
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.

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- 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)

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- 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 ¹	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 ² (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 ^{TM3} (trastuzumab) + paclitaxel (Impending competition: FDA has recently approved Tykerb ^{TM4} for HER2+ advanced breast cancer)	Test - ~\$150 Treatment - \$60,000/pt/yr	Standard of care (NCCN guidelines) Cost-effectiveness of testing methods Accuracy of Her 2 tests
Risk of adverse drug reaction/poor response to treatment	CYP2D6 ⁵	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 ^{TM6}	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 ^{TM7}	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

¹ Myriad Genetics

² Multiple FDA approved tests (IHC-HerceptTest®, Pathway; FISH-PathVysion, Her2 FISH pharmDX)

³ Genentech: HerceptinTM (trastuzumab) is a therapeutic antibody targeted at the Her 2 receptor, a component of the tumor-stimulating signal pathway.

⁴ Glaxo Smith Kline, approved March 2007

⁵ Approved tests include: AmpliChip® by Roche

⁶ Genomic Health, Inc, Redwood City, CA (CLIA approved lab, not FDA approved)

⁷ Agendia