RESULTS for LIFE
LAB TESTING: BETTER HEALTH, IMPROVED OUTCOMES

November, 2011

A new tool to tailor treatment, reduce side-effects, and manage drug costs

Genetic Tests Help Physicians Target Medication and Dosage for Cancer Patients

Important progress is being made in the battle against cancer thanks to genetic tests that help physicians better target cancer treatment. These tests identify the genetic and molecular structure both of the disease itself and the individual patient. With this information, physicians are able to select medications that are most effective in treating the individual's unique form of cancer.

Better targeting means physicians can begin effective treatment earlier and avoid treatments that have little value—and often lead to damaging side-effects. This targeted approach to cancer care is beginning to redefine traditional treatment patterns—from doing *everything* that might possibly help a patient, to doing *exactly* what is needed for the patient based on the unique molecular nature of the individual's disease.

Better targeting with genetic tests can also mean significant cost savings through more appropriate utilization and fewer adverse reactions. Cancer is already the third highest-cost condition in the US, with direct medical costs in the region of $93.2 billion annually, according to the National Institutes of Health. Oncology represents some 40 percent of total Medicare drug costs.

Quick Facts:

- Genetic tests now exist for 1,500 diseases—hundreds are used in cancer care.
- 50 genetic tests for cancer have been introduced since 2006.[a]
- Most of those are for breast cancer, colorectal cancer, multiple cancers, and prostate cancer.[a]
- Many targeted therapies exist today because of the ability of genetic tests to pinpoint genetic mutations. These include treatments for leukemia, stomach cancers, breast cancer, thyroid cancer, T-cell lymphoma, and multiple myeloma. [b]

The following examples highlight some of the ways that genetic testing is helping physicians target medications and treatment for individual patients.

Breast Cancer and Leukemia: Choosing the Right Drug

HER2 Genetic Test Identifies Patients for Breast Cancer Drug

Physicians are using a molecular genetic test combined with the drug Herceptin to tailor a more effective treatment strategy for women with breast cancer who do not respond well to standard therapies.

The test can detect an overabundance of HER2 protein on the surface of a breast cancer tu-

mor. About 30% of breast cancers are characterized by over-expression of the surface protein.[1] For these women—who usually do not benefit from standard treatments—physicians can prescribe the gene-based drug Herceptin that will bind to the protein and deactivate it. This drug has been shown to reduce cancer's spread by about 50 percent.[2] [3] As a result, women who test positive for HER2 can avoid excessive treatments that provide no value, and benefit from the treatment that fits the exact genetic nature of their illness.

A 2004 study in the *Journal of Clinical Oncology* found that use of the HER2 genetic test resulted in significant cost savings. The study found that if the diagnostic test was not done, the cost of a therapeutic dose of Herceptin for breast cancer was $79,181 per patient cured. But when the diagnostic test was performed at the outset, the cost per patient cured was $54,738. Thus, a test that cost $366 to perform yielded nearly $24,000 in savings per patient.[4]

Genetic Tests Guide Treatment for Adult Leukemia

One of the best examples of how genetic tests help physicians choose the right drug involves chronic myelogenous leukemia (CML), which often strikes adults in mid-life.

The disease is caused by a genetic rearrangement in two chromosomes that create a protein, which in turn produces excessive white blood cells. Genetic tests are able to detect the protein, thus enabling physicians to select a recently developed drug that binds to the protein and inhibits its ability to reproduce. Here again, standard chemotherapy is much less effective.

The improvement in patient health as a result of better targeting has been dramatic. Today, the estimated annual mortality rate from CML has dropped to approximately 1 percent—well below the 10 to 20 percent historically. If the current trends continue, the estimated median survival rate for CML patients will have increased from three to four years to more than 25 years.[5]

Childhood Leukemia: Deciding the Best Dosage and Timing

Genetic Tests Spark Dramatic Improvement in Childhood Leukemia

Genetic tests are having a profound impact on survival rates for acute lymphoblastic leukemia (ALL)—the most common cancer in kids—thanks to the better dosing decisions and timing of doses that they enable.

ALL represents 23 percent of cancer diagnoses among children younger than 15 years of age.[6] It occurs in about one in every 29,000 children in the United States each year.[7] The improvement in the survival rate is one of the great success stories in cancer treatment, according to the National Cancer Institute. For example:

- The current five-year survival rate is 87.5 percent; the 10-year survival rate is 83.8 percent.[8]

- Forty years ago, the five-year survival rates were less than 4 percent.[9]

Genetic testing helps fine-tune ALL treatment because there are many distinct subtypes of ALL determined on the basis of genetic profiles of the leukemia cells. The different genetic types influence prognosis and require different treatment approaches.[10]

For instance, children with leukemia cells that have certain genetic characteristics metabolize—or clear—anti-leukemia drugs more quickly than children with cells that have a different gene profile. When drugs are cleared more quickly, treatment is less effective because the drugs have less time to work.

Other children have a gene that makes them *less likely* to clear a particular anti-leukemia drug. While they have improved outcomes, they're also more likely to experience side-effects from that drug. A genetic test can enable physicians to adjust treatments accordingly, reducing the likelihood of side-effects that can prove fatal.

Although great progress has been made in the cure rates, up to 20 percent of children experience a relapse of ALL.[11] Physicians until now have had no tools to help them identify the children at risk. But scientists have recently identified mutations in a gene, called IKZF1 or IKAROS, which predicts a high likelihood of relapse. Although the researchers caution that further study is needed to determine how changes in the gene lead to leukemia relapse, the findings are likely to provide the basis for future diagnostic tests to assess the risk of recurrence. [12]

Colon Cancer: Avoiding Specific Drug for Certain Patients

Genetic Tests Determine the Best Medication for Colon Cancer Patients

In metastatic colon cancer, genetic testing helps physicians make critical medication decisions about whether a certain colon cancer drug will work for an individual patient in light of the genetic make-up of the that patient's tumor.

Patients with a normal gene called KRAS respond to a front-line cancer drug called cetuximab. However, about 40 percent of colon cancer patients have a mutated form of the KRAS gene that does not respond to this drug. In fact, if these patients take the drug, they can suffer damaging side-effects. Knowing that the patient has the KRAS mutation means that doctors can avoid prescribing ineffective drugs and expedite the use of the best alternative drug therapy.

The National Comprehensive Cancer Network now recommends that physicians test all patients with metastatic colorectal cancer for the KRAS genetic mutation before prescribing treatment. The American Society of Clinical Oncology also calls for KRAS testing for patients with colorectal cancer. The FDA requires that this front-line cancer drug include information on the label about the KRAS gene and its effect on patient response to cetuximab.

Better targeting can lead to dramatic cost savings

The economic value of KRAS testing includes reduced costs attributed to avoidance of ineffective treatment, reduced costs of managing adverse effects from ineffective therapy, and reduced overall costs of metastatic colorectal cancer.

According to an analysis presented at the 2009 Gastrointestinal Cancers Symposium, testing patients with metastatic colorectal cancer for the KRAS gene mutation prior to prescribing the drug cetuximab could potentially save the US health care system $604 million annually.[13]

Breast Cancer: Avoiding Unnecessary Treatment

Genetic Tests Help Patients/Physicians Predict Chemotherapy Benefit

Genetic tests sometimes help in guiding therapy by indicating when a therapy will provide benefit or when it is unnecessary and can be avoided entirely. This is the case with tests that can identify in early-stage breast cancer patients the likelihood of cancer recurring in the future.

When a woman is diagnosed with breast cancer, one of the hardest decisions she faces is whether to undergo chemotherapy. The decision involves a trade-off between the ability of chemotherapy to destroy any remaining cancer cells after surgery or radiation and the devastating side-effects that chemotherapy inevitably brings. This can include hair loss, nausea, heart problems, anemia, and second cancers.

Traditionally, patients and physicians were forced to make this kind of treatment decision on very limited information about risks and the likely success of treatment options. Decisions were based not on the unique nature of a patient's tumor and how it might respond to treatment, but on general estimates of how other patients with tumors of similar size or grade responded to treatment.

New genetic tests, however, provide women who have early stage breast cancer much more information to allow them and their physicians to make more-informed decisions about treatment. Such tests evaluate the activity within certain genes in the tumor and produce a score that indicates the likelihood that the cancer will recur.[14] [15] For those with higher risk, the chances of cancer recurrence are greater—hence there is a significant likelihood that chemotherapy will provide a greater benefit than harm. For those with lower risk, there may be little or no benefit from chemotherapy, and women in this group may be able to forego chemotherapy and its side-effects.[16]

Cervical Cancer: Early Detection, Improved Long-Term Outcomes

Genetic Tests Lead to Reductions in Disease Occurrence

Genetic tests for the HPV viruses that cause cervical cancer are improving diagnostic accuracy in identifying the disease at its earliest stages. The HPV DNA tests add another important screening tool to the Pap test by identifying the high-risk strains of human papillomavirus (HPV) that lead to cervical cancer. The tests can also determine whether atypical cells identified by Pap tests are actually pre-cancerous.

The increased precision of the tests in documenting true cases of cancer allows many women to avoid unnecessary procedures, such as biopsies, and the associated costs. For example, the tests can determine whether a woman with abnormal results on a traditional Pap test truly has a high-risk strain of HPV or other precancerous conditions.

The HPV DNA test is leading to improved disease-free survival and quality of life, along with reductions in disease occurrence, death, and progression to advanced cancers. The test is used by itself or in combination with Pap testing. In a Swedish study of 12,527 women, adding HPV testing at the initial screening stage increased detection rates of grade 2 precancerous lesions (abnormal cells) by 51% compared to Pap only.[17] In subsequent screenings during a four-year follow-up, the proportion of women with grade 2 or 3 lesions was 42% lower in the HPV group, as well as 47% lower for women with grade 3 lesions or cancer.

Breast and Ovarian Cancer: Prediction and Prevention

Some genetic tests help prevent disease from occurring in the first place by predicting the risk of disease before symptoms occur, thus allowing earlier treatment and preventive actions. A good example is a genetic test that identifies variations in the BRCA 1 and BRCA2 genes that increase the risk of breast and ovarian cancer.

According to estimates of lifetime risk, about 12 percent of women in the general population will develop breast cancer, but some 60 percent of women with an altered BRCA 1 or BRCA2 gene will develop the disease. Similarly, the lifetime risk of women with BRCA 1 or BRCA mutations developing ovarian cancer is 15–40 percent, versus 1.4 percent of those without these gene variations.[18]

By identifying the BRCA1 and BRCA2 mutations, genetic testing provides patients and physicians with vital information that lets them take preventive action to lessen the risk. This might include more frequent cancer monitoring, earlier treatment through surgery or preventive chemotherapy, and greater risk avoidance.

Conclusion

In many ways, genetic testing represents the future of medicine in its ability to match treatments to the unique molecular nature of individuals and their disease. The potential is dramatic—more personalized treatment, fewer side-effects thanks to better targeting, better outcomes resulting from earlier and more effective therapy, and more appropriate utilization of health care resources. From a clinical perspective, the future is very bright indeed. Many promising genetic tests are already in development that could lead to earlier diagnosis and more effective treatment for lung, ovarian, prostate, and other cancers—as well as heart disease and other chronic diseases.

But this future is already here for many patients suffering from many forms of cancer and other diseases. Genetic testing is a powerful new tool that is already making health care better, smarter, and more cost-effective.

For more information about genetic testing and the value of laboratory medicine, visit the Results for Life website at www.labresultsforlife.org. Results for Life is a national education campaign of America's clinical laboratories and laboratory professionals focused on the value of laboratory medicine.

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Endnotes for page 1 textbox:

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