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Personalized Medicine: Cancer Prevention, Diagnosis, Prognosis and Targeted Therapy

The complete sequencing of the human genome has opened up many new doors for targeted drug development and personalized, or tailored, medicine. Personalized medicine involves utilizing genetic analyses to better understand the molecular basis of a disease, and then using this information to both create more effective drug treatments and to determine which subsets of the disease population would benefit from these new treatments.[i] Personalized medicine would not only provide doctors with a genetic basis for their treatments, but it would also save thousands of patients from taking useless medication (with potentially harmful side-effects). The idea of personalized medicine is "to treat disease based on the identification of biomarkers associated with the likelihood of a drug's efficacy or potential toxicity."[ii] It would also provide a new way to assess each individual patient's risk for a disease. Individualized medicine would likely save the nation money and revolutionize healthcare; currently, "most drugs, whatever the disease, work for only about half the people who take them… [and] much of the nation's approximately $300 billion annual drug spending [is] wasted…"[iii] Personalized medicine will change the way doctors approach disease diagnosis and management.

Cancer diagnosis and treatment is one area that experts believe will be drastically altered by personalized medicine. While one cancer may appear similar to another, the

genetic bases of the two diseases could be completely different, and the appropriate treatment for one may not be right for the other.[iv] Personalized medicine would allow a doctor to use a patient's genetic composition to better understand the "molecular classification of cancer subtypes…" and "improve prognostic accuracy, target development of new therapies… and tailor selection and delivery of chemotherapeutics."[v] The first step in personalized medicine for cancer is determining the specific subset of cancer that the patient has using gene expression arrays. The second step is to use genetic information about the patient to determine both the cause of and the best treatment for the cancer.[vi]

Breast cancer is one cancer that is a model for why personalized medicine should be used. In recent years, scientists' understanding of the genetic causes of breast cancer has increased greatly. The discovery that mutations in the *BRCA1* or *BRCA2* genes lead to an increased risk in breast and ovarian cancer enables women to be tested for these mutations. Women with *BRCA1* or *BRCA2* mutations have a 40-80% lifetime chance of developing breast cancer. Tests for these mutations give each woman the ability to learn her own risk for breast cancer and any means of cancer prevention.[vii] Genome-wide association studies found seven single nucleotide polymorphisms (SNPs) that can "influence the pathologic characteristics of breast cancer."[viii] Women can be tested for these SNPs, which are all associated with certain types of breast cancer, and the treatment that best suits each woman can be determined.

Treatment for women with breast cancer is drastically changed when each treatment plan is tailored to the individual patient. Right now, "3 oncological predictive markers are in widespread clinical use…"[ix] Two of these markers are the estrogen

receptor (ER) and progesterone receptor (PR), which are used to identify women with breast cancer for whom hormone therapy would be effective. For example, women who test negative for ER rarely respond to hormone therapy. Also, other testing could be done to see whether or not a woman would benefit from certain drugs. For example, as it stands now, thousands of women with hormone-receptor positive breast cancer are taking the anti-cancer drug tamoxifen, which, for many of them, is useless.[x] This is because women with a certain SNP in the *CYP2D6* gene have poor tamoxifen metabolism, and therefore the drug has little or no effect.[xi,xii] There is currently debate over whether women should undergo *CYP2D6* testing before starting tamoxifen to learn if the drug will be effective. The third cancer marker that is tested for is human epidermal growth factor receptor (HER-2), which is used to identify women for whom anti-HER-2 therapies would be effective. The main use of HER-2 testing currently is to predict the response to the drug Herceptin. It has been shown that women who have over-expression of HER-2 respond to Herceptin, but women without over-expression of HER-2 usually do not.[xiii] These women who have low levels of HER-2 also have a lower survival rate, and it is now recommended that "patients with <20% decrease in serum HER-2/neu should be considered candidates for investigative therapies…".[xiv] Individual screening of each patient would allow a doctor to know whether or not a certain treatment would even have the possibility of being effective before determining the best course of action for their patient.

Scientific advancements have also made personalized medicine beneficial for leukemia patients. Genomic advancements have enabled new cancers and their genetic bases to be discovered. With the current technology, scientists can use "genome-scale

gene expression analyses to identify discrete disease classes not previously recognized."[xv]

Also, the way a cancer is diagnosed is changing. Previously, the type of cancer a person

had was determined based on the morphological appearance of the tumor. However, this

is not always a successful way to diagnose a tumor, since "[t]umors with similar

histopathological appearance can follow significantly different clinical courses and show

different responses to therapy."[xvi] This is because tumors that appear similar can actually

be different subtypes of a cancer. Using DNA microarrays, scientists can distinguish,

using only one test, the difference between specific subtypes of cancer, like acute

lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (see figure 1).[xvii]

These two types of acute leukemia require different treatments, so distinguishing between

the two is critical.

Just as in breast cancer, genomic testing has also made it possible to predict

leukemia patients' response to certain drugs. In the case of ALL, however, the concern is

not that a drug will be ineffective but that it can be fatal. Thiopurines are drugs used to

treat ALL, and the enzyme TMPT metabolizes these drugs. However, some patients have

little or no TMPT activity, and these patients are "at high risk of developing

hematopoietic toxicity if given standard doses of thiopurines."[xviii] There is an assay that

can test for the activity of this enzyme in patients and determine which patients are at risk

for these negative side effects.[xix] If each patient were screened for certain biomarkers, the

chances of a patient developing a toxic reaction to a drug would be greatly decreased.

The creation of such biomarker tests for lung cancer would greatly benefit lung

cancer patients. Personalized medicine for this disease, when it is created, will most

likely radically change lung cancer treatment. Currently, most lung cancer patients are

not diagnosed until the advanced stages of the disease, and the survival rate for these patients is very low. New genomic technologies, however, offer hope for the development of "more accurate tumor classification and… new diagnostic or prognostic tools."[xx] Scientists believe that the gene expression of a tumor can show the metastatic ability of the cancer, and that this gene expression profile could give doctors a better idea of the patient's prognosis. As of right now, however, there is a "lack of consensus for the molecular biomarkers that should be used to improve current histological parameters."[xxi] Once the best biomarkers have been determined, doctors will be able to determine the specific subtype of cancer a patient has and each patient's prognosis. Once this is discovered, doctors will hopefully be able to offer each individual patient a specific treatment plan based on their cancer subtype.

Colorectal cancer is another cancer that has been positively impacted by genomic advances, and personalized medicine for the familial colorectal cancers has become a reality.[xxii] Recent genetic technology has allowed doctors to determine the subtype of colorectal cancer their patient has and to decide on the proper treatment for their specific disease. If detected early, colorectal cancer is one of the most curable cancers, and genetic testing has made diagnoses more clear. Because the genetic bases of the familial types of colorectal cancer have been discovered, if one patient has a cancer, their whole family can be tested for the mutation that causes that cancer to see if they have inherited the mutation. Genome-wide association studies have identified many different regions that make a person susceptible to colorectal cancer, and in the future it is even possible that population-wide screening can be done to test an individual's susceptibility to this cancer.[xxiii]

Although it may seem that no one could argue about the benefits of personalized medicine, it actually raises many ethical concerns. The main issue with personalized medicine is that it involves examining the genetic makeup of a patient, which leads to concerns about patient privacy and confidentiality. The Personalized Medicine Coalition explains these concerns, which include:

> "the implications of being identified as predisposed to a certain condition or non-responsive to available treatments; the rights of non-consenting family members of the tested individuals… and the psychological and social effects of genetic testing for the individual tested."[xxiv]

Also, many people worry about genetic discrimination by insurance companies and employers. While the medical implications of personalized medicine all appear positive, many people have concerns over the social and emotional implications of learning one's personal genetics.

Personalized medicine for cancer allows a doctor to know each patient's risk for developing cancer, the type of cancer each patient has, and the best possible treatment for that cancer. The diagnosis, prognosis, and course of treatment for breast cancer, leukemia, and colorectal cancer have all been enhanced by genomics, and personalized medicine enables each patient to get the best care for their specific type of cancer. While more scientific advancements are needed before personalized medicine is available for lung cancer, researchers are hopeful that advancements will be made soon. Personalized medicine allows for better management of each individual's case overall, from prevention to diagnosis to treatment.

[i] "Science & Public Policy: Personalized Medicine 101." <u>Personalized Medicine Coalition</u>. (2009). <http://www.personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.php>.

[ii] De Palma, Angela. "Pharmacogenomics and the Brave New World of Personalized Medicine." Pharmamanufacturing.com. 7 March 2009. Pharmaceutical Manufacturing. <http://www.pharmamanufacturing.com/articles/2006/047.html?page=1>.

[iii] Pollack, Andrew. "Patient's DNA May Be Signal to Tailor Medication." <u>The New York Times</u>. 29 December 2008. Accessed 7 March 2009. <http://www.nytimes.com/2008/12/30/business/30gene.html?pagewanted=1&_r=2>

[iv] De Palma, Angela. (2009).

[v] Overdevest, Jonathan B., Dan Theodorescu, and Jae K. lee. "Utilizing the Molecular Gateway: The Path to Personalized Cancer Management." <u>Clinical Chemistry</u>. 55.4 (2009).

[vi] Burstein, Harold J. "Personalized Medicine and Breast Cancer Care." <u>Journal of the National Comprehensive Cancer Network</u>. 7.2 (2009).

[vii] Olopade, O.I., *et al*. "Advances in Breast Cancer: Pathways to Personalized Medicine." <u>Clinical Cancer Research</u>. 14 (2008).

[viii] Olopade, O.I. *et al*. (2008).

[ix] Duffy, Michael J., and John Crown "A Personalized Approach to Cancer Treatment: How Biomarkers Can Help." <u>Clinical Chemistry</u>. 54 (2008): 1770-1779.

[x] Pollack, Andrew. (2008).

[xi] Higgins, Michaela J., *et al*. "Pharmacogenetics of Tamoxifen: Who Should Undergo *CYP2D6* Genetic Testing?" <u>Journal of the National Comprehensive Cancer Network</u>. 7.2 (2009).

[xii] Burstein, Harold J. (2009).

[xiii] Duffy, Michael J., and John Crown. (2008).

[xiv] Belden, Heidi. "Getting personal: Genetic testing and custom-tailored drug treatments promise a sea change in pharmacy practice." <u>Drug Topics</u>. 18 September 2006. Accessed 8 March 2009. < http://drugtopics.modernmedicine.com/drugtopics/article/articleDetail.jsp?id=371868&sk=&date=&pageID=3>

[xv] Garman, Katherine S., Joseph R. Nevins and Anil Potti. "Genomic strategies for personalized cancer therapy." <u>Human Molecular Genetics</u>. 16.R2 (2007): R226-R232.

[xvi] Golub, T.R., *et al*. "Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring." <u>Science</u>. 286.5439 (1999): 531-537.

[xvii] Golub, T.R., *et al*. (1999).

[xviii] Duffy, Michael J., and John Crown. (2008).

[xix] Belden, Heidi. (2006).

[xx] Lacroix, Ludovic, Frederic Commo, and Jean-Charles Soria. "Gene expression profiling of non-small-cell lung cancer." <u>Expert Review of Molecular Diagnostics</u>. 8.2 (2008): 167-178.

[xxi] Lacroix, Ludovic, Frederic Commo, and Jean-Charles Soria. (2008).

[xxii] Cheah, Yean. "Recent Advances in colorectal cancer genetics and diagnostics." <u>Critical Reviews in Oncology/Hematology</u>. 69.1 (2009): 45-55.

[xxiii] Cheah, Yean. (2009).

[xxiv] "Science & Public Policy: Personalized Medicine 101." <u>Personalized Medicine Coalition</u>. (2009).