn screening test or to evaluate a symptomatic child (or, rarely, an adult) is conducted through the gold standard "sweat test" and/or DNA analysis.
  - Reliable sweat testing is available at CFF-accredited centers.
- Genetic counseling
  - Genetic counseling is recommended for carrier couples and families with a child diagnosed with CF or identified as a CF carrier on newborn screening.

- Genetic treatment
  - Clinical trials with gene-based therapies (e.g., replacement of the abnormal CTFR gene with a normal copy) have been ongoing since the early 1990s with limited success to date.
- Genetic research
  - Research includes studies of genotype/phenotype correlation to predict disease severity and/or response to therapy.

**What genetic service delivery or policy issues are highlighted in this case?**

- Clinical service delivery issues
  - Implementation of guidelines
    - Studies show a significant increase in use of CF mutation testing after release of ACOG/ACMG guidelines in 2001, though there is limited data about who is actually using these services. Surveys of providers suggest the majority of prenatal care providers are offering CF screening to at least some of their patients.
    - Guidelines were withheld until adequate support and educational materials were developed to improve implementation. This approach may be useful for other conditions.
    - Carrier testing in preconception settings (e.g., family planning settings) appears to be underutilized, which may reflect the general underutilization of preconception services.
  - Availability of services/providers
    - Any provider may offer CF carrier screening, sending blood or buccal specimens to centralized labs for testing. Typically, prenatal care providers (e.g., obstetricians, midwives, family physicians), who may have additional education or informational resources, provide carrier screening.
    - Comprehensive prenatal testing (e.g., amniocentesis) and genetic counseling services are available in larger metropolitan areas, which may require travel.
    - CF care centers are available in larger metropolitan areas in all regions of the country. For families living outside these areas, care coordination between local primary care providers and the CF centers is important.
    - There is a growing need for adolescent and adult services as life expectancy continues to increase.
  - Public health services
    - Implementation of state newborn screening programs and ongoing monitoring of these programs will be a continued area of policy focus over the next several years.
    - Several state-sponsored adult CF programs (e.g., Idaho, Michigan, Texas, Virginia, and Ohio) have recently faced elimination or major cuts due to state budget deficits.
- Financial/payer issues
  - Private and public insurers typically cover CF testing in prenatal and pediatric settings as per standards of care. Coverage of preconception and pre-implantation genetic diagnosis testing may be limited, but more data are needed.

- Adults with CF may have difficulty in obtaining private insurance due to pre-existing condition clauses and unaffordable premiums. They may need to rely on public insurance or state high-risk pools, which are not available in all states and have variable requirements.
- Payers may be slow to cover costs of emerging therapies. The small target population makes it challenging to build the evidence base needed to support positive coverage policies. The process of appealing coverage decisions is cumbersome and time-consuming for consumers.
- Even if payers cover treatments, consumers may be responsible for significant co-payments (e.g., 10% of inpatient costs, and 20% of outpatient treatment costs).
- Pharmacy and medical equipment companies have developed assistance programs to increase access to products; however, these programs typically have income qualifications and other restrictions.
- States may use their federal Children with Special Health Care Needs funding to pay for direct services for individuals with CF; however, this is typically the “payer of last resort”.
- Legal/regulatory issues
  - States (e.g., Florida) have attempted to pass mandates for insurance coverage of CF treatment and equipment, but these have failed due to strong insurance lobby opposition.
- Industry issues
  - Industry has a key role in developing novel tests and treatments to improve detection and care for CF. Industry faces the challenges of high costs for research and development for a limited population group, the need to make services accessible for consumers, and the desire to have profitable businesses. Patenting of products limits competition and competitive pricing, but may provide incentives for companies to develop new therapies for these conditions.
  - Genentech, the maker of Pulmozyme®, has demonstrated a commitment to patient access and to continued research into new and improved treatments.
- Consumer/advocacy issues
  - The Cystic Fibrosis Foundation, founded in 1955, has been a major driving force in the development of policies and initiatives related to CF, raising awareness, funds, and political support for the cause. This includes advocacy for genetic services programs, such as newborn screening. Though the group’s influence has been a key ingredient in progress for the disease, concerns have been raised that differential power may adversely impact resource allocation to other groups/causes (e.g., sickle cell disease).
- Research issues
  - Experience with CF points to the great value of data collection tools (e.g., the national CF registry) for monitoring and improving performance and outcomes.

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## Genetic Services Policy Project Final Report

### Hereditary Breast and Ovarian Cancer: A Policy Brief

#### **What are Hereditary Breast and Ovarian Cancers (HBOC)?**

- HBOCs are cancers associated with autosomal dominant genetic mutations with reduced penetrance.
- Individuals with these mutations have a strong predisposition to breast and/or ovarian cancer, but the risk is not absolute.
- The two most widely known genes associated with HBOC are BRCA1 and BRCA2.

#### **Who is affected by HBOC?**

- Breast cancer affects nearly 180,000 women annually, and ovarian cancer is diagnosed in more than 20,000.
- Most breast and ovarian cancers are sporadic, but heredity may account for 5 to 10 percent of these cancers diagnosed each year in the United States.

#### **What is known about the genetic contributions to HBOC?**

- *BRCA* genes were first identified in the early 1990s through studies of families with multiple cases of breast and ovarian cancer.
- Myriad Genetics, a Utah-based biotechnology company, eventually sequenced and patented the genes.
- The genes have a role in DNA repair and tumor suppression, but their exact mechanism of action remains unclear even after a decade of intense study.
- More than 800 different mutations have been identified in each of the two genes.
- Prevalence of *BRCA* mutations in the general population is estimated to be 1 in 500 to 1 in 1,000. All racial and ethnic groups may be affected, but prevalence in some groups (e.g., Ashkenazi Jewish) is higher (2 percent) than others.
- In addition to high risk mutations, family history of breast and ovarian cancer may represent:
  - Other genetic causes of BOC
  - Shared environmental causes of BOC
- Other genes and environmental influences may modulate risk in individuals with a *BRCA* mutation.

#### **What are the clinical features of HBOC?**

- Women with mutations in the *BRCA1* and *BRCA2* genes have an estimated 45-65 percent lifetime risk of developing breast cancer and 11-39 percent lifetime risk of developing ovarian cancer. (Antoniou et al, 2003) Risk is higher in Ashkenazi Jewish women with *BRCA* mutations, up to 82 percent lifetime risk of breast cancer, and 23-54 percent risk of ovarian cancer. (King et al, 2003) Colon cancer risk is also increased.
- Cancer often occurs at an early age (<50 years) and may be bilateral.
- Men with altered *BRCA* genes (particularly *BRCA2*) may also develop breast cancer and are at increased risk of prostate cancer and other cancers.

- Cancers related to *BRCA* mutations may be more aggressive than cancers not associated with *BRCA* mutations, although mortality is similar for tumors of comparable grade and stage. (Rennert, Bisland-Naggan, et al. 2007)
- Numerous factors including breast-feeding, earlier birth cohort, oral contraceptive use, and weight control are associated with decreased cancer risk in individuals with *BRCA* mutations. (Chen et al, 2006) (Jernström et al, 2004) (King et al, 2003)

### **What are the psychosocial impacts of HBOC?**

- A cancer diagnosis is often associated with fear, uncertainty, and high levels of stress. Knowing one is at increased risk for developing cancer due to a genetic mutation or other risk factor can also be stressful. The term “pre-vivors” has been coined to acknowledge the unique issues facing these individuals.
- Genetic testing for *BRCA* mutations may bring up complex family issues and emotions. Concerns about insurance and employment discrimination may affect decisions about testing.

### **What is the role of genetic services in HBOC?**

- Family and personal health history assessment
  - Families with HBOC are often identified by family history of cancer, on either the mother or father’s side of the family. Key elements of family history include:
    - Two first degree relatives with breast cancer, one with a diagnosis before age 50
    - Three or more first or second degree relatives, regardless of age of onset
    - Both breast and ovarian cancer among first and second degree relatives
    - First degree relative with bilateral breast cancer
    - Two or more first or second degree relatives with ovarian cancer
    - First or second degree relative with both breast and ovarian cancer
    - Male relative with breast cancer
    - In Ashkenazi Jewish families, any first degree relative (or two second degree relatives on the same side of the family) with breast or ovarian cancer (USPTF, 2005)
  - Having a limited number of female relatives may obscure a high-risk family history.
  - Personal histories of early onset cancer, bilateral breast cancer, or male breast cancer are red flags for possible HBOC.
  - A known *BRCA* mutation or other cancer syndrome in the family strongly suggests further evaluation.
- Risk assessment programs
  - Numerous risk models and computer based programs are available to assess an individual’s risk for having a *BRCA* mutation (e.g., *BRCAPRO*) or risk of breast cancer due to family or personal history (e.g., Gail model, Breast Cancer Risk Assessment Tool)
- Genetic counseling
  - Once an individual is identified as being at risk for HBOC or a high-risk mutation, genetic counseling by a qualified provider is recommended. Counseling involves assessment of personal risk for HBOC and discussion of HBOC, the risks and benefits of genetic testing, and the clinical and psychosocial implications of positive, negative, or inconclusive test results.

- Genetic testing
  - In the US, *BRCA1* and *BRCA2* mutation testing is only available through Myriad and is marketed as *BRCAAnalysis*<sup>™</sup>.
  - Testing options include full sequence analysis, single mutation analysis (for a known familial mutation), or multi-site analysis for common mutations found in the Ashkenazi Jewish population. Costs range from approximately \$300 to \$3,000 depending on type of testing done.
  - Testing an affected family member first increases the likelihood of finding a mutation; then subsequent family members can be tested for a single mutation.
  - Myriad requires that physicians or other licensed health care providers order *BRCA* tests to ensure that patients receive adequate information about the test and its implications.

### **What are preventive therapies for HBOC?**

- For individuals identified with a *BRCA* mutation or high risk family history, there are several options including:
  - Intensive surveillance
    - Breast-clinical breast exam, mammography, and breast MRI
    - Ovarian-vaginal ultrasound, serum CA-125
  - Bilateral mastectomy (90 percent reduction in breast cancer risk)
  - Bilateral oophorectomy (96 percent reduction in ovarian cancer risk, 53 percent for breast cancer)
  - Tamoxifen: women with a *BRCA2* mutation may benefit from this treatment, but women with a *BRCA1* mutation may not (49 percent reduction in breast cancer risk)
  - Oral contraceptives: for ovarian prophylaxis (54 percent reduction in ovarian cancer risk)
- Cost-effectiveness studies comparing the above prevention strategies suggest that bilateral oophorectomy is the most cost effective strategy with the highest quality adjusted life years (QALYs) gained. (Anderson et al, 2006)
- Recent American Cancer Society guidelines recommend annual breast MRI screening as an adjunct to mammography in women with a 20 percent or higher risk of breast cancer, including women with *BRCA* mutations and/or strong family history. (Saslow et al. 2007)

### **Who provides care for individuals with HBOC or at risk for HBOC?**

- Many different types of clinical providers may identify family history or other risk factors for HBOC, including primary care providers, genetic specialists, and cancer care specialists (oncologists, oncology nurses).
- Myriad maintains a list of “referral centers” in each state with providers who offer *BRCA* testing services. These referral centers include genetics, cancer, and breast health centers. One web-based “virtual” genetics clinic, DNA Direct, a California based company, is authorized to offer the test because they use genetic counselors and physicians in their testing process.
- Myriad also provides patient and provider education materials, risk assessment tools, and assists patients in obtaining reimbursement from insurance companies. (Myriad, 2007)

### **What costs are associated with HBOC?**

- There are no lifetime cost estimates specifically for HBOC.
- In a 2000 study, lifetime direct treatment costs for metastatic breast cancer were approximately \$60,000 for a cohort of women diagnosed with breast cancer in 1994. (Berkowitz, Gupta, et al, 2000) Newer treatments such as trastuzumab (Herceptin™), which cost upwards of \$60,000 per course, may add significantly to the cost of an individual's care.
- Estimates for cost of ovarian cancer treatment range from \$39,947 to \$50,562. (Bristow, 2007)
- According to one author, cost effective policies on genetic testing and preventive treatment may save up to \$800 million of the \$8 billion or more spent each year on breast cancer diagnosis, prevention, and treatment. (Anderson et al, 2006)

### **Who are the major stakeholders?**

- Consumers/advocacy groups
- Professional organizations/health care providers
  - Primary care providers
  - Oncologists/oncology nurses
  - Genetic counselors/cancer genetic specialists
- Academic/research institutions
- Biotechnology industry
  - E.g., Myriad Genetics
- Public and private payers
- Retail genetics
  - E.g., DNA Direct
- Government

### **What genetic service delivery or policy issues does this case highlight?**

- Clinical service delivery issues
  - Cancer genetic services are increasingly being integrated into clinical care, particularly in the oncology setting. More oncologists and oncology nurses are taking on genetic counseling functions. In addition, retail genetic services for HBOC are now available through the Internet. Extent, content, and overall quality of cancer genetic services in different settings (oncology vs. genetics clinic vs. retail genetics) has not been evaluated.
  - Recommendations, standards, and guidelines for genetic and other health services related to HBOC have been developed by numerous professional organizations. However, there is no organized system to measure or monitor performance related to these guidelines.
  - Despite increased availability of services, many people with genetic risk for cancer are not being identified and are not receiving services. This may be related to:
    - Limited public awareness of genetic risk factors and recommendations
    - Limited health care provider competency and confidence in providing genetic risk assessment, counseling, and referral
    - Health care system barriers (e.g., traditional problem-focused office visits, inadequate time, lack of electronic health tools, lack of incentives to do risk assessment, and lack of consequences for not doing risk assessment)

- Limited availability of counseling/testing services in certain geographic areas, or public and providers who are unaware of referral resources in their area
  - Of note, physicians are much more likely to pursue genetic services for cancer susceptibility if a patient requests them, highlighting the potential benefit of increasing consumer awareness about genetic risk factors. (Freedman et al., 2003)
  - Some groups (e.g., African Americans) have significantly lower rates of genetic service use, despite similar risks of having *BRCA* mutations. Additional efforts are needed to identify reasons for this disparity and to develop culturally appropriate genetic services and outreach.
  - Financial factors limit access to genetic services for HBOC. This reflects the high cost of genetic testing, lack of universal health insurance access, and variations in individual health plan coverage and reimbursement policies.
  - Innovative delivery models (e.g., computer-based counseling, group counseling) and educational programs (e.g., City of Hope intensive cancer genetics training for health professionals) may improve access and availability of services.
- Public and private payer issues
  - Many health plans are now covering genetic testing in select high-risk individuals but may not cover non-enrolled family members, may require co-pays, or may have other limitations. Medicare limits coverage to individuals with breast/ovarian cancer or a known *BRCA* mutation in their family. Medicaid may or may not cover testing.
  - Comprehensive information on current health plan coverage and reimbursement policies for prophylactic interventions is not available, but limitations on coverage may restrict patient options.
- Industry issues
  - Policymakers often point to Myriad and *BRCA* testing as an example of the adverse impact of gene patents on consumer access to health services. Industry representatives argue that the high price of tests is justified by research and development costs and the provision of educational and informational resources for consumers and providers.
  - Myriad's direct-to-consumer marketing of *BRCA* tests has raised concerns about increasing demand for services in inappropriate low-risk candidates and inadequate preparation of the medical community.
- Consumer/advocacy issues
  - Breast cancer is a high profile disease and advocacy is particularly strong. Facing Our Risk of Cancer Empowered (FORCE) is a support group created to address the unique issues of "pre-vivors."
  - Another group, the National Breast Cancer Coalition, has raised the concern that too much attention is paid to genetics and not enough to understanding environmental factors in the etiology of breast cancer. The group also states that genetic tests should only be used in well-designed clinical trials and research studies. (NBCC, 2006)
- Legal/regulatory issues
  - Individuals at risk for HBOC and providers counseling these individuals often cite concerns about potential genetic discrimination associated with positive genetic test results, despite limited evidence of actual discrimination. Federal protections against discrimination, as proposed in several recent bills, may decrease concerns in this area.

- Other areas for potentially enhanced regulation include genetic testing, gene patenting, retail genetics, and direct-to-consumer marketing.
- Research issues
  - Ongoing research is needed to evaluate clinical and economic outcomes in order to enhance the evidence base for genetic services in HBOC.
  - The role of other genes and/or the environment in breast and ovarian cancer risk is also a high priority area for research.

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## Genetic Services Policy Project Final Report

### **Multiple Congenital Anomalies: A Policy Brief**

#### **What are multiple congenital anomalies (MCA)?**

- Congenital anomalies (birth defects) are defects existing at or usually before birth.
- Infants with multiple congenital anomalies (MCA) are typically infants with:
  - two or more major malformations (e.g., a neural tube defect, cardiac defect, missing limb), or
  - three or more minor malformations (e.g., syndactyly, a club foot, abnormally formed pinnae).
- Clinical course and prognosis for MCA is highly variable and dependent on the particular anomalies or syndrome present.
- Birth defects are the leading cause of death in infants under age 1 year in the U.S., accounting for over 5,500 infant deaths annually.

#### **Who is affected by MCA?**

- Birth defects affect 3% of all newborns in the United States; 1% of newborns have multiple defects or syndromes.
- The most common condition associated with MCA is Down syndrome, which affects 1 out of 800 children and 5,500 births per year in the U.S.
- All racial and ethnic groups are affected, though individuals of low socioeconomic status (SES) may be at higher risk due to environmental or lifestyle factors. In addition, births of infants with MCA may be more common in low SES groups due to lack of access to prenatal care and termination services.
- Anomalies are present in a significant number of pregnancies that end in spontaneous abortion or elective termination.

#### **What are the genetic and non-genetic contributions to MCA?**

- Congenital anomalies may result from a number of underlying causes involving both genetic (e.g., single gene or chromosomal abnormalities) and environmental factors (e.g., maternal drug use or illness). Up to 60% of isolated congenital anomalies have no known origin.
- Many cases of MCA are associated with chromosomal abnormalities, including an abnormal number of chromosomes or aneuploidy (e.g., trisomy or monosomy) or abnormal chromosomal structure (e.g., deletions, duplications, etc.). Down syndrome is caused by an extra copy of chromosome 21 and is also known as Trisomy 21.
- Advanced maternal age is a major risk factor for MCA due to aneuploidy. This relates to the increase in chromosomal meiotic errors that occur with age. (Yoon et al, 1996)
- Numerous studies have examined the relationship between environmental pollutants and congenital anomalies, but there is little evidence of clear associations. (Dolk, Vrijheid 2003)

#### **What are the clinical features of MCA?**

- Abnormalities vary depending on the underlying cause of MCA. Common abnormalities

include cardiac defects, cleft lip/cleft palate, neural tube defects (NTDs), musculoskeletal defects, abnormalities of the eye, and gastrointestinal or genitourinary defects.

- MCA is often associated with cognitive delay or other neuro-developmental concerns.
- Particular constellations of abnormalities are associated with different syndromes.

### **What are the psychosocial impacts of MCA?**

- MCA is often associated with significant psychosocial impacts on families.
- Couples may experience internal conflicts related to religious and moral values and societal pressure to terminate affected pregnancies.
- Grief may accompany pregnancy termination and may be long lasting, even if parents feel the decision was right. (Korenromp et al, 2007)
- Post-partum depression is more common after the birth of a child with birth defects.

### **Who provides care for MCA? In what setting?**

- Many health care professionals may be involved in evaluating, diagnosing and treating a fetus or child with MCA: primary care providers (obstetrical or pediatric), perinatal specialists, clinical geneticists/dysmorphologists, genetic counselors, and varied pediatric specialists (e.g. cardiologists, urologists, neurologists, surgeons). Nurses, social workers, nutritionists, speech/hearing/physical therapists, and others may also be involved in care.
- Children with complex needs associated with MCA are likely to benefit from comprehensive coordinated care in a medical home setting.
- Public health nurses from local Children with Special Health Care Needs programs may provide home visitation or other services for affected children.

### **What are standard treatments and therapies for MCA?**

- Many pregnancies in which the fetus is identified with MCA through prenatal diagnosis are electively terminated. The termination rates vary depending on the anomalies identified. One decade-long study found termination rates of 28 percent for oral clefts and 62 to 84 percent for chromosomal anomalies.
  - Rates of elective termination are usually higher for more severe conditions.
  - Women who choose to undergo prenatal testing may be more likely to choose to terminate an affected pregnancy than women who opt not to have testing.
- For live-born infants, the prognosis and therapies depend on the nature of the condition.
- Infants with MCA usually need complex medical and surgical management. Care is tailored to clinical need and ranges from palliative care to surgical and nutritional interventions.
- Families are typically referred to health care facilities that specialize in treating children. Multi-disciplinary teams are often needed to address complex needs and coordinate care.
- MCA is often associated with cognitive or sensory impairment that may require early intervention and special education and therapeutic services.
- Increasingly, individuals with conditions such as Down syndrome are living longer, thus requiring services into adolescence and adulthood.

### **What costs are associated with MCA?**

- There are no overall estimates of costs associated with MCA because the term includes a multitude of different conditions and defects.

- An analysis conducted in 1992 provides an estimate of cost of illness for cerebral palsy and for 17 structural birth defects in the United States. For 1992, the combined estimated cost of the 18 conditions in the United States was \$8 billion. The three conditions with the highest lifetime costs were cerebral palsy, Down syndrome, and spina bifida.
- In 2004, birth defects were responsible for greater than 139,000 hospitalizations with a total cost of \$2.6 billion.

### **What is the role of genetic services in MCA?**

- Overview
  - Genetic services play a role in the detection of MCA in the prenatal and newborn settings (or later), evaluation and diagnosis of the etiology of MCA, and in counseling for reproductive decision-making. Genetic research plays a major role in elucidating the causes of MCA and the development of testing, treatment, and prevention strategies.
  - Despite the availability of prenatal screening and testing services, congenital anomalies are often not identified prior to birth. This may be due to women choosing not to have prenatal screening or testing, lack of access to such testing, or to limitations in the testing technology or users. In one study in Hawaii, less than 16% of congenital anomalies were diagnosed in the prenatal period despite high rates of fetal ultrasound use and moderate use of invasive testing. (Forrester, Mertz 2006) In another study, only 50% of Down syndrome births had the condition identified prenatally. (Benn, Egan et al. 2004)
- Prenatal screening and diagnosis
  - Expert opinion now recommends offering screening and/or invasive testing for Down syndrome and other anomalies in all pregnancies, regardless of maternal age. (ACOG, 2007) Previous guidelines recommended invasive testing primarily in women 35 years of age or older at the time of delivery.
  - Serum screening can identify fetuses at risk for MCA associated with chromosomal aneuploid (e.g., Down syndrome, Trisomy 13 or 18) or open lesions (e.g., spina bifida, omphalocele).
  - A number of different screening methods are available including:
    - Multiple marker maternal serum screening at 15 to 18 weeks gestation (using three or four markers)
    - Integrated serum screening including markers in the first and second trimester
    - First trimester screening with nuchal translucency (an ultrasound technique) and serum markers followed by second trimester serum screening for NTDs
    - Fetal ultrasound (anomalies scan) at 19 to 21 weeks gestation
  - Sensitivity and specificity of different screening protocols vary, but no protocol identifies 100% of affected pregnancies.
  - Fetal MRI, fetal echocardiographs, and amniocentesis with cytogenetic or molecular testing may follow a prenatal screen that demonstrates an increased risk of an affected fetus. A woman or couple can then make more informed decisions about the pregnancy, including continuation of the pregnancy to term or termination.
  - Women over age 35 years, and increasingly younger women, are being offered

- invasive testing as a first line procedure with chorionic villus sampling (CVS) in the first trimester or amniocentesis in the second trimester.
  - Pre-implantation genetic diagnosis may also be used with *in vitro* fertilization to identify and deselect embryos with aneuploidy or other genetic/chromosomal abnormalities that may result in MCA.
  - Future trends include the development of non-invasive procedures to obtain fetal cells for prenatal testing, and the increased use of tests such as array-based genomic hybridization/chromosomal microarray analysis (CMA) that can rule out large numbers of disorders in one test.
- Evaluation of the newborn
  - Clinical geneticists, when available, are typically involved in the evaluation of MCA, documenting malformations, signs, and symptoms in order to compare against known syndromes.
  - Several factors must be considered in assessing MCA etiology: maternal health history, prenatal history, family history, and careful and detailed physical examination of the infant.
  - Genetic testing may help to rule out or confirm a suspected single gene disorder or chromosomal abnormality if maternal and pregnancy history are inconclusive.
  - Biochemical studies, molecular testing, karyotype analysis and/or fluorescence *in-situ* hybridization (FISH) testing may help to provide a diagnosis.
  - Identification of a large number of chromosomal abnormalities that were previously undetectable through standard tests may now be detected through CMA. This is likely to increase the number of cases of MCA with an official diagnosis.
- Genetic counseling
  - Genetic counseling is indicated for pregnant women and couples who are at higher risk for an affected pregnancy based on screening tests or clinical factors or who have an affected pregnancy or child with MCA. Counseling may assist the couple in determining risk for recurrence and providing guidance and support through the diagnostic and follow-up process.

### **Who uses genetic services for MCA? Where are the gaps?**

- The exact number of women who utilize prenatal screening, diagnostic testing, and/or genetic counseling services during pregnancy is not known, though the majority of pregnant women who receive prenatal care are likely to be offered some level of screening or testing.
- The availability of improved screening techniques (e.g., serum screening and ultrasound) has led to a decrease in the use of invasive procedures. (Benn, Egan, et al. 2004)
- The impact of new guidelines recommending that all pregnant women be offered the option of invasive testing is not yet known, but has the potential to reverse trends and increase utilization of invasive testing and genetic counseling services.
- Factors associated with refusal of prenatal testing have been evaluated. In one study, women who had never had a pregnancy termination, were Spanish-speaking Latina, or who scored high on a religiosity scale were more likely to refuse prenatal screening tests. (Press, Browner 1998) In another study, lower income African American women aged 35 or greater were less likely to utilize prenatal testing, due to greater faith or fatalism and lower perceived value of testing information. Higher income women had increased test use due to lower faith or fatalism and lower perceived procedure-related miscarriage risk (Learman et al., 2003).

- A study of over 15,000 cases of birth defects in Hawaii found that genetic counseling facilities were utilized in 1,596 (10.6%) of cases. Utilization rates were higher with the presence of multiple major birth defects, chromosomal abnormalities, malformations, certain specific defects (e.g., holoprosencephaly), death of a fetus or infant, and older maternal age. (Forrester, Mertz 2007)

### **Are high quality genetic services for MCA available and accessible?**

- Availability of services
  - Prenatal screening services are available in all areas of the country, but certain procedures are only available in larger centers.
  - First trimester screening involving nuchal translucency is only available in certain medical centers, due to the technical requirements of the procedure.
  - Comprehensive prenatal testing (e.g., amniocentesis) and genetic counseling are often unavailable in smaller communities or rural/frontier areas, which may require travel.
  - California is the only state that has a mandatory state-administered prenatal screening program. All pregnant women must be offered screening and all insurers must cover the screening fee, but women can opt out.
  - Availability of medical genetics consultation for the evaluation of newborns with MCA is limited by:
    - Geographic distribution of providers in larger metropolitan areas, and
    - Relatively small total number of geneticists nationwide.
  - Chromosomal microarray technology for evaluation of MCA is currently available from a limited number of laboratories, including Baylor College of Medicine, Signature Genomics, and Perkin Elmer/Spectral Genomics. However, any physician or authorized provider can order CMA.
- Quality of services
  - Professional standards and guidelines exist for prenatal screening and diagnosis, genetic counseling, and evaluation of newborns with MCA.
  - Prenatal care performance measures have been developed to monitor compliance with some standards (e.g., offering maternal serum screening to women less than 35 years and invasive testing to women 35 years and older). Health plans may use these measures to track individual providers or medical groups. Recent changes in clinical standards will require updating of performance measures.
  - The quality of information provided to parents with an affected pregnancy is of concern to some disability advocates. Anecdotes from parents suggest that many physicians and other health care providers do not provide balanced information about the realities of raising a child with disabilities, focusing primarily on the negative aspects.
- Financial access to services
  - Public and private payers typically support coverage of prenatal screening and/or diagnostic services. Individual health plans, however, may not include prenatal care as a covered benefit or may have limitations on coverage.
  - Newer technologies such as CMA may not be covered, and companies that offer these services may require upfront payment pending insurance decisions.
  - Washington is the only state that mandates Medicaid coverage of prenatal genetic counseling.

### **What genetic service delivery or policy issues does this case highlight?**

- Current clinical policy issues and controversy revolve largely around prenatal screening and diagnosis of congenital anomalies. Trends and policy recommendations advocating earlier prenatal screening in the first trimester are based on the premise that earlier pregnancy terminations are safer. Systems are needed to assure that women and couples are given accurate and balanced information to make informed choices about these pregnancies. Availability of tests such as chromosomal microarrays that can identify large numbers of disorders, some of undetermined significance, will be a challenge for genetic counseling and informed consent processes. Disparities may increase as women who do not have access to early or adequate prenatal care will not receive prenatal testing and will not have the option to terminate affected pregnancies.
- Many disability advocates are concerned about the increased attention on prenatal screening and diagnosis, particularly for non-lethal disorders such as Down syndrome. They argue that the primary purpose of prenatal testing is for the elimination of disabilities, which devalues people living with disabilities. They believe additional resources should be allocated to support people with disabilities as opposed to preventing their births. There are also concerns that pregnant women and couples are not being given balanced information about raising a child with disabilities, leading to uninformed choices.
- Legal issues related to MCA include abortion rights and wrongful birth lawsuits, which hold health care providers liable for failing to diagnose a condition during pregnancy. Abortion regulations have the potential to decrease access to pregnancy termination, particularly in the later stages of pregnancy. Concern about liability for wrongful birth is likely to increase the use of prenatal screening and diagnosis by obstetric providers.
- Other policy issues include coverage and payment for services by private payers, academic and industry policies related to the development, pricing, and marketing of prenatal and other tests, and hospital and health system policies related to pregnancy termination (particularly for those with religious affiliation).

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## Genetic Services Policy Project Final Report

### **Sickle Cell Disease: A Policy Brief**

#### **What is Sickle Cell Disease (SCD)?**

- SCD is an autosomal recessive inherited disorder that affects red blood cells. It is one of several different hemoglobinopathies.
- SCD presents in varying degrees of severity with multi-system manifestations.

#### **Who is affected by SCD?**

- Approximately 72,000 children and adults suffer from SCD in the United States, with the highest prevalence in individuals with African ancestry.
- 1 in 500 African-American births and 1 in 1,000-1,400 Hispanic births are affected.
- An estimated 2 million people in the U.S, including 8% of African Americans, are carriers.

#### **What are the genetic and non-genetic contributions to SCD?**

- The genetic abnormality associated with SCD is a point mutation on the hemoglobin beta gene (HBB) on chromosome 11. This mutation leads to the production of an abnormal hemoglobin, referred to as Hb S.
- SCD results when an individual inherits two copies of the gene for hemoglobin S (Hb SS). The abnormal hemoglobin causes red blood cells to become deformed (“sickle shape”) when exposed to low oxygen, dehydration, or other stressors. Clusters of sickled cells block small blood vessels leading to pain and organ damage.
- SCD also encompasses disorders combining Hb S with another abnormal hemoglobin: hemoglobin C (Hb SC), sickle  $\beta$ -thalassemia (Hb S $\beta$ <sup>+</sup>-thalassemia and Hb S $\beta$ <sup>0</sup>-thalassemia), D-Punjab, and O-Arab.

#### **What does it mean to be a carrier of sickle cell trait?**

- Sickle cell carriers have one copy of Hb S, and are almost always asymptomatic.
- Rare cases of death have occurred in carriers in association with extreme exertion (e.g., athletes and military recruits). Otherwise, life expectancy for carriers is normal.
- Carrier frequency (Hb S) varies by ethnicity:
  - 1:14 in African Americans
  - 1:176 in Native Americans
  - 1:183 in Hispanics
  - 1:360 in Middle Eastern groups
  - 1:625 in Caucasians not of Middle Eastern origin
  - 1:1336 in Asians

#### **What are the clinical features of SCD?**

- Pain is a hallmark of SCD. Sickle cell crisis, or vaso-occlusion, is responsible for both acute (5-7 days) and chronic (weeks to months) pain syndromes.

- Other serious life-threatening complications include stroke, overwhelming infections with *Streptococcus pneumoniae* and *Hemophilus influenzae*, splenic and hepatic sequestration crises, and aplastic anemia.
- Additional symptoms and signs include: swelling of the hands and feet, fatigue, respiratory symptoms, acute chest syndrome, and neurological changes due to occlusion of small blood vessels in the brain.
- With disease management, most individuals with SCD now live beyond 40 years of age.

### **What are the psychosocial impacts of SCD?**

- SCD often has significant psychosocial impacts on individuals and families affected by the disease. Quality of life may be significantly impaired, particularly due to pain issues.
- Chronic pain syndromes and chronic illness behavior are major concerns, and may contribute to stigma associated with the disease.
- Cognitive difficulties and learning problems may follow neurologic events.
- Missed school and work, reliance on public assistance programs, and financial stress are common.
- Adolescents are at particularly increased risk of emotional distress and relationship difficulties.

### **Who provides care for SCD? In what setting?**

- Multiple providers care for individuals with SCD and their families including primary care providers (e.g., pediatrics, family medicine), hematology specialists, genetic specialists, pain management specialists, high-risk obstetricians, and social workers. Pediatric hematologists are often the primary source of care.
- The National Heart, Lung and Blood Institute (NHLBI) at the National Institutes of Health supports 11 comprehensive sickle cell centers in urban areas with high concentrations of SCD patients. These centers have a clinical research focus.
- Additional sickle cell clinics are available at some large academic medical centers and children's hospitals.
- The American Academy of Pediatrics stresses the importance of the medical home concept for children with SCD.

### **What are standard treatments and therapies for SCD?**

- Life-long comprehensive care is required to minimize morbidity and reduce early mortality.
- Some individuals require extensive therapies and hospitalization for the specific symptoms and complications of SCD.
- Daily penicillin prophylaxis is recommended for all children with SCD (newborn to age 5 years) to protect against life-threatening infections.
- Chronic transfusion therapy reduces the risk of stroke.
- Sickle cell pain crises are often managed with drug therapy, including narcotics.
- Coping mechanisms, adequate pain management, and cohesive family units help to prevent psychological instability and the development of a chronic pain syndrome.
- Hydroxyurea may reduce the frequency of severe pain, acute chest syndrome, and the need for blood transfusions in adults who respond to the drug. Long-term studies of hydroxyurea use demonstrate a 40% reduction in mortality. (Steinberg et al. 2003) Appropriate pediatric

dosing is under investigation.

- Bone marrow transplantation with hemopoietic stem cells, ideally from an HLA matched sibling donor, may cure SCD, but only a limited number of patients with SCD are appropriate candidates for this treatment.
- Pregnancies in women with SCD are high risk and associated with increased morbidity and mortality.

### **What costs are associated with SCD?**

- Charges for chronic transfusion for stroke prevention range from \$9,828 to \$50,852 per patient per year.
- In 2004, the average cost of hospitalization for SCD was \$6,223 with over 84,000 admissions. Total hospital costs for hospitalizations due to SCD equaled \$488 million.
- In the same year, there were 20,271 hospital discharges for children with sickle cell disease and vaso-occlusive crises with an average length of stay of 4.4 days.
- A large proportion of hospital costs are covered by public insurance, with 66 percent paid by Medicaid, 13 percent paid by Medicare, and only 15% covered by private insurance. (Steiner, Miller 2006)

### **What is the role of genetic services in SCD?**

- Overview
  - The primary role of genetic services in SCD is in the identification of carriers and affected individuals, as well as counseling for reproductive decision-making. Genetic research plays an important role in understanding the disease and in the development of new therapies.
  - Population based screening programs in the 1970s failed to differentiate between carrier status and the presence of SCD, leading to confusion and discrimination against carriers.
  - Negative perceptions associated with historical events and stigma associated with the disease in a racially disadvantaged group may continue to influence utilization of genetic services in at-risk populations.
- Newborn screening
  - Newborn screening for hemoglobinopathies using isoelectric focusing and hemoglobin electrophoresis typically identifies individuals with SCD and may identify carriers. DNA analysis may be used for follow-up in some situations.
  - Currently, SCD and other hemoglobinopathies are included in all state newborn screening programs. New Hampshire recently added hemoglobinopathies to its mandatory screening panel (previously it was voluntary).
  - Newborn screening for SCD began in 1975, and was universally endorsed when studies demonstrated the life-saving benefits of penicillin prophylaxis in 1986.
  - While most states have a policy for notifying parents of carriers identified through newborn screening programs, these policies are not uniform and follow-up services (e.g., counseling) vary between states.
- Carrier screening and prenatal diagnosis
  - Carrier screening in the preconception or prenatal period may be used to identify carrier couples. Standard of care is to offer screening to individuals and couples based on racial/ethnic background.

- Prenatal diagnosis, through chorionic villus sampling or amniocentesis and subsequent DNA analysis, may follow positive carrier screening tests. Prenatal diagnosis may offer reassurance if the fetus is unaffected or give the couple the options of preparing for the birth of an affected child or terminating the pregnancy.
- Pre-implantation genetic diagnosis is possible for carrier couples who choose to undergo *in vitro* fertilization; however, this option is expensive and not widely utilized.
- Carrier screening of athletes
  - Recent consensus statements from the National Athletic Trainers Association and the American College of Pathology (2007) recommend pre-participation carrier screening of athletes and accommodations to prevent sudden death in association with heat and overexertion.
- Diagnosis
  - Specimens with abnormal newborn screening results are retested using a second, complementary electrophoretic technique, high performance liquid chromatography (HPLC), immunologic tests, or DNA-based assay to assess the beta hemoglobin gene.
  - Given universal newborn screening, diagnostic testing to evaluate a symptomatic child is now a rare occurrence, though it is possible as some parents choose to opt-out of newborn screening.
- Genetic counseling
  - Genetic counseling is recommended for carrier couples and families with a child diagnosed with SCD or identified as a SCD carrier on newborn screening.
  - Studies suggest low rates of utilization of genetic counseling services.
  - Several states have developed “sickle cell trait counselor” training programs to increase the availability of qualified counselors.
- Genetic treatment
  - Gene therapy
  - Stem cell transplantation
- Genetic research
  - Genetic determinants that may predict response to treatments, e.g. hydroxyurea. (Ma, et al. 2007)

**What genetic services delivery or policy issues are highlighted in this case?**

- Low utilization of genetic counseling and carrier screening by at-risk individuals and couples
  - Limited public awareness of SCD
  - Limited provider awareness/attention to carrier screening, especially in non-prenatal settings
  - High “single” parent/out-of-wedlock/teen birth rates in African American population (both members of couple may not be available for testing)
- Lack of access to high quality, comprehensive treatment services, particularly for adults
  - Limited number of providers with knowledge and experience managing SCD, especially adult providers
  - Geographic limitations in comprehensive services

- Variability in use of effective treatment
- High reliance on emergency department for care
- Limited psychosocial support services
- Significant reliance on public programs/payers (i.e., Medicaid and Social Security Disability Insurance) by individuals with SCD
  - 65% of hospitalizations for SCD covered by Medicaid
  - Challenges for adults with SCD in maintaining jobs with health insurance benefits
  - Poor reimbursement by public programs may be a barrier to physicians taking on SCD patients, particularly adults
- Other issues
  - Cost, coverage, and reimbursement of emerging technology for treatment of SCD
  - Gaps in research funding support
  - Appropriate follow-up after identification of carriers via newborn screening programs/access to genetic counseling
  - Concern regarding sickle cell trait in athletes and risk of death from extreme exercise

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## Genetic Services Policy Project Final Report

### **Type 2 Diabetes and Genetic Technology: A Policy Brief**

#### **What is type 2 diabetes (T2D)?**

- T2D is a progressive endocrine disorder characterized by abnormal secretion or action of insulin, which leads to elevated blood glucose (high blood sugar).
- Elevated blood glucose results in damage to multiple organ systems over time.
- A pre-diabetes phase, with abnormal glucose tolerance or insulin response, typically precedes the development of T2D.

#### **Who is affected by T2D?**

- T2D has reached epidemic proportions in the U.S. and is increasing around the globe.
- As of 2005, 20.8 million people in the U.S. (7 percent of the population) have diabetes, including an estimated 6.2 million who have not yet been diagnosed. (NIDDK)
- Over 20 percent of the population older than 60 has diabetes.
- Prevalence is increasing in children and adolescents, particularly in association with obesity.
- Women with gestational diabetes during pregnancy are at increased risk.
- The disease is more prevalent in certain racial and ethnic groups, including Hispanics, African Americans, Native Americans, and Southeast Asians.

#### **What is known about the genetic and non-genetic causes of T2D?**

- T2D is a multi-factorial disorder, with both genetic and environmental components.
- T2D risk is increased in people with a family history of the disorder. Rare cases of early onset T2D, known as Maturity Onset Diabetes of the Young (MODY), are associated with single gene mutations. Most cases of T2D, however, are believed to be related to multiple genes, each with a relatively modest effect, acting in concert with environmental influences.
- Obesity is a major risk factor, but not all individuals with diabetes are obese and not all people with obesity develop diabetes.
- Research into the genetic causes of T2D has been an area of intense interest over the past 20 years. Though many different genes have been implicated, replication of findings has proven challenging. New techniques, such as whole genome analysis and the availability of large population-based DNA banks, have accelerated progress in this area.
- In March 2006, deCODE Genetics, a biotech company from Iceland using samples from their national population-based DNA bank, announced the discovery of a gene on chromosome 10 with a strong association to diabetes.
  - Specific variants in the transcription factor 7-like 2 (TCF7L2) gene increased risk of diabetes by approximately 1.45 times in heterozygote and 2.41 times in homozygotes with a population attributable risk of 21 percent.

- An estimated 7 percent of the general population is homozygous for high risk variant.
- Gene-disease association studies for TCF7L2 have subsequently been replicated in multiple studies and populations.
- Mutations in TCF7L2 are associated with impaired insulin secretion and increased hepatic glucose production. (Lyssenko, et al. 2007)
- Since the discovery of TCF7L2, researchers have identified a number of additional genes with connections to diabetes. None have demonstrated the same degree of risk as the TCF7L2 variants. (Sladek, et al. 2007) (Steinthorsdottir, et al. 2007) (Florez, Jablonski, et al., 2007)

### **What are clinical features of T2D?**

- Individuals in the pre-diabetes and early stages of T2D may be asymptomatic or may have a variety of non-specific symptoms, including increased thirst, frequent urination, hunger, fatigue, weight loss, irritability, and blurred vision.
- Rarely the disease may present acutely with diabetic coma, a life-threatening condition.
- Complications of T2D are associated with end-organ damage and include heart disease, stroke, blindness, kidney disease, peripheral neuropathy, and amputations.
- Diabetes was ranked as the sixth leading cause of death in 2002, primarily due to complications.

### **What are the psychosocial impacts of T2D?**

- Adequate management of T2D and/or prevention of T2D in pre-diabetics requires significant behavioral change that may be frustrating for patients and health care providers.
- Depression is a common problem in T2D and may precede development of the disease. Diabetic individuals with untreated depression have poorer glucose control, increased risk of complications, and higher health care costs.
- The psychosocial and behavioral impacts of knowing one's genetic risk for T2D is not known.

### **Who provides care for T2D and in what setting?**

- Multiple providers are involved in the care of individuals with or at risk for T2D including primary care providers (internal medicine, family medicine), endocrinology specialists, other specialists who manage complications (e.g., cardiology, ophthalmology, nephrology, surgery, rehabilitation), nutritionists, diabetes educators, nurses, social workers.
- Academic institutions and community medical centers may offer diabetes specialty clinics which provide coordinated, comprehensive care.
- Geneticists and genetic counselors are typically not involved in the care of individuals with diabetes, other than those who have a monogenic form of the disease (e.g., Maturity Onset Diabetes of the Young). Currently, one web-based "virtual" genetics clinic, DNA Direct, offers the deCODE T2™ test directly to the public. Physicians may also order the test from deCode Genetics, Inc. in Iceland.

### **What are standard treatments and therapies for T2D?**

- Maintaining tight control of blood glucose is important for preventing long-term complications.
- Key components of diabetes treatment include:

- Weight management
- Diabetic diet
- Physical activity
- Medication: oral hypoglycemics, insulin
- The Diabetes Prevention Program trials demonstrated that T2D can be prevented or delayed by lifestyle intervention (weight management, diet, and physical activity) or treatment with metformin in pre-diabetics.
- Researchers and biotechnology companies are particularly interested in developing molecular test and treatment combinations.

### **What are the costs associated with T2D?**

Total direct and indirect costs of diabetes were \$132 billion in 2002. (NIDDK)

### **What is the role of genetic services in T2D?**

- Family history assessment
  - Family history of diabetes may be identified during routine health care visits, though the extent to which this information is used in management or screening decisions is not clear.
  - The American Diabetes Association recommends screening for T2D in the following groups:
    - Every three years in individuals over age 45, particularly with BMI > 25 kg/m<sup>2</sup>
    - More frequently and at a younger age in individuals with a family history of diabetes in first- and second-degree relatives, high risk racial/ethnic groups, or the presence of other risk factors, particularly hypertension or hyperlipidemia.
  - Several risk assessment tools, such as the ADA diabetes risk score, are available to assess an individual's risk of T2D. Family history is a key component of these tools.
  - For those at higher risk or with symptoms of diabetes, the recommended screening and diagnostic test is a fasting plasma glucose (FPG).
    - Prediabetes=FPG 110-126
    - Diabetes=FPG >126
- Genetic testing
  - To date, genetic testing has not played a significant role in diabetes care or management other than in association with early onset T2D and in research settings.
  - In April 2007, deCODE Genetics, Inc. launched the deCODE T2™ test, a genetic test for the highest risk variant of the TCF7L2 gene.
    - A test is positive if it shows two copies (homozygous) for the high-risk gene variant.
    - The company's stated rationale for the test is that knowing one's genetic risk will motivate people to change their behavior and may suggest lifestyle or medication intervention in individuals with pre-diabetes.
    - The test has not been studied in clinical trials and is not subject to FDA regulation.

- The test is available through a web-based retail genetics service (DNA Direct, Inc) or it may be ordered directly from deCODE Genetics in Iceland.
  - Test costs \$300
- Evidence suggests that a panel of genes may be more useful in predicting diabetes risk than a single gene test, though there are no clinically validated or commercially available genetic test panels at the current time. (Weedon, et al. 2006)
- Several online genetics companies (e.g., geneOB) offer non-specific genetic tests for diabetes risk of uncertain benefit.
- There are currently no clinical guidelines or professional statements related to the use of genetic tests for diabetes.

### **Are genetic services for T2D cost-effective?**

- There have been no cost-effectiveness studies, nor clinical utility studies, for the deCODE T2™ genetic test.
- There have also been no cost-effectiveness studies of targeted screening for diabetes based on family history. Diabetes screening is cost-effective in individuals with cardiovascular risk factors (hypertension and hyperlipidemia), particularly in the 55-75 age group. (Cooksey, et al. 2006)

### **Who uses genetic services for T2D? Where are the gaps?**

- Currently, there are only a few anecdotes related to use of the genetic tests for T2D. The actual number of tests performed since the new test was launched is not available. DNA Direct is conducting a non-scientific survey to gauge interest in the test. A new multi-partner study, the Multiplex Initiative, funded by the National Human Genome Research Institute, the National Cancer Institute, and the National Institutes of Health, is exploring the interest of healthy young adults in a number of genetic susceptibility tests, including one for T2D. A follow-up survey of those consenting to receive the test will gauge behavior change attributable to the testing.

### **Who are the major stakeholders?**

- Consumers
  - High risk groups/disparities
- Advocates
  - American Diabetes Association
- Health care providers/professional associations
- Academic/research institutions
- Biotech/pharmaceutical industry
  - deCODE Genetics, Inc.
- Retail genetics
  - DNA Direct
- Government/public health
  - Centers for Disease Control and Prevention
    - State-based Diabetes Prevention and Control Programs
  - Health Resources and Services Administration

### **What genetic service delivery or policy issues does this case highlight?**

- Clinical issues
  - Implementation and utilization of diabetes screening programs, including family history risk assessment
  - Clinical utility/cost effectiveness of genetic tests for T2D predisposition
- Public health issues
  - Role of family history and genetic testing in population-based T2D prevention programs
- Public and private payer issues
  - Coverage of screening and prevention services
    - Diabetes Screening and Medicaid Savings Act 2007- in committee
- Legal/regulatory issues
  - FDA oversight of genetic testing
  - Regulation of direct-to-consumer marketing of genetic tests
- Biotech/pharmaceutical issues
  - Developing genetic test and medication combinations
  - Genetic risk panels
- Research issues
  - Outcomes associated with genetic testing for genetic predisposition

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**Genetic Services Policy Project**  
<http://depts.washington.edu/genpol>

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## Genetic Services Policy Project Final Report

### Genetic Technologies in the Management of Breast Cancer: A Vignette

#### *Vignette 1: Patient perspective*

Naomi Densmore is a 52-year-old, post-menopausal woman who was recently diagnosed with breast cancer through the National Breast and Cervical Cancer Early Detection Program. She did not previously have health insurance, but became eligible for Medicaid through the National Breast Cancer Treatment Program when she was diagnosed with cancer. After an abnormal clinical breast examination and mammogram, Naomi was referred to a radiologist for an ultrasound guided core needle biopsy of a suspicious lesion. The biopsy pathology revealed an invasive malignant tumor of moderate grade. Naomi was scheduled for a consultation with a breast surgeon. They discussed the surgical options of lumpectomy with radiation or mastectomy with or without immediate breast reconstruction. Naomi decided to pursue mastectomy with breast reconstruction. The surgeon first re-biopsied the tumor and confirmed the cancer diagnosis, then proceeded with the mastectomy and breast reconstruction. The axillary nodes were also removed to determine if the cancer had spread. Pathology demonstrated that the tumor was 2 cm in diameter, with grade 2 histology and positive estrogen receptors. HER2 testing and her lymph node biopsy were negative.

After her diagnosis, Naomi sees an oncologist for further evaluation and treatment. The oncologist recommends that Naomi begin tamoxifen treatment and possibly chemotherapy. For the past year, the oncologist has been using the Oncotype DX® prognostic test in similar patients as a method to determine who might be able to avoid chemotherapy. Even though the National Comprehensive Cancer Network clinical guidelines do not take a definitive position on the test, the oncologist feels it has helped determine a course of treatment in several situations. For the most part, private insurers have been covering the \$3,500 test. He knows that Medicaid has not covered this expensive test in the past, and there are significant administrative hassles involved in trying to get approval. On the other hand, Medicaid has covered chemotherapy costs, albeit at reduced rates. He decides to offer Naomi the Oncotype DX® test, but tells her that Medicaid may not cover it. He also indicates that, based on classic risk factors such as tumor pathology, she has an average risk of recurrence and that chemotherapy may or may not be of benefit.

Naomi is unsure about what course of treatment to take and turns to an online cancer support network for help. All the potential side effects of chemotherapy make her extremely nervous, but she also doesn't want to risk having the cancer to come back. She learns more about the Oncotype DX® test and how it has been useful for other cancer patients in deciding about chemotherapy. Several people online have written about a new clinical research trial using the test. She wonders why her oncologist didn't mention the trial, and if she should bring it up herself. Naomi also reads about the use of a genetic test called CYP2D6 that may predict how well she will respond to tamoxifen treatment. She wonders if this test would also be useful for her. She knows that she won't be able to afford either of these tests on her own, so she decides to ask her oncologist to petition Medicaid for coverage.

### *Vignette 2: Payer perspective*

Marianne Parker is the medical director for Medicaid in her state. She is responsible for reviewing clinical cases and approving or disapproving coverage for certain non-routine or particularly expensive tests or procedures. The need to balance costs and benefits is particularly acute for her state Medicaid program, given state budget shortfalls and growing client volumes.

Recently, Marianne has had an increasing number of cases involving requests for genetic tests associated with breast cancer treatment. First, it was HER2 testing, then Oncotype DX®, and now the CYP2D6 drug metabolism test. Because HER2 testing and subsequent treatment with Herceptin™ in HER2 positive breast cancers has been found to be cost-effective and associated with increased survival, testing using approved protocols has been covered. Up until the last few months, Marianne has denied coverage for the Oncotype DX® test, given its investigational nature and lack of clinical outcome studies. However, she notes that emerging evidence suggests the test may actually be helpful in avoiding use of chemotherapy in individuals with low risk of cancer recurrence, and therefore may reduce costs of care. Evaluation of other health plan policies suggests that the test is becoming standard of care when used in appropriate candidates. Despite lack of Food and Drug Administration (FDA) approval, Medicare has issued a positive national coverage decision for Oncotype DX®, and many other plans have entered reimbursement agreements with Genomic Health, Inc., the company that developed and performs the test. Similar tests, such as the MammaPrint® test, which the FDA approved in February 2007, are also being evaluated in clinical studies but data are less clear on clinical usefulness. Choosing between various competing tests in the future may be a challenge. Marianne decides to bring up the topic with the Medicaid Advisory Board at the next monthly meeting, and possibly revise the coverage policy on the Oncotype DX® test.

The CYP2D6 test is another story. A recent request for coverage came from an oncologist who has begun to use the test to determine which patients to treat with tamoxifen and which to treat with alternatives such as aromatase inhibitors. Marianne explored the literature on cytochrome P450 drug metabolism and genetic testing. She found an October 2006 statement from FDA indicating that the CYP2D6 gene is a predictor of tamoxifen efficacy, that tamoxifen should be relabeled to indicate that CYP2D6 poor metabolizers have a higher risk of breast cancer recurrence, and that testing is available. However, clinical experience with the test is limited. Marianne denies the request, explaining that the test is investigational and not considered medically necessary. She is convinced this is only the beginning of an onslaught of requests for genetic tests, and she is concerned that her Medicaid program is not ready to address these issues.

***Genetic services issues:***

- Rapidly emerging role of genetic technology in disease management, adding to already complex treatment options
- Limited clinical outcome studies with new genetic tests
- Variable insurance coverage for genetic services
- Complex coverage decisions requiring evidence review
- Challenges for payers, especially public payers, in balancing costs and benefits of new tests and treatments with other population health needs
- Role of coverage decisions (or anticipated coverage decisions) in clinical care
- Role of clinical trials in determining the value of genetic services
- Competition between the industry players (multiple tests with similar functions emerging)
- Relationship of industry to payers (direct lobbying for tests and treatments, which tests and treatments to cover)
- Increasing involvement of FDA in providing guidance for genetic tests
- FDA approval of genetic tests does not assure clinical usefulness
- Educational needs of consumers, providers, and payers
- Role of virtual networks in providing consumer information and support

***Case Issues for Discussion:***

1. These vignettes highlight the rapidly emerging role of genetic technology in disease management, adding to already complex treatment decisions.
  - a. What education and/or resources are needed to assure health care providers are ready to incorporate these technologies into care?
2. Health care payers often rely on technology assessments in determining which tests and treatments to cover. These assessments use criteria to determine whether there is enough evidence to suggest that a technology is safe and effective. Emerging technologies, such as gene-based prognostic assays, may appear to have benefits but may have limited evidence in clinical studies.
  - a. How can payers address this issue?
3. Medicare has implemented a “Coverage with Evidence Development” program to address promising new technologies or treatments. This program allows Medicare to extend coverage to services that might otherwise be deemed experimental, increasing access as well as clinical experience with the technology or treatment.
  - a. Could this approach work for private payers as well?
  - b. What are the benefits and risks of this approach?
4. Each state Medicaid program is different. Some services are mandated for all Medicaid programs. Genetic tests are optional.
  - a. What is the impact of lack of standardization of Medicaid policies?

- b. In developing coverage policies for genetic tests or other services, how is Medicaid different from private payers? How is it the same?
5. The Oncotype DX® test has been studied and validated using stored samples from patients with known health outcomes.
  - a. What are the potential problems with basing clinical recommendations on these studies? What are the potential benefits?
6. A new multi-center study, TAILORx, is currently recruiting patients to evaluate the Oncotype DX®, 21-gene assay, in the management of patients with intermediate risk of cancer recurrence.
  - a. How might this study impact payer coverage policies?
  - b. If the test demonstrates a clear lack of benefit from chemotherapy in specific groups, should payers be allowed to require the test to avoid paying for chemotherapy? Why or why not?
7. Currently, the Oncotype DX® test has the largest share of the market for gene-based prognostic assays for breast cancer; however, numerous companies have similar products in the pipeline. Exagen Diagnostics, Inc. has announced the development of a new fluorescence *in situ* hybridization (FISH) based breast cancer prognostic test called eXagenBC™, which it expects to cost \$700, significantly less than Oncotype DX®. The test, which will be sold as a kit, will have other advantages, including the ability to perform the test in multiple labs. As with Oncotype DX®, clinical experience with the test will be limited at first.
  - a. How might the entry of this product into the market impact Oncotype DX?
  - b. What are the implications for health care providers, who are still in the early phases of using Oncotype DX?
8. Genomic Health, Inc., the company that developed and performs the Oncotype DX® test, is working on the development of other genetic tests, although Oncotype DX® is their primary product. Despite the high cost of the test, the company does not generate enough revenue to offset costs and reports annual losses in the millions.
  - a. What implications, if any, does Genomic Health's experience have for the genetic testing industry?
9. Testing for the HER2/neu receptor gene has become a standard part of clinical care for breast cancer given the availability of targeted treatments for HER2+ cancers. Despite its high cost, Herceptin™, a monoclonal antibody directed to the HER2 receptor, is now routinely used for cancers that express the HER2 gene. The drug, which costs approximately \$50,000 per treatment course, has become a blockbuster for Genentech, the company that produces it. GlaxoSmithKline has recently announced the availability of Tykerb™, another targeted treatment for HER2+ breast cancers. Pricing is expected to be similar to Herceptin.
  - a. Is Herceptin's high price justifiable? Why or why not?
  - b. How does pricing affect access?
  - c. Does industry have a moral obligation to ensure access to effective treatments?
  - d. How might competition influence pricing?

10. Tests for genetic variants that affect cytochrome P450 drug metabolism, including tests for CYP2D6, have recently become available. Cytochrome P450 enzymes are involved in the metabolism of numerous drugs, including tamoxifen, a mainstay in breast cancer treatment and prophylaxis.
  - a. If testing for 2D6 genetic variants can show which individuals are likely to have a better or worse response to tamoxifen, is it ethical not to offer testing?
  - b. Is it reasonable to offer testing to people for whom there are no current options other than tamoxifen (e.g., pre-menopausal women)?

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## Genetic Services Policy Project Final Report

### Cystic Fibrosis: A Vignette

Mark Johnson is a 36-year-old father of two. His daughter, Madison, has cystic fibrosis (CF). Mark and his family live in a small town in Illinois.

Mark first learned about Madison's CF when his wife, Jane, was pregnant. It was their second pregnancy. Their son, Jonathan, was almost 2 years old and healthy. They had briefly discussed carrier screening during their first pregnancy, but decided to forego it because they thought their risk was low. No one in either of their families had CF, though they knew about the condition because a childhood friend of Jane's, Michelle, had had the disease. Michelle had died after a lung transplant several years before, but her younger brother who also had the disease was doing well.

This time when Jane's midwife discussed the recent newborn screening recommendations and offered the CF test, Mark and Jane decided to go ahead with it. The couple was surprised when Jane's test came back positive: she had one copy of the cystic fibrosis gene. They were even more surprised when Mark was also found to be a carrier. At that point, Jane's midwife, in consultation with a local obstetrician, arranged for an amniocentesis (amnio) in Chicago, two hours away. A genetic counselor and a perinatologist told the couple about their 25 percent risk of having an affected child and talked about the options available to them if the test were positive. The amniocentesis was performed and the amniotic fluid sent for DNA analysis.

A week later, the genetic counselor called with the amnio results. Mark and Jane were stunned. They had talked about what they would do if the baby was affected, but were still not expecting the result. Because of their beliefs, as well as Jane's friendship with Michelle, they didn't really consider discontinuing the pregnancy. After the phone call, Mark and Jane drove back to Chicago with a referral to the Cystic Fibrosis Center. The doctors, nurses, and social worker there were particularly helpful in providing information about what to expect. They discussed the challenges of raising a child with CF but were also reassuring about the exciting research being done in this area and the new treatments that were becoming available.

Despite their concerns, once Mark and Jane saw Madison, they knew that things would be okay one way or the other. They were particularly thankful that they knew about the CF before she was born so that they could be prepared, and so she could start enzyme and nutrition therapy immediately after birth. She is now 6 years old and doing so well that, even though Mark doesn't know for sure, he can't help but think the immediate treatment was beneficial. Madison is now in the 50<sup>th</sup> percentile on the growth charts, and is really active. Mark worries that she might get sick at school so he and Jane put her in a private school where they have a little closer connection to the teachers and other parents. They try their best to keep her away from germs, while still trying to lead a pretty normal life.

Currently, Madison is on a special diet, pancreatic enzymes, *recombinant DNase*, and uses a therapy vest two times a day for 30 minutes at a time. Prior to the vest, Mark and Jane were doing chest percussion, which was time- and labor-intensive. For Madison, all the treatments have been a regular part of her life; she doesn't know any differently, though she sometimes wonders why her brother, Jonathan, or other kids don't have to do the same things. The family travels up to the CF Center every three months and has been very happy with the care there. Last time they were there, they talked with the research coordinator about enrolling Madison in a new medication study. At home, Madison is followed by a local pediatrician for routine care. Mark and Jane have been pleased with his coordination of care with the CF Center. Madison has been lucky in avoiding lung infections: she has had no *Pseudomonas* and had only a brief staph infection that resulted in a short hospitalization when she was 3 years old. Other than that incident, she has avoided hospitalizations.

The Johnsons know there are a few other families in nearby communities who have children with CF, but they don't connect with them other than at special events, such as the CF walks. Their main support has been from Michelle's mother, their own family, and online support groups. People (parents and individuals with CF) from all over the country post questions and messages, which has been really helpful. Friends have also been very supportive.

After Mark's positive carrier test, several others in his family got tested too, including his parents. They wanted to know which side of the family the gene was on so that other family members would be aware of their risk. Mark's mother turned out to be a carrier. It is interesting that one of her brothers had trouble with infertility, a possible association with being a CF carrier. His sister hasn't been tested yet. She and her husband are finished having children and have decided to wait until their kids are old enough to choose for themselves whether to be tested. No one in Jane's family wanted testing. Even though their son, Jonathan, didn't have any symptoms of CF, their doctor suggested that Mark and Jane consider testing him since there was a small chance he might have the disease. He was tested and found to be a carrier. Originally, the Johnsons had planned on having three or four children; Jane, especially, wanted a big family. A couple of years after Madison was born, they discussed the possibility of pre-implantation genetic diagnosis. Because of cost and other issues, however, they decided to focus their attention on Madison and Jonathan and possibly consider adoption in the future.

Mark feels that his family has been pretty fortunate. He has a good job and good health insurance. Given the incredibly high cost of CF meds, he can't imagine not having insurance, even though he knows there are assistance programs that can help pay for medicine. He worries at times whether Madison will be able to get insurance coverage when she gets older, a concern he has heard about from the online groups. *Recombinant DNase* costs more than \$1,000 per month, not to mention all the other meds. Even with insurance, the Johnsons pay a significant co-pay on the *recombinant DNase* every month. Madison's therapy vest cost \$16,000. It took over 8 months of filing requests and appealing the insurance company's denials before they finally got it approved for partial coverage.

Mark is amazed that scientists know so much about the gene for cystic fibrosis, but don't have a cure yet. He and Jane decided to contribute to a national cystic fibrosis research fund to help find a cure. They are hopeful for the future of gene therapy and other treatments, but in the meantime,

they are glad for the technology that allowed them to identify Madison's CF so early. After talking with Michelle's mother about all the hurdles they went through before Michelle was diagnosed with CF 25 years ago at age 4, Mark has become an advocate for screening newborns for CF. Illinois was one of the states that did not screen newborns for cystic fibrosis, so when he was asked to serve on the state newborn screening advisory committee, Mark readily agreed. He is excited that the state has now decided to add CF to its screening panel. He knows there is some controversy about the value of screening all babies for CF, but he thinks if screening can find just one child with CF, it will be worth it.

## Case Issues for Discussion

1. The couple in this case chose to undergo carrier screening for the cystic fibrosis gene after the midwife discussed new screening recommendations from a professional organization. In addition to offering prenatal carrier screening to all couples, the recommendations also suggest that screening should be offered to couples planning a pregnancy. Studies indicate that while prenatal screening is being widely implemented, preconception screening is still limited.
  - a. What are the potential benefits and harms of preconception carrier screening?
  - b. What barriers exist to implementing preconception screening recommendations in practice?
  - c. What opportunities exist to overcome these barriers?
  
2. After learning that their unborn baby had CF, Mark and Jane were faced with a choice regarding continuing or terminating the pregnancy.
  - a. What factors played into their decision?
  - b. What supports would help Mark and Jane make their decision?
  
3. Madison is doing well overall.
  - c. How might this scenario differ if she was experiencing more significant health problems?
  - d. How might the scenario differ if her family situation was different (e.g., single parent, language or cultural barriers, limited education, lack of a job or health insurance, lack of geographic access to CF services)?
  
4. As demonstrated in this case, multiple providers are involved in Madison's care. Coordination of care is a significant issue, particularly in areas that do not have a specialty care center.
  - a. What systems and resources are needed to assure a close connection between community primary care providers and specialty care providers based in the CF center?
  - b. What are the potential problems if care is not well coordinated?
  - c. What educational needs do each of the various providers have?
  - d. What is the role of the medical home?
  - e. What is the role of the patient and family?
  
5. In the United States, the development of accredited cystic fibrosis specialty care centers has been touted as a model for other chronic diseases. Currently (as of 2007), there are 115 accredited centers, 95 adult programs, and 50 affiliated centers nationwide.
  - a. What are the advantages of this model of care?
  - b. What are the disadvantages?
  - c. What role does accreditation play in assuring quality of care?
  
6. Treatment for CF is costly and often includes "experimental" therapies or procedures that may or may not be covered by an individual health plan.
  - a. What is the impact of insurance coverage decisions on individuals and families with CF?
  - b. What is the role of public assistance programs?
  - c. What is the role of private assistance programs (e.g., pharmaceutical assistance programs, foundation programs)?
  - d. Why do adults with CF have particular problems with insurance coverage?

- e. What resources or services are available for adults?
  - f. Some states (e.g., Florida) have considered legislation to mandate insurance coverage of CF treatments and services. What are the pros and cons of such legislation? Why might insurance companies oppose such mandates?
7. Research is a significant component of CF care. The family in this case is considering enrolling Madison in a medication research study.
- a. What, if any, ethical concerns are associated with research in children? What protections would address these concerns?
  - b. Should risky experimental treatments (e.g., gene therapy) be withheld from children, even if there are potentially lifesaving benefits?
8. As depicted in this scenario, different family members make different choices about genetic testing.
- a. What are the indications for testing family members?
  - b. What, if any, ethical concerns are associated with testing children for carrier status?
9. The couple has considered having additional children.
- a. What is the role of pre-implantation genetic diagnosis?
  - b. What ethical dilemmas are associated with this technology for this condition and others?
10. Advocacy and political action have played significant roles in raising the profile of this disease, as well as attracting financial support for the cause.
- a. What are the pros and cons of advocacy group involvement in policy development?
  - b. What mechanisms would contribute to equitable allocation of resources for various diseases and causes?
11. Mark mentions the controversy surrounding screening newborns for cystic fibrosis.
- a. Why is universal newborn screening for CF controversial?
  - b. What are the arguments for newborn screening for CF?
  - c. What are the arguments against it?

What service delivery issues does this scenario raise?

- Geographic access to services
- Specialty care center model

What provider issues are identified?

- Multiple providers (including prenatal, pediatric, specialty)
- Coordination of care
- Implementation of professional recommendations and clinical guidelines
- Genetic testing: who and when to test

What consumer issues are identified?

- Difficult choices/ethical dilemmas related to choices
- Financial concerns: cost-sharing and out-of-pocket expenses
- Consumer advocacy/involvement in policy making bodies
- Ethical concerns about research in children
- Family issues

What payer or coverage issues are identified?

- Consumer cost sharing
- Impact of coverage decisions on consumers
- Coverage of new technologies and “experimental” treatments
- Role of public and private financial assistance programs

What industry issues are identified?

- Development and role of new treatments (e.g., gene therapy)

What policy issues are suggested?

- Newborn screening

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## Genetic Services Policy Project Final Report

### Hereditary Breast and Ovarian Cancer: A Vignette

Dr. Jamie Brown is a family physician in a mid-sized community in Oregon. She is part of a six-person family medicine group and has been in practice for 10 years.

Recently, Jennifer McCarthy presented to Dr. Brown's office for a new patient visit and well-woman check-up. Jennifer was a 25-year-old, healthy young woman of apparent Eurasian descent. Her medical history was unremarkable except for a family history of diabetes in several relatives on her mother's side and breast cancer in her mother and an aunt. Her major concern was weight gain of 15 pounds in the past two years. She was on birth control pills, which she felt contributed to the weight gain. In addition, since graduating from college three years ago, she had worked in a sedentary job that required frequent lunch meetings or after-hours drinks with clients. Her work hours made it difficult to get any regular exercise. After completing her physical exam, Dr. Brown counseled Jennifer on nutrition, physical activity, and reducing alcohol intake. She also provided patient education materials on weight management, including helpful tips for busy people and offered a referral to a dietician. As the visit was ending, Dr. Brown asked if there were any other concerns. Jennifer replied, "Well, I wonder what you think about the genetic test for breast cancer. While I was in the waiting room, I read an article about a woman who had a family history similar to mine: a mother and an aunt with breast cancer. This woman got tested through a web-based genetic testing service, and she turned out to have the gene. She had ovarian surgery and was considering breast surgery to reduce her risk of getting cancer. Should I get tested too?"

Though Dr. Brown had initially noted the family history of breast cancer, she hadn't focused on this issue given Jennifer's other immediate concerns and her young age. Dr. Brown questioned Jennifer further about her family history. Her mother, whose family emigrated from Japan to the United States, was diagnosed at age 50 with early stage breast cancer. She was doing well after lumpectomy. No one else on that side of the family had breast or ovarian cancer as far as Jennifer knew. Jennifer's paternal aunt had breast cancer and a mastectomy sometime in her early 40s. Her aunt and her father were twins and had been adopted as infants, so additional family history (e.g., ethnicity or history of cancer) was not available. Jennifer didn't think either her mom or aunt had had testing for the breast cancer gene mutations (BRCA1 and BRCA2). From Dr. Brown's recollection about cancer genetics, Jennifer's history suggested some increased risk but it wasn't clear-cut. The individuals with breast cancer were on different sides of the family, and other important data about previous generations were not available. Dr. Brown offered to do more research about the testing and suggested a follow-up appointment to further discuss the breast cancer concerns as well as check on progress with her weight control program.

At home later that evening, as Dr. Brown considered Jennifer's situation, a number of questions and thoughts came to mind: Would Jennifer or any of her family members be good candidates for the breast cancer mutation test? What additional information was needed from the affected family members? Was Jennifer's mother's Asian background a risk factor? How did her family

history fit in with other potential risk factors for breast cancer—weight, oral contraceptives, alcohol, nulliparity (no pregnancies)? Could the new electronic medical record system being installed in the family medicine office help summarize this information and provide a risk estimate based on all the factors? What would be the ramifications for Jennifer of a positive test showing that she had a mutation? Dr. Brown remembered hearing somewhere that people might have problems with insurance and genetic tests, either that insurance companies would not cover the tests or that companies might discriminate against people if they had a positive test.

After spending an hour of her evening “free time” reviewing online material from a variety of reputable sources, Dr. Brown came to the conclusion that BRCA mutation testing was unlikely to be beneficial to Jennifer at this time, particularly if the genetic status of the paternal aunt was not known. Given the aunt’s history of breast cancer at a relatively young age (<45) and lack of additional family information, the aunt might be a candidate for testing. Without data from multiple generations, an online BRCA risk calculator estimated that the aunt’s chance of having a mutation was 6.8 percent. Given the mother’s older age at diagnosis and no other affected relatives on that side of the family, the mother’s history was less concerning for a BRCA-related breast cancer. There was no evidence that the mother’s Asian background increased the risk of a BRCA mutation. Though Jennifer’s family did not appear to meet the United States Preventive Services Task Force’s evidence-based criteria for an “increased risk family,” Dr. Brown wondered if Jennifer could benefit from genetic counseling to sort through the family issues. Dr. Brown definitely did not feel competent to provide the counseling. Since there were no genetic counselors in town, Jennifer would have to make the trip to the nearest center, which was an hour away. She could also consider the web-based testing service. Dr. Brown explored the website that Jennifer mentioned and was fairly impressed with the comprehensive services that were offered, including genetic counseling and physician reports. However, the cost of testing seemed quite high (\$3,400) and might not be covered by insurance. Dr. Brown was also concerned that Jennifer might be pressured to be tested even if it wasn’t really indicated.

Given the late hour of the day, Dr. Brown decided to send Jennifer a quick email the next morning outlining her thoughts and repeating her suggestion for a follow-up visit in a few weeks. Even if they didn’t proceed with counseling or testing, Dr. Brown thought it was probably a good idea to monitor Jennifer more closely for any breast changes, encourage breast self-exam, and maybe even recommend a mammogram sometime in the next few years. Even without a BRCA mutation, Jennifer’s family history did increase her risk of developing breast cancer. A reasonable next step would be for Jennifer to contact her aunt for more information and to raise the possibility of genetic testing. Dr. Brown decided that the next time she saw her oncology colleague, Dr. Callahan, she would ask about his experience with hereditary breast cancer and if he had any additional thoughts on how to proceed.

## Case Issues for Discussion

1. As reflected in this scenario, genetic issues make up only one component of overall care and considerations in primary care practice. Jennifer's priority issue and subsequently Dr. Brown's primary concern is her weight gain; the breast cancer genetic testing question comes up almost as an afterthought.
  - a. Is the current primary care delivery system set up to adequately address genetic concerns? If so, in what ways? If not, why not?
  - b. What are alternate models that might improve identification and exploration of genetic health issues in primary care?
2. While most physicians are likely aware that genetic tests such as BRCA1 and BRCA2 exist and may be helpful in certain situations, experience and proficiency with use in practice may be limited.
  - a. What type of training and/or resources would assist physicians and other health care providers in appropriately utilizing this technology?
  - b. Do these resources already exist? If so, where?
  - c. What mechanisms exist to connect physicians to these resources and how might these connections be increased?
3. Physicians may be more aware of non-genetic risk factors for a disease such as breast cancer.
  - a. How can familial/genetic information be integrated with other risk information for accurate assessment?
  - b. What tools could assist in this process?
4. The physician in this scenario took a general family history during the exam, but spent limited time on this activity until the patient asked a specific question. Afterwards, the physician spent considerable time on the breast cancer issue, both during and after the visit.
  - a. What additional issues were brought up in the family history that the physician did not address? How should she address those issues in her future care of Jennifer?
  - b. Should this time be billable/reimbursable? Why or why not?
5. The 3-generation pedigree is a gold standard in genetic services practice. Dr. Brown did inquire about additional family history, but did not construct a pedigree.
  - a. Should this be an expectation in primary care? Why or why not?
  - b. If so, how can it be implemented in a cost-effective, time-efficient way?
6. After researching the breast cancer genetic testing issue, Dr. Brown felt that a genetic counseling visit could be beneficial for Jennifer even though evidence-based guidelines suggest that her family does not meet the "increased risk" criteria for BRCA1/2 mutations.
  - a. Under what conditions should Dr. Brown recommend a genetic counseling visit to Jennifer?
7. "Curbside" consultations are common in medicine. Dr. Brown thought that her oncology colleague might have additional information about hereditary breast cancer.
  - a. What are the potential benefits and pitfalls of such a consultation?

- b. What other types of professionals might she consult with?
- c. Are there effective models for such consultation? If so, what are they?

8. Jennifer's question about breast cancer genetic testing arose after she read an article in a popular magazine about the testing. The web-based testing service was a new concept for Dr. Brown. It was difficult to assess the quality of this retail service, and she was concerned that individuals might be pressured into testing even if they were not at high risk.

- a. Should web-based services be certified or monitored in some way? By whom?
- b. Should direct-to-consumer or direct-to-provider advertisements for genetic tests be regulated or restricted? Why or why not?

9. Dr. Brown wondered about the ramifications for Jennifer of a positive genetic test. A new term, "pre-vivor," has been coined for individuals who have a predisposition for cancer, based on a genetic risk or family history, but who have not been diagnosed with the disease.

- a. What unique concerns might pre-vivors have that cancer survivors or unaffected individuals do not have? Example resource: [www.facingourrisk.org](http://www.facingourrisk.org)

10. Dr. Brown looked for evidence-based approaches to Jennifer's care, but as is common in many clinical situations, found gaps in the available data and recommendations. She considered ordering a mammogram on Jennifer in a few years, though the literature provides limited guidance on this issue. The American Cancer Society suggests that for someone with a family history of early breast cancer, a mammogram at age 30 could be appropriate. MRI screening may also be warranted.

- a. What options could Dr. Brown recommend for Jennifer?
- b. Are there potential harms in suggesting that Jennifer undergo increased screening procedures, when her actual risk is unclear?

11. Insurance coverage of genetic counseling and testing is a potential issue for Jennifer and her family members. BRCA testing and prophylactic treatment (surgery) based on positive results are costly.

- a. What is the impact of insurance companies denying coverage for these services?
- b. Should insurance companies cover testing in non-enrolled family members?
- c. Should Dr. Brown recommend that Jennifer or her aunt avoid using insurance for counseling or testing because of concerns about potential discrimination (increased rates, etc.)?

12. The high cost of testing and follow-up services raises concerns about inequitable access to services. Studies have demonstrated that a significant number of individuals who are good candidates for BRCA mutation testing forego the test due to cost issues. This sets up a situation where individuals with resources have the opportunity to benefit from genetic testing, while those without resources do not.

- a. Is this an appropriate distribution of resources? If not, how can public policy rectify this situation?

13. The use and cost of BRCA1/2 tests are controlled by the company that developed and currently holds the patents for the tests.
- a. How does patenting affect patient access to services?
  - b. Should there be limits on the patenting of genes and genetic tests? Why or why not?

What genetic services delivery issues does this scenario raise?

- Lack of trained genetics professionals in the community
- Lack of organized referral or consultation networks (or lack of awareness of such resources)

What provider issues are identified?

- Criteria for use of genetic tests
- Educational resources: where to go for credible information, what information to collect
- Effective/efficient methods to identify high-risk individuals
- Risk interpretation tools
- Risk communication
- Evidence-based guidelines

What consumer issues are identified?

- Impact of media on patient requests
- Potential pre-vivor phenomenon
- Potential for discrimination (a real or perceived concern?)
- Getting information and sharing it with family members
- Cost sharing and out-of-pocket expenses

What payer or coverage issues are identified?

- Lack of reimbursement for time spent researching issues
- Variable coverage of preventive services, including genetic testing and prophylactic treatments
- Potential for discrimination

What industry issues are identified?

- Gene patenting

What other policy issues are raised by this scenario?

- Regulation of retail genetic services and oversight of quality
- Impact of patenting on genetic service delivery and access

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## Genetic Services Policy Project Final Report

### **Multiple Congenital Anomalies: A Vignette (1)**

Annie Klein is a genetic counselor in Alaska who focuses primarily on prenatal genetics. She works closely with Dr. James, the only perinatologist in the state.

Dr. James referred Elizabeth and Tom Bronson to Annie for genetic counseling after a series of tests indicated that their fetus was affected by multiple anomalies. Elizabeth and Tom were both 27 years old. They had been married for 3 years and lived in Sitka where they ran a small family business. This was their first pregnancy and it had been uneventful up to that point. Neither had a family history of birth defects or developmental delay. Elizabeth had no medical problems or any history of alcohol, tobacco or other substance use. At 17 weeks, Elizabeth's doctor in Sitka (a family physician with OB training) recommended a routine maternal serum screening test to check for Down syndrome and other defects such as spina bifida. Though Elizabeth and Tom were not at high risk for any problems, offering screening to all women is now standard practice.

The screening test came back two days later showing that there was an increased chance of a problem. The test was repeated for confirmation. The second test also showed an increased risk. Because there is no perinatologist in Sitka, Elizabeth and Tom were referred to Anchorage for a diagnostic ultrasound and set up an appointment for two days later. Elizabeth and Tom booked the 3-hour flight, paying the higher rate associated with last minute travel.

Once in Anchorage, the ultrasound examination revealed a female fetus that was small for gestational age (estimated at 18 weeks), with an omphalocele (abdominal wall defect), a ventricular septal defect (hole) in the heart, and a choroid plexus cyst. After discussing these results with Elizabeth and Tom and expressing his concerns that there might be a chromosomal abnormality, Dr. James recommended an amniocentesis, which was performed later that day. Amniotic fluid samples were obtained and shipped overnight to a commercial laboratory in Seattle. Chromosomal analyses by karyotyping (structural analysis of all chromosomes) and FISH analysis (rapid analysis of chromosomes 13, 18, 21, X and Y) were requested. Additional amniotic fluid and blood samples were collected for possible high-resolution chromosomal microarray testing, a new diagnostic process that allows identification of a large number of conditions, many not detected in traditional studies. At this point, Dr. James referred Elizabeth and Tom to Annie for genetic counseling. He gave the Bronsons a contact number since Annie was currently out-of-town, and he also called Annie to alert her to the case.

Annie and the Bronsons were able to connect the next day by phone after the Bronsons returned home to Sitka. Annie could tell Elizabeth and Tom were quite distraught and trying to process all the events of the past two weeks. Her role was to listen to their concerns and answer as many questions as she could with accurate information that could help them make informed decisions about this pregnancy and future pregnancies. She explained that while their histories did not put them at increased risk for having a baby with birth defects, approximately 3 percent (1 out of 33)

of all babies are born with a birth defect. Annie reviewed again the possible causes of the ultrasound findings and the fact that in many cases, the cause is unknown.

Annie discussed the various tests that were currently being done on the amniotic fluid. She also discussed possible scenarios and options for this pregnancy. If they chose to continue the pregnancy, the pregnancy would be deemed high risk and additional fetal monitoring would be advised. If the chromosome studies were normal, the large omphalocele and heart defect would suggest that ideally the baby would be delivered by caesarean section in a tertiary hospital (e.g., Seattle) where there would be immediate access to intensive treatment and surgery for the newborn. If they chose to deliver in Sitka, the baby would be flown to Anchorage or Seattle immediately after birth for treatment in a tertiary setting. If, on the other hand, the chromosomes demonstrated a typically lethal condition such as Trisomy 13 or 18, they could choose to continue the pregnancy but it was unlikely that the doctors would want to perform a caesarean section given the risks to the mother from a surgical procedure. The other option was to terminate the pregnancy.

Annie and the Bronsons discussed the pros and cons of each of these options. Tom had some concerns about termination given his religious upbringing but felt this might be in the best interest of the baby if it was likely the baby would suffer. Elizabeth worried about how they would take care of a child with complex special needs, especially in a remote area like Sitka. Annie told them about the availability of services for children with special health needs, such as public health nursing and educational programs. Tom and Elizabeth also had concerns about cost—the couple did have health insurance, but because they were small business owners, it was a high-deductible individual plan with a maximum maternity benefit. While they wanted to make the best decisions for their baby, the financial impact was very concerning to them. Already, the perinatology consultation, the diagnostic ultrasound, the amniocentesis and associated tests would add up to a significant cost. They also needed to factor in costs for travel, time away from work, etc. Annie talked with the Bronsons for over an hour and reassured them that her costs were covered as a component of the perinatal consultation. Annie informed Elizabeth and Tom that she would call back as soon as results were available.

The FISH test results came back the next day and were positive for a Trisomy 18. After talking with Dr. James, Annie notified Elizabeth and Tom of the results and discussed the importance of waiting until the karyotype came back to make any final decisions about the pregnancy. The karyotype results came back several days later and revealed a Trisomy 18, translocation type. This is a rare cause of Trisomy 18, and may result from either a balanced translocation in a parent or a “de novo” occurrence in the baby.

Annie called Elizabeth and Tom with the confirmatory results and reviewed with them information about how translocations occur, the features associated with Trisomy 18, and the fact that while 90 percent of infants die within the first year, sometimes an individual may live longer. Not having her usual visual aids was challenging, but she did her best to describe the condition over the phone. Mental retardation is a common feature in survivors. She emphasized that Elizabeth and Tom had not caused this condition by anything that they had done. Given that this was a translocation, there was a possibility that either Elizabeth or Tom could be a carrier of a balanced translocation (a silent abnormality). If one of them was a carrier, the risk for

recurrence in future pregnancies was high (1 in 4). Annie reviewed the options and offered to refer the couple to speak with others who have faced the same diagnosis. She also gave them the website information for a trisomy support group.

Elizabeth expressed relief at knowing how this happened but was very sad it happened at all, and she was concerned about the possibility that it could happen again. Tom and Elizabeth declined to speak with others since they felt they had already determined what they wanted to do: they decided to terminate the pregnancy. Annie explored this decision with them to make sure they were not feeling coerced. She also reassured them that she would share the information and their decision with Elizabeth's doctor in Sitka and he would be in touch with them about scheduling the termination procedure. She provided them with anticipatory grief counseling, recommended additional resources in the Sitka area and on the Internet, and suggested that when they were ready, she would like to meet with them again (ideally in person and before another pregnancy) to discuss further testing and recurrence risk.

Though each situation is unique, Annie finds that many of the issues, concerns, and questions that people have are the same. Being able to help people like the Bronsons sort through all the complex information and make informed decisions is very rewarding. The strength and courage of the individuals and couples that she works with continually inspire her.

## Case Issues for Discussion

1. Alaska is a frontier state with a number of unique challenges for health services delivery, including genetic services delivery.
  - a. What mechanisms are in place to address these challenges?
  - b. What additional services would be beneficial?
  
2. Multiple congenital anomalies (MCA)—the presence of two or more major abnormalities—are complex conditions. Chromosomal changes are a common cause of MCA, though often the underlying etiology (cause of disease) cannot be identified.
  - a. How does uncertainty surrounding etiology and disorder severity affect the role of screening, testing, and counseling for families?
  - b. In this case, the diagnosis of Trisomy 18 is associated with a poor prognosis. How might the case have been different if the diagnosis was Trisomy 21 (Down syndrome), for which the prognosis is less certain?
  - c. How might the case have been different if the cause of MCA was not identified?
  
3. As highlighted in this case, the identification of MCA has a significant emotional impact on the family.
  - a. What services and supports are available to assist families with these issues?
  - b. What additional services might be beneficial?
  
4. In this scenario, the presence of MCA was identified prenatally. However, in the majority of cases, anomalies are not identified until birth.
  - a. What factors contribute to delay in identification?
  - b. What additional steps, if any, could be taken to improve prenatal identification?
  - c. What challenges would Elizabeth and Tom have faced if the anomalies had not been identified prenatally?
  - d. What additional resources would they have used?
  
5. Currently, there is considerable activity in the area of prenatal screening and diagnostic testing on a number of fronts (e.g., clinical policy, research, emerging technology). Recent recommendations from the American College of Obstetrics and Gynecology (2007) suggest that screening for Down syndrome and other birth defects should be offered to all prenatal patients regardless of age or risk factors, a change from the previous emphasis on women with risk factors or advanced maternal age (>35 years). There is also a move toward earlier screening (first trimester) and newer techniques (nuchal translucency, quad screening, etc.).
  - a. What are the potential benefits of earlier and more universal screening?
  - b. What are the potential harms?
  - c. What ethical concerns do the recommendations raise?
  - d. As technology becomes available to screen for an increasing number of disorders quickly and reliably with minimal risk to mother or fetus, how will appropriate use of this technology be assured?
  - e. Who will, or who should, decide what constitutes “appropriate use”?

6. Increasingly, consumers are enrolling in health plans with high deductibles and limitations on coverage, or are unable to afford or choose not to purchase health insurance.

- a. What are the implications of this trend on consumer behavior and choices?
- b. What are the implications for demand and utilization of genetic services, including new technology?

7. Reimbursement has been a significant issue for genetic service providers, especially genetic counselors who provide time-intensive cognitive services and may be unable to bill insurance companies because they are not covered providers. In this case, Annie spends several hours on the phone with the Bronsons, but is unable to bill directly for her time. Her salary is covered by the perinatology clinic.

- a. What are the advantages and disadvantages of this reimbursement system?
- b. What alternative reimbursement systems might be considered and what would be their impact?
- c. What barriers exist to implementing alternative reimbursement systems?

What service delivery issues does this scenario raise?

- Lack of genetics professionals and other specialty services in frontier area
- Significant distance from community to needed resources
- Need for alternative service models (phone, telemedicine, electronic, etc.)
- Need for enabling services (transportation, etc.)
- Need for support resources (grief counseling, etc.)

What provider issues are identified?

- Coordination of care between providers in Sitka, Anchorage, Seattle, etc.
- Criteria for use of new technology
- Balancing patient needs and desires with available technology
- Reimbursement mechanisms for time-intensive services

What consumer issues are identified?

- Educational needs (dealing with complex information)
- Difficult choices/ethical dilemmas related to choices
- Grief and other emotional issues (potentially long-lasting)
- Need for support services (grief counseling)
- Financial concerns: cost-sharing and out-of-pocket expenses

What payer or coverage issues are identified?

- Consumer cost sharing
- Complicated health insurance plans
- Coverage of new technologies
- Reimbursement of counseling services and complex cases

What industry issues are identified?

- Development and role of new technologies (e.g., microarray testing)

What policy issues are raised?

- Ethical and societal implications related to recommendations for screening all pregnant women for Down syndrome and other birth defects

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## Genetic Services Policy Project Final Report

### Multiple Congenital Anomalies: A Vignette (2)

Marty Lewis is a genetic counselor in Washington state. She first met the Moore family when their newborn baby was being evaluated for multiple congenital anomalies. Peggy Moore was a healthy 27-year-old woman. Her husband, Jack, was 31 years old and also healthy. For the most part, Peggy had experienced an uneventful first pregnancy that included normal screening tests for Down syndrome, Trisomy 18, and neural tube defects during the second trimester. An early ultrasound exam for dates was also normal, and a second trimester ultrasound was offered but declined. At 36 weeks gestation, the Moores presented to their local hospital in Sitka, Alaska after Peggy's water broke. Fetal monitoring demonstrated that the baby was experiencing distress, so a caesarean section was performed. On delivery, Peggy's family physician who was overseeing her obstetrical care, noted a hypotonic (floppy) male infant with dysmorphic (abnormal) facial features, a cleft lip/palate, and a heart murmur. The infant was given supportive care and immediate arrangements were made to transport the child by air to Seattle, given the limited availability of tertiary services in Alaska.

Once in Seattle, the child was admitted to the Neonatal Intensive Care Unit and evaluated by a cardiologist, geneticist, orofacial team, and feeding specialist, in addition to the neonatal intensivist, and the rest of the NICU team. The cardiac ultrasound demonstrated a large ventricular septal defect. This heart defect in addition to the other anomalies suggested the presence of a syndrome. Dr. James, the geneticist, ordered several lab tests to pinpoint a diagnosis, including a traditional karyotype study. He and Marty met with the Moores to discuss other testing options including newly available chromosomal microarray (CMA) testing. The testing required blood samples from both parents and the baby. The advantage of this testing is the ability to test for multiple conditions in one test with rapid availability of results. However, health insurance plans were not yet universally covering this testing. Other options included multiple fluorescence *in situ* hybridization (FISH) tests for the most likely syndromes. The Moores decided to pursue the new testing and, after discussion with Dr. James, the family's health insurance plan pre-authorized the \$1,900 testing at 80 percent coverage.

A week later, the CMA test results came back demonstrating an abnormality (subtelomeric microdeletion) of chromosome 1p and the infant was diagnosed with 1p36 deletion syndrome. The chromosomal abnormality was not present in either of the parents' samples, suggesting a "de novo" deletion. This abnormality was not detected on the karyotype, which eventually came back normal.

Marty and Dr. James met with the Moores to discuss the results. Marty informed the couple of the low risk of recurrence and assured the Moores that nothing they did caused this abnormality. She told them that despite their lack of family history or other risk factors, 1 out of every 33 babies is born with one or more birth defects. The prevalence of this particular condition was 1 in 10,000 to 1 in 5,000; although relatively rare, it is the most common terminal deletion syndrome. Clinical course was variable, but the majority of affected children experienced

moderate to severe developmental delay and mental retardation. Seizures were a common complication but could typically be controlled with medication.

Because of financial concerns, Peggy stayed in Seattle with the baby while her husband returned to Alaska for work. During this time, Peggy began to experience significant episodes of sadness and anxiety. Concerned about post-partum depression, Marty recommended a mental health provider, but Peggy preferred to wait to see her physician when she got home to Alaska.

The infant fared moderately well and was discharged at 4 weeks of age. Arrangements were made for the baby to receive Children with Special Health Needs support services and early intervention services in Sitka. Arrangements were also made for roll-up with the geneticist who travels to Sitka twice yearly for a public health sponsored genetics clinic as well as with a neurologist and cardiologist in Anchorage. Future evaluation and treatment by the cardiac and orofacial surgery teams back in Seattle would be required. Marty provided Peggy with contact information for other families with affected children. Discharge planning included involvement of the family physician from Sitka through a conference call. Records from the infant's hospitalization were forwarded to the family physician to take over routine care.

In reflecting on the case, Marty wondered how things might have been different if the diagnosis were made prenatally. Would the Moores have continued the pregnancy knowing the prognosis? How will their son's condition affect their lives in the days ahead? Will this special child bring more joy than sorrow as similar children have done in many families? Marty made a note to contact the Moores in a week or so to check on their progress and to encourage Peggy and Jack to call upon the resources they need.

This case study highlights the following points:

- Although congenital anomalies may be identified through prenatal screening and diagnosis (maternal serum screening, ultrasound, chorionic villus sampling, amniocentesis), the test results may be normal or the tests may not be done at all (because of patient preference, provider practice patterns, etc.). In one recent study from Hawaii, only 16 percent of congenital anomaly cases were identified prenatally. Recent changes in professional screening recommendations and the availability of newer testing techniques may increase the number of anomalies that are identified prenatally. Options would then include pregnancy termination or continuation of pregnancy with enhanced fetal monitoring and ability to plan for a high-risk delivery. Pregnancy termination has numerous social, ethical and cultural implications. Cost-effectiveness studies of prenatal screening that demonstrate cost savings from screening assume that a large percentage of couples will choose pregnancy termination for affected fetuses.
- Availability of services, including genetic services, may be limited because of geography. In this case, services were not immediately available and the child/family needed transportation out-of-state. Follow-up services may also require travel (either the specialist coming to the area or the family traveling to the services). States have developed a variety of arrangements to assist with these concerns, including contracting with out-of-state geneticists and other specialists who will conduct outreach clinics on a periodic basis.

- New techniques, such as high-resolution chromosomal microarray tests that can identify a large number of conditions in one test, are emerging. These tests allow for more accurate and timely diagnosis of congenital anomalies (either in the pre- or postnatal period). Professional guidelines for use of these new technologies have not yet been established, and ethical concerns have been raised about the prenatal use of these tests.
- Multiple providers are involved in the care of children with congenital anomalies and their families, including geneticists and genetic counselors, specialists, and primary care providers. Coordination of care and support services are often needed.
- Family issues and needs are complex and vary among families. The time commitment as well as the physical and emotional strain of having a child with complex health needs can be significant. Because of hormonal changes, depression and other mental health concerns in mothers are not uncommon in the perinatal period and may be exacerbated by stress. Family separation and financial concerns are also issues in this case.

## References

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## Genetic Services Policy Project Final Report

### Sickle Cell Disease: A Vignette

Pearl Jones is a 35-year-old African American woman with sickle cell disease (SCD). No one else in her family has the disease. Pearl was diagnosed with “sickle cell anemia” when she was 3 years old after being hospitalized for a serious infection. At the time, the doctors gave her parents a dire prognosis, informing them that Pearl was unlikely to live past 18 years of age. Pearl’s diagnosis came in the mid-1970s, when the government initiated numerous publicly-funded screening programs for sickle cell. At the time, confusion about SCD and sickle cell trait led to discrimination in employment and other settings. Pearl’s parents didn’t tell many people about Pearl’s illness because they were concerned about her father losing his job if people knew about sickle cell in their family. And although Pearl’s father was employed, finances were tight, which forced the family to rely on public assistance for Pearl’s care.

As a child, Pearl had frequent hospitalizations for pain crises. She also had an episode of acute chest syndrome, a serious lung complication. Fortunately, she did not experience any strokes or other neurological complications. Growing up, Pearl missed many days of school because of her illness, but eventually earned her GED and then an associate’s degree in office administration.

Pearl and her family lived in an area where she had access to one of the ten federally funded comprehensive sickle cell centers. In this setting, she received cutting edge treatment by sickle cell specialists, treatment that was not as readily available in other community settings. In 1992, when she was 20 and having frequent pain crises, one of her physicians at the sickle cell center suggested that she enroll in a drug study. At first, her mother and grandmother discouraged her from participating given the negative history of medical experiments involving African Americans (e.g., Tuskegee syphilis studies). Pearl, on the other hand, trusted her doctors and decided to enroll. The two-year study evaluated the efficacy of hydroxyurea, a drug previously used in cancer treatment. Pearl, who was randomized into the treatment arm of the study, had a good response to the medication with significant reduction in her pain episodes. Since then, she has remained on the medication, except during her pregnancy. The medication requires that she see her hematologist on a regular basis to monitor her blood counts, since the drug may impair production of blood cells. She continues to have periodic but infrequent episodes of pain, particularly in association with stress. Several times, the pain has been so severe she has gone to the emergency room (ER) for care.

Pain has been a challenge for Pearl as it is for many individuals with SCD. The intensity of symptoms, as well as the uncertainty about when the pain will come, often takes a significant toll. Emergency treatment of pain is frequently inadequate, with many providers underestimating the need for pain medications. Pearl believes that pain played a major role in the dissolution of her marriage several years ago. She feels that her husband never really understood the disease and wasn’t able to support her during painful episodes. Her pregnancy with her now 10-year-old son was especially difficult, and left the couple emotionally drained. Pearl turned to her mother and sisters for help caring for her young son.

Several years ago, Pearl was invited to work as an office assistant for the local sickle cell association in her community. The job has grown to involve serving as an SCD patient and family advocate as well as raising funds and organizing educational programs about the disease. Despite decades of government-sponsored programs, newborn screening, and prenatal services, Pearl notes that awareness of the disease is still limited. She sees a history of disparities in funding and political support, especially in relation to other conditions such as cystic fibrosis.

As an advocate, Pearl monitors online message boards and SCD forums, and has learned about the issues that others with the disease are dealing with. Financial concerns are a frequent topic, particularly for adults. Many adults have ongoing or increasing health problems from disease complications, but they don't always qualify for public insurance programs or disability benefits. Even if they do qualify for Medicaid, it can be difficult to find a physician who will accept the low reimbursement rates along with the challenge of managing a complex chronic disease. Access to physicians and other health care providers with experience taking care of adults with SCD is also limited. Pearl's experience in the emergency room is echoed by others she communicates with online. Employment issues come up frequently as well. The disease can make it challenging to complete one's education and obtain and maintain a job with good benefits. Despite some legal protections, there is still concern about potential employment discrimination or being fired for missing work because of the illness. The message boards are not all about complaining though. Pearl is interested in recent postings about a new nutritional supplement that seems to have helped some people. She checked out the website for the product, which says the supplement was genetically engineered to work specifically in African Americans with SCD. She is a little skeptical, but who knows...this could be the wonder drug.

## Case Issues for Discussion

1. Sickle cell disease (SCD) is often used to highlight concerns about racial discrimination in health care, employment, etc.

- a. From Pearl's experience, what evidence is presented to support these concerns?
- b. How could public policy address these concerns?

2. This scenario reflects the perspective of a patient and advocate who has had access to good care through a comprehensive SCD center.

- a. How might the story differ if told by an individual with SCD who did not have access to a comprehensive care center?
- b. How might the story differ if told by a health care provider in an area with few SCD patients?
- c. How might the story differ if told by an individual with SCD if the individual relies on state assistance versus not relying on assistance?

3. Pearl finds that adults with SCD often have difficulty accessing quality services.

- a. What factors contribute to this situation?
- b. Are the issues facing adults with SCD different than issues facing other adults with chronic health conditions? If so, how are they different?
- c. What health care provider educational deficits are highlighted by this scenario?
- d. What services and supports would assure that adults with SCD receive appropriate care?

4. Pearl had frequent absences from school as a child because of her SCD.

- a. What other social ramifications are associated with this disease?
- b. Are there adequate supports to address these concerns? If not, what additional resources would be beneficial?
- c. Do you think the stigma Pearl and her family experienced in the 1970s still exists today? Please explain.

5. At the end of this scenario, Pearl hears about a new nutritional supplement that has been getting press on the online message boards frequented by people with SCD. She does additional research and finds the website for the product and seems convinced that this could be helpful to her.

- a. What are the potential benefits and harms of online message boards and other Internet resources as educational and informational sources?
- b. What issues or concerns does the nutritional supplement raise?
- c. Should such supplements be regulated?
- d. Should advertising for supplements be regulated?

What genetic service delivery issues does this scenario raise?

- Historical issues with screening programs and research projects
- Comprehensive care centers vs. community treatment (geographic disparities in care)
- Pediatric to adult transition issues

What provider issues are identified?

- Provider knowledge of disease (e.g., inadequate pain management in the ER)

What consumer issues are identified?

- Consumer knowledge base, availability and usefulness of information
- Support for social consequences of disease (e.g., divorce support groups, educational information for families)
- Concerns about racism, discriminatory treatment in health care
- Confusion regarding trait vs. disease

What payer or coverage issues are identified?

- Reliance on public assistance programs (SSI)

What industry issues are identified?

- Development of targeted therapies (“soft science” issues)

What other policy issues are raised by this scenario?

- Regulation of nutraceuticals (use of “genetics” in the marketing of nutritional supplements, lack of clinical testing for supplements)
- Differential power and resource base of different groups (sickle cell vs. cystic fibrosis)
- Education and employment accommodations, alternate arrangements
- Employment discrimination

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## Genetic Services Policy Project Final Report

### **Type 2 Diabetes: A Vignette**

#### ***Vignette 1: Patient perspective***

Marjorie Jones is a 55-year old woman who lives in southern Alabama. She was recently diagnosed with diabetes after a routine check-up with her doctor. Her blood sugar had been somewhat high in the past, but not in the diabetes range. With a history of hypertension and high cholesterol, the doctor was particularly concerned about her cardiovascular health. He recommended diet and exercise, weight loss, and started her on a small dose of metformin, an oral hypoglycemic, in addition to her blood pressure and cholesterol medications. He gave her information on the disease with a list of recommended follow-up lab tests and exams, including eye exams, foot exams, and cardiac testing. He also suggested that she attend a diabetes education class offered at the medical center.

Marjorie's father, who also had diabetes, died several years ago from complications of the disease. He had had difficulty controlling his blood sugar, and eventually lost his eyesight. He suffered from depression for a number of years. Given her father's experience, the news that she also had the disease was quite distressing for Marjorie. Would her diabetes follow the same course as her father? She had heard about diabetes being a familial disease so she worried that her own kids, three sons and a daughter, would be doomed to the getting the disease as well. According to an article she read in a recent newspaper, there was a new genetic test for diabetes that could predict whether someone would get the disease. She decided to ask her diabetes class instructor about the test.

#### ***Vignette 2: Educator perspective***

Sam Baker is a diabetes nurse educator at a large medical center in southern Alabama. Sam teaches self-management classes for individuals with diabetes and prevention classes for pre-diabetics. He also speaks frequently to community groups about diabetes risks and prevention. Alabama has one of the highest rates of Type 2 diabetes in the nation as well as high rates of obesity. Nearly 10 percent of adults in the state have diabetes, and 62 percent are at risk of diabetes because of being overweight or obese. Diabetes prevention and management are top public health priorities.

As an educator, Sam stays abreast of current research in diabetes and attends national diabetes meetings. Several years ago he read a review article about diabetes and genetics that discussed numerous possible gene-disease associations, but not much in the way of practical application. In his classes, Sam talks about the familial nature of diabetes, but focuses on the importance of healthy lifestyle for everyone, not just people with a family history of diabetes.

Sam was surprised when a genetic test for diabetes risk became available earlier this year (2007). He remembered the media reports last year when a group from Iceland discovered a major gene for diabetes and that there was a lot of hype about the importance of this discovery. He suspected that it would just be another in the long list of genes that had been associated with the condition, but wouldn't be particularly useful. Now the same group had come out with a clinical test for the risk gene.

At one of Sam's recent classes, a client asked him about the new genetic test. She was recently diagnosed with diabetes and was worried about her sons and daughter. Her father had also been diabetic. The client, an overweight woman in her 50s, thought this test might be helpful to see if her children would get the disease. Sam decided to do more research on the genetic test.

Sam checked out the company's website and learned the following information:

- The name of the test is deCODE T2™.
- The DNA-based test looks for a high-risk variant in the TCF7L2 gene.
- According to the company, a positive test (two copies of the high-risk gene variant) will increase motivation to change behavior (diet and exercise) and may suggest prophylactic medication (e.g., metformin) as a preventive strategy.
- Studies estimate that 7 percent of the population has two copies of the risk gene, and that having two copies nearly doubles one's risk of developing diabetes.
- The test is marketed as an important tool for diabetes prevention.
- Consumers can get the test directly through a web-based genetic testing service for \$300, or physicians can order it from the company in Iceland.

Sam, an avid computer user, explored a number of online resources, including several blogs, about the test. In one blog, a nurse described her experience with the test. She had already been diagnosed with diabetes and had a family history of the disease, but was interested in having the test because of potential implications for her children. Her test turned out to be negative. Was this information useful? Were her children any less at risk for diabetes? As it turns out, she was tested for free, so the cost wasn't an issue.

After reading about the test and finding no studies to support the use of the test in clinical care, Sam was pretty skeptical. He was sure insurance companies would not cover the cost of testing without more evidence of utility. Knowing how challenging it has been to get people to change their behavior, he wondered whether a genetic test that only examines one of many genes would be helpful. Could genetic testing actually have a negative effect? For instance, if the test is negative (meaning that an individual does not have two copies of the risk gene), people with pre-diabetes may think that their risk of developing diabetes is low and they may be less motivated to exercise and change their diet. And on the other hand, if the test is positive, people may think they are destined to get diabetes and not bother with making lifestyle changes. Pre-diabetics with the gene variant may opt for drugs like metformin over diet and exercise, adding to costs of care. Would a test that looks at multiple genes and gene variants be more useful, or only confuse things more?

The web-based testing service that offers the genetic test has an online survey to gauge interest and determine if people think the test will increase their own motivation to make lifestyle

changes. From Sam's experience, even if people think something will increase their motivation, it may not translate into action. He has encountered numerous people who spend \$500 or more annually on a health club membership as an incentive to exercise, but never use it.

In considering his client and her family, Sam doesn't think the new genetic test will be helpful and the cost would likely be prohibitive for many people anyway. He thinks the client's family is at risk for diabetes whether or not they have the high-risk gene and should make the lifestyle changes needed to protect themselves. Sam decides to write about the test in his monthly diabetes e-newsletter.

### **Case Issues for Discussion:**

1. In what situations might genetic testing for diabetes be indicated?
2. Would you spend \$300 on the deCODE T2™ genetic test for diabetes? Why or why not?
  - a. If you had a family history?
  - b. If you didn't have a family history?
  - c. If you had pre-diabetes?
3. What factors influence consumer demand for such a test?
4. What is the role of the media and online community (consumers and experts) in shaping demand?
  - a. Print media
  - b. Blogs
  - c. Message boards
  - d. Advertising
5. Do you think genetic tests will be helpful in getting people to change their behavior? Why or why not?
6. Should there be a requirement for genetic tests to demonstrate clinical utility prior to coming to market? Why or why not?
7. deCode, Inc. quickly turned their gene discovery into a gene test. What are the implications for other biotechnology companies? How might consumer demand for deCode's test impact the industry?
8. Communicating risk is a complicated process. What factors impact risk perception? What is the role of risk perception in genetic testing?

### **What genetic services delivery issues does this scenario raise?**

- Public and health care provider awareness and understanding of benefits and limitations of genetic technology
- Challenges associated with communicating genetic risk, variability in risk perception
- Availability of tests that have not demonstrated clinical utility, but have potential usefulness
- Need for clinical studies
- Direct-to-consumer and direct-to-provider marketing of genetic tests
- Role of media in providing information, influencing consumer behavior
- High costs of genetic technology, compared to other tests and services

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## Genetic Services Policy Project Final Report

### **Chapter 4: The Role of Cost-Effectiveness Analysis in Decision Making about Genetic Services**

As the number of genetic tests on the market has increased rapidly, so has the number of cost-effectiveness analyses evaluating genetic technologies. Our literature review identified 63 peer reviewed articles that systematically compared costs with some measure of benefit (e.g., years of life saved or gained, bad events prevented, cases detected) between 1990 and 2004 (Carlson et al. 2005; Veenstra et al., 2007).

Several factors contribute to the increase in popularity of the cost comparative studies. First, genetic technology is growing at a pace that prohibits reliance on the traditional guide to appropriate use of medical service: clinical experience. Second, the new technology often comes with a hefty price tag. BRCA1/2 testing, for example, can cost nearly \$3,500 (www.dnadirect.com). Coverage decisions of insurance companies and other third party payers have important consequences for test use, insurance premiums, and profits of both payers and test manufacturers. Third, Medicare is both a large and a public payer, without the option of either raising premiums or dropping enrollees in response to higher health care expenditures. A fourth factor is the increased amounts of public and private research funding available to conduct cost comparative studies.

This trend would appear to be strictly positive. When faced with decisions that have important clinical and economic consequences, what could be wrong with basing these decisions on careful empirical analysis? Plenty, according to a recent article published by Booz Allen Hamilton (Caruso 2008). In “The Myth of Cost-Benefit Analysis,” Caruso writes, “Cost-benefit analysis is also inappropriate for products or processes over which there are disagreements about benefits or about which outcomes are important, such as new medical technologies like genetic testing” (page 5). This chapter will draw upon both our literature review and our own cost-effectiveness analysis (CEA) of A1555G testing for aminoglycoside-induced hearing loss in cystic fibrosis patients (Carlson et al. 2005; Veenstra et al., 2007) to examine the strengths and weaknesses of cost comparative studies for genetic technologies.

#### Definitions

There are a number of approaches to cost comparative studies. All share the same basic conceptual framework: costs or negative consequences of a decision or action (e.g., administering the test) are listed on one side of the balance sheet and benefits or positive consequences are listed on the other. From this point, however, differences arise. In *cost-benefit analysis* (C/B), all costs and benefits are monetized to facilitate comparison. This approach is typically used when analysts wish to compare very dissimilar choices: Are scarce research dollars more productively invested in developing a new genetic test or a more fuel efficient car? *CEA*, by contrast, focuses on comparing decisions with sufficiently similar outcomes that they can be compared using dollars per unit of outcome. The most common outcomes used in analyses of medical technology are life years (LYs) gained or saved or quality-adjusted life years

(QALYs).<sup>1</sup> Other outcomes are also used for specific purposes, including cases detected, cases prevented, births averted, and carriers detected (Carlson et al. 2005). Thus, CEA could address a comparison between alternative means to reducing mortality: Are research dollars more productively invested in developing a new genetic test for diabetes or for breast cancer? CEA theoretically eliminates the need for analysts to monetize the value of a life—an empirically difficult and ethically challenging undertaking. We will return to this point later.

In our literature review, these two types of cost comparative approaches accounted for 19 percent (C/B) and 53 percent (CEA) respectively of the 63 studies reviewed. The remaining four studies used cost minimization, a variant of CEA. In the discussion that follows, we will focus our analysis on CEA as the most commonly used technique in the genetics area (although our comments and conclusions apply equally to cost-benefit analysis).

### Strengths

The primary strength of CEA is the logical framework it provides for decision making. This framework is applicable to most situations. The 63 studies we found analyzed genetic technologies in 13 different disease areas. CEA provides a structure through which the analyst can identify a wide range of costs and benefits associated with a particular decision or action. In our A1555G testing study, for example, we considered the adverse consequences of avoiding aminoglycosides in the presence of bacterial infections for CF patients with a positive test result for the A1556G point mutation. We also considered the possibility of mitigating aminoglycoside-induced hearing loss with hearing aids and cochlear implants.

The results of CEA can be displayed in a simple and easy to digest format, facilitating their use by decision-makers of varying levels of research sophistication. We summarized our complex CEA for A1555G testing in the one number that has become the standard in most studies (including all 14 cost-utility studies in our literature review): the incremental cost-effectiveness ratio (ICER) per QALY. In addition to its simplicity within a single study, the ICER can be compared across studies, allowing decision-makers to rationalize resource allocation broadly among different kinds of interventions that affect QALYs.

Thus, CEA is an attractive analytical model, as evidenced by the endorsement of the U.S. Panel on Cost-Effectiveness in Medicine (Carlson et al., 2005) and its widespread use in evaluating genetic technologies.

### Weaknesses

As articulated by Caruso (2008), the biggest strength of cost comparative studies—the condensing of complex processes into simplified economic terms—is also their biggest weakness. Caruso writes, “Even when conducted with the best of intentions, the method is still problematic, because it substitutes calculation for informed and considered judgment” (page 2). If the support for CEA arises from the supposition that judgment is well informed and thus well replaced by calculation, the dilemma is that the very uncertainty that renders judgment of the decision-maker ill informed most often applies equally to the researcher. The danger is that the data inadequacies and uncertainties that face the researcher can be masked in the calculation of the ICER. Because Caruso’s focus is on the use of cost-benefit analysis in the politically-

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<sup>1</sup> When QALYs rather than LYs are used, the studies are often termed “cost utility” analyses (Carlson et al., 2005).

charged regulatory arena, she outlines the many purposeful ways that inputs into cost-benefit analyses can be manipulated within a range of reasonableness to achieve a specific desired output.

But as the quote above illustrates, even for the researcher who aspires to be bias-free, there are data minefields at every turn.<sup>2</sup> In our CEA of the A1555G test, many of the most important parameters in the model, including variant prevalence and incidence and aminoglycoside-induced hearing loss severity and timing, had to be based on a paucity of data. Often even poor data for critical variables do not exist. In these cases, researchers must either omit them from the calculus or make assumptions about their value. These omissions and assumptions *necessarily* change the results. While sensitivity analyses (changing the assumptions and assessing how the changes affect the results) can offer some indication of the importance of the assumption, it does not help the researcher choose a course of action in the case where the centrality of the assumption is confirmed. Further, when data gaps suggest multiple sensitivity analyses to account for the many possibilities (in our CEA of A1555G testing, we tested multiple values for 22 variables), the study outcome becomes a matrix rather than a single number, thus obviating the virtues of simplicity and clarity.<sup>3</sup>

Even in those rare areas where the necessary data are both complete and vetted, there are still challenges. We stated earlier that the choice of CEA over cost-benefit is made to eliminate the need to place a monetary value on life in the case of medical interventions. However, for CEA to be useful as a decision-making tool, defining the outcome as cost per QALY does not escape what is essentially the same value judgment. The central value of ICER in our CEA was \$79,300. Is that too high? There is no strictly *empirical* answer. In comparison to the most commonly cited threshold of \$50,000, the answer is “yes” (Neumann et al., 2000). However, in comparison to the second most commonly cited threshold of \$100,000, it is not (Ibid). Awkwardly, there are many such benchmarks, most of which are arbitrary and without basis in theory *because they are inherently a-theoretical* (Grosse, in press). The World Health Organization proposed a threshold of \$120,300 for the U.S. in 2005 based on a multiple of GDP per capita (WHO, 2002; Eichler et al., 2004). Thresholds based on values implied by federal regulatory decision making range from \$200,000 to \$300,000 per LY (Grosse, in press; Ubel et al., 2003; Braithwaite et al., in press). Maciosek et al. report that nearly 20 percent of the clinical preventive services recommended by the U.S. Preventive Services Task Force cost more than \$165,000 (in 2000 dollars) per QALY (2006).

Finally, cost comparative studies that report an outcome as a single composite number, either a purely monetary cost-benefit ratio or an ICER per QALY, do not provide important information about the distribution of the costs and benefits across various subpopulations. That is, two interventions, both of which cost \$50,000 per QALY, may be viewed very differently by society if the benefits accrue primarily to low income children in the first intervention and high income elderly in the second. Again, there are no theoretical or empirical means of accounting for what are pure value judgments on the part of decision makers.

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<sup>2</sup> Nearly 35 percent of the 63 articles we reviewed failed to report the direction and magnitude of potential bias.

<sup>3</sup> We have not discussed the discounting of costs and benefits to account for the differential timing of each. The appropriate discount rate to use to bring all costs and benefits to present value to allow comparison of apples to apples is the subject of an entire body of literature in itself.

## Discussion

Does CEA provide any value to decision makers? Most certainly. In the words of Russell et al. (1996), “Although CEA does not reflect every element of importance in health care decisions, the information it provides is critical to informing decisions about the allocation of health care resources” (page 1177). However, this form of quantitative analysis might best be used as part of what the Committee on Risk Characterization terms an “analytic deliberative process” that elevates qualitative logic to an equal role (Caruso, 2008). Caruso describes the process as an iterative one in which “participants question value judgments and assumptions from a fresh perspective. They challenge one another’s biases and data. “They use values and judgment as a positive force to give context and authority to traditional analysis” (page 5).

There are a number of venues in which such analytic deliberation can and does take place. The deliberation is most often among technical experts—those who have knowledge about the quantitative values and/or the modeling process. However, the expertise of the medical and economic technicians does not extend to social values. Gold et al. (2007) note that decisions based solely on quantitative analysis and technical expertise are at risk of being at odds with public notions of distributive justice and equity. They argue that the public is ready (at last) to abandon the notion that health care can be consumed without limit and to engage in prioritizing what will and will not be paid for with collective dollars.

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## Genetic Services Policy Project Final Report

### Chapter 5: Analysis of Media Messages about Genetics

#### **Introduction**

Americans receive most of their information about science from the media (Hopkins, 1998; Conrad, 2001; Geller et al., 2002; Tambor et al., 2002; Young, 2002; Ten Eyck and Williment, 2003). While advances in the science of genomics have clarified a number of important questions about the relationship between genes and environment, they also have consequences for the relationship of science to the public good. How the scientific community explains significant breakthroughs to the public has nontrivial impacts on the society's quality of life (Weigold, 2001). On the other hand, the fact of the matter is that even medical professionals get much of their information about genomics from the media (Geller et al., 2003; Smart, 2003). According to Condit (2004), the media – not scientists or clinicians – provide the majority of public information about genomics.

Scholars of the topic agree that the media, perhaps more than any other slice of culture, have a significant impact on public discourse about the science of genetics and related issues (Hopkins, 1998; Conrad, 2001; Ten Eyck and Williment, 2003). In addition to informing the public, the media also may have a role in illuminating important issues that scientists or other supportive sources may gloss over, even to the point of prompting policy change (Shuchman, 2002; Holtzman et al., 2005). One reason that media influence on genomics discourse is so strong is that the public has neither an experiential basis nor sufficient science education about genomics to make reasoned decisions (Ten Eyck and Williment, 2003).

Although thousands of news stories about the promise and possibilities (both positive and negative) of genomics have been published since the 1990 announcement about the sequencing of the human genome, relatively little is known about the nature of media coverage (Cappella et al., 2005). And what is known was either published in response to the sequencing discovery, has concentrated on discerning the scientific accuracy of media coverage, or has focused on narrower concerns such as particular diseases and conditions. What is missing from the literature, we believe, is a contemporary, comprehensive, and systematic account of how the media covers genomics. As such, how the public understands (or misunderstands) science has a profound effect on its support for, or resistance to, a particular set of policies and programs.

As part of a larger project on genetic services policy, we conducted a content analysis of nearly 900 articles about genomics from 13 newspapers over a four-month period in 2006. Our goal was to capture a snapshot of what a typical media consumer might learn about genetics from reading their local newspaper. Our analytic approach is based on two related conceptual pillars. The first is what Hale (2007) terms “second-level agenda setting” and the second is framing (Goffman, 1974; Reese et al., 2005). In particular, we are interested in which genomics-related issues were covered. What prominence were they accorded? More importantly, how is genetics portrayed in the news? What frames were used to convey messages about genomics? What is the prevalence and the nature of frame elements such as messengers, attribution of responsibility

and the like (Iyengar, 1991)? In short, examining not only *what* genomics issues the media present to the public, but *how* these issues are presented, is useful to policymakers as they attempt to understand public sentiment around these complex issues.

The next section of this paper summarizes existing research literature on the coverage of genomics in the media. We then describe our methods and present our results. In the final section, we conclude with a discussion of the implications of our findings for public attitudes about genomics issues, and how these attitudes might affect the use of genetic services.

## **Background**

Because of the concern that biased or inaccurate reporting can distort public opinion, a number of researchers have focused on the accuracy of the reporting of genomics research (Conrad, 2001; Shuchman, 2002; Bubela and Caulfield, 2004; Cappella et al., 2005; Holtzman et al., 2005). While most of these studies concluded that accuracy in reporting of *facts* is reasonable, many authors note that the media are very selective in the *topics* they choose to cover (Conrad, 2001; Petersen, 2001; Condit et al., 2002; Geller et al., 2003; Ten Eyck and Williment, 2003).

A good example of media coverage focusing on a specific issue is the Ten Eyck and Williment study. These researchers explored the differences in coverage between genomics issues relating to food and those relating to medicine by conducting a content analysis of almost 3,000 articles from the *New York Times* and the *Washington Post* from 1971 (NYT) and 1977 (WP) to 2001. They speculated that the less contentious coverage of medical issues relates to the fact that the public has more comfort and experience with technology in medicine than in food, and more trust in physicians and medical researchers (who “protect” us in the former area) than in government officials and corporate researchers (who oversee developments in the latter). While there is some implicit concern about second-level agenda setting in this study, there is not a systematic examination of framing.

Examples of an issue-specific focus can be found in Hoffman-Goetz and Friedman (2005), who examined seven mainstream papers and twenty-five ethnic papers for coverage of genomics issues relating to cancer, as well as Conrad and Markens (2001), who focused on coverage of the purported discovery of the “gay gene”. Other studies have focused on the valence of the coverage. For example, Conrad (2001) found a positive frame in the coverage of genomics issues in the U.S. in the mid-1980s. Petersen (2001) reported a similarly positive frame in Australian print media coverage in the late 1990s. And some researchers have focused on contextual variables such as region; LTG Associates (2001), for instance, found both a large number of and a significant amount of geographic variation in genomics articles in 2001. There was relatively less coverage in the ethnic press, with the exception of an African-American publication in Chicago.

Racine et al. (2006) represent one of the few studies to call attention to framing (and to do so longitudinally). The authors examined the evolution of the media frames used in coverage of genomics discoveries in 749 articles in the Quebec press between 1992 and 2001. These authors found that the discourse of promise that characterized press coverage shortly after the human genome discovery gave way to public concern as ethical issues began to surface. However, as research successes increased and as public funding helped to institutionalize genomics research

in Quebec, the ethical frame gave way to an economic frame, during which time coverage increased in volume and in optimism.

### **Framing Genomics**

The concept of frames is widely cited in the scholarly literature as an important cognitive tool that allows people to make sense of the world around them (Goffmann, 1974; Snow and Benford, 1988; Schank, 1990; Gilliam and Iyengar, 2000). Lippmann's famous quote, "the way in which the world is imagined determines at any particular moment what men will do" (1921:16), was perhaps the first formulation to connect mass communications to public attitudes and preferences. Frames refer to "an interpretive schemata that simplifies and condenses the 'world out there'" (Snow and Benford, 1992:137). These narratives can be conveyed through several frame elements including values, messengers, stories, visuals, and numbers. As Charlotte Ryan pointed out, "Every frame defines the issue, explains who is responsible, and suggests potential solutions. All of these are conveyed by images, stereotypes, or anecdotes" (1991:59); put differently, frames promote a particular definition, interpretation, or evaluation of an issue (Entmann, 1993).

Iyengar (1991) provides a useful conceptual tool for understanding how responsibility for social issues can be attributed in media coverage. His work discerns between episodic coverage (focusing on discrete events and individual actors), which he demonstrates leads to individual level attribution of responsibility, and thematic coverage (detailing broader trends, context, and environment), which leads to societal attribution. Likewise, the tone of media coverage can play an important role in the presentation of public issues in the news. Cognitive linguists distinguish between reasonable tone (e.g., engaged, interactive) and rhetorical tone (e.g., polemic, defensive) in public narratives (Bales, 2002). Not surprisingly, rhetorical tone leads to little public understanding.

Framing is important in understanding public perceptions about genetics and genetic services exactly because it directs people's thinking, and ultimately, action. As noted earlier, in lieu of an experiential basis to make judgments about genomics, people must rely on other sources to get useful information about the issue. And, as a wide body of literature in the social science attests, the media becomes an important part of the calculus for public thinking about social issues. Thus it is not simply a matter of the extent of media coverage of genomics (second-level agenda setting); it is the very nature of that coverage (framing) that is significant for public understanding. Therefore, in addition to discovering what is covered and how often, we are interested in the following frame elements: attribution of responsibility (episodic v. thematic frames); messengers (who speaks?);

This study adds to our understanding by examining print media coverage of a wide range of genetics issues in the United States during the four-month period from October 2005 through January 2006. The study was conducted in the context of an exploration of the integration of genetic services into clinical practice. Thus, we are specifically interested in how the portrayal of genetics and genomics in the media might influence how people view genetic services.

### **Methods**

We conducted a content analysis of articles in 13 newspapers (2 national papers and 11 regional

papers) over the four-month period of October 2005 through January 2006.<sup>4</sup> The content of all 13 papers was searched and retrieved electronically using Proquest Newspapers. We searched the database for articles containing the following keywords: genomics; genetics; cloning; family history; gene; DNA; and pharmacology. These keywords are broader than but generally consistent with those used by other authors to locate genomics articles in the media (Ten Eyck and Williment, 2003).

We identified 1,041 articles that met our initial criteria. We eliminated duplicate articles and articles in which the keyword was used as a popular culture reference (e.g., "...Stephani set out to break free of not only No Doubt's shadow but also of blood-sucking clones like Ashlee Simpson and Kelly Clarkson...(emphasis added)" (Vaziri, 2005)). A total of 896 articles remained.

The project team created a codebook with 215 variables, including most of the variables used by Bubela and Caulfield (2004) and Ten Eyck and Williment (2003). Four coders read and coded all 896 articles. Inter-coder reliability was assured through training sessions at the beginning of the process and periodic checks throughout the coding process. Our inter-coder agreement was in the range reported for other studies in the literature (Condit, Ofulue, and Sheedy, 1998; Tambor et al., 2002).

Our code book originally contained 90 topic variables capturing the widest possible range of issues addressed by the articles. On the rule of parsimony, these were collapsed into seven broad categories that captured the spirit of the full range while creating sample sizes that were meaningful for analysis. The final topic categories are listed in Table 1 with their definitions. A complete list of topics and codes is available from the authors.

**Table 1: Topic**

Topics	
<b>Forensics</b>	all Legal from Supply of Services: forensics
<b>Social</b>	all Employment issues all Bioethics from Demand: health insurance life insurance from Social: discrimination privacy race disparities

<sup>4</sup> The newspapers are: the *Atlanta Journal-Constitution*, the *Boston Globe*, the *Advocate* of Baton Rouge, the *Chicago Tribune*, the *Houston Chronicle*, the *New York Times*, the *Orange County Register*, the *San Francisco Chronicle*, the *Salt Lake Tribune*, the *Seattle Post-Intelligencer*, the *Washington Post*, *USA Today* and the *Wall Street Journal*.

<b>Cultural</b>	all other Social issues (except discrimination, privacy, race, disparities)
<b>Cloning</b>	all Cloning subtopics (143 = 92% of cloning primary + secondary; 61 = 87% of primary)
<b>Clinical</b>	all Diseases all Supply of Services except forensics all Suppliers all Technology from Demand: consumers patients

We selected our study period to be current and sufficiently lengthy to yield a target of roughly 1,000 articles. However, we discovered that a dominant news topic during our study period was the scandal surrounding the alleged falsified data used by a South Korean cloning researcher. Because of the possibility that the relatively heavy coverage of this event might unduly bias the results, we conducted our analysis both with and without the 89 articles about this event.

## Results

Table 2 shows the distribution of our final sample of 896 articles over the 13 newspapers we selected. Thirty-one percent appeared in national papers (*USA Today*, *Wall Street Journal*, *New York Times*); nearly half (47.9%) appeared in just three newspapers: *New York Times*, *Washington Post*, and *Chicago Tribune*.

**Table 2: Distribution of Articles**

<b>Newspaper Name</b>	<b>Number of Articles</b>	<b>Percent</b>
Atlanta Journal-Constitution	42	4.7
Boston Globe	77	8.6
Baton Rouge Advocate	44	4.9
Chicago Tribune	128	14.3
Houston Chronicle	93	10.4
New York Times	171	19.1
Orange County Register	24	2.7
San Francisco Chronicle	37	4.1
Salt Lake Tribune	27	3.0
Seattle Post-Intelligencer	16	1.8

The Washington Post	130	14.5
USA Today	42	4.7
Wall Street Journal	65	7.3
Total	896	100.0

Our analysis focuses on five questions related to the coverage of genetics in the media:

- What genetics issues are covered?
- How prominent is the coverage?
- How are these issues covered?
- How is responsibility depicted?
- What is the tone of the coverage?
- Whose voices are heard?
- How does coverage vary by topic?

### ***What is covered?***

From Table 3 it is clear that the primary topic of the majority of articles fell into one of two categories: clinical (33.1%) and forensics (22.9%). In addition, there were roughly 100 articles (11%) in each of three other categories: social, cultural, and research. Only 8.1% and 3.9% of articles fell into the cloning and government activities categories, respectively.

Eliminating the 89 articles about the South Korean research scandal primarily affects the social category (42 of 101 articles in that category are eliminated) and the cloning category (43 of 73 articles in that category are eliminated). The concentration of the remaining articles in the forensics and clinical categories is increased as evidenced in the third column of Table 3.

**Table 3: Topics**

<b>Primary Topic</b>	<b>Number of Articles</b>	<b>Percent</b>	<b>Without South Korea articles</b>	<b>Percent</b>
Forensics	205	22.9	205	25.4
Social	101	11.3	59	7.3
Cultural	94	10.5	92	11.4
Cloning	73	8.1	30	3.7
Clinical	297	33.1	296	36.7
Government Activity	35	3.9	35	4.3
Research	91	10.2	90	11.2
Total	896	100.0	807	100.0

**Table: Importance of Coverage**

<b>Page Placement: Page Article Appears On</b>	<b>Number of Articles</b>	<b>Percent</b>
First Page	223	25.2
Pages 2-3	150	17.0
Pages 4 and Higher	511	57.8
Total	884	100.0

<b>Story Length</b>	<b>Number of Articles</b>	<b>Percent</b>
100-500 Words	312	35.9
501-1000	364	40.8
More than 1000	208	23.3
Total	893	100.0

<b>Origin of Story:</b>	<b>Number of Articles</b>	<b>Percent</b>
Staff Only	552	70.1
Wire Only	131	16.6
Combination Staff & Wire	105	13.3
Total	788	100

<b>Story Type: Type Classification</b>	<b>Number of Articles</b>	<b>Percent</b>
Episodic Only	352	39.5
Thematic Only	333	37.3
Partially Episodic & Partially Thematic	207	23.2
Total	892	100.0

***How is genetics covered?***

Coverage of genetics is generally in a positive or neutral tone. The figures in Table 4 indicate that the tone of only 25.3% of all articles indicates a problem. When the articles about the South Korean research scandal are eliminated, this figure drops to 20.7%. In 32.5% of all articles, attribution of responsibility for the problem (or benefit) is assigned to a specific group or person. Most frequently, responsibility is attributed to the research community and the medical profession. Responsibility is attributed to the affected individual in only 6.5% of the articles.

Fifteen percent of the articles are editorials or opinion pieces. Recommendations about a future course of action are made in 32.2% of all articles. Among those, 84.1% recommend promoting genetics and only 15.9% recommend curbing genetics activities. These numbers are only

slightly affected by eliminating the South Korean articles: 33.2% contain recommendations, of which 84.4% recommend promoting genetics activities.

**Table 4: Type of Coverage**

<b>Tone of Article</b>	<b>Number of Articles</b>	<b>Percent</b>
Problem or Problem with some Benefit	223	25.3
Neutral	280	31.8
Benefit or Benefit with some Problem	378	42.9
Total	881	100.0

<b>Attribution of Responsibility in Article</b>	<b>Number of Articles</b>	<b>Percent</b>
Yes, Responsibility Attributed	291	32.5
Responsibility Not Attributed	605	67.5
Total	896	100.0

<b>Opinion or Editorial Article</b>	<b>Number of Articles</b>	<b>Percent</b>
Yes	134	15.0
No	762	85.0
Total	896	100.0

<b>Type of Recommendation Made in Article</b>	<b>Number of Articles</b>	<b>Percent</b>
Curb + Curb with Reservations	45	5.1
Promote + Promote with Reservations	238	27.1
None (No Recommendations)	596	67.8
Total	879	100.0

***How prominent is coverage of genetic services?***

Coverage of genetics is relatively prominent, as evidenced by the figures in Table 5. A quarter of all identified articles appeared on page 1 of a news section with another 17% on pages 2 or 3. More than half of all articles (60.5%) had at least some thematic aspect to the coverage (39.5% were purely episodic) and 70.1% were written by the newspaper's own staff. Only 16.6% were stories taken strictly from a wire service. Nearly a quarter exceeded 1,000 words in length.

**Table 5: Prominence of Coverage**

**Page Placement:**

<b>Page Article Appears On</b>	<b>Number of Articles</b>	<b>Percent</b>
First Page	223	25.2
Pages 2-3	150	17.0
Pages 4 and Higher	511	57.8
Total	884	100.0

**Story Type:**

<b>Type Classification</b>	<b>Number of Articles</b>	<b>Percent</b>
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**Origin of Story:**

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**Story Length:**

<b>Story Length</b>	<b>Number of Articles</b>	<b>Percent</b>
100-500 Words	312	35.9
501-1000	364	40.8
More than 1000	208	23.3
Total	893	100.0

***Whose voices are heard?***

There were three dominant sources for the genetics articles in our sample: academics, government officials, and industry representatives (see Table 6). Non-profit organizations and those affected by the story's events provided input into 21.5% and 22.8% of all articles respectively. Consumers were rarely used as sources (3.8%).

**Table 6: Sources**

Source Type	Number of Articles	Percent of Articles <sup>1</sup>
Consumer	34	3.8
Non Profit	193	21.5
Person Affected	204	22.8
Industry	304	33.9
Government	357	39.8
Academic	367	41.0

<sup>1</sup> Indicates the number of articles with 1 or more of the source type. Articles can have more than one source type.

***How does coverage vary by topic?***

*How is the topic covered?* Given the wide range of topics, it is not surprising that coverage varies significantly across topic area. Table 7 presents the results of a crosstab analysis of an article's topic with its tone. While only 6.7% of the articles about forensics have a problem tone, nearly half of the articles about cloning (47.9%) and social issues (49.5%) do. However, these results are heavily influenced by the articles about the South Korea event. When these articles are removed, the percentage of social articles that have a problem tone drops to 36.2% and the percentage of cloning articles with a problem tone drops to 23.3%. The forensics category is unaffected as none of the articles in this category related to the South Korean affair.

On the benefit side, more than half the articles about forensics and research portray these issues in a positive light, as do nearly half the articles about clinical issues. When the South Korean articles are removed, 63.3% of the articles about cloning have a benefit tone.

Cultural issues appear to be covered reasonably neutrally, with more than half the articles bearing no evidence of either positive or negative tone. The coverage of governmental activity related to genetics is equally split between problem, benefit, and neutral tone.

Attribution of responsibility also varies by topic. Attribution is more likely to occur for articles about social issues (56.5%), cloning (53.4%), or government activities (57.1%). When the articles about the South Korean event are removed, the figures for social issues (39.0%) and cloning (36.7%) are closer to the overall average of 28%. Responsibility is much less likely to be attributed to any party for articles about forensics (25.4%) or cultural issues (19.1%). Neither of these figures is significantly affected by removing the articles about the South Korean researcher.

**Table 7: Crosstab of Topics with Tone of Article**

Topic		Tone			
		Problem or Mostly Problem	Benefit or Mostly Benefit	Neutral	Total
Forensics	Count	13	105	77	195
	% within Topic	6.7%	53.8%	39.5%	100.0%
	% within Tone	5.8%	27.8%	27.5%	22.1%
	% of Total	1.5%	11.9%	8.7%	22.1%
Social	Count	49	20	30	99
	% within Topic	49.5%	20.2%	30.3%	100.0%
	% within Tone	22.0%	5.3%	10.7%	11.2%
	% of Total	5.6%	2.3%	3.4%	11.2%
Cultural	Count	19	25	49	93
	% within Topic	20.4%	26.9%	52.7%	100.0%
	% within Tone	8.5%	6.6%	17.5%	10.6%
	% of Total	2.2%	2.8%	5.6%	10.6%
Cloning	Count	35	23	15	73
	% within Topic	47.9%	31.5%	20.5%	100.0%
	% within Tone	15.7%	6.1%	5.4%	8.3%
	% of Total	4.0%	2.6%	1.7%	8.3%
Clinical	Count	76	146	73	295
	% within Topic	25.8%	49.5%	24.7%	100.0%
	% within Tone	34.1%	38.6%	26.1%	33.5%
	% of Total	8.6%	16.6%	8.3%	33.5%
Government Activity	Count	11	11	13	35
	% within Topic	31.4%	31.4%	37.1%	100.0%
	% within Tone	4.9%	2.9%	4.6%	4.0%
	% of Total	1.2%	1.2%	1.5%	4.0%
Research	Count	20	48	23	91
	% within Topic	22.0%	52.7%	25.3%	100.0%
	% within Tone	9.0%	12.7%	8.2%	10.3%
	% of Total	2.3%	5.4%	2.6%	10.3%
<b>TOTALS</b>	Count	223	378	280	881
	% within Topic	25.3%	42.9%	31.8%	100.0%
	% within Tone	100.0%	100.0%	100.0%	100.0%
	% of Total	25.3%	42.9%	31.8%	100.0%

Whereas approximately 15% of all articles are editorials or opinion pieces, only 7.8% of forensics articles fall into this category. Nearly 25% of articles about cultural issues are op-ed pieces, as are 40.0% of articles about government activity. With regard to recommendations, articles about forensics and cultural issues are less likely than average to contain recommendations (24.4% and 19.4% respectively compared with 32.2% of all articles); articles about clinical issues are more likely to contain recommendations (38.8%), 87.6% of which are to promote genetic activities. Articles about government activities are also more likely to contain recommendations (48.4%), with 75.0% recommending promotion. These figures are unaffected by removing the articles about the South Korean researcher.

*How prominent is coverage of the topic?* There are no significant differences across topics in story placement, length, or origin. Stories about forensics and cloning are much more likely to receive episodic coverage (53.0% and 50.7% respectively compared with 39.5% overall), whereas coverage of clinical and government activities is more likely to be largely thematic (33.1% and 40.0% respectively compared with 23.2% overall).

*Who speaks about the topics?* The sources used to inform stories about the various genetic topics differ. Table 8 presents the pattern of sources by topic. Forensics articles are most often informed by government officials and affected parties, rarely by academics. Articles about social issues are sourced by industry representatives and academics, less often than average by government officials. Articles about cultural issues present many voices. More often than average, these articles present the voice of affected parties, less often than for other topics they present the voices of government officials and academics. Articles about cloning are more likely to be informed by academics, and much less likely by government officials or affected parties. Articles focused on clinical services present the voices of academics, industry representatives, and government officials. Articles about research activities are informed by very similar voices, although they are less likely to include those of affected parties. Finally, articles about government activities are, unsurprisingly, largely sourced by government officials.

**Table 8: Topic and Source**

	Government		Industry		Non Profit		Academic		Consumer		Person Affected	
	#	%	#	%	#	%	#	%	#	%	#	%
Forensics	159	77.6	54	26.4	43	21.0	15	7.3	4	2.0	77	37.6
Social	20	19.8	45	44.6	21	20.8	71	70.3	3	3.0	17	16.8
Cultural	14	14.9	34	36.2	20	21.3	30	31.9	5	5.3	28	29.8
Cloning	10	13.7	25	34.2	18	24.7	49	67.1	3	4.1	2	2.7
Clinical	101	34.0	106	35.7	62	20.9	149	50.2	10	3.4	66	22.2
Government	22	62.9	6	17.1	8	22.9	8	22.9	4	11.4	5	14.4
Research	31	34.1	34	37.4	21	23.1	45	49.5	5	5.5	9	9.9

## **Discussion**

Genetics continues to be a prominent topic of discourse in the print media. In the four months of our study period, nearly 900 articles appeared in 13 newspapers across the country. Half the stories focused on two dominant uses of genetic technology: forensics and clinical services. Discussions of social, cultural, and research issues were somewhat less prominent, with even less focus on government activities and cloning. Many of the articles about the more contentious social and cloning issues related to the scandal about falsified research results by a South Korean researcher that surfaced during our study period.

Especially when the articles about the South Korean event are removed, newspaper coverage of genetics is generally supportive and prominent, as evidenced by the tone and placement of coverage as well as the widespread use of staff writers and positive editorials. Discourse about forensics and clinical services is particularly positive, indicating widespread support for the primary applications of genetic technology. Public acceptance of these applications of genomics is implied by the largely observational coverage of these two topic areas. There are few op-ed pieces about forensics. Coverage is more event-driven as evidenced by the high percentage of episodic articles.

Coverage of the cultural issues raised by genetics, while less prominent than coverage of forensics, is more discussion-based; the higher percentage of opinion and editorial articles on these topics and lower percentage of recommendations indicates that discussion of the issues continues with no clear resolution.

The concerns over ethical and social issues prominent in the Quebec print media in the early 1990s (Racine et al., 2006) were either never shared by Americans, or have dissipated here as well. Although the public discourse about genomics will likely continue to evolve, the path to increased use of genetic services and their increasing integration into clinical practice seems virtually assured.

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## Genetic Services Policy Project Final Report

### **Chapter 6: Personal Genomics Services and Direct Access Genetic Tests**

*“The potential to discover what contributes to red hair, freckles, pudginess, or a love of chocolate—let alone quantifying one’s genetic risk for cancer, asthma or diabetes—is both exhilarating and terrifying. It comes not only with great promise for improving health through personalized medicine and understanding our individuality but also with risks for discrimination and loss of privacy” (Pennisi, 2007).*

#### **Context**

Since 2004, the market space for retail genetics has rapidly expanded and changed. Consumer, regulatory and policy interests are increasing as powerful computational technology becomes available, private and public capital flows, and the concept of personalized medicine takes hold. All of this is happening in spite of the unimpressive clinical playbook genomic research has produced so far. This review describes the environment in which personal genomics markets evolved, the types of health-related genetic tests currently available directly to consumers, and examples of how companies market such tests. We then consider issues of regulation, clinical utility, social impacts, professional organization recommendations, and public opinion, as well as policy implications related to these issues.

To a degree, personal genomics markets grew out of rising consumer activism in health care, sometimes known as consumer-directed health care. This movement aims to increase the consumer’s commitment to healthy living and monetary investment into the health care system, the latter through steadily expanding cost-sharing by employers and payers. The long-term goal is that educated, motivated consumers investing their own money will be more parsimonious in the use of scarce health care resources.

The rise of consumer markets in genomics, however, primarily stems from increasing consumer interest in genetic information, expressed in equal measures of fear, apprehension, and fascination. The press reports discoveries of genetic health and disease associations almost daily for everything from rare to common genetic disorders (e.g., restless leg syndrome to heart disease). Entrepreneurialism is also thriving, with large companies like Microsoft, Yahoo, Google, WebMD and Revolution Health launching portal and search capabilities, and start-ups like 23andMe, Navigenics, and deCODEme promoting themselves as personal genomics companies.

The blogosphere is rife with commentary and many health care newsletters have begun to track the personal genomics market. At the same time, the rapid emergence of this field is causing concern in clinical, regulatory, and oversight circles, which are already troubled by the proliferation of consumer-oriented websites with arguably over-reaching claims (Hunter et al., 2008).

## **Personal Genomics Markets**

Both researchers and personal genomics companies draw from the same pool of genetic data, yet they use and characterize these data differently. Researchers use aggregated genomic data from gene-wide association studies to identify single nucleotide polymorphisms (SNPs) associated with human variation in health and disease status. For example, SNPs may determine what a specific patient's response and/or susceptibility to a drug or disease might be. Personal genomics companies use these data when they provide customers with personalized SNP information from a portion of their own genome (about 1 percent, accounting for 95 percent or more of the genetic variation among us). Companies like 23andMe promote a service allowing customers to "see" their own genome, use interpretative information to infer their health status, susceptibilities to disease, and/or capabilities, and store their data securely with the company. Then customers can receive alerts as new tests become available to check their susceptibility and/or capability (23andMe website, 2008; DeCODE Genetics website, 2008). These companies specifically disclaim that they provide a health care or clinical service, advising their customers to talk to a physician before making any health-related decisions. At least four companies advertise SNP genome profiles, while a fifth company now offers full genome sequencing to a select few customers willing to pay \$350,000 for the service (Knome website, 2008).

The personal genomics market leaders deny that they are selling recreation or curiosity to the affluent and worried well. They argue that individuals informed of their personalized data will be motivated to minimize controllable risk factors, hence preventing or at least slowing the onset or progression of chronic disease. This premise sounds promising, but there is little evidence to support it to date. Researchers have not yet had enough experience with highly personalized risk information to know the likely answer (Multiplex Initiative, 2007).

## **Direct Access Genetics**

Positioned between conventional clinical genetic testing through labs and physicians and the personal genomics frontier are companies offering genetic tests marketed directly to consumers. To avoid confusion about the phrase "direct-to-consumer," often broadly used in reference to advertising for many health services and products, we instead will call these "direct access" genetic tests. Not all such tests have a medical purpose; websites for paternity and ancestry testing abound, and one can now send out for "infidelity testing" on suspicious clothing or personal items (The Genetic Testing Laboratories, Inc. website, 2008). An Internet search reveals a number of companies advertising direct access genetic tests for the purpose of providing health-related information (Genetics and Public Policy Center, 2008). The nature, complexity, and legitimacy of such tests vary. Consumers will find a bevy of tests from companies claiming to provide a beneficial, personalized product or intervention based on test results for nutrition, fitness, skin care, hair loss, smoking cessation, weight loss, and so on; so far these claims remain unproven. Some companies offer accepted tests or screens for genetic disorders, such as for BRCA1&2, cystic fibrosis, and hemochromatosis, which most patients continue to obtain via their physician or genetic counselor. These tests provide diagnostic or risk information that a qualified health care provider can interpret for patients, along with data to support the explanation and options for next steps in treatment, prevention, or other decision-

making. Newer tests for complex disease risk or other processes like drug response are also becoming available. While the latter tests are based on scientific data in most cases, the extent of the data varies, and the tests' clinical benefit remains unclear. These diseases typically involve multiple genetic, environmental, and lifestyle factors, as well as interactions between these factors. Available genetic tests may cover only a single gene or subset of genes involved in a given disease, while other genetic contributors remain undiscovered. Examples of this type of test include type II diabetes panels, pharmacogenomics tests, a soon-to-be-offered prostate cancer risk panel, and bipolar and mood disorder risk.

## **Business and Marketplace Issues**

In new markets there are fundamental factors related to the success and prosperity of any type of business. There are a few related to the business of health care and the science of genomics that are relatively unique.

Genetic testing companies like DNA Direct serve as a virtual delivery model for a set of genetic tests that have some evidence of clinical utility. DNA Direct provides consultation with genetic counselors and focuses on developing proprietary tools to interpret genetic risk data for consumers. Though started as a pure direct access offering, DNA Direct and other companies utilize a variety of payment models, including referrals from physicians and genetic counselors, as well as third party reimbursement when available. This distinguishes these existing businesses from personal genomics companies, such as Navigenics, 23andMe, and deCODEme, though as the latter evolve, they may compete in providing testing services.

Details are not yet available to accurately describe the business model for the personal genomics market; however, it appears to be premised on securing enough subscribing customers to develop or outsource a genetic testing service, and by aggregating data, serve as a data warehouse to which access would be sold. Beyond this, these companies intend to use their customer base, presumably on an opt-in model, to create social networking relationships, with the sites supported by subscriptions, advertising, or both. These businesses have only recently been launched and they appear to be well financed by venture capital groups and, in the case of 23andMe, by Google. But to date, there is little marketplace data to support these business models (Welch and Burke, 2008).

These business models also face several criticisms as voiced by health care providers, regulatory agencies, and consumers. In the health care community, particularly researchers and providers, many express skepticism. Public oversight and regulatory agencies are also alerted and have raised concerns regarding the direct-to-consumer marketing. Many health care providers simply discount the ability of patients and consumers either to understand their health care needs or to act responsibly when they do, and a distinct business risk for these companies arises because the dim views of too many health care providers can suppress the market.

Another area of concern is the complex nature of the underlying science and technology. When selling a financial service, the complexity lies in the instruments and tools, based on tested marketplace and economic fundamentals, with the rewards going to those who execute

effectively on those fundamentals. Conversely, in health care, and especially in genomics, the complexity lies in the underlying fundamentals of the science, a fast and moving target as genomics health care further evolves. This dynamic creates at least two business risks: betting on the science to confirm the first impressions upon which the businesses depend, and understanding that good health is ultimately far more valued as a public good than financial rewards, and therefore, more protected.

Finally, there is the issue of pushback from payers and providers about driving inappropriate and unnecessary demand. Usually a solid sign of business success is the ability to prime markets and produce demand. In health care, however, driving demand is often viewed as problematic. If significant numbers of customers use personal genomics companies and start showing up with their “genome chip” or print-outs in physician offices, the cost-containing forces within health insurance may align against such companies, and pressure for regulatory oversight may increase.

### **Marketing approaches and services**

The support services offered by personal genomics and direct access genetic testing companies vary greatly, as do the ways in which they portray the available tests. Below are some of the ways in which companies provide information or services, followed by specific examples.

Information formatting: Websites may provide “background info,” frequently asked questions (FAQs), tutorials, diagrams, videos, consent forms, disclaimers, reports that accompany results, phone consultations, and references to studies, scientific literature, news articles, or other websites. Some companies provide easy-to-follow, detailed information about the testing process, risks, and benefits, while others offer incomplete, misleading, vague, or hard-to-find information on their websites.

Information topics: Websites may provide basic information about genetic testing in general, why the advertised test might be helpful, potential results and meaning of results for each test offered, background information about the disorders for which they test, information about research related to the genes they test or products they offer, potential risk of genetic discrimination, implications for families, whether the customer can bill insurance for the test, and where to find additional resources.

Ordering tests: Customers may order tests online, by mail, by phone, through a participating provider (e.g., physician, dentist) or through another outlet (e.g., medical spa, pharmacy). Some require consent forms and/or pre-test counseling before purchasing a given test.

Support services: Support services may include a phone consultation with a physician, genetic counselor, nurse, or clinical geneticist; referral to a physician; online support group; in-person consult with a physician at a medical spa or with a “certified DNA fitness trainer”; and/or assistance in billing insurance (one company).

Current Examples: As stated above, no two companies take exactly the same approach in advertising their direct-to-consumer DNA tests. Some do share similar characteristics in their approach, as described below.

At least five companies have genetic counselors available in-house or through a partner company for pre-test and/or post-test counseling by phone. The tests these companies offer include more established medical genetics tests, newer complex disease tests, and genome scans, all of which consumers may purchase directly online. None of the five offer an intervention product based on test results.

DNA Direct offers a variety of tests, including single-gene disorders like cystic fibrosis and hemochromatosis, as well as newer tests like the deCODE Type II diabetes panel and drug response testing (DNA Direct website, 2008). For each test, the user-friendly website offers thorough background information about the disease and addresses such questions as how the testing works, what information it provides (including mutations for which it tests), who is an appropriate candidate for the test, pros and cons of testing, whether insurance covers the cost, and other test or condition-specific issues. The cost to order a test includes pre- and post-test counseling, or consumers can purchase counseling separately before deciding to pursue a test. DNA Direct requires pre-test counseling before ordering certain tests—breast and ovarian cancer risk, infertility, and recurrent pregnancy loss—but not for others. Consumers may also purchase post-test counseling for results not obtained through DNA Direct, such as genome scans from 23andMe and deCODE, or seek counseling to get a second opinion about whether genetic testing is appropriate for them. The website shows names, degrees, biographies, and photographs for the company’s genetic counselors and medical director. To obtain results, users log into a secure website to view a personalized report about the results and what they mean, along with information about the disease, next steps, family issues, and where to go for additional resources. Here they may also access a letter to share with their physician that explains results, genetic disease factors, limitations of genetic testing, diagnosis, patient care, treatment, population and family risks, and lists literature references.

Navigenics advertises a genome scan for SNPs related to 18 diseases or conditions listed on its website (Navigenics website, 2008). For \$2,500, consumers can purchase “Health Compass,” which includes the scan, a personalized report, genetic counseling to review results, guidance about talking to a physician about results, and a year-long subscription for online report access and updates about new genetic research and other medical studies. Consumers may renew their subscriptions for \$250 per year. The website provides information about the testing and follow-up process both in print and as a video. The scan looks for markers associated with the 18 conditions, selected on the basis of three criteria: prevalence (affects at least one per one thousand in the U.S.), ability to take preventive action (e.g., lifestyle changes, medications), and a disease-marker association study published in a peer-reviewed journal. Consumers have the option not to receive results for certain conditions if they so desire. Navigenics creates a personalized, online report that only the consumer may access and emails the consumer when the report is ready. Tools built into the report allow the viewer to compare results with the general population for each condition. The company designates a genetic counselor to review results with the consumer, who may contact the counselor as many times as needed during the membership period. The company also encourages sharing results with a physician.

A few companies require that consumers order the test through a provider or affiliated partner, although they do not provide genetic counseling.

Suracell offers a DNA test reputed to relate to five cell aging processes: methylation, inflammation, glycation, oxidation, and DNA repair (Suracell website, 2008). To purchase the test, consumers complete an online consent form and use the website to locate a local affiliated medical spa, doctor's office, or wellness center where they obtain the DNA kit. A few weeks after submitting a DNA sample, the customer receives a results report with color-coded graphs indicating low, medium, or high "gene efficiency" in each of the five areas. Neither the report nor the website specify which genes the test includes. Based on the test results, the report then outlines the numbers and types of Suracell nutraceutical pills, available for purchase online, to take each day. For questions about results, Suracell recommends contacting a Suracell partner physician, or a genetic counselor; the consent form has a link to the National Society of Genetic Counselors website.

Psynomics markets two tests, one for mutations in the GRK3 gene and one for a serotonin transporter gene (Psynomics website, 2008). Studies (described, but not cited, under the "physician" tab) have associated the former with bipolar disorder and the latter with response to serotonin-based drugs. The company intends these tests for patients who already show symptoms, and therefore require physician involvement. On the consent form, customers vouch that they have been diagnosed with a psychiatric disorder and have discussed the test with their physician. After processing a customer's mail-in saliva collection kit, Psynomics sends results to the customer's physician rather than to the customer directly. In addition to the allele results, the 5-page results report includes information about DNA testing in general, the genes tested, limitations of testing, results interpretation, and what results mean for the patient's family. The consent form also notes that these particular gene tests have only been validated in populations of Caucasian, European ancestry.

Several companies provide information about the test results and may encourage consumers to consult a physician or genetic counselor, but do not provide interpretation beyond the information available on their website or in the results report.

Consumer Genetics offers two test panels related to caffeine response and asthma medication response (Consumer Genetics website, 2008). The website tells consumers that the former can affect their fertility and risk of heart attack, and that people with "a certain gene" could reduce their risk of heart attack 22 percent by drinking 2 to 3 cups of coffee per day, but stops short of actually recommending any action. For the latter test, the website quotes studies (references provided) about how patients with certain genotypes do not respond as well to particular ingredients commonly used in asthma medications. Although one could conclude that it may be beneficial to choose a medication without those ingredients, the company again stops short of recommending a specific action. The website states that results for either test, provided in a one-page, technical-sounding report, "will allow you to make a more informed decision about your health." Similar to other companies, the disclaimer states that Consumer Genetics does not intend its tests to be used for diagnosis or treatment, only for information, and that clients should consult their own physician or health care provider about the results.

CyGene suggests that taking its genetic tests will “help you take more control of your healthcare” (CyGene website, 2008). The website offers tests for glaucoma and macular degeneration, metabolic health assessment, osteoporosis, thrombosis, and athletic performance, using a mail-in cheek swab kit. Clients can log onto the website with a password to obtain a personalized report that includes results, interpretation, discussion of other risk factors, lifestyle/behavior recommendations, and more information about the disease(s) for which they obtained genetic testing. The report also recommends that clients discuss results with their physician.

As described for Suracell above, many companies sell a product or intervention tailored to consumers, based on results of genetic tests that they market online. Several companies focus on diet, either for general health or for weight-loss; other areas include skin care and smoking cessation.

Dermagenetics, a Genelink, Inc. company, advertises customized skin care products based on the results of its DNA test for “key skin aging genes” that are not specified on its website (Dermagenetics website, 2008; Genelink website, 2008). The site discusses results of a clinical trial that, according to the company, proves the effectiveness of its product, although the study has not been published in a peer-reviewed journal. Customers place an order for the personalized product online or through a participating spa, after which the company sends an at-home DNA cheek swab kit. The lab processes the kit and uses results to determine which extra ingredients to add to its basic skin crème formula, then sends the finished product to the consumer. Dermagenetics does not provide any results or interpretation of the DNA test itself.

g-Nostics, a UK-based company, offers a DNA test for genes it says affect nicotine breakdown (CYP2A6) and brain reaction to nicotine (DRD2) (g-Nostics website, 2008). In the FAQs, the website cites 14 journal articles related to the genetics of nicotine addiction. After ordering the test, available online or in UK pharmacies, g-Nostics mails clients a finger-prick/blood spot DNA kit and asks them to complete an online questionnaire. The company uses the DNA test and questionnaire results to create personalized quit programs. While waiting for results, clients begin a motivational course in preparation for the personalized program they start a few weeks later. The course also includes online peer support.

A few companies provide surprisingly little information about the genetic tests they sell online directly to consumers. A person could easily order a test from one of these companies without any understanding of what the results would mean.

Health Tests Direct offers over 400 types of blood tests, including a few DNA tests: cystic fibrosis carrier screen, Factor V Leiden, and MTHFR (Methylenetetrahydrofolate reductase) (Health Tests Direct website 1, 2008). The website has an alphabetical list of tests and prices, but does not provide any information about indications for obtaining a test. The company touts its service as a way to “save 40-70%” of the usual cost for blood tests by eliminating a doctor visit and insurance and billing costs (Health Tests Direct website 2, 2008). Clients pay up front, and then have blood drawn at a participating, state-certified clinic that they can find through a zip code-based search on the company’s website. It refers clients to an independent, peer-

reviewed website (not affiliated with the company) for information to interpret test results, and describes how to navigate the site to find information about the meaning of test results. Customers may purchase tests online or by phone.

Graceful Earth sells an ApoE test for Alzheimer's Disease (AD) risk (Graceful Earth website 1, 2008). A small-print, easy-to-miss link on the online order page takes the customer to a page of FAQs, which provides some information about the ApoE gene and how the company's lab processes DNA from the mail-in saliva kit. This page focuses heavily on AD risk, briefly mentioning but not explaining the connection to cardiac health. The page also contains misleading information about the meaning of results, labeling an E4/E4 genotype as "severe risk" for Alzheimer's Disease and atherosclerosis. Studies suggest that the E4/E4 genotype increases the risk of Alzheimer's Disease; however, to categorize this increase as severe may be viewed as an overstatement (National Institutes of Health, 2008). In addition, the website states that the test is an important prevention tool, because "in cases where the disease is already in progress, you can stop the disease in its early stages" (Graceful Earth website 2, 2008). In fact, nearly all peer-reviewed studies indicate that AD cannot be prevented or stopped from progressing, even with medication. The website states that several publications show that lifestyle changes reduce the risk of developing AD, but does not provide any references. It does not give an example of a results report or describe how the company makes test results available.

## **Clinical Issues**

To health care providers, information that does not lead to known and effective treatments and good outcomes of care lacks clinical utility, and could also create problems through a mix of misleading marketing and uninformed consumers. Not all genetic disease factors have been identified. Some providers worry that if consumers' results do not show an elevated risk for a given condition at known loci, they might incorrectly assume they have no genetic risk, and hence neglect healthy behaviors. Similarly, providers are also concerned about false negative lab results, which are especially worrisome if a consumer's genetic profile inaccurately shows low risks for life-threatening and compromising conditions. This concern was recently heightened when a study of the reliability of lab results showed wide variation on reported testing results (Matthews, 2008).

Although some direct access genetic testing companies advise customers to consult a physician about their results, physicians may lack sufficient knowledge about genetics to appropriately interpret test results. In focus groups conducted in Washington State in 2002, primary care physicians reported feeling challenged in maintaining knowledge of technical and scientific advances in genetics (Gibson et al., 2003). Participants noted that "Patients are getting information and asking questions that I can't answer. It's hard to keep up with them," and "You're always concerned that there's a test you haven't heard about." As we suggest in our Chapter 8 recommendations, public programs and regulation to increase capacity for training genetic services specialties as well as increase genetics content in all medical training would help address this challenge.

Lastly, as the utility of genetic testing increases, especially with the rapid pace of diagnostic development underway, health care providers may sense competition and intensify calls for more stringent regulation. Physicians, among all health care professionals, can effectively incite regulatory action.

### **Ethical, Legal, and Social Issues**

A range of concerns arise for the bioethics community, from paternalistic (harms outweigh benefits) to dismissive (can't hurt, or buyer beware). One frequently expressed concern is that consumers at increased risk for a serious disease will either become fatalistic because they fail to recognize the probabilistic nature of genetic data (except for a few highly penetrant conditions such as Huntington Disease), or, conversely, may neglect their health if their genomic profile seems benign.

For those who worry that only the well-off will have access to genetic services, direct access tests could offer a lower-cost alternative to traditional services. Rather than having to pay for physician visits as well as a test, consumers may order a test directly online. On the other hand, these tests still often cost a few hundred dollars, a price that remains out of reach for many. Though some companies provide a phone-order option, consumers usually need Internet access and familiarity navigating websites to read the testing information. Bypassing a physician or genetic counselor visit may leave consumers confused about the meaning of their test results, unless they choose a company that provides counseling services; however, additional services add to the cost of the test. Direct access testing might improve access for some, but it remains unclear whether benefits will outweigh harms.

Legal issues include discrimination by employers and insurers on the basis of definable risk, although this concern may diminish given the passage of the Genetic Information Nondiscrimination Act (GINA) in April 2008. To date, there is very little settled law with respect to the rightful uses of genetic information because the issues had raised only marginal concerns until recently.

Genetic discrimination can be shown by communities and social systems, not just by employers and insurance companies, though its forms are different. People with presumed genetic defects and disorders have faced stigmatization. Genetic information can affect family relationships as well as personal, reproductive, and end-of-life decisions. Even with GINA in place, many consumers will remain concerned about protecting the privacy of their genetic information. People with disabilities are increasingly apprehensive about biological "stratifications". One concern is that much of the accumulation of genetic information could lead us down a slippery slope if it becomes the fodder for engineering human perfection (Sandel, 2007).

Ultimately genetic data alter our sense about our identities. These technologies are more disruptive culturally and socially than they are disruptive to business and economic models. Hence, personal genomics markets are fundamentally marked by uncertainty because of the disruptive nature of the products being offered. All the evidence points to a niche market: even

if the price point for rendering a customer's genome comes down, as predicted, to \$1,000 in ten years, personal genomics markets are indisputably elite.

On the other hand, there may be social and health benefits worth waiting for. Will providing personalized risk information be a motivational factor strong enough to cause consumers to actually reduce their risk factors through lifestyle practices? We do not have these answers yet because we have not studied the subject enough. But if positive outcomes can be achieved using specific, individualized data, it would be of even greater significance if those outcomes could counter the heavy tolls of the most common chronic diseases—diabetes, obesity, cardiovascular conditions and cancer—affecting the developed world, and increasingly, the developing world.

## **Regulation**

Though there is ongoing debate and discussion at the federal level about strengthening the regulation of genetic testing, there is not yet a clear consensus. At root is the question of which model of oversight applies: should personal genomics markets be regulated as clinical services and hence fall under the scrutiny of the U.S. Food and Drug Administration (FDA) and state licensure requirements? Or, should they be considered a commercial concern, regulated as a consumer information business like financial services where the issues of full and fair disclosure, protections against fraud, and truth-in-advertising apply?

Two government agencies hold some authority to regulate genetic testing in the United States: the Centers for Medicare and Medicaid Services (CMS), per the Clinical Laboratory Improvement Amendments Act of 1988 (CLIA), and the FDA. The FDA reviews medical devices for safety and effectiveness; this includes test kits such as those used to collect cheek swab or saliva DNA samples, but not the in-house tests run on the samples once they reach the lab. To obtain CLIA certification, a lab must meet “standards for quality assurance, record maintenance, proficiency testing, personnel qualifications and responsibilities, and quality control” (Secretary’s Advisory Committee on Genetics, Health, and Society, 2007). With the exception of cytogenetics, however, CLIA does not recognize a specialty area for genetic tests, nor does it address the clinical validity of lab tests (Hudson et al., 2007). Thus, although the lab results may accurately report a patient’s genotype for loci tested, no federal agency has certified that these results are useful to the patient. On their websites, companies advertising direct access genetic tests typically emphasize any CLIA or FDA approvals that apply to their services and products, sometimes with wording that could mislead consumers into thinking that the approvals apply more broadly than they do.

The Federal Trade Commission administers a variety of consumer protection laws. Its Division of Advertising Practices enforces federal truth-in-advertising laws, including such areas as “claims for foods, drugs, dietary supplements, and other products promising health benefits” (Federal Trade Commission website, 2008). In July 2006, the FTC issued a consumer warning about at-home genetic tests, based on a Government Accountability Office (GAO) study of nutrigenomics tests from four companies (Federal Trade Commission, 2006; U.S. Government Accountability Office, 2006). The report found that “the results from all the tests GAO

purchased mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers.”

New York State requires companies offering personal genomics services and direct access genetic tests to obtain a permit. In April 2008, the New York State Department of Health sent letters to 23 companies to notify them of the state’s permit requirement (Winnick, 2008). Taking matters into their own hands, parents filed a class-action lawsuit against a company for refusing to give promised refunds after providing incorrect baby gender results from their DNA test on mothers’ blood (Lawyers and Settlements website, 2008). It will be interesting to see whether additional lawsuits involving similar or other aspects of direct access tests arise.

In Chapter 8, we recommend several policy steps to help address the issues above. The government could assure that the FTC, FDA, and state attorneys general achieve their mission of preventing harm and fraud, and monitor the accuracy of lab results by regulating “home brew” genetic tests. They could consider licensing retail genetics companies and regulating direct-to-consumer advertising for genetic services to gain more control over the information companies provide to consumers. The government could also facilitate federal interagency discussions about additional policy actions.

## **Evidence and Utility**

A Centers for Disease Control and Prevention (CDC) pilot project, “Evaluation of Genomic Applications in Practice and Prevention” (EGAPP), aims to assess the evidence for and utility of specific genetic tests for clinical practice (National Office of Public Health Genomics website, 2008; EGAPP website 1, 2008). The project’s recommendations may help guide consumers who consider ordering direct access genetic tests. The working group issued its first recommendation in December 2007 regarding cytochrome P450 polymorphism testing to inform treatment for adult depression using selective serotonin reuptake inhibitors (SSRIs) (EGAPP Working Group, 2007). The group did not find enough evidence linking CYP450 testing to clinical outcomes for adults treated with SSRIs to recommend for or against using the test to inform treatment initiation. Taking into consideration other factors suggesting potential benefit or harm of testing, the group felt the potential for harm was greater and discouraged using the test until more clinical data becomes available. The working group has pending recommendations for several other tests they have reviewed: gene expression profiling tests for breast cancer treatment, mismatch repair gene testing for Hereditary Nonpolyposis Colorectal Cancer, and genomic tests for ovarian cancer detection and management (EGAPP website 2, 2008). The group is currently reviewing a multi-gene cardiovascular disease panel for risk assessment and lifestyle management, as well as a gene test to predict colorectal cancer patient response to irinotecan therapy (EGAPP website 3, 2008). Tests under consideration for future workgroup review include several currently being offered direct to consumer, such as ApoE for Alzheimer’s Disease risk assessment, MTHFR for cardiovascular disease prevention and management, and two genes related to type II diabetes risk (EGAPP website 4, 2008).

In a recent article, researchers reviewed evidence of gene-disease associations for the genes tested by seven companies offering predictive genetic profiling and personalized interventions or

products online (Janssens et al, 2008). Of the 56 genes (69 variants), they found meta-analyses for 32 genes; only 38 percent of these meta-analyses showed a statistically significant association. The researchers noted that these associations were mostly modest, and were often tied to a different disease from those for which the companies advertised online as the purpose of testing. For some of the 56 genes, the authors found a single study showing gene-disease association, but no replicated findings to show sufficient evidence of the association. The researchers believe that a meaningful genetic risk profile would require an understanding of gene-gene interactions beyond current knowledge, and found current evidence “insufficient to support useful applications.”

## **Professional Organization Statements**

The American Society of Human Genetics (ASHG), the American College of Medical Genetics (ACMG), and the National Society of Genetic Counselors (NSGC) have all issued statements about direct access genetic testing. ASHG’s statement makes specific recommendations about the type of information companies should provide about their tests, how professional organizations should educate their members about direct access tests, and changes that CMS, the FTC, and the FDA should make to improve regulation (Hudson et al., 2007). The ACMG statement lists minimum requirements it believes should be in place for any genetic testing protocol, including direct access tests. It recommends involvement of a genetics expert to order and interpret the test, a clear statement of scientific evidence for a test, and lab accreditation by CLIA, but also calls on consumers to fully inform themselves about the meaning of test results and the security measures in place to protect the privacy of their results (American College of Medical Genetics, 2008). The NSGC statement expresses concern that consumers may not receive appropriate input from a knowledgeable health care provider when ordering a direct access genetic test, though acknowledges that this model of testing may increase access for some people. The statement lists nine issues that NSGC urges consumers to review prior to ordering a test, including topics of materials and information, informed consent, referrals to genetics professionals, privacy safeguards, and laboratory credentialing (National Society of Genetic Counselors, 2007).

## **Consumer opinions**

In 2003-2004, the Washington State Department of Health conducted a series of 15 community focus groups to discuss genetic discrimination, equity of genetic services, and newborn screening. In the course of discussions, the topic of at-home genetic tests and related issues arose several times (Washington State Department of Health, 2005). On the positive side, participants thought that direct access tests could help improve access to genetic testing, ensure privacy of results, provide useful information, and perhaps be affordable and easy to use. “I like it,” one respondent commented. “There’s privacy. I can do it right there and then.” Another participant drew a comparison to at-home HIV testing, a model for assuring confidentiality. Concerns about at-home kits included licensing, regulation, test accuracy, and availability of help to interpret results. The latter was their primary concern; some participants worried that they might panic without counseling. They also wanted to know if the FDA approved the tests,

asked if results would be accurate, and expressed worry about contamination. One participant said that if she received positive results, she would go see her physician because she would not trust the information.

One scenario that participants specifically considered in some of the forums involved testing for a gene variant that would confer higher risk of developing Alzheimer's Disease (AD). Although the test scenario described to participants was not direct access, the information they requested and their comments about different possible results could easily apply to the ApoE AD risk tests currently offered online. Their discussion highlights the importance of providing accurate information. Participants requested additional information about 1) the accuracy of the test; 2) who is available to interpret the results and what their qualifications are; 3) who has access to test results (e.g. insurance companies); 4) whether insurance companies can deny coverage after a positive result; 5) the cost of the test; and 6) if AD can be cured or effectively treated. Some participants felt that there was no benefit in getting tested if one could not take any action in the case of a positive result. If people who feel that way read the misinformation on one company's website, claiming that "you can stop the disease in its early stages," they might reach a different decision about testing. Others in the focus groups thought that since the genetic test lacked predictive certainty, a positive result would be equivalent to a positive family history. Those who favored taking the test thought it could help someone emotionally and financially prepare for the future. They also felt that a support system to help understand and deal with results would be critical.

## **Conclusion**

The prospect for genomics technologies illustrates why genomics has been called a "terrible gift" (Carlson and Stimeling, 2003). The potential benefits are exciting and profound, but along the way, society will have to deal with social, cultural, and economic uncertainties. Thus far, companies offering direct access genetic tests or personal genomics services have faced little regulatory oversight. Consumer and professional organization opinions about such services agree about the importance of regulation, accurate and complete information, and counseling by qualified providers to explain results. While a few companies provide sufficient information and support to satisfy these needs, the majority fall short in one or more areas. For now, it appears that consumers are on their own to navigate the many genetic testing options available to them on the Internet. The opportunities to improve public health are increasingly evident, but our social uncertainties are deep and linked to a fear of excessive entrepreneurialism in the health care setting. Our economic uncertainties, on the other hand, arise out of the complexity of the underlying science and how to scale demand for first generation genetic service technologies that are limited to those who can afford them for now, but, guided by cogent public policy, could eventually be more accessible and far reaching.

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## Genetic Services Policy Project Final Report

### Chapter 7: A Changing Health Care World

Genetic services are delivered within a continually changing health care system. There is a rich literature on the challenges and opportunities facing the health care system at the beginning of the 21<sup>st</sup> century, and the changing economic and political context in which they have evolved. Among the trends forecast by most observers are:

- increased consumer cost-sharing for health insurance as employers continue their retrenchment from broad-based coverage;
- increased enrollment in Health Savings Accounts (HSAs), both as consumers choose this option and as alternative options are removed;
- increased transparency of information, both about the business and the content of health care services, from the Internet and through multi-media advertising;
- increased presence of national and international corporations in health care markets;

Walk-in clinics—both freestanding and inside retail establishments such as Target and CVS—are proliferating. The Convenient Care Association reports that there were 800 retail clinics in November 2007, with that number projected to be 1500 by the end of 2008 (Wood, 2008).

- growth in the number and variety of venues outside a doctor's office where health care services can be obtained;
  - increased attention to the needs and desires of consumers;
  - growth in the variety of non-MD professionals offering health care services;
  - increased use of electronic technology to provide both information and services, including by government agencies; and
- growth in medical outsourcing, including patient travel for treatment overseas.

Genetic services markets will be similarly affected by these trends—in some cases, disproportionately so.

Whole Foods, United HealthCare, and Aetna only offer coverage to employees through HSAs. National surveys of employers suggest that more than 30 percent of large employers were considering adding an HSA option in 2007 (Cauchi, 2006).

An estimated 55,000 Americans were treated at Thailand's Bumrungrad Hospital in 2005, 83 percent of whom received non-cosmetic procedures (Kher, 2006).

### **Implications for Genetic Services**

Two powerful forces will affect developments in genetic science and their application to genetic medicine: evolving health care markets, and rapid advances in information technology (IT). These forces interact, particularly as health care facilities and professionals adopt IT advances such as electronic medical records and electronic billing. Recommendations about the

appropriate role of government in guiding the translation and implementation of genetic advances must have as their underpinning a very clear understanding of the implications of these forces for the financing and delivery of genetic services. As a starting point to develop these recommendations, we summarize the unique characteristics of genetic services.

### ***Unique characteristics of genetic services***

*Family Based.* While many medical conditions affect family members indirectly because of their concern for the patient and their potential role in caretaking, genetic conditions have a much more direct effect. Genetic conditions may ripple through families in increasingly predictable ways. A woman's knowledge about her susceptibility to breast cancer has implications for her sisters and her daughters. A couple's carrier status for sickle cell disease has implications for the health of the child it might wish to have. Genetic science is helping to identify the conditions that have an important genetic component, although specific genetic characteristics often interact with environmental factors in inducing illness.

*Information Heavy.* Information is at the core of genetic services. All genetic services provide information directly, and most of them (given the family connections) have implications for information that might affect the decisions of others. In some cases, most notably for indigenous populations, genetic information can have implications for an entire group.

*Social Effects.* Genetic information affects not only decisions about medical treatment, but also reproductive and other life decisions. Genetics, perhaps more than other areas, challenges our social beliefs. This is particularly true around issues that affect reproductive decisions. For example, genetic services such as pre-implantation genetic diagnosis (PGD) and prenatal testing, which offer women choices about their pregnancies, present ethical dilemmas that sometimes have to be settled in courtrooms after the expenditure of many resources and much angst.

*Privacy and Confidentiality.* Because of the family connections and predictive power of genetic information, privacy and confidentiality are even more critical in this area than for other forms of clinical information. Fear of insurance and employment discrimination has led many states to adopt anti-discrimination legislation. Congress is also struggling with this issue, as evidenced by the fact that anti-genetic discrimination legislation has been introduced, but not passed, in every Congress from 1996 until 2008, when the Genetic Information Nondiscrimination Act of 2007 was signed into law on May 21, 2008 (S.358; H.R.493). Providers have concerns about the legal implications of how genetic information is handled. Physicians may have a duty to warn family members of patients whose genetic test reveals a hereditary illness, compromising the expected confidentiality of the patient/provider relationship (Offit et al., 2004). In addition, providers may be subject to wrongful birth and other lawsuits for not offering genetic tests whose results might have changed patient decisions (Caulfield, 2001).

*Checked Cultural History.* Genetic information takes on special meaning in some ethnic and cultural communities because of its previous misuses. The African American community's experience with the mishandling of sickle cell disease information affects its view of genetic information and genetic services (Tapper, 1999). Native American communities are often concerned about the impact of genetic information on their views of family connections,

legal status of tribal affiliation, and origin beliefs, in addition to worries about misuse and discrimination (Foster et al., 1999).

*Genetics in the Media.* As with many new technologies, genetics and genetic services are receiving a great deal of attention in a broad array of public media (Gilliam et al., 2006). Newspaper and magazine articles on various aspects of genetics abound, ranging from art and ancestry to new treatments for genetic conditions. Genetics, particularly in the areas of forensics and paternity, play a frequent role in the storylines of popular television programs. Advertising of genetic services targeted directly to consumers is increasing. Not surprisingly, the messages offered by the media vary in content, tone, and accuracy, and play into consumers' views of genetic services in as yet unknown ways (Conrad, 2001; Geller et al., 2003).

*Provider Issues.* Genetic conditions, perhaps more than many other medical conditions, involve providers in many specialties ranging from genetic counselors to board certified specialists. Communication across the different provider groups is essential to treatment quality and outcomes; however, it is challenged by differing professional cultures, differing levels of knowledge about genetic conditions (not always in proportion to years of formal training), and differing reimbursement methods and levels. Further, the distribution of genetic specialists is quite uneven geographically, increasing the difficulty of adequate communication.

#### ***Implications for consumers of genetic services***

In the 21<sup>st</sup> century, consumers expect and will increasingly receive personal information that is digital, virtual, and mobile. Consumers will seek this information from an increasing array of sources—professional, commercial, public, and consumer-based (i.e., from other consumers), both domestic and international. As the number and type of information sources increase, so will the variability of the accuracy and applicability of the information. The availability of trusted “integrators” and interpreters of the information – such as genetic counselors – will be important. Consumers without access to this interpretive resource, either virtual or face-to-face, will be left to sift through and synthesize complex information on their own.

Although general medical information (facts about specific diseases and treatments) is now readily available on the Internet, personal medical information has been slower to emerge in an electronic format. However, increased penetration of the electronic medical record and increased use of electronic communication for patient/provider interactions will change that (Asbrand, 2007). As consumers become more adept at using electronic means of obtaining and interpreting information, they are likely to become more comfortable with seeking genetic services from electronic sources. Susceptibility testing, such as for the heritable breast cancer gene mutation BRCA1/2, is currently available online from a variety of vendors, some of whom also offer electronic or telephonic genetic counseling services. Myriad Genetics clearly believes in the power of direct to consumer messaging, having engaged in several advertising campaigns for its BRCA1/2 tests (Myriad Genetics, 2007). A recent and controversial entrant is a genetic test for bipolar disorder developed by a psychiatric geneticist at the University of California, San Diego, that retails for \$399 (Wohlsen, 2008). It adds to the more than 1,000 genetic tests that have become available to consumers over the Internet in recent years. In addition, companies like 23andMe offer to provide a complete sequencing service for individuals (23andMe website).

Some segments of the consumer population will be at a disadvantage in a world of electronic information, most notably those without convenient and affordable access to the Internet, those with language and literacy issues, and those for whom privacy and confidentiality issues make electronic communication of personal medical information uncomfortable or impossible.

### ***Implications for providers of genetic services***

Perhaps the most obvious implication of this future for medical providers will be the loss of relatively exclusive control of patient information. Patients will expect electronic access to their own medical records. In addition, traditional providers of genetic services will find themselves practicing in collaboration – or in competition – with a wider variety of providers across a larger geographic area.

Genetic conditions are currently treated by a diverse array of medical and genetic providers. However, the changing health care context suggests an increased presence of alternative care providers (e.g., naturopaths and midwives) in primary care. This development would add to professional culture differences, and increase training and knowledge differences.

A world of electronic information will change the impact of geographic imbalances in the supply of genetic services providers. In communities with appropriate infrastructure, electronic and virtual service delivery can afford consumers in isolated areas access to specialized genetic services providers. Telemedicine demonstration projects will provide useful evidence about the opportunities and challenges of this form of virtual delivery (Columbia University, 2000). Cross-state licensure issues are among the barriers that must be sorted out before telemedicine can reach its full potential. Finding mechanisms for provider reimbursement for virtual and electronic services is another challenge.

The growth of multi-specialty clinics located off the campuses of traditional hospitals may work well in genetic services markets. Existing multi-specialty clinics that treat genetic conditions may already fit this model.

### ***Implications for the financing of genetic services***

Increased availability of electronic information and increased comfort with electronic and international commerce in health care will interact with changes in health care financing. Although estimates of the pace of health savings account growth differ across analysts, there is little dispute that HSAs will be a rising force in the next decade. Approximately 4.5 million individuals are currently enrolled in HSAs, and most surveys report roughly 50 percent of employers are offering HSAs or are planning to offer them in the near future (Trapp, 2007). Federal legislation to increase the tax advantages of HSAs, coupled with many state and federal government initiatives to encourage HSA enrollment among government employees, provide evidence of the public sector's commitment to the concept.

The growth of HSAs will shift billions of dollars of health care spending into the hands of consumers. As a result, forces that directly affect consumer demand for genetic services will play an important role in determining which services are used, how often, and by whom. These forces include direct to consumer advertising and Internet-based information as well as the counsel of health care professionals. Recent gender and ethnicity-oriented advertising of

vitamins and other supplements suggests that advertisers may seek to segment product markets if this appears to increase product sales and revenue (Payne, 2006).

As consumer-controlled dollars increase as a percentage of health care spending, restrictions placed on the coverage of certain services by traditional insurance products will become less important. This has particular relevance to the area of genetic testing and counseling, and decisions of families to seek testing for heritable conditions. Existing insurance policies generally cover neither genetic testing nor counseling for family members of enrollees, nor services from retail genetic service providers; however, these restrictions will be less important to families with HSAs.

Another spillover effect of an increased percentage of consumer-financed care is that disparities in access to health care and consequent disparities in health will worsen unless there are adequately financed public programs to support lower income consumers. Public programs are typically more cautious in their coverage of non-essential services and technologies. Thus, the beneficiaries of these programs may be unlikely to have access to the full range of genetic services.

### ***Implications for research***

Most observers agree that the growth of HSAs will increase the already growing trend of “commodification” of health care (Geyman, 2004). The impact of increased reliance on economic markets to distribute services will have implications for medical research. In particular, investors are likely to be more interested in new technologies that have direct appeal to consumers with resources at their disposal. Experience with television advertising of certain prescription pharmaceuticals supports this notion. Empirical observation suggests that technologies aimed at reproductive decisions and outcomes will command significant researcher attention. Policy decisions regarding the design and funding of the catastrophic insurance policies that must accompany HSAs will affect investors’ interest in treatments for rare diseases and very expensive technologies. If coverage of these services is restricted – perhaps through a requirement of evidence of effectiveness – investment in these services may fall. The implications for research directed at particular sub-populations are not yet clear, but will likely have increasing importance.

### ***The role of government***

The role of government is generally to alter markets in which independent decisions of market players (e.g. consumers and suppliers) yield results that violate social values. Developing genetic services markets are likely to heighten a number of existing policy concerns and generate some new ones.

*Provide Essential Market Infrastructure.* A primary role of government is to provide the infrastructure that allows markets to function. The basic infrastructure components include transportation corridors (safe roads, shipping lanes, and airways), a stable currency, and a court system that upholds legal agreements. In the future, Internet access may be added to the necessary components of publicly provided market infrastructure—a new “corridor” across which significant levels of commerce take place. Supporters of bio-banking initiatives might add

appropriate access to genetic data as a necessary component of at least the research enterprise in this area.

Even (perhaps especially) markets that function well largely serve those with resources. A consequence of relying on markets to deliver genetic services will be to heighten existing disparities in access to these services between those who have resources and those who do not. Thus, it could be argued that a necessary component of market infrastructure is a mechanism to address these disparities to a degree that comports with social values. It falls to government to provide and monitor this mechanism.

*Provide Information.* A frequent objection to the use of markets to ration complex personal services is the difficulty that consumers often have in obtaining sufficient information to make informed decisions. This is true for most health care services; it certainly is true for genetic services. Our traditional approach in other health care markets is to substitute external standards (e.g., professional licensure and facility accreditation) for complete information.

An increasing amount of commerce will occur outside the boundaries of current government jurisdiction. This will happen for several reasons. First, technology is expanding at a more rapid pace than public policy. The unregulated “home brew” genetic tests are an example of a technology that appeared, probably purposefully, outside the lexicon of existing regulation of laboratory tests. We can expect other new technologies to push regulatory boundaries as well. Second, the evolution of the structure of genetic services markets (along with health care services markets in general) is reducing the role of the traditional physician provider. The provision of genetic tests through department stores and over the Internet, often without the involvement of a genetic counselor, provides an example in this area. While Congress is considering legislation that would insert some government oversight into retail genetic services markets, none currently exists (Javitt and Hudson, 2006). Finally, as international markets for health care services increase, we can expect that this will include genetic services. The “nighthawk” model for radiology services (remote reading of radiology images, usually done overseas) would apply well to the performance of genetic tests. Some international outsourcing already exists for reproductive and other genetic services whose use in the U.S. is restricted and/or expensive (South Asian Women’s Forum, 2006).

These changes in technology, market structure, and venue suggest that an increasing volume of genetic services will be provided without the customary protections of regulation, physician oversight, or U.S. authority. An important government role in a more *caveat emptor* world will be as purveyor of easily accessible, high quality, unbiased information about services and providers. Service providers, too, will have increasing information needs as both the science and the organization of markets becomes more complex. Both consumers and providers will need access to information about what government programs exist to assist them. Because government activity in the area of genetics spans many agencies and departments at both the state and federal levels, coordination and communication among relevant government bodies would improve their collective efforts.

Finally, government can play a role in speeding the translation of basic science discoveries into clinical applications and in mediating scientific controversies. Convening experts to create

evidence-based practice guidelines or to generate scientific consensus is a mechanism that the federal government has used for this purpose.

*Monitor the provision of information by private sector entities.* Participants in active markets generate large amounts of “information.” Much of this information is provided in the form of product and service advertising, some of which is regulated by the FTC. However, there are other more subtle (and less regulated) mechanisms to influence consumer and provider behavior, including the activities of pharmaceutical sales representatives and public statements by commercial entities and advocacy groups on the Internet, in public forums, and through news outlets. While the FTC’s ability to adequately monitor formal advertising is limited by resources and the lack of specialized expertise, no government agency has oversight authority over these other mechanisms of influence. Thus, government has an additional role in expanding its ability to monitor the information generated by an increasingly commercial genetic services sector.

Enforcing, and where necessary creating, regulations to ensure the confidentiality of genetic information (both publicly and privately generated) and preventing its use for insurance, employment, or other discrimination is also an important government activity. When individuals fear how their genetic information might be used against them, they are both less likely to seek genetic services and less likely to participate in genetics research.

*Promote balanced competition.* Commercialized genetic services markets will serve consumers best when productive competition is encouraged and destructive competition is limited. Productive competition can be fostered by removing inappropriate barriers to entry, preventing subsets of professionals or commercial entities from monopolizing information, and maintaining a level regulatory playing field. Destructive competition can be limited by assuring transparency, monitoring market outcomes, and constantly balancing the benefits of market barriers (e.g., regulation) with their costs and side effects.

*Encourage innovation.* Innovation in a market has the potential to create new value. In genetic services markets, this can mean improved health and increased access to information with which to make life decisions. Innovation is generally the result of investments in research.

The government can play multiple roles in fostering innovation. At the most basic level, appropriate patenting policies that balance positive incentives for private investors and researchers with the needs of those who use the outcomes of research are essential. Existing patent laws, for the most part, were created in the late 19<sup>th</sup> century in an entirely different scientific and market context. Updating patent laws to reflect the realities of the 21<sup>st</sup> century would likely improve this balancing.

Maximizing the value of innovation also involves appropriate application of scientific discovery. This is facilitated through appropriate and even-handed regulation of emerging technologies to assure their safety and provide information to guide their efficacious use.

Important innovation can occur in the delivery as well as the creation of genetic services. Government can foster market structure innovation through both regulations that do not restrict it

unduly and creative reimbursements that reward it. Pilot and demonstration projects are often used for this purpose, as well as evidence-based modification of public purchasing strategies.

Government funds a large share of medical and genetic science research. If publicly funded research is to produce the highest public value, funding policies must reflect social priorities.

*Provide a forum for discussions of social values.* Genetic services raise many ethical, social, and cultural issues. An important role of government is to facilitate public discourse about these issues. Because not all social values have equal voice in a market-oriented environment, it falls to government to assure that all voices are at the table and all values are considered. Finally, it is the responsibility of government to incorporate the social values that emerge from these conversations into public policy.

*Lead by example.* Government at all levels has an important influence on markets through its purchasing power. The coverage decisions of Medicare, Medicaid, public employee benefits, and other government programs have a substantial direct effect by increasing (or decreasing) demand for covered (or excluded) services in a large population. Public decisions often have the important secondary effect of establishing a standard of coverage for private insurers. This double impact applies not only to the list of covered services, but also to provider payment mechanisms (e.g., direct reimbursement of genetic counselors) and conditions of coverage (e.g., tiered pharmaceutical benefits).

State and federal governments can be cognizant of their significant influence on genetic services markets when they design public program benefits, both with regard to consumer incentives/requirements and provider incentives/requirements.

### ***Conclusion***

The changing organization and financing of the health care sector provides both opportunities and challenges for genetic services delivery in the next 20 years. Traditional means of guiding consumer decisions through professional and government oversight will be less available and therefore less relevant. Thus, government agencies at all levels must adapt their strategies to the evolving context to assure that public values continue to be served by genetic services markets.

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## Genetic Services Policy Project Final Report

### Chapter 8: Recommendations

There is consensus among genetic services experts and advocates that the field of genomics holds the potential to advance a more powerful, preventive, and in some cases cost-effective personalized medical care system. One of the goals of the **Genetic Services Policy Project** was to develop a set of policy recommendations to address the barriers to integrating genetic services into the health care delivery system, thereby facilitating the achievement of this potential. In previous chapters, we described the nature of existing genetic services; how, where, and by whom they are delivered; who receives them and who pays for them; the evolution and likely future of genetic services; and policy challenges in their equitable and appropriate delivery. In this chapter, we present our recommendations for public policies that address the barriers to integration that we identified.

Throughout the work of the GSPP, we sought input from our national Advisory Committee. Because committee members work in sectors of the health care industry that are differentially affected by the evolution of genetic services, their input into the final recommendations was particularly valuable. Prior to the final Advisory Committee meeting in May 2007, we circulated a set of federal policy recommendations derived from our research. After lengthy collective and small group discussions at the meeting, we asked members to indicate their sense of the relative priority that should be given to each recommendation. We carefully considered this input from the Advisory Committee as we developed the recommendations and priorities that follow.

Table 1 presents the nine recommendations that we believe have the highest priority for federal government action. We have grouped them into four categories that represent different public policy tools that can be used to influence markets:

- Use the convening/facilitating power of government (C/F),
- Use public insurance programs to model effective genetic services purchasing strategies (PI),
- Use public programs to create opportunities (PP), and
- Use the regulatory power of government to constrain/guide markets (R).

**TABLE 1**

<b>HIGHEST PRIORITY RECOMMENDATIONS</b>
<i>Convening/Facilitating (C/F)</i>
Convene experts and consumers to create guidelines and recommendations regarding the delivery of genetic services
Facilitate interstate licensure

<b><i>Modeling Effective Purchasing Strategies Through Public Insurance Programs (PI)</i></b>
Provide education and decision-making tools regarding genetic services in public insurance programs
Pay for genetic counseling/counselors in public insurance programs
Pay for care coordination and multidisciplinary treatment in public insurance programs
<b><i>Provide Educational Opportunities Through Public Programs (PP)</i></b>
Provide public education programs about genetic services for consumers/enrollees
Integrate genetics into educational curricula for current health professional students
Provide public education programs about genetic services (e.g., CME courses) for health care providers
<b><i>Regulate Genetic Services Markets (R)</i></b>
Prohibit genetic discrimination

*Convene Experts and Consumers to Create Guidelines and Recommendations Regarding the Delivery of Genetic Services.* The introduction of genetic services (e.g., genetic tests) often precedes an accepted evidence base to guide their use. Expert opinion can (must) serve as the next best alternative. Thus, the convening function of the federal government can play a central role in the development of standards and guidelines for appropriate use of genetic services. Because the field of genetic services involves values as well as science (e.g., the value of information to guide future health care decision-making), consumers and advocates as well as experts must be included in the discussions.

*Facilitate Interstate Licensure.* Health professionals often favor licensure programs to protect their professional markets and therefore their economic interests. However, the state-based programs restrict the mobility of genetics professionals, restrict reimbursement of unlicensed professionals (e.g., genetic counselors), and seriously complicate electronic and telephonic consultations across state boundaries. The fast-rising demand for genetic literacy among clinicians, given the shortage of genetic services professionals, especially in rural areas, makes this policy question much more central. While the federal government does not have jurisdiction over this state regulatory function, it can facilitate discussions of mechanisms to provide for interstate licensure.

*Modeling Effective Purchasing Strategies Through Public Insurance Programs.* The federal government can have a major impact on the delivery of genetic services through effective purchasing strategies in public insurance programs such as Medicaid, Medicare, and the Federal Employees Health Benefits Program. What these programs choose to provide (e.g., education and decision-making tools regarding genetic services) and pay for (e.g., genetic counseling, care coordination, and multidisciplinary care) has not only a direct effect on a large portion of the market, but also influences the behavior of private insurance plans.

*Provide Educational Opportunities Through Public Programs.* Participants in the health care system can only use genetic services appropriately if they are aware of what services are available and how they can/should be used. The federal government can affect the integration of genetic services through the creation and funding of public programs that educate consumers and providers (current and future) about genetics and genetic services.

*Prohibit genetic discrimination.* Evidence is mounting that people’s fears about genetic discrimination reduce their willingness to seek genetic services. Opponents of legislation to protect the privacy of genetic information and prohibit discrimination argued that there are few documented cases of discrimination actually occurring. However, for the purpose of increasing the use of genetic services, the evidence is less important than the perception: if people *worry* that results of genetic tests will be used against them, the impact on utilization is the same. To the extent that passage of the Genetic Information Nondiscrimination Act (GINA) will allay these fears, it will contribute to the goal of appropriate genetic services utilization and integration. According to even its supporters, the passage of GINA is an important step in this direction, but one that may need improvement over time.

Table 2 presents additional recommendations that address six issues that arose prominently from our work:

1. How can the federal government promote evidence-based decision making for genetic services?
2. How can the government protect consumers from harms that might arise in genetic services markets?
3. How can the government promote innovation in genetic services and their delivery?
4. How can the government address social and distributional issues around genetic services?
5. How can the government increase the supply of providers with genetic training and expertise?
6. How can the government assure access to genetic services for rural populations?

Again, we grouped these recommendations into the four categories reflecting the policy tools that each one embodies.

**TABLE 2**

<b><i>Issue 1: How can the federal government promote evidence-based decision making for genetic services?</i></b>	
C/F	Encourage research data coordination through NIH
PI	Cover only clinically/cost effective care in public insurance programs
PI	Use data from public purchases to create an evidence base for genetic services research
PP	Fund research on clinical application/utility and cost effectiveness of genetic services
R	Require evidence-based assessment for approval of new technologies

***Issue 2: How can the government protect consumers from harms that might arise in genetic services markets?***

C/F	Facilitate interagency (e.g., HRSA, CDC, CMS, NIH) discussions about genetic services delivery and policy
C/F	Evaluate the need for broad regulations regarding direct to consumer advertising and/or retail genetic services
C/F/R	Assure that FTC, FDA, and state attorneys general carry out mission of preventing harm and fraud
R	Regulate “home brew” tests
R	Consider licensing retail genetics companies

***Issue 3: How can the government promote innovation in genetic services and their delivery?***

PI	Pay for telemedicine and electronic genetic services in public insurance programs
PI	Integrate genetic services information into electronic medical records in public insurance programs
PI	Reward innovative genetic service delivery models in public insurance programs (e.g., reimbursing telephonic genetic counseling services)
PP	Fund demonstration projects on telegenetics
PP	Fund research on the impact of genetic delivery system innovations

***Issue 4: How can the government address social and distributional issues around genetic services?***

C/F	Provide forums for discussion of financial, ethical, legal, social implications (FELSI); assure all voices are at the table
PI	Include genetic services in public programs for low income populations
PI	Provide insurance coverage for children with genetic conditions transitioning into adult services
PP	Fund research on access to genetic services
PP	Fund research on ethical issues related to genetic services

***Issue 5: How can the government increase the supply of providers with genetic training and expertise?***

PP	Increase capacity in training pipeline for genetic services specialties
PP/R	Increase genetics content in all medical training

R	Require genetics CME for physician licensure
<b><i>Issue 6: How can the government assure access to genetic services for rural populations?</i></b>	
PI	Pay for telemedicine and other electronic genetic services in public insurance programs
PP	Use loan-forgiveness model for rural providers with genetics expertise

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### Appendix A: Dissemination Activities

Dissemination of results has been a major component of the **Genetic Services Policy Project**. The dissemination activities have taken many forms, from peer-reviewed publications and workshops to informal articles and presentations. The GSPP has attained a high rate of acceptance for peer-reviewed submissions—85 percent, or 34 out of 40. Project personnel have also taken part in 15 informal presentations and six written dissemination activities. Finally, we have held four in-person meetings of the national advisory committee, produced quarterly newsletter updates, and provided website resources. A summary count follows; see Appendix A.1 (page 3) for a full list.

#### Genetic Services Policy Project Dissemination Activities

- 8 published articles (peer-reviewed)
- 3 published articles (not peer-reviewed)
- 12 poster presentations (peer-reviewed)
- 14 formal presentations, including 7 workshops
- 15 informal presentations
- 6 informal written dissemination activities
- 6 peer-reviewed submissions that were not accepted
- 13 formal communications with advisory committee, including 4 annual face-to-face meetings

GSPP has produced eight peer-reviewed publications in the following journals: *American Journal of Managed Care*, *American Journal of Public Health*, *Genetics in Medicine*, *Health Affairs*, *Journal of Health Politics, Policy and Law*, and *Maternal and Child Health Journal*. Articles include topics such as economic analyses and evidence-based assessments of genetic services, genetics policy, utilization trends of genetics clinics, and genetic counseling for children with special health care needs. The 12 peer-reviewed posters address similar subjects. A list of article titles and authors is included in Appendix A.1.

GSPP has given a number of formal presentations. The conference organizers include American College of Medical Genetics, American Public Health Association, Centers for Disease Control and Prevention, Genetic Alliance, National Institutes of Health, and World Research Group. Dates and titles of presentations are included in Appendix A.1.

With the assistance of many members of our Advisory Committee, we developed a series of workshops that were delivered at meetings and conferences of some of the key trade associations represented by our advisors: AdvaMed, America's Health Insurance Plans, American Hospital Association, American Medical Association, Association of Genetic Technologists, Biotechnology Industry Organization, and Child Health Corporation of America. Between November 2006 and October 2007, we delivered seven workshops. The workshops allowed us to directly disseminate our work to hundreds of providers, managers and executives

in the health care delivery system. The response to our material was excellent, and those who attended felt that this was a very efficient method of dissemination. For those workshops that conducted evaluations, GSPP's presentations received consistently positive feedback. The presentation and evaluation materials from each workshop appear in Appendix A.2 (page 9).

Project personnel have also participated in a number of informal presentations to audiences such as the Western States Genetic Services Collaborative, the National Coordinating Center for the Regional Genetics and Newborn Screening Collaborative Groups, Washington State Genetics Providers Group, Washington State Perinatal Advisory Committee, the Institute of Medicine Cancer Policy Forum, and units within the University of Washington, the National Human Genome Research Institute, and the National Society of Genetic Counselors.

GSPP has taken advantage of informal opportunities to disseminate written materials to the National Conference of State Legislatures, the National Newborn Screening and Genetics Resource Center, and several chief medical officers. We sent a letter to the Secretary's Advisory Committee on Genetics, Health and Society, responding during the public comment period to the draft report, "Policy Issues Associated with Undertaking a Large U.S. Population Cohort Project on Genes, Environment, and Disease." We also had an informational display table at the National Society of Genetic Counselors' Annual Education Meeting. In addition, our website showcases GSPP's project updates and resources.

In sum, our dissemination activities have reached a broad audience on a range of topics related to genetic services. Our materials have been well received, as evidenced by our high publication success rate and the uniformly positive evaluation of our presentations.

## Appendix A.1: Complete List of Dissemination Activities

### ***Papers and Articles (peer-reviewed)***

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
October 2005	Article	Economic analyses of human genetics services: a systematic review	<i>Genetics in Medicine</i> . 2005 Oct;7(8):519-523.	Josh Carlson
October 2005	Article	The Case of BiDiI: A Policy Commentary on Race and Genetics	<i>Health Affairs</i> , web exclusive, October 11, 2005	Rick Carlson
April 2006	Article	Toward Evidence-based Assessment for Coverage and Reimbursement of Laboratory-based Diagnostic and Genetic Tests	<i>Am J Manag Care</i> . 2006;12:197-202	Rick Carlson, David Veenstra
February 2007	Article	Genetic Counseling, Insurance Status, and Elements of Medical Home: Analysis of the National Survey of Children with Special Health Care Needs	<i>Maternal and Child Health Journal</i>	Grace Wang
April 2007	Article	The role of genetics in the provision of essential public health services	<i>American Journal of Public Health</i> 97(4):620	Grace Wang
October 2007	Article	Utilization trends of genetics clinics excluding prenatal services in Washington State, 1995 to 2004	<i>Genetics in Medicine</i> . 9(10):713-718.	Grace Wang, Cindy Watts
October 2007	Article	Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes	<i>Genetics in Medicine</i> . 9(10):695-704.	Dave Veenstra
February 2008	Article	Preemptive Public Policy for Genomics	<i>Journal of Health Politics, Policy and Law</i> 33: 39-51	Rick Carlson

### ***Papers and Articles (not peer-reviewed)***

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
July 2004	Article	Describing GSPP	National Society of Genetic Counselors' newsletter <i>Perspectives</i>	Deb Lochner Doyle Amber Roche
May 2005	Article	Describing GSPP	Association of Maternal and Child Health Programs newsletter <i>Pulse</i>	GSPP personnel
June 2006	Article	Third Party Payer Perspectives	Health Industry Forum Foundation	Rick Carlson

**Posters (peer-reviewed)**

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
May 2005	Poster presentation	A Systematic Review of Economic Evaluations of Genetic Testing Technologies	International Society for Pharmacoeconomics and Outcomes Research in Washington, D.C.	Scott Ramsey
July 2005	Poster presentation	A Systematic Review of Economic Evaluations of Genetic Testing Technologies	International Health Economics Association in Barcelona, Spain	Scott Ramsey
October 2005	Poster presentation	Organization, Administration and Funding of State Genetic Services Programs	American Society of Human Genetics Annual Meeting in Salt Lake City, UT	Grace Wang
March 2006	Poster presentation	Pharmacogenomics and aminoglycoside-induced hearing loss in cystic fibrosis patients	American College of Medical Genetics Annual Clinical Genetics Meeting in San Diego, CA	Julie Harris
September 2006	Poster presentation	Utilizations of Genetics Clinics in Washington, 1995 – 2004	University of Washington Annual Gathering of Health Sciences Schools incoming students	Grace Wang
November 2006	Poster presentation	Factors associated with need and use of genetic counseling: An analysis of the National Survey of Children with Special Health Care Needs	American Public Health Association Annual Meeting in Boston, MA	Grace Wang
November 2006	Poster presentation	Policy implications of cost effectiveness analysis for genetic testing: A case study	American Public Health Association Annual Meeting in Boston, MA	Julie Harris
November 2006	Poster presentation	Integrating Personalized Medicine into the Health Care System: A Comprehensive Study of Stakeholder Groups	American Medical Association meeting	Patricia Deverka (GSPP Advisor)
November 2006	Poster presentation	Through the media lens: Analyzing the news messages Americans receive about genetics	National Society of Genetic Counselors' Annual Education Conference in Nashville, TN	Amber Roche
November 2006	Poster presentation	Integrating genomics into the healthcare system: opportunities for collaborations by stakeholders	National Society of Genetic Counselors' Annual Education Conference in Nashville, TN	Grace Wang Amber Roche
November 2006	Poster presentation	Proving Genomics: A Workshop for Physicians	Accepted – Society of Teachers of Family Medicine Annual Spring Conference in April in Chicago	Rick Carlson
March 2007	Poster presentation	Utilization Trends of Genetics Clinics in Washington State, 1995 to 2004	American College of Medical Genetics annual meeting in Nashville, TN, in March 2007	Grace Wang

### **Formal Presentations and Workshops**

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
September 2005	3 Panel presentations	Payment and reimbursement	Access to Quality Testing for Rare Disorders: National Institutes of Health (NIH) National Conference in Rockville, MD	Rick Carlson
March 2006	Presentation	Evaluation of Genomic Applications in Practice and Prevention (EGAPP) assessment of genetic testing; program review and follow-up	Centers for Disease Control and Prevention in Atlanta, GA	Rick Carlson
March 2006	Presentation	Stakeholders' Perspectives on the Delivery of Genetic Services	American College of Medical Genetics Annual Clinical Genetics Meeting in San Diego, CA	Rick Carlson, Deb Lochner Doyle
July 2006	Presentation	Personalized Medicine Landscape: challenges and opportunities for consumers	Genetic Alliance Annual Conference in Bethesda, MD	Rick Carlson
October 2006	Presentation	Quality, Access, and Sustainability of Biochemical Genetic Testing	Joint National Institutes of Health (NIH) Office of Rare Diseases – Centers for Disease Control and Prevention in Atlanta, GA	Rick Carlson, Michele Puryear
November 2006	Presentation	A model for determining the budget impact of expanded newborn screening	American Public Health Association Annual Meeting in Boston, MA	Wylie Burke
November 2006	Presentation	Genomics Stakeholder Workshop	American Medical Association meeting	Rick Carlson, David Veenstra
November 2006	Presentation	Genomics Stakeholder Workshop	AdvaMed meeting – Molecular Diagnostics: Development, Regulation, & Reimbursement	Rick Carlson, Jeff Bauer (GSPP advisor)
April 2007	Presentation	Transforming Health Care: The emergence of Genetic Services in Medicine and Health Care	Child Health Corporation of America	Rick Carlson
May 2007	Presentation	Proving Genomics: What Do Payers and Providers Need?	BIO (Biotechnology Industry Organization) International Convention, Boston, MA	Rick Carlson, Jeff Bauer (advisor)
June 2007	Presentation	Proving Genomics	Association of Genetic Technologists' Annual Meeting, Denver, CO	Rick Carlson, Deb Lochner Doyle
June 2007	Presentation	Proving Genomics: A Workshop for Payers	America's Health Insurance Plans Annual Meeting in Las Vegas, NV	Rick Carlson
July 2007	Presentation	Integrating Genomics: What Do Hospitals Need?	American Hospital Association / Health Forum's Leadership Summit in San Diego, CA	Cindy Watts
November 2007	Presentation	Integrating Medical Genetics and Genetic Testing to Enhance the Value of Healthcare Delivery and Disease Prevention	Genetic Testing & Genetic Risk Assessment for Health Plans, World Research Group	Rick Carlson

### ***Informal Presentations and Workshops***

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
May 2005	Presentation	Year 3 proposal narrative as background for a task force	National Society of Genetic Counselors' Genetic Services Delivery Task Force	Daragh Conrad (GSPP Advisor)
September 2005	Web cast presentation	Financing of Genetic Services based on GSPP State Genetics Profiles data	National Coordinating Center for the Regional Genetics and Newborn Screening Collaborative Groups	Deb Lochner Doyle
September 2005	Conference participation	Genetics and newborn screening services	National Coordinating Center for Regional Genetics and Newborn Screening Collaborative Groups in Washington, D.C.	Grace Wang
September 2005	Presentation	Project update	Western States Regional Genetics Collaborative meeting in Las Vegas, NV	Amber Roche
December 2005	Discussion / presentation	Integrating genetic services into current system	Joint Centers for Disease Control and Prevention-Group Health Cooperative meeting in Seattle, WA	Rick Carlson
February 2006	Presentation	Assessed databases, described GSPP activities	GeneTests in Seattle, WA	Rick Carlson
March 2006	Presentation	GSPP state genetics profiles, case studies, and cross-cutting policy format	Washington State Genetics Provider Group in Kent, WA	Deb Lochner Doyle
June 2006	Presentation	Project update	HRSA offices in Washington, D.C.	Rick Carlson
June 2006	Discussion	Reimbursement policy	National Human Genome Research Institute	Rick Carlson
June 2006	Utility, infrastructure	Developing guidance process for evidence-based coverage decisions regarding genetic services	Diagnostic developers and payers	Rick Carlson
June 2006	Briefing attendance	A Bill to improve and expand the use of molecular genetic tests and therapeutics	Senator Barack Obama's staff in Washington, D.C.	Rick Carlson
October 2006	Presentation	Update on the work of the Genetic Services Policy Project	Western States Genetic Services Regional Collaborative Summit	Amber Roche
October 2006	Presentation	Preemptive Public Policy for Genomics	UW Dept of Health Services Policy Seminar Series	Rick Carlson
February 2007	Presentation	Genetic Services Policy Project findings	Washington State Perinatal Advisory Committee	Deb Lochner Doyle
March 2007	Presentation	Billing and reimbursement issues for genetic services	Institute of Medicine Cancer Policy Forum	Deb Lochner Doyle

### **Informal Written Dissemination**

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
August 2005	Fact sheets	GSPP overview	National Conference of State Legislatures Annual Meeting in Seattle, WA	Candi Wines
September 2005	Fact sheets	Genetic Services Policy Project overview	Requested by and sent to 7 advisors and chief medical officers	Candi Wines
September 2005	Template – state genetics profiles	State genetics profiles and GSPP overview	Sent to National Newborn Screening and Genetics Resource Center	Candi Wines
October 2005	Flow chart diagrams	Organization, Administration and Funding of State Genetic Services Programs	Sent to National Conference of State Legislatures for a booklet they are creating	Grace Wang
July 2006	Public Draft Comment Letter	Comments on public draft of SACGHS' report: Policy Issues Associated with Undertaking a Large U.S. Population Cohort Project on Genes, Environment, and Disease	Secretary's Advisory Committee on Genetics, Health, and Society	GSPP personnel
November 2006	Display table	GSPP State Genetic Profiles, Fact Sheets, Informational Tear-away Sheets	National Society of Genetic Counselors' Annual Education Conference in Nashville, TN	Amber Roche

### **Submissions That Were Not Accepted**

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
June 2005	Panel presentation	Impact of genetic services on disparities in vulnerable populations	Submitted to Grantmakers in Health	Rick Carlson
October 2005	Panel presentation	The role of genetic services in health care: barriers and opportunities	Submitted to American Society of Human Genetics Annual Meeting	Deb Lochner Doyle
October 2005	Article	Expenditures for Genetic Services in the United States: An Overview	Submitted to <i>Health Affairs</i>	Grace Wang
January 2006	Article	Stakeholders' perspectives regarding genetics and genetic services in the United States	Submitted to <i>Clinical Genetics</i>	Grace Wang
January 2006	Panel presentation	Policy Research on Genetic Services: New Science Meets Old Paradigm	Submitted to Academy Health Annual Research Meeting	Carolyn Watts, Deb Lochner Doyle
April 2006	Poster	Promoting Health by Integrating Genomics into the Healthcare System: Opportunities for Collaborations by Stakeholders	Centers for Disease Control and Prevention annual National Health Promotion Conference	Grace Wang
Continuous	Website	GSPP updates and resources	GSPP's website	GSPP personnel

**Dissemination to the Advisory Committee**

<b>Date</b>	<b>Activity</b>	<b>Topic</b>	<b>Venue</b>	<b>Primary Person</b>
September 2004	Presentations / Conference	Update to Advisory Committee on GSPP Year 1	Annual Advisory Committee Meeting, Washington D.C.	Project personnel
April 2005	Presentations / Conference	Update to Advisory Committee on GSPP Year 1	Annual Advisory Committee Meeting, Chicago, IL	Project personnel
June 2005	GSPP update	Annual summary sent to advisors	Via email	GSPP personnel
September 2005	GSPP update	Quarterly communication with advisors	Via email	GSPP personnel
November 2005	GSPP update	Quarterly communication with advisors	Via email	GSPP personnel
April 2006	Presentations / Conference	Update to Advisory Committee on GSPP Year 2	Annual Advisory Committee Meeting, Washington D.C.	Project personnel
June 2006	GSPP update	Annual summary sent to advisors	Via email	GSPP personnel
August 2006	GSPP update	Quarterly communication with advisors	Via email	GSPP personnel
February 2007	GSPP update	Quarterly communication with advisors	Via email	GSPP personnel
April 2007	GSPP update and review	Quarterly communication with advisors	Via email	GSPP personnel
May 2007	Presentations / Conference	Update to Advisory Committee on GSPP Year 3	Annual Advisory Committee Meeting, Washington D.C.	GSPP Personnel
August 2007	Backgrounder distribution	Backgrounder on Pharmacogenomics for the Pharmaceutical and Biotechnology Industries: Basic Science, Future Scenarios, Policy Directions	Mailed a copy of backgrounder to each GSPP advisor	Rick Carlson
October 2007	GSPP update	Quarterly communication with advisors	Via email	GSPP personnel

**Appendix A.2: Summary of Evaluations from Genomics Workshops**

<b>Organization</b>	<b>Conference Title</b>	<b>Location, Date</b>	<b>Workshop Title</b>	<b>Presenters</b>
American Medical Association	2006 Interim Meeting of the AMA House of Delegates	Las Vegas, NV November 12, 2006	Proving Genomics: A Workshop for Physicians	Rick J. Carlson, JD, Genetic Services Policy Project  David Veenstra, Pharm D., PhD, Genetic Services Policy Project
AdvaMed	Molecular Diagnostics: Development, Regulation, and Reimbursement	Washington, DC November 16, 2006	Proving Genomics: A Stakeholder Workshop	Rick J. Carlson, JD, Genetic Services Policy Project  Jeffrey C. Bauer, PhD, Senior Vice President, ACS Healthcare Solutions  Paul Campbell, Managing Director, EBG Advisors
Child Health Corporation of America	Strategic Planning and Business Development Forum	Los Angeles, CA April 26, 2007	Transforming Health Care: The emergence of Genetic Services in Medicine and Health Care	Rick J. Carlson, JD, Genetic Services Policy Project
Biotechnology Industry Organization	BIO International Convention – New Ideas: Bold Ventures, Global Benefits	Boston, MA May 6-9, 2007	Proving Genomics: What do Payers and Providers Need?	Rick J. Carlson, JD, Genetic Services Policy Project  Jeffrey C. Bauer, PhD, Senior VP, ACS Healthcare Solutions  Paul M. Campbell, MS, Managing Director, EBG Advisors
Association of Genetic Technologists	32 <sup>nd</sup> Annual Meeting	Denver, CO May 31-June 3, 2007	Integrating Genetic Services into Mainstream Health Care	Rick J. Carlson, JD, Genetic Services Policy Project  Debra Lochner Doyle, MS, CGC, Genetic Services Policy Project
America's Health Insurance Plans	Annual Meeting	Las Vegas, NV June 20-22, 2007	Proving Genomics: A Workshop for Payers	Rick J. Carlson, JD, Genetic Services Policy Project  Allan J. Ebbin, MD, MPH, Vice President, Healthcare Quality and Education, Sierra Health Services
American Hospital Association	2007 AHA/Health Forum Leadership Summit	San Diego, CA July 22-24, 2007	Integrating Genomics: What Do Hospitals Need?	Carolyn Watts, PhD, Genetic Services Policy Project  Marc Williams, MD, Director, Clinical Genetics Institute, Intermountain Healthcare

***American Medical Association Evaluation***

Audience: 70 senior level physicians

Evaluation: The AMA used its own evaluation form following the presentation.

	Strongly Agree			Strongly Disagree	
	1	2	3	4	5
The program was well organized.	31	23	3	2	1
The learning objectives were adequately addressed.	25	26	4	4	0
I can now discuss the evolving technology of genomics.	12	31	14	3	0
I can now describe the current scope of genetic testing services.	13	31	13	3	0
I can now discuss the findings and policy recommendations of the Genetic Services Policy Project.	8	25	18	5	2
I can now describe the clinical utility of personalized medicine.	13	32	13	2	0
I can now identify the uses of genetic data for predictive testing.	10	31	14	5	0
I can now describe the fundamentals of pharmacogenomics.	15	30	12	3	0
	Yes			No	
Did you perceive any commercial bias in the presentation?	1 (No explanation given)			54	

**Comments/Suggestions:**

Several “outstandings.” “Excellent, exciting program.” “More of the same.” “Update annually.” “Excellent presentations by Rick Carlson and David Veenstra.” “Very Good, thanks!” “Very interesting – Good to get real scoop on what is/isn’t out there and how rapidly (or not) this is likely to unfold.” “No current impact.” “Great speakers, excellent information, well done!” “Tough topic, very complex.” “Great discussion.” “Liked combination of speakers and having socio-economic context for the technical information.” “Good overview – not much news.” “I have a real interest in slow metabolizers and that was very helpful.” “Wish more physicians attended and participated. This is an important field. Thanks for the good handouts.”

“Expand discussion of prediction testing. How can technology help people alter their lifestyle?” “Less quotations and predictions, more about present facts and uses.” “More details.” “Mention proteomics.” “Provide list of references.” “Explore more generalized genetic testing (mitochondrial DNA) in exploring racial/genetic background of individuals. “Time lapse prediction” “Longer, more depth” “Information that is currently not available, more specifics re: testing and uses.”

TOTAL OF 64 CME forms returned.

### *AdvaMed Evaluation*

Audience: The audience numbered about 200, and was comprised of senior managers, mostly marketing, product and business development from various diagnostic companies.

Evaluation: AdvaMed did not conduct presentation evaluations.

### *Child Health Corporation of America Evaluation*

Audience: 30 strategic planning and business development employees

Evaluation: CHCA collected written comments and feedback from attendees:

- Engaging - intriguing - thought provoking – GREAT
- Thank You Thank You Thank You - Brilliant, Helpful, Fabulous
- Very enlightening, Excellent, liked his approach. We need to keep this item on our agenda for future meetings.
- Would have liked more time.
- Very interesting!
- Unclear how message can be taken back for some sort of implementation.
- Wonderful view of the future.
- Awesome - though provoking.
- I'd love to hear more on this - maybe do some roundtables on it?
- This was a very informative and thought provoking lecture.

### *Biotechnology Industry Organization Evaluation*

Audience: There were approximately 300 biotechnology executives in attendance.

Evaluation: BIO did not conduct presentation evaluations.

### *Association of Genetic Technologists Evaluation*

Audience: There were approximately 20 genetic technologists in attendance.

Evaluation: AGT conducted its own presentation evaluations.

	Excellent 4	Good 3	Fair 2	Poor 1
Speaker Preparation	9	1	0	0
Level of Seminar	7	3	0	0
Length of Seminar	7	3	0	0
Effective Presentation of Materials	7	3	0	0
Usefulness of Handout Materials	4	5	0	0

#### **What is the most valuable insight gained from this seminar?**

- What we do as clinical medicine is a small part of the overall medical system.
- A look at genetics in overall healthcare system.
- The issues of current and future delivery. This was an excellent presentation.
- This should be repeated next year – presented to entire conference attendance in Houston.

- Public perspective, policy and pharmaceutical impact for PGX.
- Impact of personalized medicine.
- The whole lecture was very educational.
- So much information available.
- We need to educate more about genetics.

**Will you use information gained in this seminar in your professional position?**

Yes: 8                      No: 1

**What was your main motivation for attending this particular seminar?**

- To be educated on how genetics will eventually effect the medical system.
- Clinical background as well as cytogenetics and concerns about how the science reaches the public and how to educate providers.
- To learn more about genetics.
- Topic relevance.
- PGX status.
- Interested in the topic.
- Interest – coevolution of genetics with medicine.
- To be more educated about the field.

**Did this seminar meet or exceed your personal goals and expectations?**

Yes: 9                      No: 0

**Why or why not?**

- Very thought provoking.
- It was easy to follow along and full of lots of information.

***America's Health Insurance Plans Evaluation***

Audience: There were approximately 150 managed care executives in attendance.

Evaluation: AHIP conducted a short evaluation:

Both speakers received the same scores (Good is a 3 on a scale of 1 to 4).

Speaker Effectiveness:    Good  
 Presentation Content:     Good  
 Value to Organization:    Good

***American Hospital Association Evaluation***

Audience: There were approximately 30 hospital leaders in attendance.

Evaluation: AHA conducted a short evaluation:

Excellent:                  2 responses  
 Very Good:                5 responses  
 Good:                        7 responses  
 Satisfactory:              1 response

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## Genetic Services Policy Project Final Report

### **Appendix B: Analysis of GINA Through the Advocacy Coalition Framework**

The Genetic Information Nondiscrimination Act of 2007 (GINA) would have seemed to be legislation with no impediment to passage in the 110<sup>th</sup> Congress. Previous versions of GINA had passed the Senate by big margins in 2003 (108<sup>th</sup> Congress) and 2005 (109<sup>th</sup> Congress). President Bush had been favorable to passage and had indicated that he would sign the legislation into law.

The House of Representatives passed GINA in February 2007 by a wide margin. The House version of GINA, sponsored by Representative Louise Slaughter (D-NY), had been blocked in previous years by the Republican leadership that controlled the House. Democratic control of the House following the 2006 midterm Congressional election s cleared the way for house passage and – or so it seemed – quick passage in the Senate.

And yet as of the spring of 2008, GINA had not come to a vote in the Senate and there was no apparent prospect of a Senate vote on GINA in the near future. Indeed, there seemed a substantial likelihood that the 110<sup>th</sup> Congress would adjourn without the Senate having taken up this legislation that it had passed twice before by wide margins, and that – this time – the House *had* acted upon. When the 2007 version of GINA had been enacted by the House and sent on to the Senate for consideration it was subjected to a “hold” by Senator Tom Coburn (R-OK), and Coburn’s objections (based on objections to GINA raised by business interests and the U.S. Chamber of Congress) seemed to be irresolvable.

Then, in early April, 2008, there began to be indications that after a year with no visible activity, behind-the-scenes negotiation by a very persistent Senator Ted Kennedy (D-MA) – with the constant support of pro-GINA interests led by the Center for Responsible Genetics and the Genetic Alliance – was leading to a compromise that would move GINA to a vote in the Senate. On April 24<sup>th</sup> the Senate passed a modified version of GINA by a vote of 95-0. On May 1<sup>st</sup> the House passed the Senate version of GINA by a vote of 414-1, and the legislation was signed into law by President’s Bush on May 21, 2008.

Why GINA was floundering in the 110<sup>th</sup> Congress bears examination as a case study of national policy-making, a study of the manner in which interest groups affect policymaking, and a study of the agenda-setting that occurs at the federal policy-making level. In particular, GINA as a case study illustrates the value of Paul Sabatier’s Advocacy Coalition Framework as a shorthand method for understanding the policy process.

#### **An Introduction**

For citizens to have meaningful participation in the US political economy, they must find ways to act and speak collectively. Interest groups represent the freedom to join together with others to make political contributions and demands. These groups must impact the politicians and bureaucrats who serve as our policymakers, within the structure of our governing institutions.

Two concepts have come to describe our governing institutions and the intersecting activities of interest groups: political subsystems and issue networks.

The concept of the political subsystem is recognition that much of our policy-making takes place at levels below the three classical branches of American government, predominately at the administrative level. Surrounding the activities of this administrative state are issue networks, loose structures involving various bureaucrats, interested academics and professionals, and interest group representatives, all with a mutual interest in matters of policy-making within the subsystem.

As agenda-setting raises issues to the level of policy-making probability, these interested parties and interest group representatives form advocacy coalitions to stake claim to influence on the politics and policies at issue. Political and policy entrepreneurs also respond in such agenda-setting moments, to try and stake claims of influence on the policies at issue.

### **The Genetic Information Non-Discrimination Act of 2007**

There has been concern over issues of “genetic privacy” (protection against the misuse of genetic information by employers and health insurers) for over twenty-five years (Hudson, 2007). Some states enacted statutes in the 1970s that prohibited discrimination in health insurance underwriting based upon positive sickle cell and other genetic traits. Interest in these issues increased dramatically when Congress funded the commencement of the Human Genome Project in 1990. The first consideration of federal legislation – the 1990 Human Genome Privacy Act – was directly tied to the beginning of the Project. With the conception of the Human Genome Project, efforts were led by the Center for Responsible Genetics, based in Cambridge, Massachusetts, to get state legislation enacted that would prohibit the use of genetic information to deny healthy individuals insurance or employment. Broad legislation was passed in California, but vetoed by Governor Pete Wilson, who expressed concern for adverse effects on employers providing employee health insurance. Broad state legislation was adopted in Oregon, and went into effect in 1995, but even with regard to that legislation the potential for adverse employment and health insurance actions remained.

As scientific research continued throughout the 1990s leading to the completion (in 2001) of the mapping of the genome, debate continued over concerns that the ultimate predictive medical advances to be gained by the Human Genome Project would pale by comparison to the negative impacts of the use of genetic information by employers and health insurance underwriters. Some commentators pointed out that state legislation regarding health insurance underwriting would not apply to self-insured employers because of the preemption provisions of the federal ERISA statutes, and that protection under the Americans with Disabilities Act is incomplete (absent “subterfuge,” selective insurance underwriting is not prohibited discrimination).

After the collapse of the Clinton health reform efforts in 1993, and the shift to Republican control of the House of Representatives in the 1994 election, the 1995/1996 congressional term saw the introduction of new health (and genetic) privacy legislation. Four pieces of legislation introduced that session addressed issues of genetic privacy and discrimination, and the issue was addressed during committee hearings on the Health Insurance Reform Act of 1995, introduced by Senator Nancy Kassebaum (R-KS).

This last development is significant, because the Health Insurance Reform Act of 1995 was a major component of what became the Kassebaum-Kennedy Health Insurance Reform Act of 1996, ultimately adopted as the Health Insurance Portability and Accountability Act of 1996 (HIPAA). While the major purposes of HIPAA were to “reform” the small group and individual health insurance markets nationwide, this effort mostly has been unsuccessful in that policy-making sense. The most far-reaching effects of HIPAA have come from Title IV of the Act, which established the regulatory procedure and authority for the Department of Health and Human Services to adopt what became The Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule”) *if* Congress did not adopt medical privacy legislation within three years of HIPAA’s enactment on August 21, 1996.

Congress did not do so, and so during the Clinton administration, HHS proposed a Privacy Rule and released it for public comment on November 1999. The Department received over 52,000 public comments and adopted a final rule published (effective) December 28, 2000. In March 2002, under the Bush administration, HHS proposed and released for comment modifications and a proposed, new “final” Privacy Rule, and received over 11,000 public comments. The new version of the Privacy Rule was published August 14, 2002, and became the Privacy Rule effective for regulatory purposes.

In its report on the Health Insurance Reform Act of 1995 (the original Kassebaum bill) the Senate Committee on Labor and Human Resources clearly noted that for policy reasons, “health status” and “medical history” covered by the act should be read broadly to include genetic information. As such, the rule-making process that led to the Privacy Rule could have – in classic subsystem operation – resolved many of the concerns regarding genetic privacy. Ultimately, this did not happen. The Privacy Rule as adopted, after an extensive comment process, excludes a group health plan with less than 50 participants administered solely by an employer, but more importantly it excludes from protected health information “employment records that a covered entity maintains in its capacity as an employer.”

While the rules could have been drafted to address broader health insurance and employment privacy and discrimination concerns, they ultimately were not. This circumstance led directly to the introduction by Representative Slaughter (D-NY) and Senator Snowe (R-ME) of the Genetic Information Non-Discrimination Acts of 2003, 2005 and 2007. Further analysis of these events demonstrates how advocacy coalitions attempted to work within the political subsystem on both sides of the issue to influence the ultimate policy outcomes in the HIPAA Privacy Rule, and how in the aftermath, genetic privacy advocates have found policy entrepreneurs to serve as their allies in an attempt to resolve these issues at the macro-policy level.

### **GINA and the Politics of the Policy-Making Process**

In April of 2007, immediately following House passage, Senator Kennedy issued a report on the Genetic Information Nondiscrimination Act of 2007 as Chairman of the Senate Committee on Health, Education, Labor and Pensions (the HELP Committee). This extensive report tracked the origins and history of this legislation from the early 1990s forward.

The report identified the purpose of GINA as:

The purpose of this legislation is to protect individuals from discrimination in health insurance and employment on the basis of genetic information. Establishing these protections will allay concerns about the potential for discrimination and encourage individuals to participate in genetic research and to take advantage of genetic testing, new technologies, and new therapies. The legislation will provide substantive protections to those individuals who may suffer from actual genetic discrimination now and in the future. These steps are essential to fulfilling the promise of the human genome project.

As to health insurance, GINA would prohibit discrimination in health insurance in employer-sponsored group plans, health insurers in the group and individual policy markets, Medigap and state and local (non-Federal) government health plans. GINA would increase existing (ERISA) protections and supplement other protections to restrict the use of genetic information obtained by insurers in processing reimbursement. GINA would further prohibit insurers from requiring genetic testing and would restrict the use of genetic information in insurance underwriting.

As to employment GINA prohibits the use of genetic information in employment decisions by employers, unions, employment agencies and training programs. If an employer obtains genetic information it shall be considered confidential and treated by the employer as such.

These protections, the Kennedy Report notes, are about perception as much as reality; there is no real documentation of discrimination in insurance or employment, rather the “expressed belief” is documented in a series of surveys that insurers and employers *will* discriminate if they gain possession of genetic information. Some legal protections currently exist, but there are gaps in federal legislation and in the availability of existing state protections.

The HELP Committee of the Senate has been conducting hearings on genetic nondiscrimination since 1995. In 1996, as part of the passage of HIPAA the Senate prohibited discrimination against any individual enrolled in a group health plan because of health status, including health status based on genetic information.

HIPAA did not directly address medical privacy; the legislation provided that HHS must issue regulations on comprehensive medical privacy if Congress did not pass comprehensive medical privacy legislation by August 21, 1999. Congress did not do so, although the Senate HELP Committee continued to hold hearings on genetic discrimination in health insurance and employment. After the adoption of the HIPAA Medical Privacy regulations by HHS, the HELP Committee and the Senate as a whole have considered genetic nondiscrimination legislation which is broader in application than the HHS regulations, as noted in earlier discussion of the Genetic Information Nondiscrimination Act of 2007.

### **Policy-Making Theory**

Several academics (Salisbury (1992); Berry (1997); Browne (1998)) have observed that the activities of interest groups, and their impact on federal policy-making, began to shift significantly in the 1980s. Correspondingly, the actions of members of Congress and of the administrative bureaucracy have shifted significantly as well. Coalitions are much more

important than prior to the 1980s. In illustrating modern policy-making, the Advocacy Coalition Framework (ACF) is a very productive tool.

Over twenty years ago, political theorist Terry Moe posed what he viewed as a central question in American political analysis: how do you construct a proper theory of political organization and structural choice in the context of political uncertainty? As he noted, the problems are many and the task is complex. Most critically, we must attempt to explain policy change and learning through examination of the reality of political organization and structural choices (Moe, 1980).

Also twenty years ago, Paul Sabatier first described the theoretical structure he labeled the Advocacy Coalition Framework (ACF). There have been other theories of the policy process proposed and developed over the same twenty year period; policy theorizing of this type has blossomed. But through the evolution of thinking about the ACF, Sabatier and others – most notably Sabatier’s partner Hank Jenkins-Smith – have developed one analytical tool to use in answering Moe’s central questions (Sabatier, 1993; Sabatier and Jenkins-Smith, 1993; Sabatier, 1999; Sabatier and Jenkins-Smith, 1999).

### **Policy Change in the ACF**

Sabatier has a central purpose of his own in developing a theory of the policy process: “The process of policymaking includes the manner in which problems get conceptualized and brought to government for solution; governmental institutions formulate alternatives and select policy solutions; and those solutions get implemented, evaluated and revised ... Given the staggering complexity of the policy process, the analyst *must* find some way of simplifying the situation in order to have any chance of understanding it.” And so, he argues, we have a need for theories of the policy process – ways of simplifying the manner in which we look at the process of policy-making in order to better understand it.

Since the original 1988 article in which Sabatier proposed the ACF, he and Jenkins-Smith have continued to develop this “theoretical lens on public policy,” revising it every “six years or so (1993, 1999, 2006).” The ACF views the central element of policy analysis to be the examination of “policy change,” the evolution of policy-making over time. This encompasses the “formulation, implementation and reformulation of policies through the process of “policy-oriented learning. “

The locus is actors in the policy subsystem, dealing with a policy issue over a period of a decade or more. These policy actors form the advocacy coalitions that are at the center of the framework. Each coalition has a central, shared belief system, a “set of basic values, causal assumptions, and problem perceptions”, and each coalition, based upon this shared belief system, shows a “degree of coordinated activity over time.”

The primary task is to “identify the conditions under which a productive analytical debate between members of *different* advocacy coalitions is likely to occur.” This examination focuses upon three variables: 1) the level of conflict over an issue 2) the “analytical tractability” of the issue and 3) the nature of the subsystem itself.

Recognition of the stability of core belief systems and the centrality of these belief systems to policy actors is also a critical element of the ACF.

### **Policy Subsystems and the ACF**

The ACF focuses analysis first on the institutional setting for action: the policy subsystem. Focusing on this setting helps explain changes in beliefs and policies among actors, as well as the manner in which actions are “shaped and constrained” by larger governing systems in which political subsystems are placed.

A useful way of looking at governing systems is in terms of macro-policy or “high politics” systems, below which are policy or micro-policy subsystems. Major decisions that may change the political power structure in a major policy area are macro-policy decisions which the ACF has labeled external system events. These decisions often result from an inability to resolve policy issues at a lower level.

Micro-policy systems are “relatively hidden” policy systems where government policies of limited public interest, often in areas of technical complexity, arise. At this level are networks of policy actors and decentralized power structures. Communications are informal, but frequent among subsystem actors, which include interest group representatives, government officials and their staff, bureau and agency personnel, non-governmental policy specialists, and interested media members.

These policy subsystems are a form of “functional representation,” and policies of regulation or redistribution that can be resolved without resort to new macro-political legislation are addressed at this level. It is at this level that interest group conflict – through the actions of advocacy coalitions – most frequently manifests itself. A subsystem can be “dominant,” that is controlled by a small number of actors with significant influence and control over policy outcomes, with stable relations among policy actors. Alternatively a subsystem can be “competitive,” with coalitions in constant competition for control.

Recent work by political scientists of the historical institutionalism school is consistent with this aspect of the methodology of the ACF. Kathleen Thelen (1992) and Margaret Weir (1992) have argued respectively that “institutions evolve (with) shifts in the political coalitions on which they rest to inspire or compel changes – sometimes abrupt and discontinuous but more often incremental and cumulative,” and that historical attention is needed to “the organizational substructure of politics, particularly to processes of issue definition and coalition building among nonelite actors.”

These observations are particularly apt given Moe’s work on political uncertainty and structural choice. The most significant issue, Moe would argue, is “not simply to get the policies and structures (an interest group) wants in the current period, but also to design them in such a way that they have the capacity to survive and prosper in an uncertain political future.”

### **The Organizational Politics of Actors, Interest Groups and Coalitions**

Actors within policy subsystems often have multiple functions, operating as actors with political expertise and beliefs, as representatives of interest groups or other identifiable organizations

operating within the subsystem and acting as advocacy coalition members. In these capacities actors seek to influence policy, to avoid political uncertainty – or at least to cope with it – and to influence structural choices. All of these functions are influenced, in ACF theory, by each actor’s belief systems, and by the organizational and interest group dynamics that are tied to the formation of advocacy coalitions.

In the American system of politics, collective opposition to change is easiest to organize and advance. Action to effectuate change is much more problematic; it requires agreement on purpose, goals and tactics. As each of these elements becomes more specifically focused, more energy and resources have to be expended in agreement on a common purpose and a course of collective action. For instance, contrast the concerted efforts in opposition to the Clinton administration’s 1993 attempts at health reform (see Chapter 5 of Theda Skocpol’s *Boomerang: Health Care Reform and the Turn Against Government* (1997)) with the several decades of effort by earlier reformers that led finally to the 1965 adoption of Medicare (see Chapters 1-5 of Theodore Marmor’s *The Politics of Medicare* (2000)).

As the ACF has evolved, there have been attempts to address these collective action problems. According to ACF theory, collective action is enhanced by sharing the expense of a common effort to effectuate change (the “transaction costs”), and a common enemy tends to create allies. Policy change is much easier to resist or deflect than to accomplish. Regulation is more easily effected than re-distribution, and “self-contained” regulation (such as legislation of prohibition) is more easily effectuated than regulation by bureaucratic activity over time. A certain amount of political uncertainty can be removed through “self-contained” regulation, as it tends to set into place what might be called “political property rights.”

### **The Input of Policy Entrepreneurs**

Policy Entrepreneurs (PEs) are policy actors that propel political and policy changes. They transform existing coalitions and add new dimensions to policy debates in the effort to effect policy change. In many instances this function will be served members of Congress who decide to take on “national” issues, issues with a scope that extends well beyond the interests of their immediate constituency. In national policy-making it is not necessary to be in Congress to serve as a policy entrepreneur, but members of Congress are uniquely positioned to take on these tasks.

These efforts are critical in defining ideas and moving them through the policy process, looking for opportunities to effect positive policy change and seizing these opportunities when presented. PEs “frame” an issue to move it to the proper level of attention in policy-making institutions together with the interest groups that they mobilize or with which they ally. They interject “new dimensions of evaluation” into otherwise conservative policy institutions through what Schattschneider (1960) first labeled “conflict expansion.”

For conflict to “expand” to the level necessary for policy change to occur, “new definitions” of policy problems and solutions must be interjected into the policy process. New interests will be activated to participate in the policy process as the conflict over the need for policy change “expands.” In cases where subsystem control of an issue serves to inhibit policy change, PEs redefine the issue to de-stabilize subsystem control. Redefinition serves the purpose of reframing issues in familiar terms and values such as “privacy” or “nondiscriminatory” or “equitable.”

The ACF focuses much of its attention at subsystem levels of policy-making in order to provide an analytical framework that can view policy change as a product of a process that occurs over as much as a decade or more. At the same time, the ACF recognizes that policy change happens for a reason, not for its own sake. Either the activities occurring within a political subsystem gradually reflect a recognition that policies need to be changed or at least adjusted (policy learning), some significant “shock” external to the subsystem literally forces change to occur, a shock “internal” to the subsystem precipitates change through the disruption of control by a dominant coalition, or the actors within a subsystem negotiate change.

One other circumstance can cause policy change to take place: the inability of subsystem actors to effect necessary changes leads policy entrepreneurs to seek change at another level of policy-making.

When we examine the case of the Genetic Information Non-Discrimination Act, we will see an example of a perceived need for change that advocacy coalitions could not resolve at the policy subsystem (in this case administrative agency) level. This being the case, the contest over policy change has moved to Congress, in part because change has been effectuated in no other way.

### **The ACF and Interest-Group Theory**

Consideration of policy-making is helped by an understanding of two additional concepts: interest-group theory and agenda-setting. Questions have been raised about the “assumption” implicit in the ACF that collective action by members of an advocacy coalition is a given. Interest – group theory will help resolve these collective action concerns, and also help provide a link to an understanding of the nature of agenda-setting.

A connection has been formed between the study of interest groups and the ACF in the work of Andrew McFarland. McFarland’s work on the political process theory of interest groups in a pluralist system has been developed over almost forty years (1969 to present), finding its most thorough exposition in his 2004 book *Neopluralism, the Evolution of Political Process Theory*. As noted in *Neopluralism*, while a great deal of work has been done in the study of interest groups, the classic focus has been on why individuals join groups and how groups maintain an organizational structure. McFarland notes that Baumgartner and Leetch, in their 1998 book *Basic Interests: the Importance of Groups in Politics and Political Science*, argued that more theoretical work should be directed to the study of the “role of interest groups in the policy process.”

For twenty years, McFarland has argued that the best way to understand the role of interest groups in the public policy process is through the application of the theory of triadic power. Under this theory – adapted from the work of James Q. Wilson (1973) – the government policy process takes place in specific policy areas. Economic producers (P) organize to lobby for rents in their area of economic production. Countervailing interests (CV) organize to compete with and oppose the interests of P. Administrative agencies with greater or lesser autonomy (AA) control much of the policy process in each area of production, and the unit formed by these three interests creates a “power triad” in the area of production.

McFarland's theoretical work has evolved from and expanded on the concept of triadic power, which is still at the core of his work; added to this are the concepts of routine politics and high politics, and the idea that the focus of the policy subsystem "cycles" from one to the other. Routine politics is the normal, day-to-day decision-making and administration within a policy area. High politics is the political process of policy or administrative structural change.

McFarland's concept of interest-group cycles is adapted from Schlesinger's thinking in *The Cycles of American History* (1986). McFarland's basic argument is that the actions of interest groups, in addressing specific issue areas, go through cyclical phases. In periods of routine politics producer groups are commonly in control, leading to periods of excessive control and leading to popular discontent. This is followed by a transition period during which countervailing power groups coalesce, followed by a period of high politics in a reform cycle. During reform cycles countervailing power groups and autonomous government agencies respond with corrective policy-making, after which another transition phase occurs in which matters recede from the public agenda, producers maintain their constant efforts for control and another era of producer dominance follows before the cycle revolves again.

In *Neopluralism*, McFarland brings his study of interest group participation in the policy process to fruition. In doing so, he finds the ACF to be the most useful theory for purposes of studying how interest groups participate in, and influence, the policy process. Political process theory, McFarland argues, should address three questions. Who has the power here? How is policy made in this area? What are the activities of interest groups in this area? The answers, he argues, are best arrived at by recognizing the power of an analysis using the triadic concepts, agenda-setting as seen through the interest-group cycle theory, and the tools of the ACF.

In applying the ACF to interest groups, McFarland first observes that the ACF acknowledges the utility of Hugh Hecla's (1978) concept of issue networks which McFarland refocuses as "policy networks." A policy network is an ad hoc communication network of interest group participants, bureaucrats, public officials, academics and interested media members interested in a common set of policy areas. Secondly, from within a policy network, and remaining relatively stable over a long term, are advocacy coalitions. These operate to influence the processes within policy subsystems. The common beliefs that hold advocacy coalitions together are not only material interests as Sabatier and Jenkins-Smith had noted (and McFarland reinforces), but extend to core social and political values as well.

### **Agenda-Setting, Interest Groups and the ACF**

Interest-group cycles theory is a theory of political agendas. One of the driving forces in agenda-setting as it affects interest groups is the impact of political cycles on the content and timing of policy agendas. John Kingdon's influential theories of agenda-setting utilize a policy network concept as well, labeling these networks "policy communities." In Kingdon's work (1995), the existence and activities of these policy communities becomes critical to problem recognition, problem definition, the generation of policy proposals, and the selection of policy alternatives. The ultimate question becomes, is there a problem that needs a solution?

Conceptually, McFarland notes, this is consistent with ACF theory. The evolution of the perspectives of members of a policy network or community is, Kingdom recognizes, one of three

major contributors to the setting of governmental policy-making agendas, along with significant , or triggering” public events that accelerate problem recognition, and the effects of political events and processes.

Some policy communities, Kingdon observes, are close knit and some are more fragmented. A close-knit policy community shares a commonality of outlook, orientation, vision; a fragmented community tends to be relatively unstable and lack a shared sense of structure. Close-knit policy communities have a greater impact on the policy agenda, and fragmented communities less so. But surrounding each “area of policy concern” (Kingdon’s description) – the policy subsystem, where policy problems emerge and are matched with alternative policy solutions – such a community exists. And in turn, as problems emerge and rise higher on the public agenda, the impact of the interested policy community on resulting policy outcomes becomes more significant.

Kingdon poses a straightforward question: How does the list of potential alternatives for public policy choices get narrowed to the ones that actually receive serious consideration? There are, he says, two classes of answers: alternatives come to life and evolve in what he calls the “policy stream” (again, analogous to the policy subsystem), and it is policy specialists that work within a particular “policy area” (again, a subsystem) that are engaged in the narrowing process.

Kingdon describes three agenda-setting and alternative-selection processes through which policy-making will occur: “the inexorable march of problems pressing on the system,” “the gradual accumulation of knowledge and perspectives among the specialists in a given policy area,” and “political processes.” The second of these processes would originate in a policy subsystem. Policy-making through the other two processes would originate at the levels earlier described as macro-political. At all three levels McFarland’s cycles of excess and reform, routine and high politics, will occur.

When Congress is involved in the policy-making process some additional agenda-setting elements will apply as well, including some elemental agenda differences in the Senate and the House. These will become relevant to the analysis in due course.

### **Agenda-Setting in the U.S. Senate**

One of the early, pre-eminent observers of interest groups was Jack Walker (See “The Origin and Maintenance of Interest Groups in America,” *American Political Science Review* 77: 390-406 (1983). In his 1977 article, “Setting the Agenda in the U.S. Senate: A Theory of Problem Selection” he addressed the significant restrictions on the opportunities for members of the US Senate to move individual agenda interests. These opportunities are restricted by a variety of factors:

The Senate's capacity to shape its own agenda is increasing, but members are still able to exercise little discretion over the scheduling of items for debate. Much of the business transacted by the Senate is either mandated by the Constitution or required for the maintenance of the vast federal establishment. Each year a budget must be assembled, innumerable amendments made to existing statutes, and presidential appointees confirmed or rejected. In addition, the daily schedules of

individual Senators are jammed with activities – subcommittee hearings, talks with constituents, lobbyists or reporters, roll calls on the Senate floor, consultations with staff members – that originate with other people and are virtually unavoidable. Little time and energy remain for reflection or the promotion of new legislative departures (Walker, 2007).

In addition, Walker points to what he labels “sporadically recurring problems” – issues that must be addressed because of prior legislation (typically reauthorization items) or administrative oversight. The Senate, Walker observes, tends to respond even more than the House to the exigencies of the moment, leaving little opportunity to address the type of priority that GINA represents: establishment of broad policy statement, particularly in the absence of a perceived crisis. Walker has posited three “features or conditions,” the presence of which would tend to significantly increase the probability of a legislative item successfully appearing on the Senate’s discretionary agenda: actual (not theoretical) impact on large numbers of people, convincing evidence that a serious problem will be addressed (again, actual not theoretical) and an easily understood solution exists, has been identified and is being adopted.

If all three of these desirable characteristics are clearly present, the likelihood increases significantly that the matter will get space on the Senate’s agenda, though this is by no means guaranteed. Matters not meeting all of the observed elements have virtually no chance. Senator Kennedy’s report, discussed earlier, virtually establishes the failure of GINA to meet Walker’s observed agenda-setting standards: the problem that GINA was designed to address was prospective and theoretical, not representative of a clear and present necessity.

### **Looking at GINA with a Theoretical Lens**

The Council for Responsible Genetics is a genetic professionals group formed 25 years ago to “foster public debate about the social, ethical and environmental implications of genetic technologies.” As such, it is an advocacy coalition with a set of beliefs generally consistent with efforts to “work through the media and concerned citizens to distribute accurate information and represent the public interest on emerging issues in biotechnology.”

A major player within the Council for Responsible Genetics, and in seeking passage of GINA, was the Genetic Alliance. In describing itself, the Genetic Alliance says that it is “a coalition of more than 600 advocacy organizations serving 25 million people affected by 1000 conditions.” The existence of the Genetic Alliance is premised on the legitimacy of the coalition perspectives discussed thus far. Founded 20 years ago, the Genetic Alliance was intended to facilitate the formal linkage of what has grown to over 600 organizations, each of which constitutes an interest group dedicated to building the capacity of these organizations to address issues of concern to “the genetics community.”

Many of the advocacy organizations that had joined the Genetic Alliance had been formed to link together people with a personal interest in defined genetic diseases that - while devastating in their effects on sufferers – impact very limited portions of the US population. By themselves these groups had limited resources and found it virtually impossible to impact broad public policies. But 20 years ago the organizers of the Genetic Alliance could see the potential for

significant developments in genetic research, and the attendant emergence of a wide array of policy issues that would be of significance to each of these smaller advocacy groups.

The Genetic Alliance openly avows “leveraging the voices of its members in formal communication with governmental officials and agencies” and the “application of organizational network theory” in advancing the interests of its member advocacy organizations. The Genetic Alliance is literally an advocacy coalition as defined by Sabatier, organized around a central, shared belief system. The Alliance has enumerated this shared belief system, in its mission statement, its statement of its central philosophy and consistently in its position statements over the course of its history.

Both of these coalitions joined in an open fight against what they labeled “genetic discrimination.” What is “genetic discrimination” as these coalitions have defined it in this policy dialogue? An employer’s use of genetic information to make hiring and firing decisions would be genetic discrimination. An insurance company’s denial of coverage based on genetic test results would be genetic discrimination. These coalitions centered themselves around a belief that genetic information must not be used to discriminate in insurance underwriting or in employment decisions.

GINA was the subject of discussion and public dialogue among many of the small groups and the researchers which were first concerned about genetic discrimination, and the establishment of genetic privacy, in the late 1980s and early 1990s. In classic fashion issue networks emerged surrounding the genetic research that was being done at the time, as it began to show promise and receive public funding. Through the development of policies by the Equal Employment Opportunity Commission (EEOC) under the Americans with Disabilities Act, the enactment of HIPAA, the medical privacy Final Rules under HIPAA and the debates over GINA 2003, 2005, and 2007, advocacy coalitions have operated within classic issue networks centered on genetic issues.

### **The Continuing Call to Arms**

The ACF is a model that supports, and conforms to, much of the best work on interest group theory, in that its primary focus is on the coalition-building that is most influential at the administrative level. Moreover, as a model of the policy process, the ACF emphasizes the difficulty of influencing policy-making at the Congressional level by any means, including coalition-building. As long observed by political observers, coalition-building can best marshal forces at the Congressional level to create opposition to the adoption of new policies.

The interest groups that had set passage of GINA as a priority had to continue to try and influence Congress in a positive way. But as interest group theorists and application of the ACF demonstrate, the task at hand was a daunting one. Robert Salisbury and Jeffrey Berry, in contemporaneous articles in 1989 and 1990 both observed that the sub-governments and iron triangles that political scientists had observed from after World War II until the mid-1970s had begun to disappear in the early 1980s, replaced by the issue networks discussed earlier. And both observed, as Salisbury put it, that the result was a substantial increase in interest group activity in Washington with less, not more, impact on Congressional policy-making. And as William P. Browne documented in the early 1990s, a further result has been that members of Congress have

reverted, if you will, to being most concerned about constituent issues and not broad policy issues that don't sell "back home."

These were the impediments that the proponents of GINA faced. Attempts to gain passage of the type of broad, general policy-making that GINA represented are daunting, even if the nature of the policies in question would seem to be lacking in controversy.

### **How GINA Came to Pass into Law – and What We Can Learn**

The proponents of legislation that would create a national policy of genetic privacy and prohibit genetic discrimination mounted what turned out to be an almost two-decade effort to accomplish this end. First, those that had similar interests in the passage of such legislation began public dialogue about the issue in classic issue networks. There was opposition over the years from business and insurance interests, though not in a consistently organized fashion due to the lack of any apparent agenda-setting event that would catalyze an effort to make genetic discrimination issues emergent.

Still, citizens groups concerned about a myriad of possible genetic-based medical advances aligned with researchers concerned with the need for research volunteers who were not inhibited by issues of genetic discrimination to argue for protective legislation. The arguments were first centered at the political subsystem level of administrative agencies (EEOC, HHS), and then moved to the level of Congressional macro-politics as the proponents gained more and more converts, eventually reaching to members of Congress.

This is the policy change that Sabatier and McFarland have theorized about in arguing the merits of the ACF as a method for analyzing the evolution of public policy. An examination of the long development of the policy momentum that led to the passage of GINA in the 110<sup>th</sup> Congress would seem to bear out the legitimacy of the ACF.

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## Genetic Services Policy Project Final Report

### **Appendix C: Case Study of Intermountain Healthcare’s Clinical Genetics Institute**

#### ***Why the Case Study Approach?***

The field of genetic services is a relatively new one; some organizations are embracing rapid growth in this area while others are moving more slowly. In such a new and varied field where there is as yet no standard response, it is helpful to use a case study approach to examine clinical integration of genetic services. The primary advantage of this approach is that the smaller unit of analysis allows for an exploration that is more detailed, more specific, and therefore more meaningful. It is also useful in facilitating examination and analysis at the level of the organization. Our purpose is to study the integration of genetic services into clinical settings.

In selecting a site for a case study, we sought organizations that are intentionally integrating genetic services into their clinical pathways. Intermountain Healthcare, located in Salt Lake City, Utah, provides many useful characteristics for a case study. The city itself, and Utah generally, is particularly conducive for such research because of several factors: the strong cultural interest in family history, the availability of an extensive body of medical records linked to family pedigrees, public willingness to participate in biomedical and public health research, investment in biotechnology as an economic base, and the presence of the University of Utah and various commercial enterprises. “Because Utahns tend to have large families and keep extensive genealogy records, they are ideal partners for investigating human genetics” (Eccles Institute of Human Genetics website). In addition, the traditionally low rates of tobacco and alcohol use and relatively homogenous demographics of the population minimize variation of many of environmental and socioeconomic contributors to disease and provide “a much cleaner data set,” according to University of Utah instructor Deborah Neklason. “It means [researchers] can more easily separate genetic influences from other, lifestyle-related causes of illness” (Sussingham).

Intermountain Healthcare was selected as the site of the case study largely because it is a leading integrated health care system that is interested in genetics. Intermountain began exploring means of integrating genetic services in 2004, culminating in the creation of the Clinical Genetics Institute (CGI). We chose to use CGI as the basis for a case study in part because of its surrounding conditions and a commitment by top administrators to integrate genetic services in an explicit program. In addition, Intermountain’s structure as a payer and provider allows for the study of multiple facets: as the payer and provider, as the payer for other providers, and as the provider for other payers. The fact that Intermountain offers both clinical care and insurance products provides an opportunity to study the integration of genetic services from the perspectives of health care providers, hospital administrators, and payers.

#### ***Narrative about Utah and Intermountain***

The state of Utah is an interesting outlier in statistical measures, a state in which the population tends to be younger, more educated, and healthier in many regards than the national averages. The population has a higher percentage of Caucasians—in fact, Utahns of northern and western

European ancestry were the population chosen to represent Caucasians in the International HapMap Project (National Human Genome Research Institute, 2006)—a strong cultural interest in genealogy and willingness to participate in research, and widespread economic investment in the life sciences and biotechnology industries. Salt Lake City is home to the state government, a public university, many for-profit businesses and nonprofit organizations, the Church of Jesus Christ of Latter-Day Saints (often referred to as the LDS or Mormon Church), and Intermountain Healthcare. The teachings of the LDS Church—the importance of genealogy and family history, healthy living, education, and volunteering—are reflected in many of these anomalous trends.

While traditionally home to a relatively homogenous citizenry of Caucasian residents, conservative values, and lower than average cost of living and wages, things are starting to change. Immigration, cost-of-living, and salaries are increasing (Key Informant A, 2006), and liberal views are becoming more common in the urban area (Key Informant B, 2006). Salt Lake City, the capital, seems to be changing more quickly than the rest of the state. Divides in political views, coupled with the competing priorities of life sciences, infrastructure development, and education, may lead to tensions in the future over the proper role of genetic services.

The state government is conscious of Utah's relatively high birthrate and how that affects both the recently expanded newborn screening panel and Medicaid budgets. Medicaid finances nearly one-third of the state's births, which is lower than the national average of more than 40 percent (Statehealthfacts.org website). Disproportionate shares of Medicaid enrollees in Utah live in a few outlying communities comprised mainly of members of the Fundamentalist LDS Church. FLDS members often practice plural marriages (polygamy) and family intermarriage. The twin towns of Hildale, Utah, and Colorado City, Arizona, have higher rates of poverty than their state averages: 33 percent of city residents receive food stamps, compared to less than 5 percent in Utah and 7 percent in Arizona (Zoellner, 1998). The cities also have the world's highest incidence of fumarase deficiency, a rare genetic disorder that causes severe mental retardation, which genetics experts attribute to the practice of cousin marriage (Szep, 2007).

There is growing interest in research into birth defects and the genomic contribution to chronic disease; the University of Utah is conducting bench science in this area. In 2006, the U.S. Centers for Disease Control and Prevention awarded a \$2 million, five-year grant to a new Intermountain Center of Excellence for Infection Prevention Strategies (INTERCEPT), a partnership between Intermountain Healthcare, University Health Care and the Veterans Affairs Salt Lake City Health Care System, for a joint study on health information technology and infection prevention (University of Utah, 2006).

Intermountain Healthcare, with its companion insurer SelectHealth, is one of the largest health systems in Utah, and one of the top-rated integrated health care systems in the country. Despite occasional concerns about market share and antitrust regulations, the state generally perceives Intermountain in a positive light. Given a growing national interest in genetics in the last decade, Utah's rich and unique genetics-related resources, and an integrated data system, Intermountain Healthcare saw an opportunity to develop genetic services capacities with an emphasis on prevention, clinical utility, and cost-effectiveness.

### ***The Clinical Genetics Institute***

Intermountain Healthcare has been working to integrate genetic services into the broader health care delivery system through its Clinical Genetics Institute (CGI). In spring of 2004, several Intermountain executives began discussing the idea of such an institute. The Clinical Genetics Institute was the brainchild of three Intermountain Healthcare physicians and was supported by the administration. Some touted genetics as the “next big thing,” while others described it as “the ultimate preventive medicine” (Key Informant C, 2006). Despite an enthusiastic task force at the beginning of the process, within a year one of the three promoters passed away and one retired from active practice. Although the institutional support for CGI remained, the clear vision and focused energy were lost. The administration hired a director with prior experience in genetics clinics, who brought his own vision of how best to integrate genetic services.

CGI’s past: During key informant interviews in the summer of 2006, we discovered that there is little consensus on CGI’s original purpose and that its role within Intermountain was not clearly articulated in the beginning. One member of the senior leadership team recalled that the purpose of CGI was to do genetic research and discovery to strengthen clinical care programs, and to serve as the broader base of genetics information. Another leader believed CGI was created both to serve as a central genetics resource for Intermountain and to evaluate genetic tests.

CGI in the present: We first interviewed key informants during the summer of 2005. Little was known about the Clinical Genetics Institute, which had only begun a few months earlier. During our expanded follow-up interviews in the summer of 2006, we noted no new large-scale activities. There was, however, the addition of the Adult Genetics Clinic, a monthly clinical diagnosis activity within CGI. We found that, within and outside of Intermountain Healthcare, knowledge of CGI’s activities and purpose was limited and often conflicting.

In an attempt to evaluate whether the CGI had a significant impact on clinical services, claims data were also reviewed. Specifically, data were compiled based on CPT codes (service codes) for genetic testing, genetic counseling and consultation for conditions consistent with the clinical case studies used in this project (e.g., breast/ovarian cancer, cystic fibrosis, sickle cell disease and multiple congenital anomalies) over a three year period (calendar years 2004-2007). Analysis of these data revealed no significant changes in service utilization or claims over this time frame. It may be that more time would be necessary to see any service trends and/or these data accurately reflect the changing focus of the expectation of the CGI.

Although most people within Intermountain Healthcare spoke highly of CGI’s leadership, few were able to articulate its specific activities, and many outside stakeholders had not heard of CGI. One Intermountain senior manager thought CGI’s primary purpose was to evaluate the counseling and payment issues surrounding new genetic tests and to develop protocols for clinical use. The respondent, who did not know any details, thought of CGI as a “system interface” for genetic activities and speculated that it might be working with the oncology program. The respondent believed that CGI’s impact lies in helping to surface the future of genetics across the Intermountain system, facilitating genetic counseling in the oncology program, helping people understand the need for guidance regarding new genetic tests, and serving as the impetus for enacting that structure. The staff of CGI saw its role as promoters of genetic services, though the original plan for CGI was to provide critical technology assessment.

When asked whether CGI is meeting expectations, a senior manager responded with uncertainty as to what to expect, noting that things are moving “at a snail’s pace” (Key Informant C, 2006). However, the manager also recognized that it can be difficult to get people involved and was pleased with the progress CGI has made so far. Another manager, responding to the same question, answered that CGI seems to be consistent with company expectations but was not personally sure what to expect. Representatives of the affiliated insurer, SelectHealth, seemed to have a more specific idea of CGI’s activities, a view that was not echoed by other groups and individuals. They saw a distinction between the types of genetic test analyses performed by CGI and SelectHealth. There is a difference between the payer perspective of cost-effectiveness and the clinical perspective of clinical utility; SelectHealth worked with CGI to align benefit design with clinical needs. SelectHealth representatives described their relationship as “cordial and collaborative” (Key Informant D, 2006). Others with whom we spoke did not seem to know what CGI does. Health plan physicians saw CGI’s role as educating physicians once technology assessment decisions were made.

CGI’s future: One senior leader envisioned CGI playing a larger clinical and basic research role, performing crosscutting education, and conducting technology assessments in the future. Another manager predicted that CGI’s role would be as a collaborator, potentially with the University of Utah or Sorensen Molecular Genealogy Foundation, and would offer education “in a big way” (Key Informant C, 2006).

The three original promoters of CGI envisioned that it would conduct research to guide the policy of Intermountain and SelectHealth in using new genetic tests. The director, however, developed a broader set of activities for CGI that was more in line with his interests and experience; the shift in focus coincided with the center’s change in leadership. Without the involvement of two of CGI’s original promoters, the driving impetus became less immediate and the focus less clear, leaving CGI staff to figure out their place within the broader organization. As of the 2006 interviews, CGI had not reported to the Board formally and had only talked informally with an immediate supervisor on a somewhat regular basis. The supervisor had a generally positive view of CGI, but did not keep track its actual activities. As in most organizations, this case illustrates a few basic principles: communication is key; commitment of leadership is necessary; and the mission and vision must be clear and consistent.

CGI faces an organizational/structural difficulty because of the fact that most clinical programs at Intermountain are organized vertically, yet CGI is conceptually horizontal, cutting across many programs. Its current strategy is largely to be present, to attend meetings and present ideas. In particular, CGI has recognized the inadequate supply of genetic counseling and has been a champion of additional genetic counselor capacity.

The intent of the case study was to analyze how one organization worked to integrate genetic services into the health care delivery system. By examining both the Clinical Genetics Institute’s challenges and opportunities, other organizations will be better able to anticipate potential obstacles, capitalize on opportunities, and differentiate which factors are specific to CGI and which are more universally applicable.

### ***Challenges for the Clinical Genetics Institute***

If the Clinical Genetics Institute may be viewed as a fledgling organization (though the Intermountain system itself has been in existence for decades), its staff has faced challenges similar to those of many new initiatives. Such issues include the commitment of leadership, the clarity and consistency of the mission and purpose, organizational structure and funding, communication with key stakeholders, and external factors such as the economy, legislation, and community demographics.

Internal Challenges: Among the primary challenges in a new initiative are to retain leadership support and involvement; to balance limited resources with other initiatives within the organization; to possess the full range of necessary expertise; and to negotiate disagreements with internal and external stakeholders. CGI had a strong start because of the enthusiasm of its proponents and an executive-level decision to support the start-up of CGI. Once the original backers of CGI left Intermountain, however, much of the drive dissipated. The administration did not curtail CGI, but it did not actively support it either, causing (allowing) CGI's staff to fly under the radar and work to create a niche for themselves.

The diminished institutional support for CGI did not necessarily reflect an actual reduction in interest; rather, competing initiatives garnered more attention and fiscal resources. For example, Intermountain invested in a new data system and began construction of a new flagship hospital, both of which diverted significant available funding and administrative resources. The creation of Intermountain's new data system limits the addition of family history information in the current medical record system; this has hindered CGI's plans in delivering genetic services. Additionally, CGI's resources are limited by having a small staff. Though staff members display evident enthusiasm and have relevant experience, their expertise covers only a part of the broad scope of operating a clinical genetics institute within an integrated health care system. If, in accordance with the original vision, CGI were to develop new models of education and outcomes research, it is questionable whether they would have sufficient resources and background to fully develop the research and implement its findings.

Some disagreement exists, both external and internal to Intermountain, regarding the purpose of CGI. Some perceive an overlap between CGI's mission and activities that other groups are already performing. There is also disagreement about whether Intermountain needs increased genetic counseling capacity, and where the additional genetic counselors would be located administratively and physically. The delicate balance of collaboration and competition between Intermountain Healthcare and the University of Utah's medical facilities further complicates this disagreement. The lack of clear purpose and uniform stakeholder understanding hampers efforts.

The Clinical Genetics Institute does not currently have an established, measurable set of outcomes to justify expenditures and make a case for expanded capacity. The units of assessment—number of clinical services, percent increase in patient volume, reports of technology assessments, etc.—are yet to be determined, but will soon be needed to be able to assess its impact and strategically plan for the future.

External Challenges: Other challenges arise outside of the organization's direct control, such as legislative actions, regulatory changes, and the culture of the broader community. CGI and

Intermountain Healthcare have not been immune to these challenges. Intermountain, as the largest provider of health care services and health insurance in the state of Utah, has faced periodic charges of antitrust violations. Although a 2006 legislative task force reported that Intermountain did not use unfair business practices, sensitivity about its market share remains (Argue et al., 2006). Partially in response to those concerns, Intermountain's health care and insurance plans changed their names in 2005: Intermountain Health Care and IHC Health Plans became Intermountain Healthcare and SelectHealth. One of Intermountain's challenges will be to remain cognizant of the external pressures that precipitated the renaming.

Like all health care organizations, Intermountain must operate in a changing regulatory environment. Utah is one of only a few states in the country to require genetic counselor licensure, which creates new opportunities and issues for reimbursement for licensed counselors. The original version of the law required genetic counselors to have graduated from a currently accredited program. This proved problematic, however, for those who attended a program that was accredited at the time of their graduation but has since lost accreditation or ceased operations. The law was later revised to allow for a temporary license provision.

The state legislature voted down a so-called "any willing provider" bill in 2005. Approximately half of all states have "any willing provider" laws. The law typically means that health insurers must accept contracts with any willing health care provider in the geographical service area, as long as the provider is "qualified under state law" and "willing to meet the terms and conditions set forth by the insurer" (National Conference of State Legislatures).

Intermountain's insurance side, SelectHealth, offers three network HMO plans and a fourth preferred provider organization (PPO) plan. The enactment of an "any willing provider" law would have altered the structure and dynamics of SelectHealth's plans by mandating that it open its provider networks to any willing provider.

Finally, CGI is conscious of the opportunities and limitations posed by operating within the bounds of what is culturally acceptable in Utah. Staff personnel remain mindful of the connection between genetic services and reproductive decision-making, as well as the predominantly pro-life culture in the state.

### ***Opportunities for the Clinical Genetics Institute***

Internal: The Clinical Genetics Institute has several opportunities, particularly the continued support of an administration that sees CGI as a long-term investment. CGI recently reconstituted its advisory board, creating an opportunity to clarify its mission and define its message. In addition, although the new flagship hospital, heart and lung center, and trauma and critical care facilities compete with CGI for Intermountain's internal resources, they also draw external attention to Intermountain and provide more opportunities for clinical research and integration. There are also opportunities for collaboration with the genetic counselor program at the University of Utah and the state Genetics Advisory Committee.

Another advantage is Intermountain's structure. With clinics across the state and the rise of telemedicine, CGI is well positioned to deliver clinical genetic services and counseling over a broad geographic area. Because Intermountain is an integrated system, there is a seamless

transition from primary care to specialty follow-up care. This may facilitate better integration of genetic services. Intermountain also has mechanisms for integration and provider education that surpass many other organizations. With this system already in place, CGI can widely disseminate its content more easily than if it had to create new educational opportunities.

CGI could serve as an intermediary player, encouraging Intermountain and UU to move from competition to collaboration. One interviewee suggested that CGI could provide guidance regarding insurance coverage decisions for genetic services; currently, if the UU sees an Intermountain patient, SelectHealth generally will not pay for it.

External: Utah state government activities may provide opportunities for the Clinical Genetics Institute. The reconstitution of CGI's governing body coincided with that of the state Genetics Advisory Committee. The activities of the two may provide fodder for discussions and recommendations. Additionally, the requirement for genetic counselor licensure provides opportunities to advance the field of genetic counseling, which is a key component of CGI's work. Licensure allows for the possibility that genetic counselors could bill directly for their services, which may increase reimbursement and attract more genetic counselors to the state. An influx of genetic counselors would increase opportunities for collaborative training and delivery, particularly if genetics becomes an important component in all medical specialty training programs. The resulting billing information may provide data for research into how genetic counseling is used, whether it is cost-effective, and what other effects it may have.

CGI may be in a unique position to create a business case for providing genetic services in general and genetic counseling in particular. Because of the research and clinical practice possibilities, CGI and Intermountain could provide national models for effective genetic services integration.

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## Genetic Services Policy Project Final Report

### **Appendix D: The Emerging Landscape of Genetic Services**

#### **Introduction**

Historically, medical genetics services focused on “genetic” diseases – diseases for which genetics is the major causal factor. Increasingly, however, genetic information is becoming relevant for common complex diseases, and provides therapeutic opportunities unrelated to inherited risk. This shift has implications for the work of genetics professionals and the knowledge needs of other health care professionals. Because many new genetic tests and technologies are already available for clinical use and many more are expected to become available in the near future, this shift also poses important challenges for health care policy-makers.

Genetic services are offered in several different locations within the health care system. For the most part, however, they are currently a component of specialty referral services. A significant portion of genetics services occur in designated medical genetics clinics, often located in academic medical centers. Major factors determining where services are provided are the clinical manifestations of the disease for which services are provided, the nature of the available treatments, current screening recommendations, and reimbursement policies.

Many early innovations resulting from genomic research will enhance currently existing genetic services, creating pressure on genetics professionals to expand their availability or delegate certain services to other health professionals. Increasingly, genomic research will also provide tests and technologies that are most appropriately integrated into primary care and other parts of the health care system. Some will challenge the current delivery of health care in fundamental ways.

#### **Current genetic services**

##### Services prompted by clinical presentation or the nature of treatment

Each medical specialty provides diagnosis and treatment of a subset of rare genetic diseases, based on their clinical presentation. Retinal dysplasias are seen by ophthalmologists, hereditary ataxias are seen by neurologists, porphyrias are seen by gastroenterologists and dermatologists, and so on. Because these disorders are rare, even within specialty care, specialists with the appropriate expertise are often located in academic medical centers or other sites of tertiary referral care. Many of these centers also have specialized units that provide care for genetic disorders that do not fall readily into a single specialty domain, such as metabolic disorders and congenital malformations. Some genetic diseases are both common enough and unique enough in their care requirements to have dedicated clinical units; examples include specialized clinics for patients with cystic fibrosis, sickle cell disease, hemophilia, and the muscular dystrophies.

The pathway to care is influenced by the type of symptoms and by treatment options. Some disorders are highly treatable – for example, multiple endocrine neoplasia type 2 (MEN 2) and hemophilia. For others, treatment has steadily improved but continues to fall short of definitive control – for example, cystic fibrosis. Treatment for many genetic disorders is still predominantly palliative – for example, the muscular dystrophies. Referral for discrete components of care may occur, such as surgery for MEN 2. Care may sometimes be provided through a partnership between a specialty center, genetics professionals and the primary care provider. In this model, the patient may be seen periodically – e.g., once a year – in the referral center for consultation, with day to day care provided by the primary care provider.

#### Services prompted by screening

- (1) *Newborn screening* Some genetic disorders require the initiation of treatment in infancy, with good prospects of a healthy outcome if treatment is started early enough. This reality led to the creation of state newborn screening programs, to identify affected infants prior to the onset of symptoms and refer them to the appropriate specialty care.
- (2) *Prenatal screening* Several genetic tests are currently recommended for routine prenatal screening, including maternal serum measures to identify increased risk for neural tube defects and Down syndrome; carrier screening for cystic fibrosis, sickle cell disease and thalassemias; and carrier screening panels for women of Ashkenazi Jewish ancestry. These tests, when positive, may be followed by prenatal diagnostic testing to determine whether the fetus is affected.

#### Genetic counseling

Genetic counseling is an important adjunct service in all of these clinical settings. After a diagnosis is made, whether by clinical presentation or as a result of screening, genetic counseling provides families with the opportunity to learn about the inheritance pattern of the disorder, the risk for other family members, and genetic testing options. Reproductive genetics is an important focus of genetic counseling services. For genetic disorders that are severely disabling and lack definitive treatment, some parents are interested in the use of genetic testing to prevent births of affected children. Clinical geneticists and genetic counselors assist parents to understand their reproductive options. Carrier tests for many autosomal or X-linked recessive diseases can identify couples who are at risk to have an affected child. Prenatal diagnosis is available for many of these genetic diseases, to determine whether a fetus is affected. These tests can be used to inform the use of selective abortion or assisted reproductive technologies, including pre-implantation genetic diagnosis to prevent the birth of a child with specific genetic disease. Care is provided through collaboration between clinical genetics and perinatal medicine; often genetic counselors are located in a prenatal clinic to assist in the delivery of these services.

Genetic counseling can also assist in identifying affected family members so that appropriate health care can be provided. For example, if a young woman with breast cancer is determined to have a BRCA mutation, other family members can be tested to determine whether they have inherited the mutation, so that appropriate cancer screening or prophylactic surgery can be offered. Similarly, a diagnosis of hemochromatosis should prompt evaluation of other family

members at risk – in particular, siblings of the affected person – so that appropriate phlebotomy treatment can be initiated.

### **Evolving role of the genetics professional**

The American College of Medical Genetics defines medical genetics as “a branch of biomedical science that studies the relationship between genes and health,” clinical genetics as “a primary medical specialty focused on health and illness of individuals and their families,” and a clinical geneticist as “a physician who specializes in genetic disorders and conditions”. Genetics professionals include clinical geneticists (MDs with clinical genetic training), nurse geneticists (RN), genetic counselors, who may have MS, or PhD degrees, and laboratory geneticists.

The role of the clinical geneticist has evolved over time and encompasses a range of clinical roles (Table, page 9). The typical example of a clinical geneticist is that of a dysmorphologist evaluating children with developmental delay and/or birth defects for genetic disorders. In fact, the clinical geneticist can also be involved in prenatal diagnosis, diagnosis and treatment of metabolic diseases, diagnosis of single gene disorders, evaluation of both children and adults with neurologic and neuromuscular diseases, cancer, or infertility, and evaluation of genetic traits involved in common diseases (Williams, 2001).

In the past, the focus of clinical genetics was to help establish a diagnosis for patients with rare genetic disorders and conditions. Even in the absence of treatment, a diagnosis can provide some benefits to the patient, including the elimination of unnecessary tests, risk information for reproduction and family members, and prognostic information (Williams, 2001). Except for metabolic diseases, treatment was not part of the role of the clinical geneticist. In recent years, clinical geneticists have become increasingly involved in the management of the patients they diagnose. There is also reasonable hope that the research focused on single gene diseases will bear fruit in more definitive treatments for at least some diseases. The recent publication of guidelines and monographs about the management of genetic syndromes speaks to this growing role (Cassidy and Allanson, 2004; Trotter, 2005; Kishnani, 2006). Clinical geneticists now help coordinate long-term follow-up, periodic evaluation for known complications, and supportive treatments.

Not surprisingly, the earliest clinical benefits of the Human Genome Project are in the form of more and better tests for genetic diseases. Diagnosis is becoming increasingly more accurate with the aid of DNA-based testing. The increasing availability of diagnostic tests for genetic disorders makes it increasingly impractical for the clinical geneticist to be involved in the provision of all such tests. Some of these tests have already been taken up by non-genetic specialists, like BRCA1/2 testing by oncologists or HNPCC testing by gastroenterologists. To ensure that the use of genetic tests by non-genetic specialists is successful, these providers need to be knowledgeable about the most common genetic conditions they face, about the interpretation of the genetic tests they use, and about the type of information and counseling needed when providing such tests (Greendale, 2001). Some specialty clinics have hired genetic counselors to provide counseling to patients undergoing genetic tests, although genetic counselors are not trained to diagnose conditions.

## Emerging genetic tests

Clinical geneticists have not typically been involved in what is now called “genomic medicine,” i.e., the use of risk information about genetic susceptibility to disease or pharmacogenomic profiles in practice. Although these tests provide information with potential implications not only for the patient being tested but also for his/her family members, such tests are usually not accompanied by genetic counseling. Practice standards, including the evidence needed to justify test use, are not yet established, nor is the role of genetics professionals, either in setting practice standards or in assisting other clinicians by means of educational efforts, consultation, or counseling.

### Pharmacogenomics

Pharmacogenomics represents one of the most promising clinical applications of genomic research. Testing for gene variants associated with drug response has the potential to improve both the safety and the efficacy of drug treatment. In the most widely anticipated use of pharmacogenomics, testing would occur before prescribing commonly used drugs to assure that the appropriate drug is chosen based on the patient’s likelihood of adverse reactions or response. The level of evidence required to justify routine use of pharmacogenomic tests is not yet established; in particular, there is controversy concerning the need for randomized controlled trials to assess the outcomes of pharmacogenomically assisted prescribing. Once this approach is determined to be useful, clinicians will need to be educated in its use.

An important question in the evaluation of pharmacogenomic testing is whether it poses significant personal or social risks. Testing is focused on informing drug prescribing, but many pharmacogenomic tests provide ancillary information, defined as information unrelated to drug response, such as predisposition to diseases for which the individual is not currently seeking treatment or does not manifest symptoms, or prognostic information that is not informative for treatment. The implications of this information for informed consent or appropriate use of pharmacogenomic tests is not yet resolved. Conceivably, some pharmacogenomic tests could pose sufficient risks to make genetic counseling a consideration.

Some pharmacogenomic tests will be introduced as a component of a new therapeutic. An example is testing *Her-2-neu* amplification in breast tumor tissue, in order to determine if the patient is a candidate for Herceptin therapy. To the extent that testing measures acquired as opposed to inherited genetic change, as in this example, the potential risks of the testing process are reduced (Haga and Burke, 2008).

### Gene expression profiling

Gene expression profiling represents another new genetic testing strategy. As with testing for *Her-2-neu* amplification, this testing approach has been used to measure acquired genetic change. For example, Oncotype Dx and MammaPrint are two currently available tests that measure gene expression in breast tumor tissue, in order to predict likelihood of breast cancer recurrence. As with pharmacogenomics, the appropriate evaluation of these tests is not yet resolved. Oncotype Dx has been proposed as a means to determine which women with early stage breast cancer require chemotherapy, based on large scale retrospective analyses. The need for prospective evaluation of testing outcomes is a matter of debate. This form of testing is

presumed not to involve genetics professionals; however, it is conceivable that future gene expression profiles could measure inherited rather than acquired variation, with broader genetic implications.

### Genetic susceptibility testing

Genetic susceptibility testing also raises questions regarding evaluation and appropriate use. When is genetic risk information useful and when is it harmful? Who decides? In light of the large volume of risk information that will flow from genomic research, these questions are critically important for health care policy. An important question is whether susceptibility tests should be viewed as helpful information, evaluated primarily for their predictive value, versus measures of risk that should be used only if they are proven to lead to interventions that improve health outcomes. Factor V Leiden, one of the few genetic susceptibility tests now in clinical use, illustrates the challenge: the test is widely ordered despite the fact that there is no evidence to suggest that FVL testing should routinely direct clinical management or will improve health outcome. This observation could be interpreted to mean that the test is being used inappropriately, or that it is providing information that clinicians and patients find of value. In addition, FVL testing will rarely identify individuals with very high inherited risk (e.g., FVL homozygotes), for whom specific therapy and referral to genetic counseling may be appropriate.

Consideration of genetic susceptibility testing leads to fundamental inquiries about the purpose of health care, incorporating how broadly “health” and “health outcomes” should be defined, and the limits that should be set on the use of health care resources. Genetic susceptibility testing also poses questions about delivery of care, including the degree to which current systems of primary care can be better focused on prevention. And to the extent that prevention can be made a central focus of primary care, rigorous questions will need to be asked about the value added by knowledge of genetic risk: e.g., if the health care system were already maximizing efforts to promote healthy diet, how would knowledge of genetic risk for diabetes or coronary artery disease assist patients or providers?

Storage and retrieval of genetic susceptibility information also pose challenges. The information will need to be readily accessible in all places where a patient receives health care if it is to be maximally effective. At the same time, appropriate privacy protection will be essential.

### **Provision of services**

As discussed above, genetics professionals provide a range of services to assist families and other clinicians to care for patients with genetic diseases (Table). Patient care for rare genetic diseases is likely to be best in centers with substantial experience treating these disorders. Often the specialty center is the only source of care within a state or large geographic area. The provision of genetic services relies on appropriate referral to genetic services, effective coordination of specialty services, and interdisciplinary management of patients with genetic disorders.

Since genetics professionals are not involved in primary care, they rely on other providers for patient referral. The provider seeing the patient for an initial complaint must recognize the

possibility of a genetic disease and know where to refer the patient. For this reason, primary care providers and local specialists need sufficient background knowledge of genetics, and appropriate access to point of service information, to make appropriate and timely referrals.

Particularly as advances are made in diagnosis and treatment of genetic disorders, specific referral to genetic services, from both the specialty center and primary care, is also important. Clinical geneticists are most likely to know if a diagnostic test is now available for a condition previously diagnosed on a clinical basis, or if new treatments or surveillance strategies are now available for a given condition. Clinical geneticists often play a key role in diagnosis and are increasingly playing a role in guiding and coordinating patient management, as discussed above. Furthermore, a specialist may be able to provide disease management after diagnosis but may be unprepared to counsel the family about mode of inheritance, genetic testing options for family members at risk or other services, such as prenatal diagnosis and other reproductive options.

Another issue is the need for genetics professionals with the expertise to provide services to adults with rare genetic disorders. This need stems from recently improved survival rates for many genetic disorders and the greater importance placed on long-term follow-up and management, as discussed above.

One of the biggest challenges in the delivery of genetic services is effective coordination of the different components of service for patients with genetic diseases and their families. This challenge encompasses communication between different specialties to ensure effective sharing of care among primary care provider, specialty provider, and clinical genetics. It often includes the challenge of coordinating across significant distances, and taking into account different funding mechanisms for the different components of care. This challenge is often poorly addressed in the current U.S. health care system.

To address this need for effective coordination of care for patients with genetic disorders, interdisciplinary clinics organized around a specific genetic diagnosis or family of diagnoses have been developed, like specialty clinics for cystic fibrosis, neuromuscular diseases, or PKU. Other interdisciplinary clinics are organized around broader diagnostic categories, some of which may have a genetic origin. Examples include hearing loss clinics and maxillo-facial clinics. Depending on the diagnosis, the geneticist may be asked to play a coordinating role. Progress in understanding the genetic contribution to common diseases is likely to lead to a new kind of referral clinic in which a multidisciplinary team, incorporating genetics professionals, provides care. The geneticist will likely be brought in as an expert or consultant to address specific issues about diagnosis, interpretation of genetic susceptibility test results, and counseling. Such clinics already exist in cancer genetics, for example.

### **Location of services**

Genetic services are usually provided in clinical genetics clinics based in academic medical centers or tertiary referral centers. One of the important reasons for locating clinical genetic services in academic medical centers is that they are poorly reimbursed. Often it is possible to deliver them effectively only because the salaries of the genetic counselors and clinical

geneticists are largely covered by research activities, with clinical care representing only a small fraction of their effort.

The increasing numbers of genetic tests now available will result in greater demands for the services of genetics professionals. Efficiencies may be hard to achieve in the absence of innovative approaches to support; for example, genetics professionals can often provide effective consultation to primary care providers and specialists via telephone and email, to allow them to complete the initial stages of work-up in a patient suspected of having a genetic disease. This consultation can limit inappropriate referrals and reduce time demands on genetics clinics, but is not usually reimbursed.

### **Barriers to integration of genetic services in practice**

The evolving role of the clinical geneticist must find a balance between the trend for clinical geneticists to be increasingly involved not only in diagnosis but also in offering guidance on patient management and letting other health professionals take on the diagnosis and treatment of some genetic disorders because the clinical genetics workforce is limited in numbers. Although some common genetic disorders are already mostly under the care of other health professionals (for example, cystic fibrosis), it will be difficult to decide, among some other disorders, which ones need to be diagnosed and/or managed by clinical geneticists and which ones can be taken on by other specialties. Clinical geneticists are not the first to struggle with what should be the boundaries of their practice (Greendale and Pyeritz, 2001). This dilemma has been compared to the one faced by infectious disease specialists in the last century. As new tests and antibiotic treatments became available, infectious disease specialists started to focus on the diagnosis of complex cases and less common disorders, as well as the use of the newest therapies, while the most common diseases and their treatments were dealt with by primary care providers and other specialists (Guttmacher, 2001). The advent of new technologies led to a redefinition of the specialists' role, not their disappearance.

For clinical geneticists to continue providing services, reimbursement issues must be resolved. Current reimbursement practices do not cover the costs associated with the provision of genetic services (Pletcher, 2002). The majority of clinical geneticists receive at least part of their income as a salary, and only 6% receive most of their income from traditional fee for service (Pletcher, 2002). In clinical genetics, patient evaluation, counseling, and education require more time than in other specialties, but reimbursement does not reflect this (Howell, 2002). Furthermore, counseling services provided by genetic counselors are often not reimbursed. Genetic counselors must be paid out of other sources of income. Academic clinical genetic laboratories used to be an important source of income for clinical genetics services, but competition from commercial laboratories has made them less profitable. Clinical genetic services cannot be maintained in the long run using the current reimbursement practices.

Because clinical genetics services are located in tertiary care centers, they rely entirely on referral from other providers for their practice. Primary care providers and other specialists need to be aware of the availability of genetic services in their area. They also need to be better educated about appropriate use of genetic services and indications for referral to a clinical

geneticist (Taylor, 2003). Clinical geneticists might need to come up with new ways to provide services to increase their visibility and availability; the use of phone or telemedicine consultations with providers and/or patients could reduce the number of unnecessary referrals while increasing the number of cases addressed by the clinical geneticist.

Because the number of clinical geneticists and other genetics health professionals is limited, some areas have little or no access to genetic services. Incentives must be in place to attract more qualified individuals into the field of clinical genetics and more genetic professionals to underserved areas. The use of telemedicine could also increase access to genetic services in underserved areas, but assumes that there are genetic professionals elsewhere who have the time and resources to offer telemedicine consultations. It must also take into consideration that not all services can be provided using telemedicine, and that a subset of patients will still have to travel to see the genetics specialist at a tertiary care center. In considering these challenges, however, the emerging uses of genetics testing and technology need to be considered. Some are readily integrated into existing health care while others may require specific efforts to define appropriate use and the role of genetics professionals.

### **Other innovative uses of genomic technology**

Genetic technology has also entered the health care system in a different way, as the source of improved health care tools for various health care problems, often based on genomics analysis of pathogens. The most obvious example is the use of DNA-based tests to identify microbial pathogens, providing more accurate and rapid means to determine the cause of many infectious diseases. Typically, the testing process itself is simple, requiring no specialized expertise.

Innovative genome-based therapeutics are also part of this trend. For example, fomiversen, an antisense oligonucleotide that binds to the messenger RNA of an essential protein of cytomegalovirus, can inhibit protein expression. It has proved to be an effective therapy for cytomegalovirus infections of the eye in AIDS patients. More innovations of this kind are likely; in general, they will be integrated into health care by the same route as non-genetic technical innovation, generally by direct comparison to the technology they are replacing, and will not necessarily change the structure or process of health care delivery.

### **Conclusions**

Although clinical geneticists still “specialize in genetic disorders and conditions,” there have been tremendous improvements in their knowledge about these disorders and the tools at their disposal to diagnose and treat them. As the role of the clinical geneticist evolves to integrate these advances into clinical services, their relationship with other providers will change.

Primary care providers and other specialists need to be aware of the availability of genetic services, learning how and who to refer for genetic evaluation. In addition, clinicians not trained in genetics will need to develop the skills to use certain genetic services independently – notably pharmacogenomics and genetic susceptibility testing.

Clinical geneticists have to develop new ways to increase access to their services in a context of limited resources, and also participate in the development of robust practice standards for the use of genetic tests and technologies in other clinical settings, in partnership with the appropriate medical specialties. Interdisciplinary collaborations will become more common. Reimbursement practices will have to change to reflect these new developments to sustain the provision of genetic services.

**Table: Roles of Genetics Professionals**

	Clinical roles	Usual site of practice
Clinical Geneticists	<ul style="list-style-type: none"> <li>• Diagnosis of genetic disease</li> <li>• Consultation regarding clinical management</li> <li>• (Rarely) primary care of patients with genetic disease</li> <li>• Supervision of genetic counselors (not required in all states)</li> </ul>	<ul style="list-style-type: none"> <li>• Academic medical centers</li> </ul>
Genetic counselors and nurse geneticists	<ul style="list-style-type: none"> <li>• Evaluation and counseling of patients related to risk for genetic disease in themselves or family members</li> <li>• Counseling before and after genetic testing</li> </ul>	<ul style="list-style-type: none"> <li>• Academic medical centers</li> <li>• Specialty referral clinics</li> <li>• State-supported genetics clinics</li> </ul>
Genetics laboratory professionals	<ul style="list-style-type: none"> <li>• Perform or supervise laboratory procedures for genetic tests</li> <li>• Interpret test results</li> </ul>	<ul style="list-style-type: none"> <li>• Academic medical centers</li> <li>• State laboratories</li> <li>• Commercial laboratories</li> </ul>

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