Overview

Introduction

When you are diagnosed with cancer, your life changes in many ways. One of these changes may be hearing new, unfamiliar terms from your doctor concerning your diagnosis and your treatment choices.

One of the new terms you may begin to hear is **"personalized medicine."** What does this really mean, and what are its possible implications for your cancer treatment? In this section of our website, we will help you understand this increasingly used term and the many important considerations it may raise for you and your healthcare team.

We will break this discussion into the following sections:

- **Personalized medicine and you**
- **Understanding tissue (biospecimen) issues**
- **Ethics**
- **Molecular diagnostics**

The Big Picture

Personalized medicine is increasingly becoming a goal of healthcare. It is a medical model in which treatment decisions are based on each person's unique**:**

- **Clinical information** (physical examination, past medical history, symptoms, family history, lab and other test results, etc.)
- **"OMIC" biomarkers** (genetic, genomic, proteomic, metabolomic biomarkers, etc.)

- **Environmental information** (e.g., exposure to environmental factors, lifestyle choices, and personal and cultural values)

Because these factors are different for every person, the nature of diseases—including their onset, their course, and how they may respond to drugs or other interventions—is as individual as the patients themselves.

The goal of personalized medicine is to enable your healthcare providers to focus on the multiple factors that make you "you." Current research is focused on classifying many cancers into subgroups based on different characteristic "omic" profiles and then considering additional characteristics specific to your cancer to optimally treat you as an individual.

Although this may not appear fully "personalized," as it is based on defined subgroups, it is an important improvement over treatment based on the overall characteristics of one large group with no differentiation based on molecular patterns.

The promise of personalized medicine is to enable accurate predictions concerning a person's:

- Risk of developing a disease
- Disease progression
- Response to treatment

The effectiveness of personalized medicine requires translation of biomarker findings into precise diagnostic tests and targeted therapies.

It's All About You

It's important to remember that personalized medicine is not only about "omics," but is also about you, the healthcare consumer. Every person is different in multiple ways, including their diets, lifestyle choices, levels of stress, exposure to

environmental factors, and their individual DNA. Many of these variations play a role in health and disease. People also have different cultural and personal values, all of which must be recognized and respected as you work together with your healthcare team in determining your treatment decisions..

➔ **The choice is yours:** Please note that you can read this portion of our website from beginning to end, or you can skip directly to those sections that you find of the most interest. As with all areas of our website, this section is written to provide you with both informational and supportive resources that may help you through your cancer journey.

For further information on personalized medicine, we encourage you to visit the following sections of our website:

- **Personalized medicine and you**
- **Understanding tissue (biospecimen) issues**
- **Ethics**
- **Molecular diagnostics**

Personalized Medicine And You

Introduction

Receiving a cancer diagnosis is an emotional time that is often scary, confusing, and Overwhelming; your life changes in many ways.

One of those changes is trying to learn new terms concerning your type of cancer, medical tests, and treatment options. For many patients and family members, it may seem as if the medical team is speaking an entirely different language, using words and acronyms that you've never heard before.

One of the terms you may come across is **"*Personalized Medicine.*"** In this section of our website, we will help you understand this increasingly used phrase and the important implications it may have for you and your treatment decisions.

What Exactly IS "Personalized Medicine"?

The overarching promise of personalized medicine is to optimize medical care and outcomes for each individual. It recognizes that the best treatments, medications and dosages, and preventive strategies may differ from person to person-resulting in customized patient care. [1]

Personalized medicine is about **you**, the patient, the healthcare consumer. It is a medical model in which treatment decisions are tailored to the individual patient.

The goal for personalized medicine is to:

- Identify genetic differences that predict an individual's **possible side effects** from a drug—*does this patient have an increased risk of developing specific adverse effects with this drug treatment?*
- Develop genetic tests that predict an **individual's response** to a drug—*will this drug be effective for this patient?*
- **Identify biomarkers** – *does this patient have a biomarker that can diagnose, treat, or be used to monitor them?*

Human DNA may be approximately 99% similar across a population, yet just as with zebras, that remaining one percent allows us to each display our individual "stripes." The goal of personalized medicine is to treat "you."

Important Background Information

If you are a patient advocate, a medical professional, or anyone who wants the details of the terms and science discussed below, *please click here.*

We have a large section on these details but have them available through a link to keep the content flowing for those newly diagnosed patients who are not interested in the science.

Tumor markers:

Tumor markers (also called biomarkers) are substances found in the blood, urine, stool, or tissue that are produced by cancer cells. Tumor markers may indicate or suggest the presence of cancer. Different tumor markers may be present for different types of cancer.

The **ideal marker** would be a blood test for cancer in which a positive result would only occur only if there were a cancer present. This **ideal marker** would also indicate the stage of the cancer and possible response to treatment. In addition, it, would be easy to measure.

Tumor markers can be used for several purposes:

- Screening a health population or a high-risk population for the presence of cancer
- Making an early diagnosis of a specific type of cancer
- Determining the probable outcome of a patient's disease
- Monitoring a patient during the course of surgery, radiation therapy, or chemotherapy
- Monitoring a patient in remission

No current test meets all these requirements. Most tests today have problems with false positive and false negative results. For more information about this click here:

http://cisncancer.org/research/new_treatments/tumor_markers/how_it_works.html

Tumor markers can be classified into two groups:

1. **Cancer-specific markers** are related to a particular type of cancer. The tumor itself produces the marker. Cancer-specific markers can be useful in the follow-up of treated patients to track progress of the disease or response to treatment. Examples include:

    a. CEA (which may be used to monitor patients treated for colorectal cancer)

    b. CA19-9 (initially developed used in colon cancer, but found to be very sensitive for pancreatic cancer)

    c. CA-125 (a marker that may be used to monitor women with the most common type of ovarian cancer during and after active treatment).

2. **Tissue-specific markers** are related to specific tissue. Elevated levels may suggest abnormalities of specific tissue, such as the presence of cancer. An example is:

    a. PSA, which may be elevated in the blood when there is *non*-cancerous prostate growth or with prostate cancer. In addition, PSA also tends to be elevated in older men and in cases where there is inflammation or infection of the prostate.

Tumor markers are <u>not</u> always reliable for the following reasons:

- Normal cells as well as cancer cells can make most tumor markers.
- Tumor markers may also be associated with noncancerous conditions.
- Tumor markers are not always present in early-stage disease.
- People with cancer may never have elevated tumor markers.
- Even when tumor marker levels are high, cancer may not be present.
- Tumor markers that may be helpful in monitoring some cancer patients during and after treatment most often are *not* reliable in detecting cancer.

Because abnormal tumor marker levels may only suggest the presence of cancer, other scientific tests are usually required before confirming a cancer diagnosis.

Genetics

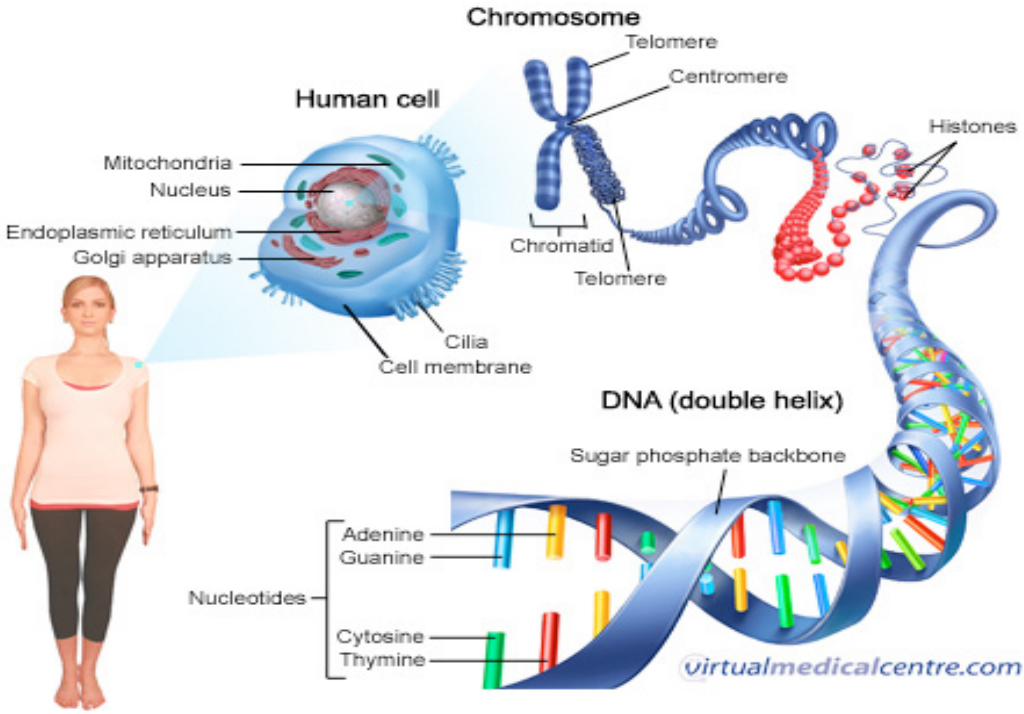
Genetics is the science of genes and the transmission and variation of inherited traits—in other words, the process by which parents may pass certain genetic traits to their children. Characteristics determined by genes range from eye color, hair color, and height to inheritance of or predisposition for specific diseases.

"Genome" refers to an organism's complete set of DNA, including all of its genes. In humans, a copy of the entire genome – which is more than 3 billion DNA base pairs – is contained in every cell that has a nucleus.

Genomics

Genomics is the study of a person's complete DNA sequence – including genes and "noncoding" DNA segments in the chromosomes and how those genes interact with each other, as well as the internal and external environments they are exposed to.

This includes the study of gene mutations, both those that are passed from parents to children (inherited) and those that happen during your lifetime (somatic). It is these mutations that contribute to the development and spread of cancer.



Pharmacogenetics

Pharmacogenetics is a specialty field within the study of genomics. It is generally regarded as the study of genetic variation that can affect an individual's responses to certain drugs. Pharmacogenetics uses information about a person's genetic makeup, or genome, to help determine the drugs that are likely to work best for that particular person and/or that may be likely to lead to certain adverse effects.

For certain drugs, pharmacogenetics may help to determine whether patients are **rapid or slow metabolizers** (referring to how long the drug stays in your body) as well as whether they are **responders or non-responders** (meaning whether the drug works for you).

Having the ability to predict a person's individual response to a drug, both in terms of therapy benefit and the likelihood for adverse events, will play a crucial role in:

- Preventing the use of a drug that is likely to cause serious effects for a particular patient without benefit

- Guiding the selection of optimal therapies that are most likely to benefit a specific patient

Deaths from drug side effects are one of the top ten leading causes of death, so this field is very important.

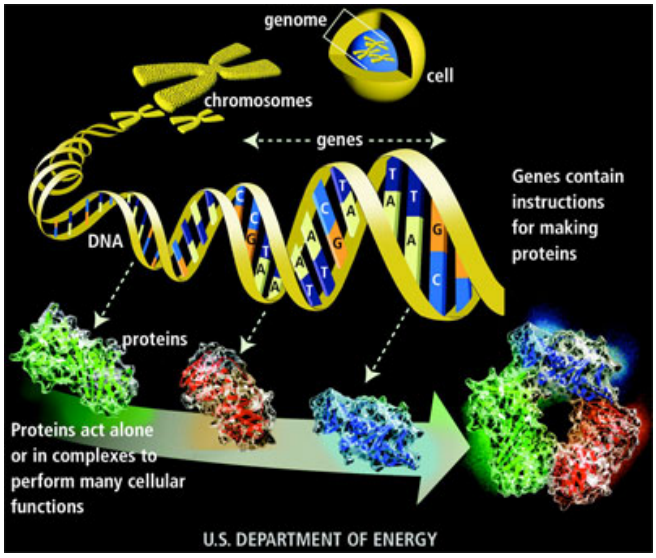
Epigenetics

For decades, scientists and doctors assumed that cancer was caused by irreversible damage to some critical stretch of DNA within one's genome. But in the last few years, a much more complex picture has emerged, one that shows that some cancers are caused by epigenetic changes–tiny chemical tags that accumulate over time and can turn genes on or off rather than mutate them.

The word "epigenetic" literally means "in addition to changes in genetic sequence." It is used to refer to any process that alters gene activity without changing mutating the DNA sequence. Experiments show that epigenetic changes, unlike mutations, can be reversed.

Proteomics

Proteomics is the study of the structure, functions, and interactions of proteins. While genes are the "recipe" of the cell, containing all the instructions for assembly, proteins are the products of these recipes, functioning as the cellular engines that drive both normal and disease physiology.



Proteomics is much more complicated than genomics. While an organism's genome is more or less constant, the proteome – or set of proteins expressed by the genome – differs from cell to cell and from minute to minute, depending on the activity of specific genes.

This makes interpreting protein measurements very difficult.

Image Courtesy of U.S. Human Genome Project

A breakthrough in cancer treatment was the discovery that tumors "leak" proteins and other molecules into blood, urine, and other accessible body fluids. The greatest promise for the early detection and treatment of cancer is to collect such fluids from patients and test them for the presence of cancer-related molecules, called cancer biomarkers or tumor markers.

Although protein biomarkers hold great promise, there are significant challenges to consider:

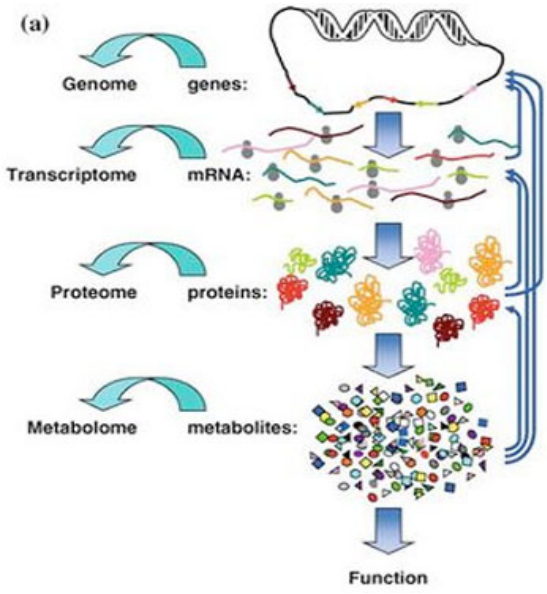
- The vast number of proteins that exist in the body can make it difficult to identify and describe them.
- Proteins are continually moving and undergoing changes.
- Proteins exist in a wide range of concentration in the body.
- Lack of standardization – Laboratories across the county collect, store, and study proteins in different ways. This lack of standardization makes it difficult to accurately compare results from one laboratory to another.

Metabolomics

Metabolomics is the systematic study of the unique chemical fingerprints that cells leave behind. More specifically, it is the study of how your body responds to drugs, environmental changes and diseases. Metabolomics is an extension of genomics (study of genes) and proteomics (study of proteins).

If metabolomic information could be translated into better diagnostic tests, it might have the potential to impact clinical practice, and it might lead to more targeted biomarkers that improves care.

If



you move from the top of the image to the bottom you get more precise information on what is happening in your body. So metabolites are a closer marker to how cells are functioning than genes or proteins.

Therefor, measuring them may be more helpful in improving disease detection, treatment and monitoring than measuring either genes or proteins.

Image courtesy of Royston Goodacre School of Chemistry, The University of Manchester

Making it Personal

Every person is different in multiple ways, including in what they eat, the types of stress they experience, exposure to environmental factors, their genes, and factors other than changes in DNA that alter gene expression.

Many of these variations play a role in health and disease. Personalized medicine allows your healthcare provider to focus his or her attention on what makes you "you," instead of depending on generalities.

Personalized medicine uses each person's unique combination of genetic, clinical, and environmental information.

It allows accurate predictions about a patient's:

- Susceptibility of developing a disease
- Probable course of that disease
- Response to treatment

Image provided by CISN archives. All rights reserved.

Currently diagnosis is symptom driven. New molecular tools may identify disease subtypes that cannot now be clinically determined and provide doctors with information on disease outcome, which will help them make better treatment decisions with their patients. These tools may also provide doctors with information on which drugs their patients may respond to.

One goal of personalized medicine is to identify genetic variations or mutations as well as changes in gene or protein expression that can be linked to a response from a specific medical intervention.

Understanding the genetics of each tumor will change how researchers test new drugs and clinicians use them. The challenge is to establish the technology to support the necessary clinical research. [2]

The hope is that more cancers can be treated with targeted therapy that spares healthy cells and only kills the targeted cancer cells. This should lead to fewer side effects, better survival outcomes and perhaps even fewer secondary illnesses caused by initial treatment.

To truly wipe out cancer cells within the body, it is not enough to have effective drugs that target some of the cancer growth pathways. It is essential to have a way of monitoring the cancer itself so drug therapy can be adjusted to match the tumor should it evolve.

Putting the "P" in "Personalized": *Personalized Medicine is …*

Predictive: *Uses molecular and diagnostic tools to predict each individual's health risks and outcomes*

Preventive: *Emphasis on wellness to prevent or lesson disease*

Preemptive: *action-oriented, individualized health planning.*

Personalized: *Each person's clinical, genetic, and environmental profile*

Participatory: *Empowers patients to participate in their own care*

What is the Promise of Personalized Medicine?

The promise of personalized medicine is that cancer treatment for each person will be as **individualized** as the person himself or herself.

Personalized medicine takes into consideration that all human diseases have both molecular and environmental components. The study of genetic variation has proven

to be more complex than imagined. Proteomics and Metabolomics are still in the early stages of study and are not yet used routinely in the clinic, but the potential is great.

Personalized medicine has the potential to:

Image curtsey of CISN archives

- Reduce traditional "trial-and-error" therapy
- Reduce adverse drug interactions
- Improve the selection of drug targets
- Reduce time, cost, and failure rates of clinical trials
- Revive drugs that failed clinical trials with heterogeneous patient populations and retest in specific subgroups
- Identify reliable tumor markers that detect disease early
- Shift the emphasis in medicine from reaction to prevention
- Reduce the overall cost of healthcare

Personalized medicine is about "**you.**" It includes all of your traditional clinical medical information, combined with your "omic" information, and is influenced by your interaction with your environment.

> As the uniqueness of individual tumors become clear, it is now understood that even the right combinations of drugs will fall short as resistance develops and responses are not durable. Studies have found up to a 40% difference between primary and recurrent lesions.
>
> Science must be able to distinguish mutations that are drivers of disease and therefore targetable, from those that are merely present. Personalized medicine is working on this now. [3]

Personalized medicine pays attention to your needs and customizes care in response to what you say; everything from your reports of specific symptoms to descriptions of personal goals and quality of life.

The ultimate in personalized medicine care integrates your personal story with the best science.

Challenges in implementing Personalized Medicine

The journey has begun, according to experts in this area of research but many roadblocks remain that could stall progress. [3] Even when the science has been perfected, the successful implementation of personalized medicine is dependent on several factors:

- There is a critical need to educate health professionals. The science of genetics that is traditionally taught in medical schools remains limited, with little or no discussion of complex "omic" information.
- The implementation of personalized medicine requires government support and regulatory oversight, as well as public vetting of ethical issues.
- Medical records systems must be structured to accept genetic data and to be integrated with the patient's existing health record in a way that facilitates its use in clinical decision-making.
- For personalized medicine to become a reality, the need for tissue continues to be critical for research and must be donated by willing, informed individuals.

Direct-To-Consumer Marketing

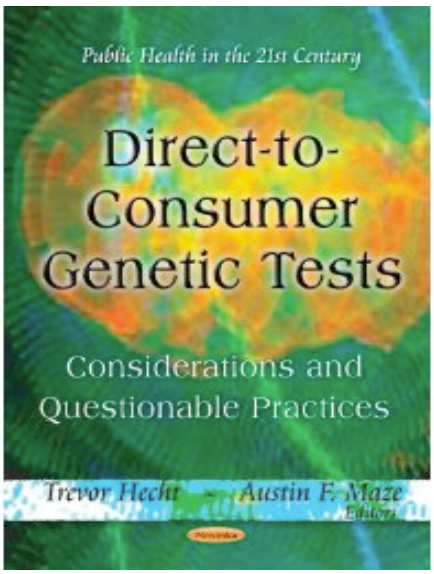
There is an increasing movement to – market – medicines and medical care directly to the consumer. Ads on television and in the print media are constantly encouraging us to purchase a particular supplement or medication, claiming it can cure us of many ailments.

In addition, for many years, patients have been taking their own blood sugar levels and
blood pressure readings, and current technology is creating more and more products we can use in our own homes to monitor our health. In fact, if we choose to, we can even test our own DNA.

But the question is, what should we do with all this information? Direct-to-consumer genetic tests are not designed to provide a clear-cut "answer" as if one is pregnant or not pregnant.

The information received from genetic tests can be extremely complex and is best understood with the help of both doctors and genetic counselors who know you,
Your medical history, your family history, and other crucial details.

Please think carefully before you take this type of step



It is vital that consumers be educated about their role as medical consumers, particularly as the field of personalized medicine information grows.

Image curtsey of CISN archives

It will also be essential for all stakeholders to create an environment that is favorable to the basic research required for innovation of effective personalized medicine solutions and the translational and clinical research necessary to bring such solutions from the research bench to the bedside.

Stakeholders include:

- Diagnostic and pharmaceutical companies
- Governmental and regulatory bodies
- Payers
- Physicians
- Patient groups.

Where does Personalized Medicine Stand Today?

If you were to ask your Primary Care Provider (PCP) this question, your answer would include information on your symptoms, lab test results, lifestyle, environmental exposures, and possibly the molecular biomarkers for your specific cancer. However, should you ask your Oncologist this same question, much of the information you'll receive will concern molecular biomarkers.

Since you located this site based on your interest in cancer, we will focus on biomarkers in this section. The arrow below illustrates the many different areas that may be affected by using biomarkers in personalized medicine.

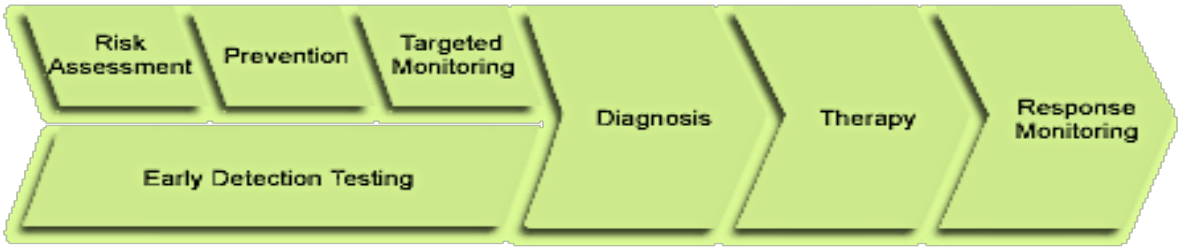


Image from the Personalized Medicine Coalition:
http://www.personalizedmedicinecoalition.org/sciencepolicy/personalmed-101_overview.php

We will briefly discuss all of these areas below and will cover them each in more detail as you move through this section of our website.

Early Detection Testing

As shown in the diagram above, early detection testing includes ***Risk Assessment***, ***Prevention,*** and ***Targeted Monitoring***. Although early detection testing will continue to be based on the risk averaged from a large population sample, the hope is that new tools will enable screening tests such as mammograms and colonoscopies to be more accurate and find disease earlier when it is easier to treat.

Risk Assessment

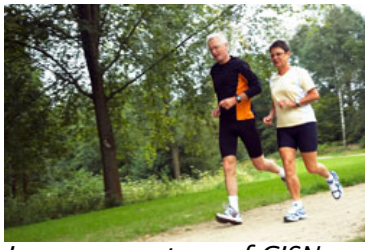
New forms of risk assessment will determine which people carry a genetic variation that may increase their risk for developing cancer. Enhanced means of risk assessment will improve the ability to make informed life choices that may decrease a person's risk. When individuals are found to have known

variations, they should be monitored more closely based on evidence-based guidelines.

Prevention

Although our genes influence our risk for cancer, **much** of the difference in cancer risk is due to factors that are not inherited. Although there is little you can do if you do have a specific genetic mutation, there are still steps that you **can** take to reduce your risk of developing cancer.

Such measures include avoiding tobacco products, keeping a healthy weight, staying active throughout life, and eating a healthful diet, all of which may reduce a person's lifetime risk of developing cancer. These same behaviors are also associated with a lower risk of developing heart disease and diabetes.



Images courtesy of CISN archives

Although we all have the ability to make healthy choices, the social, physical, and economic environments in which we live may positively or negatively impact our ability to "stick with" our well-intended plans. Nevertheless, is it important to realize that **you** are in control. [4]

Targeted monitoring

Personalized medicine introduces the ability to use markers that may signal risk or detect disease before symptoms appear. Women with certain BRCA gene variations have an increased risk of developing breast cancer.

Increasing the frequency of mammograms may be recommended to help early detection, or preventive surgery or chemoprevention may be considered for possible risk reduction. Genetic markers are also currently being used to facilitate safer and more effective drug dosing and scheduling. [3]

Diagnosis

Fulfilling the promise of personalized medicine requires that these findings be translated into precise diagnostic tests and targeted therapies.

In current practice, cancer diagnosis is primarily based on symptoms (clinical presentation) and by your pathology report. New molecular tools may help to

characterize cancer subtypes that cannot currently be distinguished clinically and may provide predictive information concerning disease outcome, aiding in guiding treatment decisions.

Below are types of testing now being used to provide your doctors with the information they need to make an accurate diagnosis of your cancer type and stage.

Hereditary Gene Testing

Personalized medicine is being used today in the testing of inherited genetic mutations. For example, specific BRCA1 and BRCA2 gene mutations are implicated in familial breast and ovarian cancer. Genetic testing can be provided to determine individuals at increased cancer risk due to such BRCA mutations, which may prompt more intense monitoring and consideration of prophylactic therapy.

Somatic Gene Testing

Personalized medicine is now being used to detect "somatic" or non-inherited mutations in cancer. Somatic mutations refer to acquired gene mutations or DNA changes that occur after conception. Some examples are the following:

- Mutations of the KRAS gene in advanced colorectal cancer are predictive of a poor response to therapy with anti-EGFR (anti-epidermal growth factor antibody) agents, an important finding that now guides treatment decisions for patients with and without KRAS mutations

- The discovery of a chromosomal translocation in chronic myelogenous leukemia (CML), led to the development of a new drug called Gleevac that targets the enzyme produced as a result of that mutation.

Diagnostic testing – a few examples

- Oncotype DX is a diagnostic test to detect patterns of genetic abnormalities within tumors. These patterns predict the probable rate of recurrence and can help guide treatment decisions. This test is available for both breast and colon cancers. *For more information on this click here.*

  The **Onco*type*** **DX®** Breast Cancer Assay is a diagnostic test that assesses a patient's tumor tissue at a molecular level. It analyzes the activity of a specific group of genes to predict the likelihood of chemotherapy benefit and recurrence risk in early-stage, estrogen-receptor-positive, invasive breast cancer.

  Onco*type* DX® Colon Cancer Assay is a new multigene expression test that also examines the activity of specific genes in a patient's tumor sample to assess the likelihood of recurrence following surgery to remove stage II colon cancer. Both tests provide individualized information

concerning the biological makeup of the patient's tumor, helping to guide important treatment decisions.

- Testing for the overexpression of Her2 gives physicians information to make treatment recommendations.
- **HER2-neu testing** may also be conducted for advanced cancer of the stomach or the junction where the esophagus meets the stomach (gastroesophageal junction), as the FDA has approved treatment with trastuzumab in combination with specific chemotherapy agents for these HER2-neu positive cancers
- Testing for estrogen and progesterone status also helps determine treatment recommendations.
- In patients diagnosed with invasive breast cancer, a tumor sample is typically tested to determine **hormone receptor status of estrogen and progesterone** as well as whether there is **overexpression of the gene HER2-neu.** Such testing provides important prognostic information concerning how aggressive the tumor may be and in guiding treatment decisions.

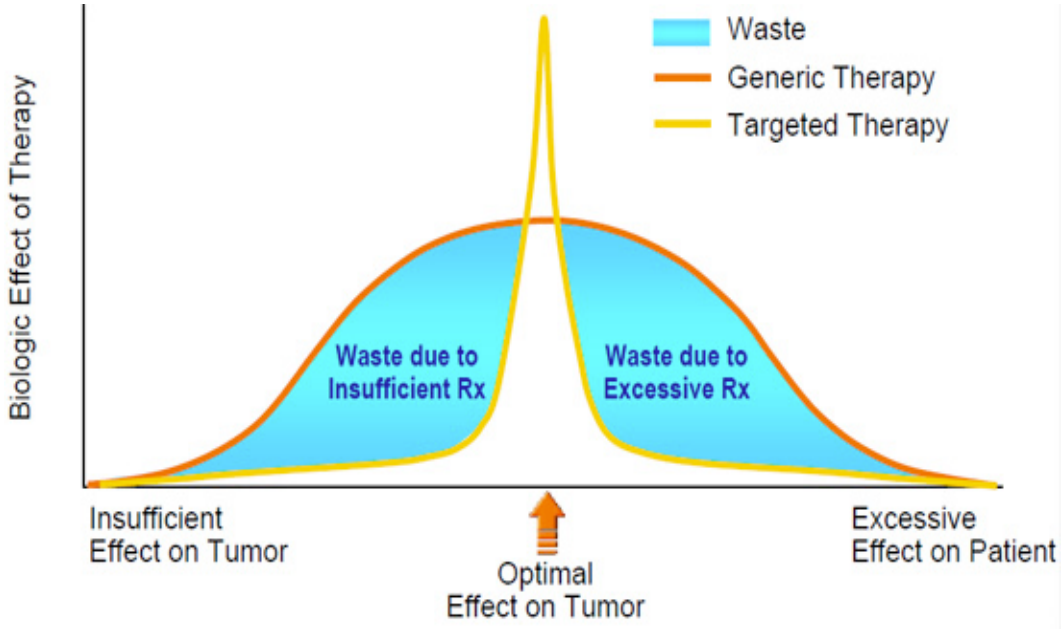
  Patients with estrogen- and/or progesterone-positive breast cancers may benefit from anti-hormone therapy as part of their treatment, such as with tamoxifen or aromatase inhibitors. Those whose tumors are HER2-neu positive may be candidates for treatment with anti-HER2 agents, such as trastuzumab (Herceptin®), which targets the HER2-neu protein

Therapy

New molecular tools may also provide doctors with information on which drugs their patients may or may not respond to and/or the likelihood of their developing adverse effects associated with certain agents.

Targeted Therapy

Targeted therapy is the use of agents designed to target specific mutated molecular pathways in a subset of patients with a given cancer type.



Examples include the following:

- As noted earlier, trastuzumab (Herceptin®) and additional anti-HER2 agents may be used to treat patients with HER-2-neu positive breast cancer and cancers of the stomach and gastroesophageal junction.

- Also mentioned earlier, imatinib (Gleevec®) is used to treat chronic myeloid leukemia that has the Philadelphia chromosome.

- Using a whole genome screen to identify genes active in cutaneous T-cell lymphoma (CTCL), scientists found that presence of the protein HR23B predicted response to the drug vorinostat (Zolinza®).

- 5-fluorouracil (5-FU) is a commonly used chemotherapy agent. Dihydropyrimidine dehydrogenase (DPD) is the primary enzyme that determines the breakdown of 5-FU. Some people have genetic variations, causing the DPD enzyme to be less active or inactive, limiting the metabolism of 5-FU.

As a result, people with such DPD mutations have a higher risk of developing severe or even fatal reactions to 5-FU. Screening for DPD mutation and direct measurement of DPD activity prior to treatment with 5-FU will enable proper adjustment of dosage to prevent a dangerous adverse reaction.

Response Monitoring

To truly wipe out cancer cells within the body, it is not enough to have effective drugs that target some of the cancer growth pathways. It is important to have a way of

monitoring the cancer itself, so that drug therapy can be adjusted should the tumor change or evolve.

Response monitoring may be done by measuring **tumor markers** (biomarkers).

Summary

The term "cancer" refers to more than 100 different diseases. For most cancers, the molecular characteristics have not yet been fully classified, nor are there known or validated markers for early detection, treatment planning, or targeted therapy.

A cancer diagnosis is still based largely on structural and functional (morphological) examination of tumor biopsy specimens. Yet this approach has significant limitations in predicting a specific tumor's potential for progression and response to treatment. Personalized medicine hopes to change this.

Personalized medicine includes clinical, 'OMIC,' and environmental information

Again, remember that personalized medicine is "about you." This includes all of your traditional clinical medical information, combined with your 'OMIC' information, and is influenced by your interaction with your environment.

Personalized medicine will address the following issues:

- **"Risk assessment** – what is your risk of developing cancer in your lifetime?
- **Screening** – do you have cancer?
- **Differential diagnostics** – what is the precise classification of my cancer?
- **Prognosis and staging** – compared to other people in my classification, how aggressive is my cancer, and what are the implications for treatment?
- **Treatment selection** – how do a range of therapies compare for me with respect to efficacy and safety?
- **Treatment monitoring** – is my therapy having the desired effect with acceptable toxicity and optimal quality of life?
- **Surveillance** – is there still no evidence of disease?"

Quote from: www.genomichealth.com

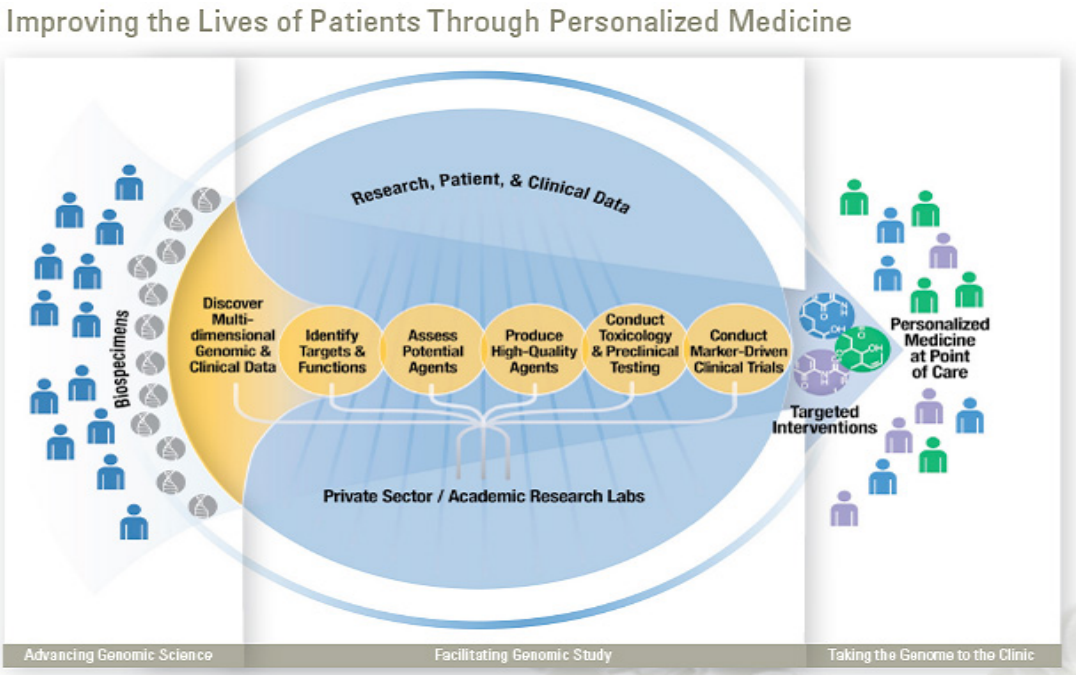


Image courtesy of the National Cancer Institute

Questions to Ask Your Doctor

- Is there a targeted therapy for my type and stage of cancer?
- Are there any specific tumor marker tests that you would recommend in my case?
- Have you already had any tumor marker tests conducted for me?
- How are these tests performed?
- If I should in fact have these tests, how often should I have them?
- If I have abnormal levels of a particular tumor marker, what does that mean?
- Would having elevated levels affect my treatment?
- Do you recommend using tumor markers in my follow-up care?
- Is it possible for me to donate my tumor tissue for future research?

Tumor markers are recognized as a promising tool that may lead to early diagnoses of cancers and more targeted treatments.

References

1. **Ginsburg, GS, Willard, H.** Geomic and Personalized Medicine, Foundation and Application. Transl Res.2009 Dec.154(6):277-877 Epub 2009 Oct 1.

2. **Baselga, J**. Personalized Medicine: Are we Hunting for the Holy Grail? Personalized Medicine in the Future. 2011 European Multidisciplinary Cancer Congress. Abstract 2 – Presented September 24th, 2011

3. **Mills, GB**. Challenges to implementation of personalized cancer therapy. 2011 European Multidisciplinary Cancer Congress. Abstract 3 – Presented September 24th ,2011

4. **American Cancer Society** www.cancer.org/ACSGuidelinesonNutritionPhysicalActivityforCancerPreventionwww.cancer.org/health/eathealthygetactive/

Resources

Chatterjee, S. Cancer Biomarker: Knowing the Present and Predicting the Future (Fut. Oncology 2005)

Curtis, C etal, Nature doi:10.1038/Nature 10983,2012

Khoury,MJ etal, Health Affairs Nov/Dec 2008 27/6/1600+1611

Mayo Clinic www.mayclinic.com/health/personalizedmedicine/Ca00078

National Cancer Institute BRCA1 and BRCA2 Fact Sheet NCI website http://www.cancer.gov/cancertopics/factsheet/risks/brca

National Cancer Institute website Definition of Personalized Medicine www.cancer.gov/dictionary?cdrId=561717

The Case for Personalized Medicine – 3rd Edition. www.PersonalizedMedicineCoaliton.org/sites/default/files/files

University of Oxford http://www.herc.oc.ac.uk/research/somatic

Understanding Tissue Donation

Introduction

If you've received a cancer diagnosis recently, you may be surprised to learn that in many cases, treatment options have not greatly changed over the past 15 to 20 years.

For many types of cancer, surgery, usually followed by radiation, chemotherapy, and/or hormone therapy, continues to represent the "standard of care".

Personalized therapy, consisting of a treatment with an agent that targets a specific molecular alteration in the cancer, may be available for treatment in a small subset of cancers, but this depends on whether specific molecular biomarkers have been identified for the particular tumor type.

In order to broaden the reach of personalized medicine to greater numbers of cancer patients, biomedical research requires help from patients, researchers, and the pharmaceutical/biotechnology industries.

- Patients need to be provided with information that helps them understand the importance of biospecimen donation; this may then persuade them to participate and donate.

- Researchers must continue to focus on identifying meaningful cancer biomarkers.

- Stakeholders must work together to identify successful means of creating additional tissue banks to facilitate and expedite the biomarker discovery process.

- Private industry, including pharmaceutical and biotechnology companies, must continue to focus on developing targeted treatments and the molecular diagnostics needed, besides conducting clinical trials to study agents' safety and efficacy.

All are crucial to fulfill the promise of personalized medicine!

For that reason, in this section, we will discuss the use of biospecimens for research.

"Biospecimens" refers to biological materials including tumor tissue, normal tissue, skin, blood (serum and plasma), hair, urine, saliva, and buccal cells (swabbed from the inside of your cheeks). All of these samples can serve as DNA sources.

Image courtesy of the University of Miami School of Medicine

For consistency in this discussion, most of the examples described will refer to solid tumors in the cancer setting. Because the term "tissue" is often used interchangeably with the term "biospecimen" and is a more familiar term, the rest of this section will refer to biospecimens as tissue.

Why tissue is needed

Cancer research would not be able to move forward without donated human tissue. Such research plays a crucial role in addressing the full spectrum of healthcare concerns regarding cancer, including:

- Prevention
- Early detection
- Diagnosis
- Treatment

In addition, as discussed throughout this module, this research has been critical to the discovery and development of biomarkers that have already made a tremendous impact in improving the diagnosis and treatment of specific types of cancer (see section on Personalized Medicine).

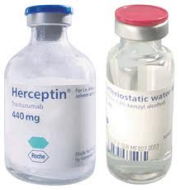
In this setting, research on human tissues enables research into:

- The identification and validation of biomarkers and the creation of biomarker tests (assays) that may predict response to a particular treatment (often called companion diagnostics).

- The identification and validation of biomarkers that improve the ability to predict individual prognosis, e.g., the presence or lack of the estrogen receptor (ER) in breast cancers. Tests that are used to measure these biomarkers are referred to as "molecular diagnostics".

Below are examples of research successes made possible by tissue donation:

Biomarkers Found	**Agents Developed**
BCR-ABL	Gleevec (CML)
HER2/neu	Herceptin (breast cancer)
K-RAS	Cetuximab (colon cancer)



C-kit	Gleevec (GIST)
EGFR	Iressa (NSCLC)
B-RAF	Zelboraf (melanoma)

For more information on these agents, please click here

Biomarkers Identified and Agents Developed

- **BCR-ABL**, an abnormal gene produced by a specific chromosomal rearrangement or "translocation", known as the Philadelphia chromosome. The altered BCR-ABL protein resulting from the Philadelphia chromosomal rearrangement is overexpressed (amplified) in most cases of chronic myelogenous leukemia (CML). Imatinib (Gleevac®) specifically targets or blocks (inhibits) the abnormal BCR-ABL protein, which is a type of protein known as a "tyrosine kinase receptor."

- **HER2-neu**, a protein on the surface of cells that is overexpressed (amplified) in approximately 25 to 30% of breast cancers and in some cancers of the stomach and the junction where the esophagus meets the stomach (gastroesophageal junction). HER2 protein overexpression leads to uncontrolled cell growth and division, and HER2 positive cancers tend to grow faster and be more aggressive than HER2 negative cancers. Trastuzumab (Herceptin®) is an agent known as a monoclonal antibody that targets the HER2 receptors, which may help keep the cancer from growing.

- Mutations of the **KRAS gene** in advanced colorectal cancer have been found to be predictive of a poor response to agents that target the epidermal growth factor receptor (EGFR), such as cetuximab (Erbitux®). EGFR is often overexpressed in colorectal cancers. The KRAS gene is involved in many EGFR pathways, and it is thought that KRAS mutations may be a possible barrier to the effects of anti-EGFR agents. Such findings are important in guiding treatment decisions for patient with and without KRAS mutations.

- C-KIT is a protein (tyrosine kinase receptor) that is mutated and abnormally activated in cells in gastrointestinal stromal tumors (GIST). The agent imatinib (Gleevec®) is a tyrosine kinase receptor inhibitor, which blocks the C-kit receptors, inhibiting cell proliferation. (As noted above, imatinib is also used in the treatment of patients with CML caused by overexpression of the abnormal tyrosine kinase receptor protein BCR-ABL.

- Patients with non-small-cell lung cancer who have mutations in a specific region of the **EGFR gene** have had an improved response to treatment with gefitinib (Iressa®) compared to patients without such mutations.

  Researchers have found that gefitinib interacts with the EGFR protein precisely in the region where the EGFR gene is mutated. Most patients with malignant melanoma, an aggressive skin cancer, have mutations of a gene called B-RAF. In those patients, the agent vemurafenib (Zelboraf®) inhibits B-RAF activity, inhibiting cell proliferation.

Cancer research takes place in many different types of facilities:

- Academic medical centers
- Community hospitals
- VA hospitals
- Pharmaceutical and biotechnology companies
- Government medical centers within the National Institutes of Health (NIH)
- Military biomedical research centers
- Centers of physical sciences.

Most, if not all, of these entities have a need for human tissue for research purposes, even when they do not have direct interaction with patients or research participants. Thus, it is important that people who may be able to donate tissue are fully informed about this aspect of research.

Tissue From Your Diagnosis

Your Pathology Report

Tumor tissue is routinely removed (or "biopsied") and analyzed to confirm or rule out a cancer diagnosis. A pathologist performs such analysis on fresh tissue, frozen tissue, or tissue that has been fixed in formalin (a preservative). The pathologist then performs the "histological examination;" (histology refers to the anatomical study of the microscopic cellular structure and function of tissues).

Histological examination may determine:

- Whether the tissue sample is sufficient to make a diagnosis. For example, does the sample contain a necessary number of tumor cells and not just normal fat cells and supporting tissue (stroma)

- Whether the tissue sample is benign, pre-cancerous, or cancerous

- What specific cancer type is found

- Tumor grade, based on a system that classifies cancer cells according to how abnormal they appear under the microscope as well as the likelihood of tumor growth and spread.

- Histological grade, based on how closely the tumor cells resemble normal cells

- Nuclear grade, based on the rate of cell division and the shape and size of the nucleus in the abnormal cells

- Whether there are areas of degenerating cancer cells (necrosis)

- Whether additional tissue will need to be removed (margin status)

- Other characteristics of the tissue requiring identification by assays

Medicare, Medicaid, and most insurance policies require that such analysis be performed in a CLIA-certified laboratory. The objective of "CLIA," or Clinical Laboratory Improvement Amendments, is "to ensure quality laboratory testing" and covers approximately 225,000 laboratory entities throughout the United States.

The pathologist documents the above information in a report, called a pathology report so that you and your medical team can use this to determine your individualized treatment plan.

After the Diagnosis, Some Tissue Remains

The pathologist stores remaining formalin-fixed tissue that is not needed for your diagnosis and embeds it in a small paraffin (wax) block. The storage of these blocks ensures their availability for outside consultations, medical-legal cases, and any necessary subsequent testing.

(These photos are taken from the website of the National Surgical Adjuvant Breast and Bowel Project, http://foundation.nsabp.org/NSABP_Pathology_Photos.aspx)

Should a patient require additional studies, the pathologist can slice additional

formalin-fixed, paraffin-embedded sections for this use.

It is possible that the newly-cut slices may not capture exactly the same cellular picture that was seen in the initial slide sample.

In addition, a hospital may not keep the blocks after a certain length of time, although it is possible that they may still be useful to the patient should subsequent treatment become necessary. State regulations determine the length of time that is required for archiving tissue samples, and such regulations vary from state to state. Generally, academic medical centers archive tissues longer than community hospitals do so. Some facilities never discard tissue samples.

Formalin-fixed, paraffin-embedded (FFPE) tissue is one of the most widely used methods of preserving and archiving clinical samples. Hospitals, tissue banks, and research laboratories worldwide currently hold over a billion tissue samples. (1)

Organizations like the Joint Commission and the College of American Pathologists issue guidelines and recommendations for the storage of tissue samples at hospital pathology units.

This photo shows pathologist S. Paik in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Tissue Repository. Tumor blocks are held in similar archives in hospital laboratories around the world.

Moving Forward

The work performed by today's cancer research scientists has moved far beyond the histological examination performed by the clinical pathologist. They focus their efforts on the diagnoses and treatments of the future. They use sophisticated technology to conduct molecular analysis and to analyze the genetic makeup of normal and tumor tissue, the proteins expressed, specific genes, and proteins that drugs can target. They need tissue to make this research possible.

Common Misunderstandings

Many clinical studies that require tissue involve studying genes. The term "genetic research" is not restricted to research on gene changes that cause inherited cancers. Unfortunately, some patients may refuse to participate in studies or to donate tissue due to this misunderstanding.

Rather, genetic research is an umbrella term that can include research into inherited genetic mutations, acquired (somatic) genetic mutations, and common genetic variants that may predict risk of disease, response to treatment, risk of side effects from a treatment, or confer protection from a disease.

Hereditary genetic mutations, such as mutations of the BRCA1 or BRCA2 gene associated with increased risk of breast, ovarian, and other cancers, can be passed down from parent to child over generations. In contrast, a somatic or acquired genetic mutation occurs during a person's lifetime and is not passed down to children.

In addition, people often do not understand that tissue donated by patients with a specific disorder may be used in the future not only for research on the disease in question, but also for research on other diseases and by researchers at different institutions.

(See "Consensus Statement: Informed Consent for Genetic Research on Stored Tissue Samples," JAMA 1995). Informed consents for patients who are interested in participating in clinical studies, undergoing surgery, and/or donating tissue include information about the future use of donated biospecimens.

Opportunities to Donate Tissue

There are various ways to donate tissue. As explained earlier, your pathologist uses tissue taken at the time of your biopsy and/or surgery to help make a diagnosis. There is often remaining tissue that you can donate to help researchers better understand cancer and/or to identify new biomarkers that may ultimately lead to new drugs.

Always consider asking your doctor if you can donate your extra tissue.

Extra Diagnostic Tissue Donation

Patients with small tumors may not be candidates for donating tissue. But in most cases, tissue remains after that used for diagnosis. For obvious reasons, many patients find it easier to donate blood, urine, saliva, and hair for research. However, the need is greatest for solid tumor tissue, particularly for rare cancers or rare subtypes of common cancers.

Active research centers routinely request permission from patients to use tissue that will be removed during surgery but will not be needed by the pathologist for diagnostic purposes. Patients may give their permission when they sign their informed consents for surgery.

CISN Tip: *If you are unsure whether you have consented to donate your tissue, locate your consent for surgery and read the fine print. In the days, hours, and minutes leading up to surgery, some patients may be reluctant to read about the possible side effects of anesthesia or surgery and/or may later forget the details provided during the consenting process.*

Clinical trial tissue donation

Patients enrolled in clinical trials increasingly are receiving requests for tissue in the informed consents for their studies or as a separate consent addendum. These studies may require tissue samples to help identify the genetic or protein targets of an investigational drug or to determine the characteristics of individuals who respond best or who do not respond at all to the research agent. Such studies are referred to as “correlative studies.”

Correlative studies tend to be exploratory in nature. Depending on the clinical trial design and other factors, they may require or request fresh tumor material, blood, or urine. In addition, some might request a tissue sample from the patient’s FFPE tumor block.

As noted above, different states vary in the length of time required for the archiving of tumor blocks. Once this time lapses, many hospitals, particularly community hospitals, discard the blocks to make room for new ones. Some research centers have

created “discarded block programs” that permit them to obtain such blocks for research purposes, and many research hospitals never discard tumor blocks at all.

Extra Tissue Samples

Some studies will request additional biopsies. In such cases, researchers may request access to the initial tissue sample (obtained during biopsy or surgery) and a second or possibly additional tissue samples at later times based on specific criteria.

This is most frequently encountered in research studies that assess whether a particular drug or treatment has caused changes in the tissue that may predict response.

Confidentiality:

Identified or De-Identified Tissue Specimens

Tumor tissue often can be “**identified,”** meaning that the hospital or research center is able to link the information derived from the material to the specific patient. In such cases, researchers can access information about the patient’s diagnosis, treatments, and outcome.

Tissue samples may also be **“de-identified,”** meaning that they are provided to researchers without any information that could identify the tissue donor, consistent with HIPAA regulatory procedures. HIPAA refers to the Health Insurance Portability and Accountability Act, which includes provisions concerning the security and privacy of health data.)

Linking Patient Tumors with State Cancer Registries

Some research takes place without patients’ knowledge. Once a pathologist’s analysis of a tissue specimen is completed and a cancer diagnosis has been made, the

anatomic pathology laboratory information system (LIS) transmits the diagnosis, which is a "reportable event," to the hospital cancer registry and the state cancer registry. The state cancer registry creates a record of the patient's cancer in the cancer registry record.

State-based cancer registries are data systems that collect, manage, and analyze data about cancer cases and cancer deaths.

Established by Congress through the Cancer Registries Amendment Act in 1992 and administered by the Centers for Disease Control and Prevention (CDC), the National Program of Cancer Registries (NPCR) collects data on the occurrence of cancer, the type, extent, and location of the cancer, and the type of initial treatment.

Factors Affecting Tissue Quality

The conditions under which tumor tissue is collected, fixed, preserved, and stored is also an ongoing focus of research, since donated tissue is an invaluable resource.

The life cycle of tissue

All tissue taken from the bodyundergoes a series of steps that must be standardized, documented, and carried out accurately to ensure that the tissue is useable for research. We will discuss each of these steps below.

- Collection
- Processing
- Storage
- Analysis

The image below demonstrates these steps:

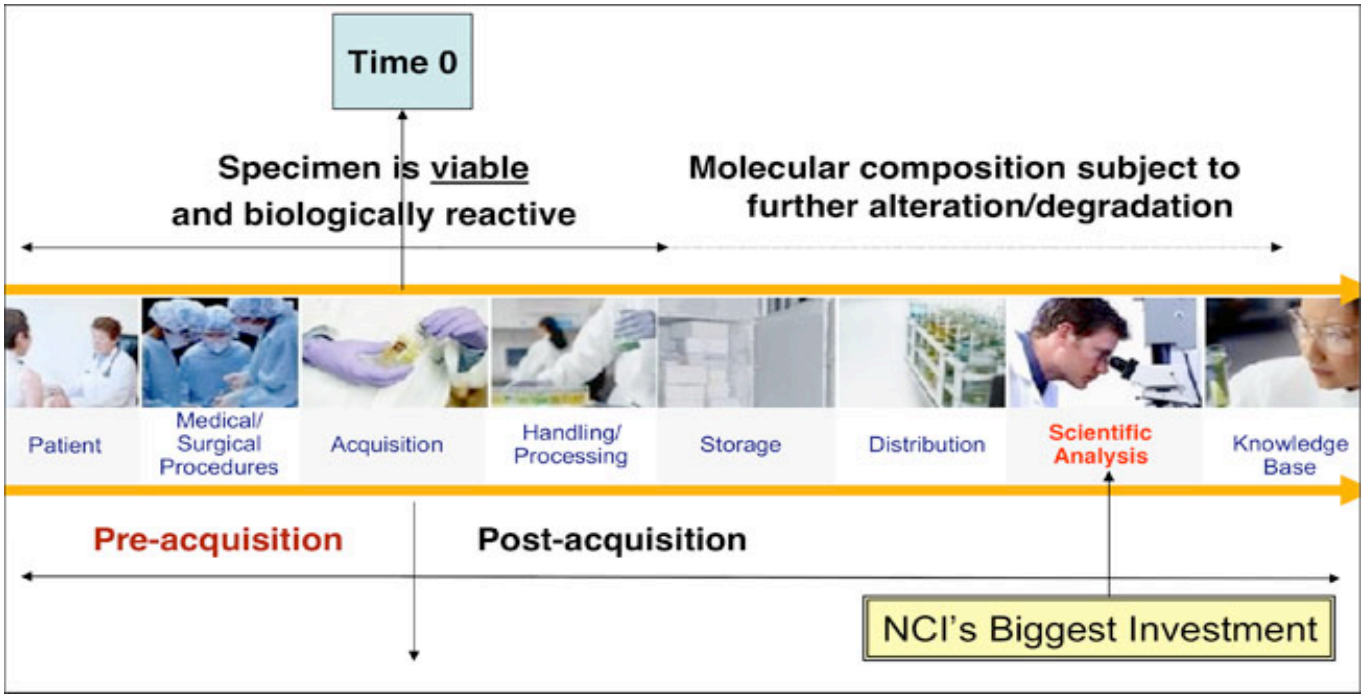


Image curtsey of the National Cancer Institute

Collection

This term refers to how tissue is obtained from an individual. At the collection stage, there are multiple factors that can affect the biomarkers present in your tissue. Called pre-analytes, these factors may affect the tissue before it is processed, stored, or analyzed.

One study that sought to evaluate the frequency and nature of mistakes made in a laboratory found that pre-analytic mistakes constituted 68% of all errors.

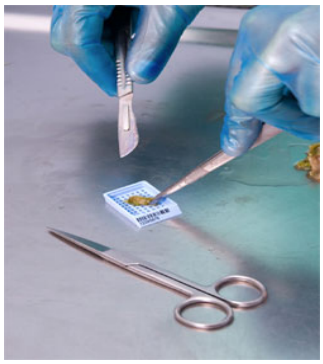
Some examples of pre-analytic factors include the use of anesthesia during surgery. The compounds used for anesthesia can infiltrate the blood supply and tumor tissue and affect its composition.

Clamping of the veins and arteries during surgery represents another pre-analytic factor. Clamping to reduce bleeding deprives the tumor of its blood supply, thus altering the quality and attributes of the tissue, and has the potential to affect the biomarkers that will be measured in the tissue. The presence of specific biomarkers and the ability to measure such markers effectively is important because it may suggest whether specific treatments are right for a particular patient.

Successful tissue retrieval requires the surgeon's hand-off to knowledgeable personnel who can handle the tissue appropriately. A trained responsible individual must transport the tissue from the operating room to the lab where it will be preserved.

Processing

Once the tissue is collected from the body, the next step is called processing.



This refers to the handling of the tissue to prepare it for testing or storage.

Laboratory technicians must be available in a timely manner to preserve the tissue or otherwise handle it for clinical or research purposes. Temperature, time, and the fixative used all play a crucial role in proper processing.

For example, it is important to consider the temperature of the lab in which the tissue is held while awaiting preservation; the temperature of the storage facility; the effects of freezing and thawing, including multiple instances of freezing and thawing the same sample; the amount of time spent in fixative; and the time spent in storage, since long-term storage can lead to degradation of the sample.

The optimal conditions for tissue collection, processing, and storage will depend on the tissue type, the assays that need to be performed, and whether the tissue will be used for a clinical (diagnostics and treatment) or a research application.

Storage

Tissue is often stored in large facilities called biobanks that may be located within hospitals, research centers, or private facilities.

Though research units that store biospecimens may differ, at a minimum, they include some form of cryogenic (freezing) facility for tissues that must be kept frozen and a shelving and identification retrieval system.

Some units may also be linked to data sources that provide information about the variables to be studied (type of disease, outcome, treatment received, individual characteristics).

In its "Best Practices for Biospecimen Storage," the National Cancer Institute calls for:

- Standardized protocols for storage, depending on the tissue type extracted (e.g., wet tissue, frozen tissue, paraffin-embedded tissue, blood, serum, urine) and the biomolecules to be analyzed (e.g., RNA, DNA, proteins, lipids).

- Security warnings that will monitor the function of the storage equipment and alert personnel to any power failures

- Limiting biobank access to specific individuals who are knowledgeable about privacy procedures.

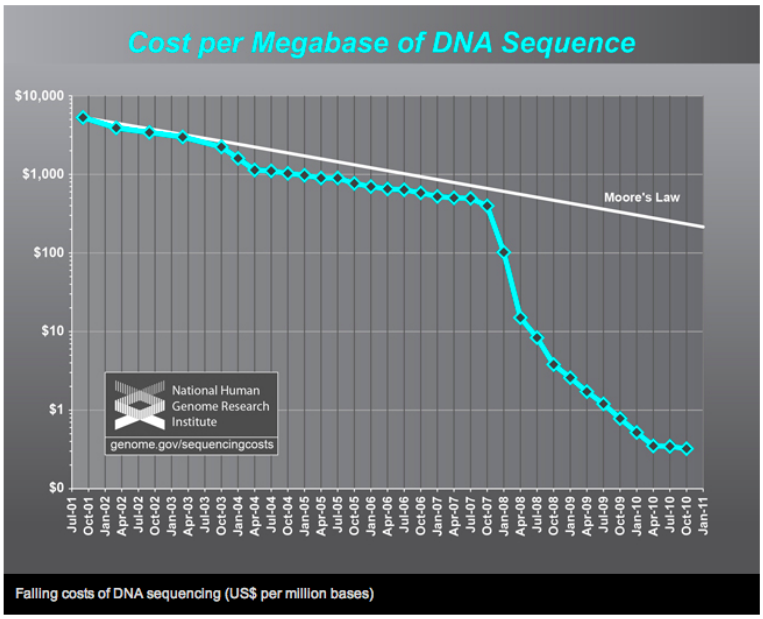
The guidelines, which are extensive, are located at

http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf.

Analysis

Tissue testing or analysis also needs to be standardized to enable accurate comparison of results.

Advances in genetic sequencing and molecular analytic technologies have increased the call for high-quality biospecimens. Some analyses can be performed with minute amounts of tissue. Tests that previously could only be performed with fresh tissue can now be conducted with paraffin-embedded tissue.



As shown in this slide from the National Human Genome Research Institute, the cost of DNA sequencing has dropped significantly since the mapping of the human genome.

The analysis of each biospecimen generates an enormous amount of data. This type of research also requires numerous specimens to note trends in patient cases.

Daniel MacArthur, a UK-based geneticist who writes about "consumer genomics" and blogs at genomesunzipped.org, noted in the February 21, 2011 issue of *Wired Magazine*, "Our ability to create genetic data is rapidly out-stripping our ability to store and analyze it."

Following is a discussion of additional hurdles that must be overcome on the path to personalized medicine.

The importance of standardization

Both clinical and tissue research needs to be standardized at all the stages listed above. Many groups and agencies are involved in working to achieve this.

The National Cancer Institute (NCI)'s Office of Biorepositories and Biospecimen Research has noted that, "The lack of standardized, high-quality biospecimens has been widely recognized as one of the most significant roadblocks to the progress of cancer research."

The NCI has also conducted a review of the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. This review resulted in a document entitled, "**NCI Best Practices for Biospecimen Research."** Comprehensive in scope, it identifies technical, operational, ethical, legal, and policy best practices to "ensure a level of consistency and standardization across biospecimen resources."

For more information, please visit: http://biospecimens.cancer.gov/practices/ or https://cabig.nci.nih.gov

Informed Consent

As stated earlier, there is a tremendous need for cancer patients to donate tissue for cancer research. If you are interested in doing so, you will be asked to sign an informed consent document. It is important for you to understand the issues below, so that you can appropriately balance any potential risks with the possible benefits.

The phrase **"informed consent"** refers to the process of communication between a patient and a physician to help the patient understand a proposed medical intervention and results in the patient's authorization or agreement to undergo a specific medical intervention (American Medical Association).

In the context of research, it applies to a legally effective process indicated in the United States Health and Human Services Code of Federal Regulations (45 CFR 46.116 and 45 CFR 46.117)...

- In which a research participant or a legally-authorized representative receives all information necessary to make an informed decision,
- that has facilitated his or her understanding of what has been disclosed by providing the ability to ask questions about the research and through having questions asked of him or her to measure understanding,
- and that promotes a voluntary decision.

The informed consent process will include discussion of the fact that information gained from patients' tissue donations might not benefit the patients personally, but may provide important data that ultimately could benefit patients in the future.

An informed consent document should include the following items:

- What kinds of data will be collected and how the data will be used and stored
- The patient's willingness to be contacted about the use of his or her biospecimens and/or data in future research studies
- Any benefit or potential risk to the patient, the patient's family, and his or her community, e.g., whether there is a risk of stigmatization and discrimination based on research results
- Whether individual or aggregate research results will be released to the patient, the family, or the provider and, if so, the mechanism for communicating such results
- The type of research that will be conducted, e.g., concerning specific cancer type or looking at all possible disease conditions
- Possible benefit to the investigator or institution and information concerning potential conflicts of interest
- How the patient can discontinue participation and withdraw consent

Ownership

While it is agreed that pathology departments within hospitals and medical centers are the "recognized legal guardians" of tumor blocks, the ownership of tissue question persists. This question also arises when scientists determine that tumors could prove useful for research purposes, in particular, to generate a "cell line."

A recent bestseller entitled *The Immortal Life of Henrietta Lacks* by Rebecca Skloot chronicles the story of the first research cell line, called HeLa, created from the cells of a woman whose very aggressive cervical cancer took her life. The cell line made early advances in biomedical research possible, but ultimately prompted crucial questions about our beliefs and ethics.

It is important to note that many informed consent documents for use of tissue specimens will include template language that grants permission to the researcher for establishment of a cell line from the tumor of the patient/research participant. This document most often includes language declaring that the donor of the tissue has no right to any products resulting from the research.

Questions for Your Doctor About Donating

"The informed consent says that the researcher will perform genetic research. What does this mean?"

Many individuals are unclear about the meaning of the term, "genetic research." Ask whether the research involves genes involved in inherited disease and if there are potential consequences for your privacy. In many cases, the research may focus on acquired genetic alterations, genes that may predict response to a specific treatment, common genetic variations called SNPs (single nucleotide polymorphisms), the silencing of genes that may confer risk or protection (epigenetic alteration), or other aspects.

"Should I donate tissue?"

When deciding whether to participate in research or donate tissue, it is important to do so knowledgeably and comfortably. The overwhelming majority of research participants have done so without adverse consequences.

Ask your doctor about the nature of the research to be performed and any potential risks. Protect yourself by noting any possible conflicts of interest.

"Does the investigator or the institution have a financial interest in the research?"

Institutions allow researchers to receive small amounts of money from pharmaceutical and biotechnology companies to conduct the research. Any amount in excess of this constitutes a "conflict of interest." More frequently, institutions prohibit researchers with a financial stake in the research from taking part in the study.

"If I donate tissue, how do I know if my identity will be linked to the tissue or de-identified?"

Ask the physician or researcher whether the hospital/research center will be able to link the information derived from the material to you or whether the tissue specimens will be de-identified and have all links to you as the patient/research participant removed.

Linking is often an option on the informed consent document, but be sure to check with your doctor to clarify this point. Although de-identified samples may be more protective of your privacy, they do not provide researchers with the ability to access your medical records to see how your cancer responded to treatment. This lack of ability to match the research done using your tissue with your outcome slows down the advance of personalized medicine.

De-identified specimens must meet two criteria to be exempt from the federal requirements for the protection of human subjects.

1- The samples must be in existence at the time the research begins (no procurement for the sake of the research study).

2- Identifiers must be irretrievably removed from the information or samples that will be studied.

(Taken from 45 Code of Federal Regulations §46.101(b)(4) 1994)

US federal regulations allow for de-identified specimen collection without formal informed consent from the patients whose samples are included. Some studies have indicated that patients prefer to support biobanks that give them the opportunity to opt out.

"Will the information about my tissue be made available to me?"

This will depend on the type of research study. In many cases, research takes a long time to complete and researchers may prefer not to commit to this extra step.

"What are my rights?"

The law stipulates that you can withdraw from a study at any time. You can also withdraw your tissue donation.

CISN Summary

Current research strategies are greatly enhanced by the contribution of tissue by patients – those with cancer and those without.

This is the only way science can make advances in "personalized" medicines so doctors can treat tumors based upon specific targets.

Resources

http://www.cancer.gov/cancertopics/factsheet/Information/donating-tissue-research

The National Cancer Institute Office of Biorepositories and Biospecimen Research

http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html

References

Weining Tang et al, "DNA Extraction from Formalin-Fixed Paraffin-Embedded Tissue, Cold Spring Harbor Protocols, 2009.

Dry, S, "Who Owns Diagnostic Tissue Blocks?, Lab Medicine, February 2009, Volume 40, Number 2

Consensus Statement: Informed Consent for Genetic Research on Stored Tissue Samples, Journal of the American Medical Association, December 13, 1995

The Center for Disease Control (CDC) Website, www.cdc.gov/cancer/npcr

Sandusky, G, Dumaual, C, and Cheng L, "Human Tissues for Discovery Biomarker Pharmaceutical Research: The Experience of the Indiana University Simon Cancer Center – Lilly Research Labs Tissue/Fluid Biobanks", Veterinary Pathology 2009 46:2

Compton, C, Ph.D, "Getting to Personalized Medicine: Taking Out the Garbage" Cancer October 15, 2007, Volume 110, Number 8

Sherman, ME, Figueroa, JD, Henry, JE "The Susan G Komen for the Cure Tissue Bank at the IU Simon Cancer Center: A Unique Resource for Defining the "Molecular Biology" of the Breast, Cancer Prevention Research, 2012;5:528-535.

Brothers, KB, Morrison, DR, Clayton, EW 2011. Two large-scale surveys on community attitudes toward an opt-out biobank. American Journal of Medical Genetics Part A 155;2982-2990

Langseth, H, Luostarinen, T, Bray, F, Dillner, J, "Ensuring quality in studies linking cancer registries" Acta Oncologica, 2010;49:368-377''

ETHICS

Introduction

It is important for newly-diagnosed cancer patients and their family members to understand the ethical implications of personalized medicine. Although some patients may currently benefit from research that has already identified targeted therapies for their specific cancer types, this field is relatively new, and much work is still in progress.

Therefore, patients may need to consider the following questions:

- If available, should they have a genetically-based test to determine the possibility of benefiting from a specific targeted therapy?
- If a patient is diagnosed with a cancer associated with known inherited genetic mutations (e.g. specific mutations of the BRCA1 or BRCA2 gene in breast cancer, ovarian cancer, and other cancer types), should family members receive genetic testing to help determine their risk?
- Should patients agree to donate their tissue for research?

In assessing these options, lit is important for cancer patients to understand the implications that such decisions may hold for them and their family members.

Stakeholders

Although personalized medicine holds great promise, the associated challenges are not limited to the science behind it. Several public policy and ethical challenges exist that must be addressed before personalized medicine can fulfill patient needs safely and effectively..
All stakeholders must be actively engaged in overcoming these challenges, including:

- Physicians
- Hospitals and cancer centers
- Private insurance companies
- Medicare and Medicaid
- Drug and biotech companies
- State governments
- Federal government
- Advocacy organizations
- And, of course, patients.

All stakeholders must work together to study carefully the multiple ethical, legal, and social issues raised by this research to help fulfill the promise of personalized medicine while ensuring patient protection and preventing any misuse of new genetic technologies and information.

The Promise

The overarching promise of personalized medicine is to optimize medical care and outcomes for each individual.

It recognizes that the best treatments, medications, dosages, and preventive strategies may differ from person to person--resulting in customized patient care.

Personalized medicine takes into consideration that all human diseases have both molecular and environmental components. The study of genetic variation has proven to be more complex than previously imagined, but is steadily moving forward. Proteomics and Metabolomics are still in the early stages of study and are not yet used routinely in the clinic, but the potential is great.

Traditional Care Model

Traditionally, during a doctor's visit, patients would explain their symptoms, answer questions concerning their past and present medical history, report their family medical history, and in some cases may undergo diagnostic procedures, such as x-rays and blood tests. Patient diagnosis and treatment are determined based on clinical presentation, medical history, lifestyle factors, and test results.

Future Care Model

Personalized medicine is an evolving model of healthcare delivery that determines appropriate treatments based on each patient's unique characteristics. A significant difference between personalized medicine and the traditional model of care is the use of an individual's genomic information, where molecular data is used to determine appropriate treatments. (Steele, 2009).

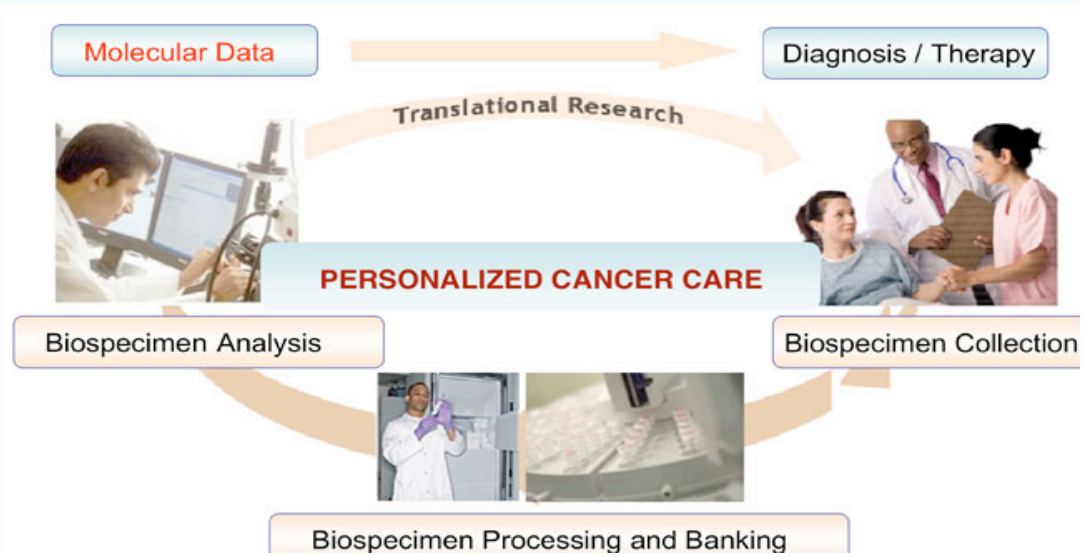


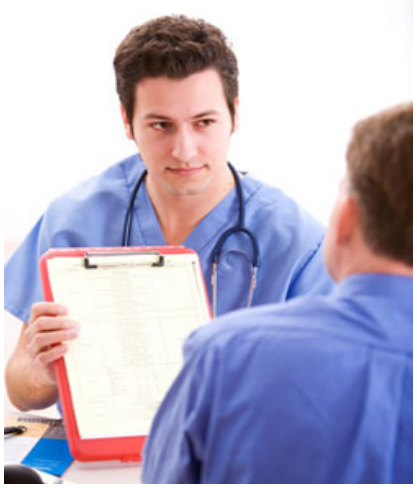
Image Courtesy of the National Cancer Institute

Expected Improvements

The current model of bringing a drug from "the bench to the bedside" is slow and costly (Rochman, 2012). With increasing understanding of the human genome and the molecular level of disease, there is increasing potential for more efficient, effective methods to successfully treat the right patients with the right therapies at the right time.

Patient awareness issues

Genetic information is biologically linked to individual identity, making personalized medicine an intimate and serious process. Although the promise of improved outcomes is real, there will be much more information about each person's genomic makeup in their medical records.



Today and on an ever-increasing scale, every person seen by a doctor will encounter either choices made for them or choices they will be asked to make about genomic data gathering.

Image courtesy of CISN archives

Routine Clinical Care

1. As part of every cancer patient's diagnosis, genomic testing is already being done on their cancer tissue and documented in their pathology report.

   Many more of these tests will become routine as the field progresses. Individuals will not be asked for permission to test, as the information will be seen as necessary for correct diagnosis and staging. **This information will be in their medical record and linked to them.**

   For example:
   - Hormone status of tumors: i.e., ER + or –
   - Genomic mutations present, i.e., KRAS, Her2-neu

2. Patients may, in addition to the automatic testing now done for diagnosis, ask for genomic tests that reveal if inherited mutations (BRACA1,2) are present. Or they may request biomarker or genomic tests (such as Oncotype DX) that may provide more detailed information about their cancer. **This information will be in each patient's medical records and linked to them.**

Research

1. As part of their cancer surgery, patients may be asked to donate additional tissue for biomarker research. Sometimes this "ask' is buried in the surgery consent document and not specifically discussed. So be sure to either read the document or ask if your tissue will be used in cancer research. **This data may or may not go in a patient's, medical record so it may or may not be linked to them – patients must ask.**

2. Patients may be asked and agree to participate in a clinical trial to test new therapeutics'. Usually tissue donations that will be used to look for biomarkers will be part of the clinical trial. **This data may or may not go in a patient's medical records so it may or may not be linked to them – patients must ask.**

Patients who are considering participating in genetic research should fully understand the purpose of such research and the expected outcomes. This information should be provided during the informed consent process.

A "Patient Friendly" Informed Consent

Personalized medicine depends on tissue (biospecimen) research to identify new biomarkers. Patients may be asked to consider participating in a clinical trial and to donate tissue for the purposes of the study. Or they may be asked to donate tissue as part of providing their consent for surgery. In the latter scenario, it is important to note that the consent for tissue donation may be buried in the surgery consent form. Patients may also ask their doctors directly whether they can donate tissue.

Many agree that the consent process is generally not "user friendly" for patients. Informed consent documents often include lengthy and complex terminology written in scientific, medical, and legal language.

People are often unfamiliar with and may be easily intimidated by such terminology.

Image courtesy of CISN archives

The consent process may therefore be overwhelming and confusing for some patients, particularly following a cancer diagnosis when emotions may run high, thoughts may be scattered, and a person's ability to think logically may be clouded by the need to make many challenging and life-altering decisions.

What Patients Need to Understand

If patients consent to donate their tissue, they should have a full understanding of how their genetic biospecimen and data will be used, including:

- What research will be conducted for the present study and in future studies
- What benefits may result from the research
- How the information will be used and what information may be revealed about participants who donated their tissue for this research
- Which entity owns the donated tissue

It's crucial for patients to ensure that they receive a clear, thorough explanation during the consent process and that they ask the questions listed above.

Doing so will help to achieve truly "informed consent" and to prevent inappropriate use of genetic specimens and related data.

Image from CISN archives, all rights reserved

For more detailed information on the topic of tissue donation, please go to our section on tissue donation.

Ethical Challenges

History has shown that genetic information can be used for good or for bad purposes.

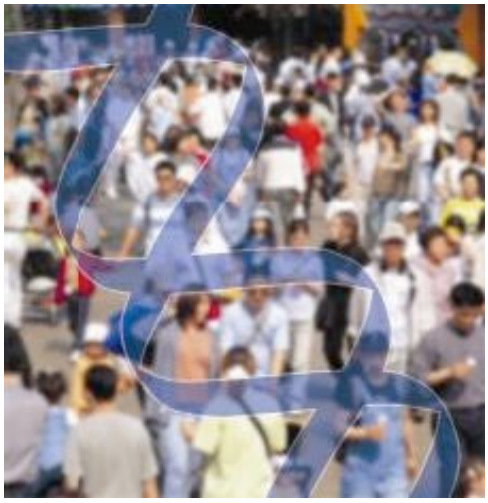
With the technological advances seen in the last several decades, genetic information now can be used to enhance cancer risk prediction, diagnosis, and treatment.

Personalized medicine relies heavily on the use of genetic information and tumor biomarkers to determine cancer molecular subtypes and to predict an individual's response to particular therapies (McKinnon & Anderson, 2011).

Access

Access to Targeted Therapies

Fulfilling the promise of personalized medicine must take into account the question of access—that is, which members of society will actually have access to targeted therapies and whom will benefit most (Fleck, 2010).



Many people are without health insurance today, and many more have insurance plans with only the most basic coverage.

How can access to personalized medicine be provided to everyone? Is access for everyone a reasonable goal? Is it an attainable one?

There will likely be several levels of personalized care. If universal access is a goal, what level is acceptable? Is a tiered system ethical, where those who cannot afford to pay receive some level of service, while those who can afford the associated costs receive more comprehensive care? If the level of access will resemble that provided by our current healthcare system, this may be unacceptable to some people whose needs are not met.

Disparities in access to treatment, cancer-related health status, and health outcomes are the result of multiple factors in addition to genetics, including social factors such as income, education, occupation, geographic residence, etc. (Wolinsky, 2011). All are crucial considerations that must be taken into account by all stakeholders

Access to Test Results

The question of access to genetic test results and how the information is used also raises ethical and legal issues related to personalized medicine (Vickers, 2006).

If patients seek to know more about their genetic makeup, what are the implications for their family members?

Do family members have a right to learn about the patient's genetic results or the choice to refuse receipt of such information? Such questions need to be considered and discussed before testing is performed.

Image from CISN archives, all rights reserved

Access to Data

Risk prediction is an important component of personalized medicine, but it requires a fairly large sample of individuals. One of the most promising methods of risk prediction is achieved through the use of data collected by hospitals.

This is called a "secondary use" of health data, since it is not being used for its original purpose of making a diagnosis about the patient from whom it was collected (Hawkins, 2010).

There are additional potential secondary uses, including assessment of data for pharmacogenomic drug development, another important goal of personalized medicine.

In these cases, people other than patients and their medical teams have access to patient genomic data to work on solutions that may help others in the future. Policies must be developed to allow such data sharing while protecting patient confidentiality and preserving the right to opt-out of these uses.

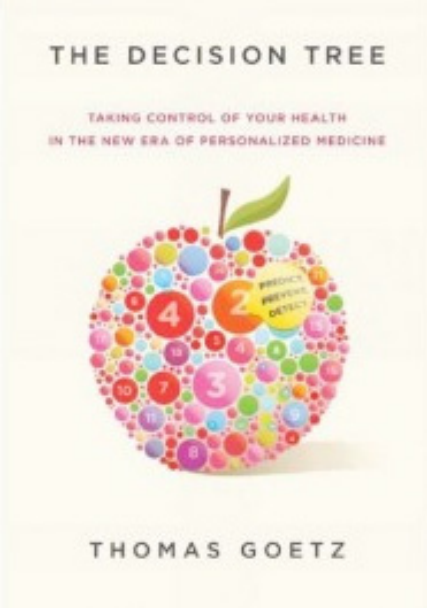
Image from CISN archives, all rights reserved

Access To Genetic Counseling

Deconstructing a disease at its molecular level and developing an effective targeted therapy is a remarkable feat that once would have been viewed as science fiction. But today, personalized medicine is a reality for some patients and may soon become possible for many more. Accordingly, there is a crucial need for a well-equipped and appropriately trained professional workforce to help patients understand their choices.

Genetic counseling is a complex process intended to guide individuals through an intimate, life-altering, and sometimes painstaking decision-making process. The profession requires a highly-specialized knowledge and skill base to educate and help people effectively through multifaceted decisions about their own health and possibly the health of their relatives (Owens et al., 2009).

Because decision making after a cancer diagnosis can be extremely difficult, genetic counselors must be able to assist individuals effectively without seeking to fulfill their own agendas (Lebel, 2005). They should maintain an impartial and unbiased attitude about their patients' personal beliefs, values, and goals. Genetic counseling should always accompany research that discloses genetic information.



However, some people may not be willing and/or capable of processing technical risk-assessment data obtained from new "omic" tests (Annes, Giovanni, & Murray, 2010).

Decision-support tools will also be essential to guide treatment decisions based on such test results, as the psychological impact of this type of information may be complex.

Image courtesy of Wired magazine Executive Editor Thomas Goetz

Oncology nurses should have basic knowledge at least concerning genetics and genomics, since they serve at the front line of cancer research and are often the "go to" person for patients with questions and concerns. (Lea, Read, & Williams, 2011).

Just as personalized medicine is evolving, so too will the roles and responsibilities of genetic counselors and the need for an adequate workforce of these professionals. There is concern that even healthcare providers in general may lack sufficient understanding about genetics, though many are still expected to provide genetic-related clinical information and services (Owens et al., 2009).

Privacy

Ensuring adequate protection of patient privacy is another crucial area that must be addressed before many people will be willing to take advantage of personalized medical care. Most agree that patients have a right to keep details about their health confidential from most people and entities. But how far does that right extend? Does it cover information about a person's genetic makeup?

For example, if a patient's genetic information is collected for use in risk profiling or diagnosis, should he or she be committed to allowing the use of the data for diagnosing and profiling others? When patients donate tissue for risk profiling, they are often asked for such permission. While this can be done without patient identifiers, this information is in effect "personally identifying," so it can never be truly anonymous.

Yet secure data sharing is absolutely necessary to develop the field of personalized medicine and the knowledge base around it.

This measn the need exists for a number of entities to have access to these biospecimens, including researchers, clinicians, and pharmaceutical companies.

While this may be necessary to enhance the benefit of personalized medicine, mass accessibility to biospecimens increases public concern about privacy and confidentiality (Hawkins, 2010).

There are three important safeguards needed concerning genetic information:

1) A thorough and transparent consent process about potential risks and benefits

2) The ability to isolate genetic information from electronic health records (EHRs) during information exchange. The inclusion of such data in EHRs is crucial, but privacy concerns must be addressed.

3) Addressing the inadequate protection against genetic discrimination offered by the Genomic Information Nondiscrimination Act (GINA) (Francis, 2010).

Discrimination

One of the possible significant barriers to genetic testing is the fear of discrimination from an insurer, or even worse, an employer. This fear has been indicated in several polls, including a Harris Poll in 2002.

Many patients fear genetic discrimination using information obtained from an individual's genome. Genetic non-discrimination laws have been enacted in most US states, and at the federal level, by the Genetic Information Nondiscrimination Act (GINA).

GINA prohibits insurance companies and employers who offer group insurance from discriminating on the basis of potential genetic conditions for asymptomatic individuals. However, because it does not control insurance rates for those diagnosed with a genetic disease (Clayton, 2003), this is inadequate protection.

Even with this legislation in place, the fear of genetic discrimination prevents some individuals from undergoing genetic testing (Clayton, 2003). Some individuals even pay for testing themselves to prevent their insurers from learning which genetic tests they have had and result they've received.

Along with the translation of personalized medicine into clinical practice and the currently inadequate protections in place comes the possibility that insurance companies will use genetic information to deny or discontinue coverage in the future.

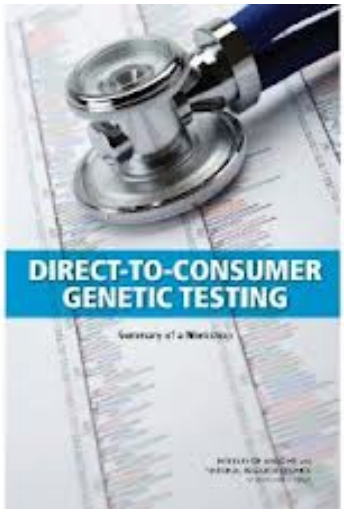
This is a very real concern that again must be addressed by all stakeholders.

Patients who are interested in donating their tissue must be sure to discuss any privacy concerns they may have with their doctors.

Other Important Issues

Direct-to-Consumer Testing

Traditionally, genetic tests have been available only through healthcare providers, such as physicians, nurse practitioners, and genetic counselors. Healthcare providers ordered the appropriate tests from a laboratory, collected and sent the samples, and interpreted the test results, so that patients would receive the support they needed when their results were disclosed.



"Direct-to-consumer" genetic testing refers to genetic tests marketed to consumers via television, print advertisements, or the Internet also known as "at-home genetic testing."

Such testing provides specific genetic information directly to a patient without necessarily involving a doctor or insurance company in the process.

Because there is little regulation of these commercialized tests, there is the risk of obtaining inaccurate results and unsupported clinical interpretation, since physicians do not yet know how to assess results from home tests. Furthermore, the clinical utility of these results remains undetermined (Khoury, et al., 2008).

If left unaddressed, the use of direct-to-consumer genetic testing may become increasingly problematic. The general public and health professionals at all levels need further understanding of genetics overall, as well as genetic testing and its implications, to adequately prepare our society for personalized medicine (Ojiha & Thertulien, 2005).

Biobanks

Biobanks are used to process and store collections of human biological tissue specimens and related health data. These biospecimens are important in increasing the understanding of the many aspects of disease, including disease risk prediction, prevention, identification, diagnosis, and treatment.

As noted previously, there are numerous ethical, social, and legal considerations that must be taken into account concerning biobanks including, but not limited to,

informed consent, confidentiality, secondary use of sample data over time, return of results, and data sharing (Hawkins, 2010).

Biobank repositories vary in size, research scope, sample types, availability of related healthcare information, collection procedures, and funding sources.

Image courtesy of Duke University

Although there is strong societal support for innovative medicine like genomics and pharmacogenomics, they cause major concern around potential loss of privacy and social discrimination (Hawkins, 2010).

Additional considerations surround the collection, use, and storage of biospecimens.

For example:

- How will donors be protected if there is accidental release of information?
- Once a sample is donated, who has the right to ownership?
- What occurs if a biobank closes or is bought out by another company?

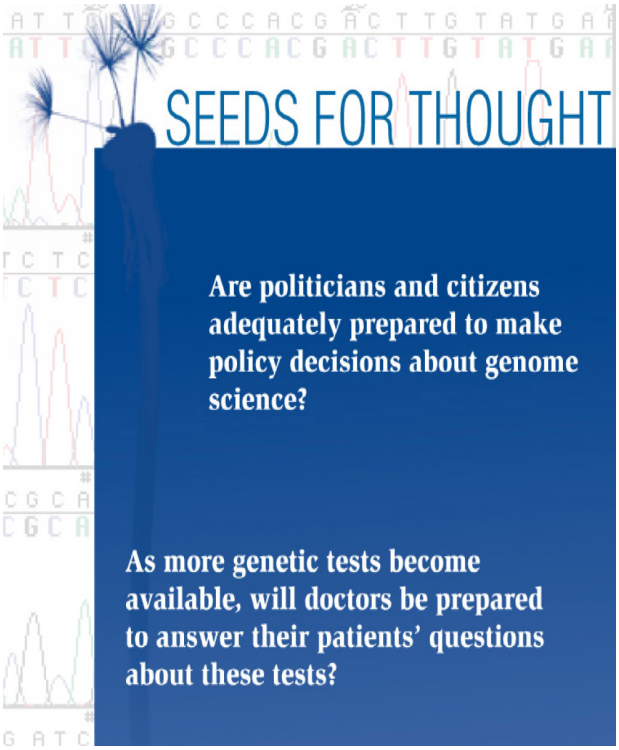
Though these important questions remain unanswered, technological advances in personalized medicine will continue to increase the need for biospecimens.

Summary

As an evolving medical model, personalized medicine, promises to offer safer and more effective cancer treatments by "matching" drugs to a person's individual information at the molecular level--the individual's "molecular fingerprint."

Though the promise of personalized medicine is exciting, there are several associated ethical considerations that must be resolved.

Major challenges associated with personalized medicine include:



- Privacy concerns
- Access to testing
- Access to results
- Cost of targeted therapy
- Prevention of genetic discrimination
- Clear informed consent
- Psychosocial impact
- Access to genetic counselors
- Access to decision-aid materials

Image courtesy of National Human Research Institute

Comprehensive informed consent is necessary to ensure that research participants understand risks to privacy. Genetic counselors play a crucial role in helping to educate patients about genetic privacy concerns as well as guiding them through complex, life-altering decision-making regarding cancer treatment and outcomes.

All stakeholders must be actively engaged in addressing the important ethical and public policy issues surrounding personalized medicine.

References Cited

Annes, J. P., Giovanni, M. A., & Murray, M. F. (2010). Risks of presymptomatic direct-to-consumer genetic testing. *New England Journal of Medicine, 363*(12), 100-101.

Clayton, E. W., (2003). Ethical, legal, and social implications of genomic medicine. *New England Journal of Medicine, 349(6)*, 562-569.

Evans, J., Dale, D. C., & Fomous, C. (2010). Preparing for consumer-driven genomic age. The *New England Journal of Medicine, 363(12)*, 1099-1103.

Fleck, L. M. (2010). Personalized medicine's ragged edge. Retrieved March 3, 2012 from http://www.thehastingscenter.org/Publications/HCR/Detail.aspx?id=4854.

Francis, L. P. (2010). You are born with your genes: Justice and protection against discrimination in the use of genetic information. *Mount Sinai Journal of Medicine, 77*, 189-196.

Hawkins, A. K. (2010). Biobanks: Importance, implications and opportunities for genetic counselors. *Journal of Genetic Counseling, 19*, 423-429.

Khoury, M. J., Berg, A., Coates, R., Evans, J., Teutech, S. M., & Bradley, L. A. (2008, November/December). *Health Affairs, 27(6)*, 1600-1611.

Lea, D. H., Skirton, H., Read, C. Y., & Williams, J. K. (2011). Implications for educating The next generation of nurses on genetics and genomics in the 21st century. *Journal of Nursing Scholarship, 43(1)*, 3-12.

Lebel, R. (2005, November). Ethical issues in cancer genetics. Atlas of Genetics and Cytogenetics in Oncology and Haematology. Retrieved March 3, 2012 from http://AtlasGeneticsOncology.org/Educ/EthicCancerGenet30029Es.html.

McKinnon R., & Anderson, C. (2011). Transforming pharmaceutical education to accelerate the acceptance and implementation of personalized medicine. *American Journal of Pharmaceutical Education, 75*(6), 1-2.

Ojha, R. P., & Thertullen, R. (2005). Health care policy issues as a result of the genetic revolution. Implications for public health. American Journal of Public Health, 95(3), 385-388.

Owens, T. A., Tabangin, M. E, Huether, C. A. Bowling, B. V., & Warren, N. S. (2009). High school biology/life science teachers' presentation of genetic counseling and health care career options in their classroom. *Journal of Genetic Counseling*, 18, 275-286.

Rochman, S. (2012). Clinical trials game-changer? *Cancer Today, 12*, 26-29.

Steele, F. L. (2009). Personalized Medicine: Something Old, Something New: So What's New? *Personalized Medicine. 6*(1), 1-5. Retrieved May 6, 2012 from http://www.medscape.com/viewarticle/586267_5.

Vickers, A. J. (2006). Whose data set is it anyway? Sharing raw data from randomized trials. Trials, 7(15). Retrieved April 12, 2012 from htt;//www.trialsjournal.com/content/7/1/15.

Wolinsky, H. (2011). Genomes, race and health. *EMBO Reports, 12*, 107-109.

Molecular Diagnostics

Introduction

"Molecular diagnostics" is another term that you may never have heard of before your cancer diagnosis. Since it's difficult to discuss personalized medicine without talking about molecular diagnostics, we have an entire section on the topic. We will therefore discuss the meaning of "molecular diagnostics" and how it may affect your treatment choices.

Simply put, molecular diagnostics includes all tests and methods used to identify a disease or the likelihood of developing a specific disease by analyzing biomarkers (*DNA*, *RNA,* or *proteins*).

Once particular biomarkers are identified using a molecular diagnostic, your doctor could learn important information about the biology of your cancer, helping him determine treatment decisions specific to your case.

Right now biomarkers that can be matched to targeted treatments have not yet been identified and validated for all cancer types. But, research is ongoing to detect such markers and to introduce additional successful targeted therapies for different cancers.

Molecular diagnostics techniques may include the following:

- Stand-alone genetic tests
- Biomarker tests
- Companion diagnostics [1]

CISN stock image, all rights reserved

We will discuss each of the items listed above to provide you with a better understanding of their purpose.

Molecular diagnostics is becoming more important in clinical research to:

- Select patients for targeted therapies based on their molecular profiles.
- Modify the dose of a drug so that it matches each patients needs.
- Assess early response to therapy and/or to monitor patients during treatment.
- Identify an individual's risk of developing adverse drug reactions.
- Guide treatment decisions. [2]

For example, patients with malignant melanoma and metastatic lung, breast, or brain cancers are now routinely being offered a "molecular diagnosis" in some clinical centers, enabling their doctors to select targeted treatments.

- Malignant melanoma is no longer viewed as one disease, but instead can be classified by its genetics; a gene called BRAF has been found to be mutated in approximately 70 % of cases.

- Non-small-cell lung cancer (NSCLC) may be associated with mutations in a number of genes, including the epidermal growth factor receptor (EGFR) gene, the KRAS gene, as well as rearrangements of the ALK (anaplastic lymphoma kinase) gene.

Background

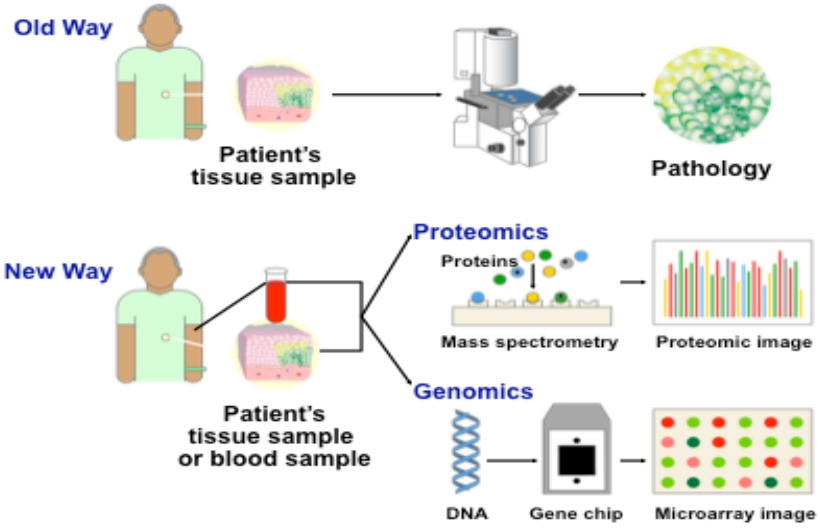
The human body is made up of trillions of cells that "talk" to one another to keep you healthy. Normal cell growth requires a communications network that functions properly. This network is an extremely complex system of protein pathways. The genetic changes associated with cancer result in changes in proteins that disrupt the cells' communication network.

As cancer develops, these altered proteins cause normal cell "'talk" to become distorted, disrupting normal communication and ultimately leading to uncontrolled tumor growth.

The challenge once cancer is diagnosed is to locate these rebel genes and proteins that have hijacked normal cellular communication and correct the problem before it

becomes life threatening. This requires analyzing the *molecules* inside the cell using molecular diagnostics.

Before the use of molecular diagnostics, doctors primarily classified cancer cells primarily according to their appearance under a microscope (pathology). Molecular diagnostics assesses the interactions of genes (genomics) and proteins (proteomics), identifying gene and protein activity patterns in cancerous cells. Using technology such as *mass spectrometry* and *gene chips*, molecular diagnostics is able to identify genes active in cancer, separating them from the others in cells.



Reminder:

Genomics is the study of all the genes in a cell or organism.

Proteomics is the study of all the proteins made by those genes.

Image courtesy of the National Cancer Institute

Molecular diagnostics identifies the gene and protein activity as "expression patterns" or "molecular signatures. These molecular signatures improve your doctor's ability to diagnose cancer, characterize different molecular subtypes, and recommend specific targeted therapies for you.

Why Molecular Diagnostics Are Important

The medical community has recognized the importance of molecular diagnostics for several decades, and this field is especially important to cancer care. Molecular diagnostics has already improved cancer diagnosis and treatment techniques for some cancers, and research is continuing on others.

Potential uses of molecular diagnostics *Image courtesy of Diagno Cure*

The image above shows the many areas in which molecular diagnostics may be used. This spans the entire scope of cancer care, beginning with risk assessment and moving through to surveillance after diagnosis and treatment.

Clinical implementation of molecular diagnostics

Even though the incidence of cancer and the number of cancer deaths remain high, novel cancer molecular diagnostics are allowing physicians and pathologists to diagnose cancers more accurately, identify subgroups, and select targeted and individualized treatment regimens.

Although the traditional pathological examination of cancer remains an essential clinical tool, newer technologies such as *microarrays*, *RT-PCR*, *mass spectrometric proteomic analyses*, and *protein chips* are being used more often, although not yet routinely used everywhere or for all cancer types.

By evaluating patterns and changes in genes, researchers have discovered that cancers named according to the organ in which the cancerous cells reside are in fact many different types of cancer.

Studies have shown that what had been considered a single type of cancer based on how the cells appear under a microscope, can be two, three, or even more subtypes, each with a distinct molecular signature (expression) pattern. This may mean that each subtype needs to be treated differently.

Some examples of how molecular diagnostics is used

Example One: Grouping patients based on their molecular signatures – Lung Cancer

Using microarrays, researchers discovered that the most common type of lung cancer, called lung adenocarcinoma, is actually several distinct types of cancer, each with its own gene signature pattern. Having the ability to distinguish these signatures is crucial information, as each responds most effectively to different treatments.

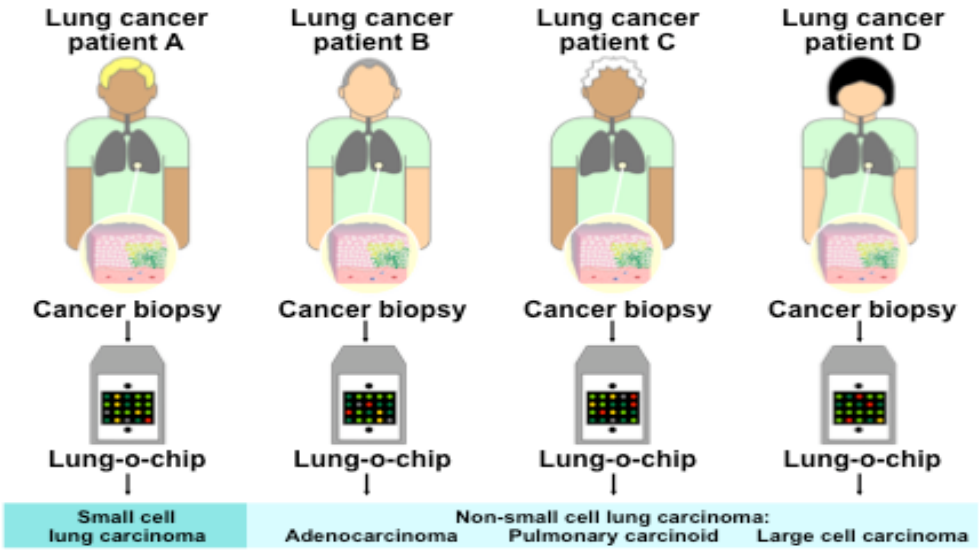


Image courtesy of the National Cancer Institute

As you can see from the image above, a gene chip can identify distinct types of lung cancer. This may explain why in the past some lung cancer patients responded to a specific treatment while others did not. One drug does not fit all.

Example Two: Modify the dose of a drug, based on your molecular profile:

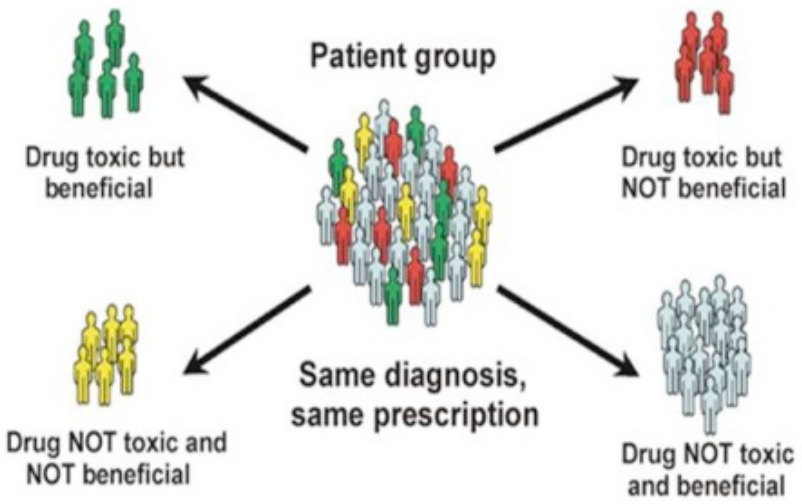
CISN image all rights reserved

Today, a drug dose may be determined by a number of factors, including using body height and weight. But research is finding that a person's molecular profile may be a better predictor of how much of a drug a patient requires to receive benefit with minimal side effects.

Example Three: Identify which patients will benefit from a specific drug and those who are at risk for adverse reactions:

Pharmacogenetics is a science that examines the inherited variations in genes that determine drug metabolism and response. [3]

Using this strategy will help to identify which patients will not benefit from a specific medication and/or who are at risk for serious drug reactions, providing crucial information on proper treatment for each individual.



This image demonstrates how molecular diagnostics can help to identify individuals with the same diagnosis who will benefit most from a specific medication and those who should receive alternative treatment.

Image courtesy of The National Cancer Institute

Example Four: Use molecular diagnostics to guide treatment decisions:

Gene predictor formulas may be better than current methods in identifying patients with poor prognoses. If patients predicted to have poor outcomes can be accurately identified early, their treatment may be appropriately altered. See image below:

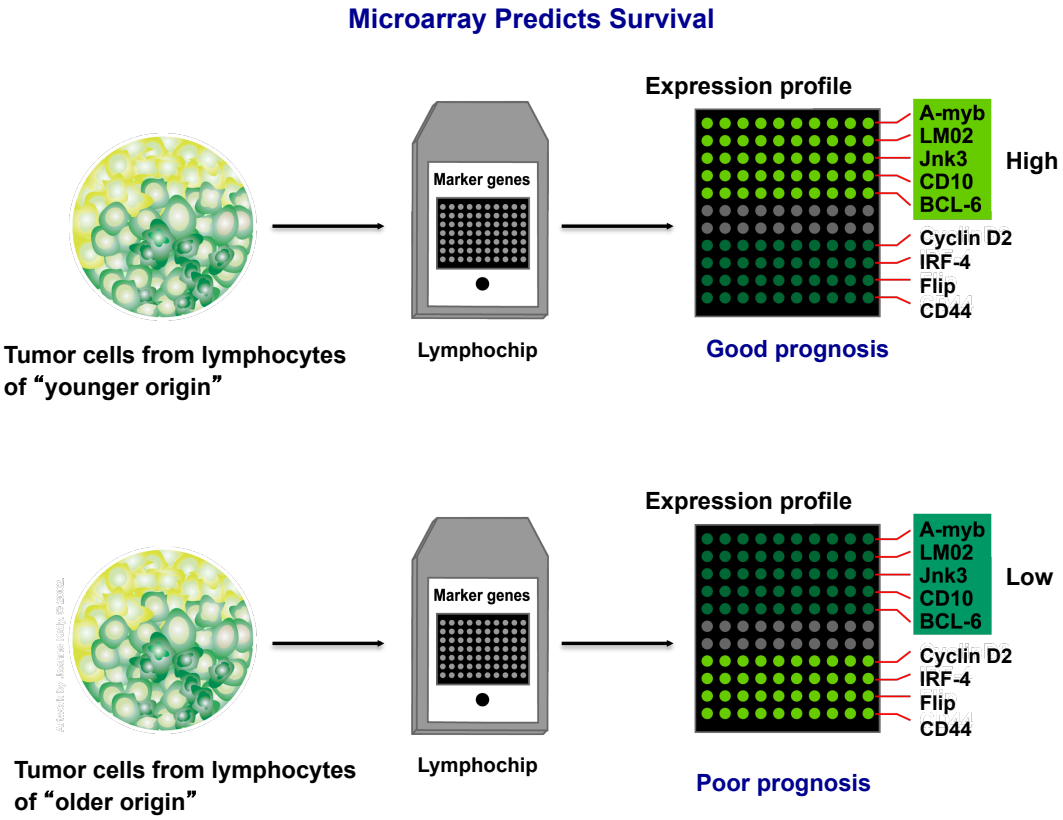


Image curtsey of the National Cancer Institute

Types of Molecular Diagnostics

As stated earlier, there are several types of molecular diagnostics: genetic tests, biomarker tests, and companion diagnostics. The terms "genetic tests" and "biomarker tests" are often used interchangeably, but we are presenting them here separately. You may find them in either category when researching this topic. Companion diagnostics are a separate category and will be discussed as such.

GENETIC TESTS

A few examples of successful molecular diagnostic genetic tests are:

Myriad Genetics: BRACAnalysis®

Assesses the risk of developing breast or ovarian cancer associated with inheriting mutations in the BRCA1 and BRCA2 genes by DNA sequencing

Genomic Health: Onco*type* DX® Breast Cancer Assay

Predicts benefit of chemotherapy and risk of recurrence in estrogen-receptor-positive, HER2-neu negative breast cancer patients by assessing gene expression levels of 21 genes from tumor tissue.

BIOMARKER TESTS

For many tumor types, *biomarkers* represent an important shift in cancer care. These biologic indicators are increasingly being used to help physicians screen, diagnose, and monitor patients. Certain biomarkers may help in prognostic evaluation, assessment of treatment response, and monitoring for disease recurrence.[4]

Predictive vs. Prognostic Biomarkers

Following are several examples of biomarkers that may be categorized as "prognostic" or "predictive":

Prognostic Biomarkers provides information about the patient's overall cancer outcome, regardless of therapy, for example:

- **HER2-neu** expression in breast cancer, cancer of the stomach, and cancer of the junction where the esophagus meets the stomach (gastrointestinal junction)
- **MSI** (microsatellite instability) in colorectal cancer
- **NPM1 and FLT3** mutations in acute myeloid leukemia (AML)
- **Onco*type* Dx®** in breast cancer and colon cancer

Predictive Biomarkers provide information about the effect of a treatment and may be predictive of response, resistance, or toxicity, for example:

- **Epidermal Growth Factor Receptor (EGFR)** to determine whether a solid tumor (e.g., of the lung, colon, head or neck, pancreas, or breast) is positive for EGFR

overexpression, guiding treatment

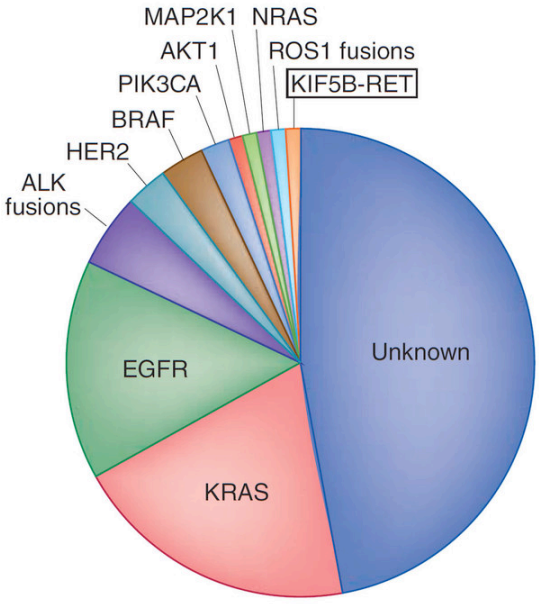
- **KRAS** mutations in colon cancer
- **BRAF** mutations in colon cancer and malignant melanoma
- **HER2-neu** expression
- **CYP2D6** genetic variants that may be associated with decreased metabolism of the medication tamoxifen to its active form (endoxifen). (In women with estrogen-receptor-positive breast cancer, it has been suggested that reduced metabolism of tamoxifen may reduce its effectiveness in reducing the risk of recurrence. However, the clinical trial results to date have offered contradictory findings.)
- **UGT1A1, DPYD, TYMS** testing for gene mutations that predict sensitivity to specific chemotherapy drugs

A predictive biomarker may or may not be a target for therapy.[5]

Emerging Biomarkers

In addition to well-established biomarkers--such as KRAS and EGFR in colorectal and lung cancer and HER-2-neu and ER/PR in breast cancer--many new biomarkers are being investigated in multiple tumor types. Some biomarker studies have started to show promising data, but validation of such markers will require multiple steps, possibly taking many years of research.

Example: Non-Small-Cell Lung Cancer **(NSCLC) gene mutations**



This image illustrates how far we have come in identifying mutations in Non-Small-Cell Lung Cancer (NSCLC).

Remember that NSCLC is just one of several lung cancer types. This image shows that there are many different gene mutations that may be associated with NSCLC, further complicating how best to treat a specific patient.

Although we have gained knowledge in recent years concerning KRAS and EGFR mutations in NSCLC, much remains to be learned about the other markers identified on this image.

Image from Pao et al, Nature Medicine 18,349-351 (2012)

COMPANION DIAGNOSTICS

As discussed above, the term '"molecular diagnostics" is a general one that includes all tests and methods used to identify disease or risk for disease by analyzing molecules, such as DNA, RNA, or proteins.

In contrast, "companion diagnostics" is a term used to describe a type of molecular diagnostic test that is developed by a drug company at the same time that their new drug is being developed. Patients will be tested with this molecular diagnostic before treatment to see if they will respond to the new drug.

This approach promises to improve overall outcomes, while reducing less effective care and adverse events.

The use of a companion diagnostic is becoming more common in predicting drug effectiveness and optimal dosage. According to experts, this will eventually become the norm. "It's a new field, and it's growing," says Peter Tolias, executive director of the Institute of Genomic Medicine at the UMDNJ-New Jersey Medical School.

Although the use of companion diagnostics is a relatively new concept, as more biomarkers are being discovered and validated, it's challenging the concept of "one size fits all" in drug development and promises to change the way drugs are discovered, developed, and marketed. It is hoped that the day will come when analysis of blood or tissue samples may determine whether cancer patients will respond to a specific drug.

In this illustration, "Responders" to the medication are depicted on the left and "non-responders" are shown on the right.

Image courtesy of Ventana Medical Systems

In the last five years, most of the major pharmaceutical companies have established new programs for companion diagnostic products. "In the olden days, they never used to worry about who their drug was going to be functioning in, or who's going to have an adverse effect," Tolias says.

However, the tide has changed, and pharmaceutical companies are now increasingly focused on developing new agents that can target only cancer cells, and providing

companion diagnostics to identify those patients who may benefit most, those who are unlikely to benefit, and/or those who at most risk for adverse effects.

This image depicts the process used by Industry to identify a biomarker and then to develop both a drug that targets the marker as well as a molecular diagnostic to test for the biomarker in patients.

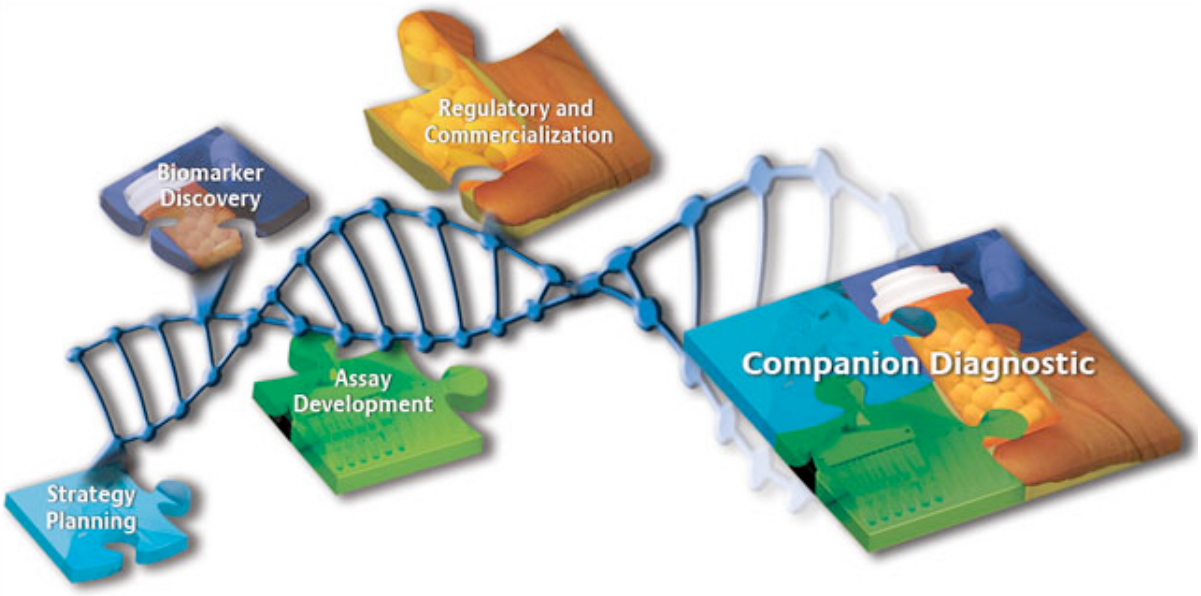


Image courtesy of Asuragen

Potential Advantages of Molecular Diagnostics

The use of molecular diagnostics in practice has been referred to as personalized medicine. Research that identifies unique gene and protein patterns associated with different cancer types will lead to the definition of new classifications and subtypes based on their molecular signatures.

Though this has the potential to improve cancer research, diagnosis, and treatment, the development of new therapies will require customized approaches to many cancer types and subtypes.

Using Expression Patterns to Choose Treatments

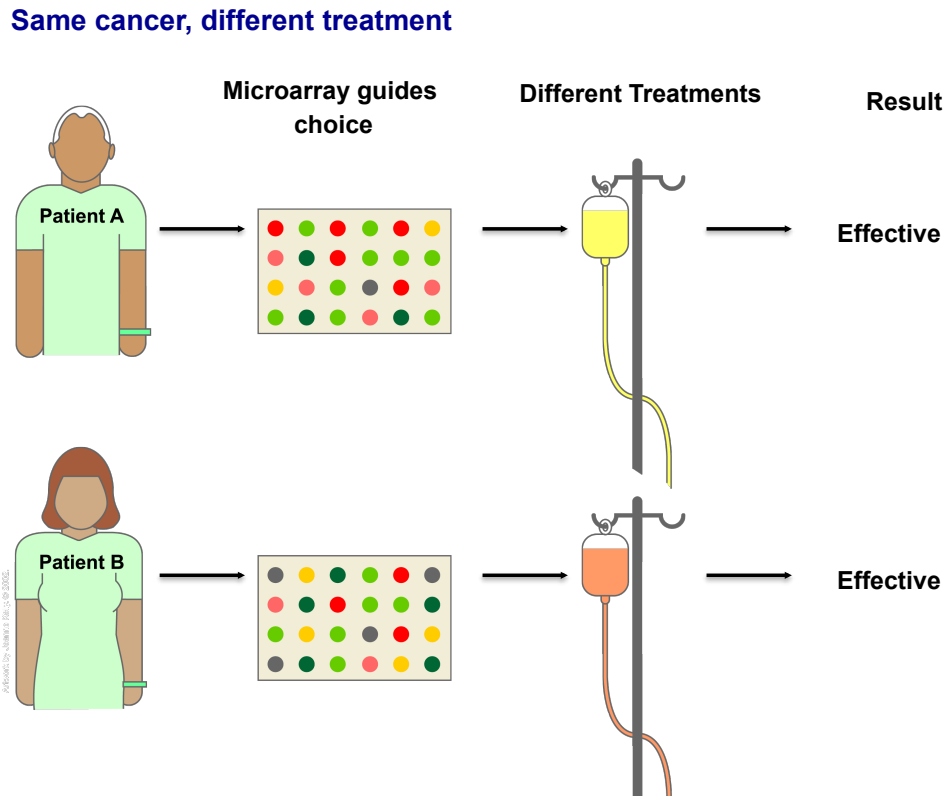


Image courtesy of The National Cancer Institute

With the advent of microarrays, research has entered an entirely new level of sophistication. This technology allows researchers to study patient populations, collecting expression patterns of tumors that can then be documented, validated, and finally translated for general use by individual doctors and patients.

In the future, your doctors may also be able to predict your response to chemotherapy or radiation, based on your "molecular signature/expression signature". This could eliminate much of the clinical "guesswork," when deciding among multiple therapies that have been approved for a specific cancer type.

Summary of potential advantages

- Enhanced methods to screen the general public for specific cancers
- Accurate early diagnostic methods

- Identification of biomarkers that may lead to tailored treatments with improved effectiveness

- Reduced side effects from unnecessary treatments

- Improved tools to accurately monitor for treatment effectiveness and/or likelihood of metastasis or recurrence.

- Enhanced quality of life

Potential Problems With Molecular Diagnostics

Despite the rising costs associated with new drugs, industry is committed to providing a more targeted approach to medical treatment.[6] It's suggested that more personalized prescribing may lead to impressive financial benefits, as an estimated 40% to 70% of patients currently may not respond to available treatments for conditions such as depression, asthma, diabetes, arthritis, and cancer.[7]

However, many new therapies will be more expensive to develop, because research funds may not be available for cancer subtypes that affect small numbers of people, thus providing less opportunity for profit.

Food & Drug Administration (FDA) regulations have specified that companion diagnostics used to direct drug therapy choice should:

- Be considered Class III medical devices
- Follow the Premarket Approval (PMA) process, which is the strictest level of FDA device review and one that typically requires appropriately designed and conducted clinical trials.[8]

Recently, the FDA released a draft guidance document to clarify its position on the use of non-FDA-approved molecular tests in labs reporting clinical results.

The development and clinical validation of molecular diagnostic clinical tests deserves the same level of thoroughness as required for drug development. In addition, they must be offered at a realistic cost that reflects both their clinical value and the costs associated with their development. [9]

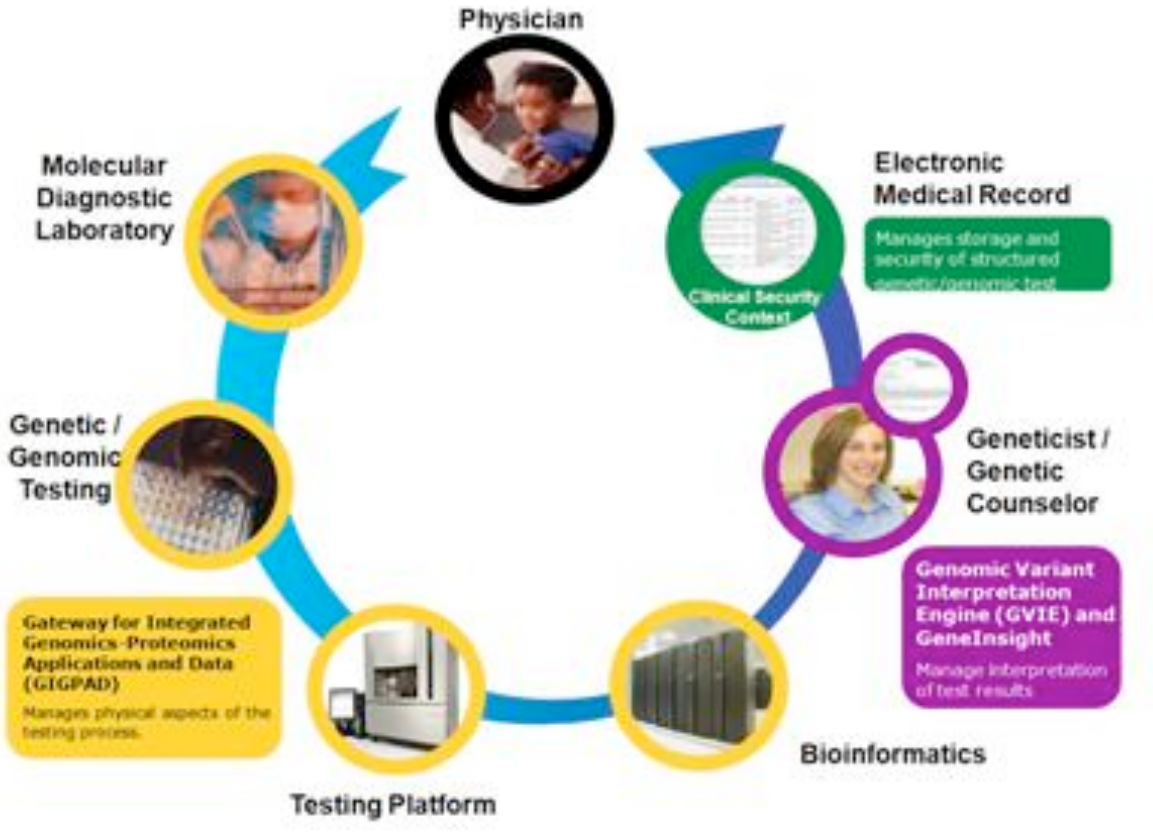


Image courtesy of Health & Human Services.gov news

Summary of challenges for implementation:

1) The need to link all relevant data obtained sfrom genetic and molecular testing into the electronic medical record, requiring secure, well-operated, health information technology infrastructure. (see image above.)

2) Of major importance to the success of personalized medicine is how samples are collected, tested, and validated. Please go to "How Cancer is Studied /Translational Research / Biospecimen Issues" on this web site for more information on this topic.

3) High costs associated with discovery, development, and regulatory approval

4) The need for standardization and biomarker validation

5) Lack of availability at all medical centers

What Is The Availability of Molecular Diagnostics?

Those molecular diagnostics that are currently available remain relatively limited. In addition, many may be expensive, perhaps with the exception of the Pap smear, which has long been effective in detecting early-stage cervical cancer.

However, some molecular diagnostic tests are currently used as or are becoming standard care. See examples given in earlier in this section under "biomarker tests." In addition, some treatments developed through research on molecular diagnostics, have been approved by the FDA for use in specific types of cancer.

Molecular diagnostics may also be available through participation in clinical trials (research studies in people). Health insurance companies may or may not provide coverage for specific molecular diagnostics.

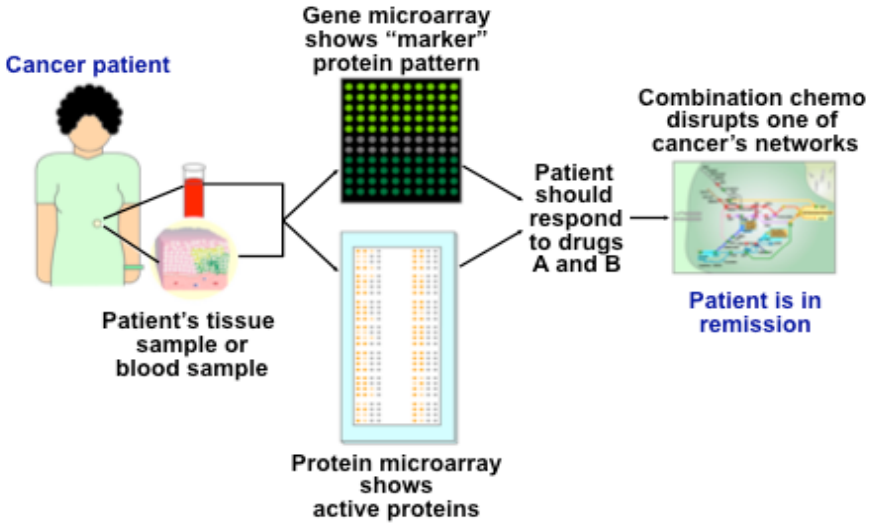
Ask your oncologist about molecular diagnostics for your diagnosis and whether an appropriate targeted agent has been approved or is under study for your specific cancer type.

What Is The Future of Molecular Diagnostics?

Future research may focus on developing molecular diagnostics to create a scenario such as the following:

A cancer patient visits her oncologist and gives a few drops of blood or a biopsy specimen. After analysis of the blood or tissue samples, she is told that her genetic expression pattern shows a specific subtype of disease.

Meanwhile, another expression pattern predicts that her genetic profile should respond well to chemotherapy regimens A and B with minimal side effects.



During her treatment, protein expression patterns are used to ensure her treatment is effectively disrupting the targeted cellular pathway in her tumor.

Image courtesy of the National Cancer Institute

After treatment, additional gene and protein expression patterns verify that the cancer is in remission. (Excerpted from The NCI Understanding Cancer Series)

A Multidisciplinary Approach Is Needed

Many clinicians have neither the training nor the time to assess the clinical significance of biomarker variants that have been identified in patients. For this reason, molecular diagnostic laboratories typically employ genetic professionals who interpret test results and produce text reports describing the significance of any genetic variants identified.

The process of generating such reports can be time-consuming and expensive, so streamlining and automating portions of the process through information technology (IT) can be valuable. IT can also help standardize result reporting by reducing variability between the ways in which different geneticists might interpret the same results.

Conclusion

Personalized medicine, including the molecular diagnostic tests that provide information to your healthcare providers, may ultimately revolutionize cancer prevention, diagnosis, treatment, and follow-up.

Although there are many pathways involved in most tumors, making targeted therapy more complex than originally thought, this emerging approach continues to offer great promise, such as in the following:

- The ability to make more fully informed medical decisions
- Higher probability of desired outcomes
- Reduced probability of negative side effects
- Increased pro-active focus on prevention and prediction of disease rather than primarily reaction
- Earlier disease intervention than previously possible

But it is important that all stakeholders' needs are met:

- Healthcare providers desire easy-to-access, easy-to-use molecular testing services.
- Payers require cost-effective options.
- Patients must receive the optimal treatments for themselves.
- We all need molecular testing to be reliable and of a high standard of quality to ensure accuracy and robust results.

CISN Summary

Molecular diagnostics are becoming important tools for cancer detection and sub-typing. The expansion into the pharmacogenomics and therapy decision tree areas will have major implications for both industry and patients.

New technologies are needed to deliver greater sensitivity, faster turnaround, and smaller platforms (testing machines) if they are to become part of disease treatment monitoring as well as diagnostics. If this can be achieved, it will also open the door to move from the dedicated diagnostics laboratory to the physician's office.

Molecular diagnostics are particularly applicable to:

- The early detection of cancer,
- Optimizing drug therapy by better defining a patient's need,
- Predicting clinical outcome from a specific drug, and
- Determining metastatic potential.

For More Information

- American Association for Cancer Research. Molecular Diagnostics in Cancer Therapeutic Development: Fulfilling the Promise of Personalized Medicine http://www.aacr.org/home/scientists/meetings--workshops/molecular-diagnostics-in-cancer-therapeutic-development.aspx>
- National Cancer Institute. Understanding Cancer Series: Molecular Diagnostics http://www.cancer.gov/cancertopics/understandingcancer/moleculardiagnostics>
- A more technical version of molecular diagnostics written by the CISN: http://cisncancer.org/research/new_treatments/molecular_diagnostics/index.html

References:

1. Tufts Center for the Study of Drug Development. Personalized medicine is playing a growing role in development pipelines. *Impact Report: Analysis and Insight into Critical Drug Development Issues*. 2010;12(6).

2. George Poste, David P. Carbone, David R. Parkinson, Jaap Verweij, Stephen M. Hewitt, and J. Milburn Jessup. Leveling the Playing Field: Bringing Development of

Biomarkers and Molecular Diagnostics up to the Standards for Drug Development, Clin Cancer Res; 18(6); 1515–23. 2012 AACR.

3. One size does not fit all: the promise of Pharmacogenomics. Just the Facts: A Basic Introduction to the Science Underlying NCBI Resources, National center for Biotechnology Information. Available online at: http://www.ncbi.nlm.nih.gov/About/primer/pharm.html

4. Tufts Center for the Study of Drug Development. Personalized medicine is playing a growing role in development pipelines. *Impact Report: Analysis and Insight into Critical Drug Development Issues*. 2010;12(6).

5. Excerpted from a talk by Karen Rasmussen, PhD, FACMG, Clinical Molecular Genetics. *Maine Center for Cancer Medicine,* Scarborough, Maine

6. Davis J, Ma P, Sutaria S. The microeconomics of personalized medicine. *McKinsey Quarterly*. *http://www.mckinseyquarterly.com/The_microeconomics_of_personalized_medicine_2527*. Updated April 2009. Accessed July 26, 2011.

7. Spear BB, Heath-Chiozzi M, Huff, J. Clinical application of pharmacogenetics. *Trends Mol. Med.* 2001;7(5):201-204.

8. Food and Drug Administration. FDA/CDRH Public Meeting: Oversight of laboratory developed tests (LDTs), July 19-20, 2010. *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm*. Updated September 17, 2010. Accessed July 26, 2011.

9. George Poste, David P. Carbone, David R. Parkinson, Jaap Verweij, Stephen M. Hewitt, and J. Milburn Jessup, Leveling the Playing Field: Bringing Development of Biomarkers and Molecular Diagnostics up to the Standards for Drug Development, Clin Cancer Res; 18(6); 1515–23. _2012 AACR.