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## Genetic Services Policy Project

### **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>3</sup> (trastuzumab) + paclitaxel  (Impending competition: FDA has recently approved Tykerb™ <sup>4</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/po or 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>6</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>7</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-HerceptTest®, Pathway; FISH-PathVysion, Her2 FISH pharmDX)

<sup>3</sup> Genentech: Herceptin™ (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

### **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

### 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>TM</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

### **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. (Kupperman, Learman, et al.

2006)

- 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 services 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

### 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 influenza*, 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

### **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
    - Health Disparities Diabetes Collaboratives
  - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health

**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

### 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

### **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 copay 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

### 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

### **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

### 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

### 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

### **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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