



# Precision Medicine in Oncology

TUTORIAL FOR RESEARCH ADVOCATES

Research Advocacy Network

*Advancing Patient-Focused Research*

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# Chapter 1: Overview of Precision Medicine in Oncology

## What's In This Tutorial?

This tutorial offers readers an overview of precision medicine as it applies to the field of oncology. In this chapter, we define precision medicine and explain its goals and challenges. Then we'll briefly discuss the hallmarks of cancer and define some key terms before examining levels of evidence as they apply to precision medicine.

Chapter 2 covers the role of genomics in precision medicine. Chapter 3 examines clinical trials designed for precision medicine, and Chapter 4 discusses the targeted therapies that are precision medicine's ultimate goal. Chapter 5 addresses molecular diagnostics and their role in precision medicine. The final chapter summarizes some of the many ways cancer research advocates can apply the information learned in this tutorial to advance cancer research and improve patients' lives.

Separate tutorials developed by the Research Advocacy Network are available for several of these topics and will be of interest to readers who want to deepen their understanding of issues related to precision medicine. Visit [www.researchadvocacy.org/general-resources/tutorials](http://www.researchadvocacy.org/general-resources/tutorials) for more information.

**Precise:** (1) Exactly or sharply defined or stated; (2) minutely exact; (3) strictly conforming to a pattern, standard, or convention; (4) distinguished from every other.

SOURCE: MERRIAM-WEBSTER ONLINE DICTIONARY

## What Is Precision Medicine?

According to the U.S. National Institutes of Health (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." Although the term precision medicine is relatively new, the concept of precision medicine is not. For instance, a basic and long-established example of precision medicine is blood typing to match donated blood with patients who need transfusions. For more than a century, we've known that transfusing the same type of blood reduces the risk of complications for recipients and results in better outcomes. Precision medicine is sometimes described as the opposite of the "one-size-fits-all" approach to medical care, which focuses on strategies developed for an average or typical patient. In the one-size-fits-all approach, two patients with the same type and stage of cancer might receive identical treatment, despite individual differences that make the treatment more effective for one patient but less effective, or not effective at all, for the other.

Precision medicine is also contrasted with the empiric approach to medical care. In empiric medicine, patients receive the treatment that generally works best for most patients with the same disease or condition. If that treatment doesn't work well, an alternative treatment might be tried. If that fails, other treatments might be considered and tried until a clinician exhausts all the options. Precision medicine, oppositely, begins with testing and analysis of the individual patient to determine at the outset which approach will work best.



## Precision Medicine and Personalized Medicine: Is There a Difference?

The term “precision medicine” is often used interchangeably with the older term “personalized medicine” and the two terms have similar meanings, although some experts disagree about whether they are exact synonyms.

The National Academy of Sciences prefers the term precision medicine because personalized medicine is more likely to be misunderstood as referring to treatments and preventive strategies developed for a single individual. Instead, the key idea is developing strategies that can be precisely matched to individual characteristics that subgroups of patients share. Even so, you may hear both terms—precision medicine and personalized medicine—used to mean much the same thing.

## Goals, Challenges, and the Precision Medicine Initiative

The goal of precision medicine is to improve health care by finding new treatments and preventive approaches that are effective for specific individuals based on their distinctive characteristics, while avoiding costly care that’s unnecessary or ineffective and might cause harmful side effects. Precision medicine will probably not completely replace standard approaches to cancer care; instead, it will give us new and better options for some patients. Recent scientific developments, such as faster, more affordable genomic sequencing and more powerful computer technology, have made precision medicine more feasible now than ever before. Precision medicine has already begun to revolutionize cancer prevention and treatment through strategies targeted to individuals with specific characteristics.

An example of one such characteristic is the BRCA genetic mutations. Women with one of these mutations are at significantly increased risk of developing breast or ovarian cancer. Armed with this knowledge, they might now opt to have preventive surgery or undergo additional screening procedures to detect a cancer in its earliest, most treatable stages. Actor, filmmaker, and humanitarian Angelina Jolie-Pitt made headlines a few years ago with her announcement that she had a BRCA mutation and underwent surgical removal of her breasts and ovaries in hopes of avoiding the disease that claimed the lives of her mother, grandmother, and aunt.

Precision medicine’s role in oncology will continue to grow in coming years, thanks in part to an initiative launched by President Obama in November 2015. The Precision Medicine Initiative (PMI) includes a \$215 million federal investment to accelerate the development of precision medicine. PMI’s initial focus will be on cancer treatment and prevention, and it will expand in the future to include an array of other diseases and conditions. A key part of the initiative will be building a “cancer knowledge network,” a database of molecular and medical information that will be shared by researchers, physicians, and patients.

Even so, precision medicine presents enormous challenges: Researchers have just begun the task of identifying and understanding the biology behind innumerable characteristics that make patients and their cancers unique and finding treatments that precisely target those characteristics. What’s more, scientists recently discovered that different tumors within the same patient can have different characteristics, meaning that treatment might need to be targeted at each tumor, rather than each patient. But as one scientist pointed out, precision medicine is a marvelous opportunity to “work hard at work worth doing.”



Angelina Jolie has been public about her *BRCA1* mutation.

Photo credit: "Angelina Jolie by Gage Skidmore 2" by Gage Skidmore. Licensed under CC BY-SA 3.0 via Wikimedia Commons.

## The Hallmarks of Cancer and Why They Are Useful

In a groundbreaking article published in 2000 in the journal *Cell*, a pair of cancer researchers outlined 6 key characteristics that cancer cells have in common and that set them apart from other cells. More than a decade later, they expanded the list to include a total of 10 “hallmarks of cancer.”

Cancer cells differ from normal cells in that they demonstrate the following abilities:

1. Sustained, self-sufficient growth signals
2. Insensitivity to signals that inhibit growth
3. Ability to evade programmed cell death (apoptosis)
4. Ability to replicate indefinitely
5. Re-programming energy metabolism
6. Avoiding destruction by the immune system
7. Ability to generate sustained blood supply (angiogenesis)
8. Ability to invade tissue and metastasize (spread to other areas)
9. Genetic instability
10. Tumor-promoting inflammation

From Hanahan D, Weinberg RA. Hallmarks of cancer. *Cell*. 2000;100:57-70; and Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.



Adapted from Conley, Barbara. “Precision Medicine.” Research Advocacy Network Advocate Institute Webinar, May 2015

These hallmarks are what enable cancerous tumors to grow, spread aggressively, and survive. However, they also make cancer cells distinct from normal cells and therefore susceptible to being targeted and destroyed. The hallmarks are important because they represent ways to precisely target cancers and thereby defeat them.

## Defining Key Terms

### What Is a Biomarker, and When Is It “Actionable”?

Biomarkers (shorthand for biological markers) are any characteristic of the body that can be measured as a way to evaluate health. In the past, biomarkers were primarily physiological indicators like blood pressure, heart rate, and body temperature. More recently, the term has become more associated with molecular biomarkers, such as genes, proteins, and antigens. For example, prostate specific antigen (PSA) is a biomarker detectable in blood that suggests a man might have prostate cancer if levels of the antigen are elevated. *HER-2/neu* is a genetic biomarker that is associated with aggressively growing breast cancers. The terms biomarker or marker and molecular diagnostic are sometimes used interchangeably.

Biomarkers are classified as either actionable (meaning that they can be used to guide or enhance patient care) or not actionable (if they are not useful for making healthcare decisions).

Actionable biomarkers can be further broken down into prognostic and predictive subgroups. A prognostic biomarker is one that provides information about the likely course of the disease. For example, a PIK3CA mutation suggests a worse prognosis in *HER2+* breast cancer. A high PSA when prostate cancer is diagnosed is also a prognostic biomarker. Although such information might not seem helpful or actionable, it can enable some patients to by-pass certain treatments that would probably not be beneficial to them or that could have serious side effects and only limited benefits.

In biology and medicine, "molecular" refers to genes, proteins, and other cellular molecules. A molecule is the smallest particle of a substance that has all of the physical and chemical properties of that substance.

Predictive biomarkers tell whether a particular treatment is likely to help a patient or not. An example of a predictive biomarker is the *BRAF V600E* mutation in melanoma. Melanoma patients whose tumors had a *BRAF V600E* mutation that were treated with the *BRAF* inhibitor, vemurafenib, have shown dramatic responses. Unfortunately, not very many predictive biomarkers have been identified yet, but those that we do know about are very valuable in guiding treatment.

Biomarkers have other specific applications in the field of oncology, too. The table below summarizes the various ways biomarkers can be used to guide cancer care.

### Uses of Biomarkers in Oncology

Use of Biomarker	Description
<b>Risk assessment:</b>	To help a person determine how likely he or she is to develop cancer; can be used to help decide whether a person should undergo more intensive screening or take preventive measures. For example, <i>BRCA 1</i> and <i>2</i> tests can be used for assessing breast and ovarian cancer risk.
<b>Screening:</b>	To help identify cancer at an earlier stage than would have happened without the test. For example, screening mammography can be used to detect early, and often very treatable, breast cancers.
<b>Diagnostic:</b>	To help diagnose a cancer, perhaps before it is detectable by other, conventional methods. For example, beta-HCG (beta-subunit human chorionic gonadotropin) tests can assist in diagnosing testicular cancer.
<b>Prognostic:</b>	To forecast how aggressive the disease process is and/or how a patient can expect to fare in the absence of therapy. For example, prostate-specific antigen (PSA) may be used as a <b>prognostic biomarker</b> when evaluating patients with prostate cancer to assess the likelihood of cancer progression.
<b>Predictive:</b>	To help identify which patients will respond to which drugs. For example, epidermal growth factor receptor ( <i>EGFR</i> ) mutations may be used as a <b>predictive biomarker</b> when evaluating non-small cell lung cancer patients to select patients for anti- <i>EGFR</i> drug therapy.
<b>Monitoring:</b>	To determine how a patient is doing over time, either on or off therapy. For example, cancer antigen 125 ( <i>CA 125</i> ) may be used as a <b>monitoring biomarker</b> when assessing patients with ovarian cancer to evaluate disease status or burden.

For a more detailed discussion of the different types of biomarkers and some examples of each, you may want to consult the document titled *Biomarkers in Cancer* available for download from the Research Advocacy Network Web site ([www.researchadvocacy.org](http://www.researchadvocacy.org)).

### What Are “Driver” and “Passenger” Mutations?

A driver is a molecular alteration in a cancer that is necessary for the cancer’s development or survival, and therefore is a suitable target for destroying the cancer. Drivers are distinguished from passengers, which are other molecular changes that are not critical to the tumor’s survival, and are simply “along for the ride.” Passengers are not useful targets for cancer therapies, but they can still be useful biomarkers. In other words, passengers can provide information about a cancer, but not necessarily a means of stopping or destroying it.

### Levels of Evidence in Various Biomarkers

For a few cancer biomarkers, we have both an approved diagnostic test for the detection of that biomarker and an effective targeted treatment. For a companion diagnostic and a matched therapy to have a “strong” level of evidence is primarily dependent on whether or not the biomarker with the matched therapy were shown to be predictive in well-designed prospective clinical trials.

An example of a biomarker with strong evidence to support testing and treatment is the *c-kit* genetic mutation, which is detected in some types of gastrointestinal cancers. In more than half of cases, gastrointestinal stromal tumors (GIST) with the *c-kit* mutation can be effectively treated with the drug imatinib. Imatinib inhibits the cancer-promoting activity of that particular mutated gene, and so represses GIST in patients with the mutation. Thus, the evidence for treating GIST that have the *c-kit* mutation using imatinib is strong as demonstrated in prospective clinical trials.

There are several biomarkers with diagnostic tests and treatments that also show a high or strong level of evidence, but in many other situations, the evidence is weak or still being investigated.

For example, when there is only a single case report of a targeted treatment working well for a patient with a particular biomarker, the evidence is considered much weaker. In situations like this, the patient is sometimes referred to as an exceptional responder, and researchers must investigate whether other patients with the same biomarker will respond the same way or not.

Similarly, when a predictive biomarker test is still being evaluated in clinical trials, the evidence for that test is still under investigation and holds less weight compared to FDA approved biomarker tests that are widely used on the market. And when a test or treatment has not yet reached clinical trials (for example, if it is still being evaluated in animals or in cells in laboratory settings), the evidence is considered weaker still.

The next chapter looks at clinical trials, explaining how they are designed and how they will help unlock new breakthroughs in precision oncology.

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# Chapter 2: Genomics and Precision Medicine

## What is Genomics?

Genomics is the study of multiple genes working together to perform a specific function. In the past, researchers tended to focus on single genes because they didn't have the capability to study many genes and their functions simultaneously. Genomics requires sophisticated computer technology and laboratory methods that have only been developed fairly recently. (For example, in the past decade, new and more affordable technology for sequencing DNA has become available.) The term "oncogenomics" refers specifically to the study of genes within cancers.

## Genetics and Genomics: What's the Difference?

Genomics is distinguished from genetics, which is more broadly the science that deals with heredity and variation of organisms. Genetics often refers to the study of single genes, one at a time, whereas genomics considers multiple genes.

Here's one way to think about genetics vs. genomics as the terms might apply to cancer:

Consider Susan, a woman with a family history of breast cancer but no personal history of cancer. If Susan decides to have a test to determine whether she has a specific mutation of one of the two *BRCA* genes that confer a higher risk for developing breast cancer, that would be described as a genetic test.

Marybeth, on the other hand, recently received a breast cancer diagnosis. She opts to have comprehensive testing of her tumor to look for a variety of mutations that might help guide her treatment. This type of testing is called genomic testing.

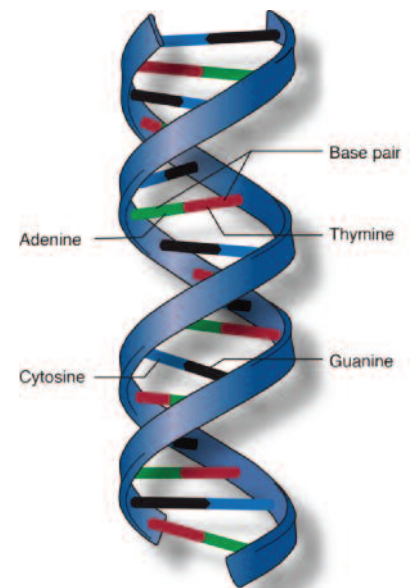
## A Short Refresher on DNA, Genes, and Genetic Mutations

Deoxyribonucleic acid, more commonly known as DNA, is the chemical that makes up our genes. DNA forms long strands called chromosomes, which are found in all of the body's cells except some blood cells. Normal human cells have 46 chromosomes, with about 2 meters of DNA packed inside them.

All DNA is made up of just 4 chemical units, known as nucleotide bases. The nucleotide bases are adenine, cytosine, thymine, and guanine. Each of these bases matches up with just one other nucleotide base: Adenine pairs with thymine, and guanine pairs with cytosine.

If you envision DNA as a twisted ladder (the familiar "double helix"), the base pairs form the rungs of the ladder. Altogether, we each have about 6 billion nucleotide bases, or 3 billion base pairs. That's 3 billion steps on each individual's DNA ladder, so to speak.

A gene is simply a section of DNA that carries the coded instructions for making the machinery cells need, such as a protein or enzyme, that is necessary for life. The proteins that DNA codes for perform all the various tasks that keep cells healthy and functioning properly.



This graphic shows the double helix, twisted ladder structure of DNA and the individual nucleotide bases that pair to form the rungs of the ladder (adenine, thymine, guanine, and cytosine).

*Image credit: Darryl Leja, NHGRI, [www.genome.gov](http://www.genome.gov).*

There are approximately 20,000 genes in a human DNA sequence. Intriguingly, most of our DNA (about 97%) is not functional, meaning it does not carry codes for making proteins. Researchers aren't certain what these noncoding areas of DNA do, but presumably they serve some as-yet-undiscovered purpose.

The vast majority of our genes are identical to every other human being's genes, but there are small genetic differences between us. In some cases, the genetic variations are helpful or don't make any noticeable difference. In other cases, they account for a minor difference, such as hair color or height. And in some cases, the difference can cause disease or greater susceptibility to disease, such as cancer.

Variations in genes can take several different forms. A single nucleotide base can be changed, added, or missing; groups of nucleotides can be affected; portions of chromosomes can be moved; or whole chromosomes can be affected. By far the most common type of variation is a change in just one nucleotide base, which is also known as a single nucleotide polymorphism or SNP (pronounced "snip").

Changes in DNA, whether good, bad, or neutral, occur in a variety of ways: We can inherit them from our parents, they can be the result of errors that occur when DNA replicates to make new cells, and they can occur as a result of exposure to harmful substances, such as viruses and bacteria, toxic chemicals, and radiation. Usually, an alteration in a single gene isn't enough to cause a cancer. It often takes alterations in several genes that affect the way cells grow and reproduce to trigger development of a cancer.

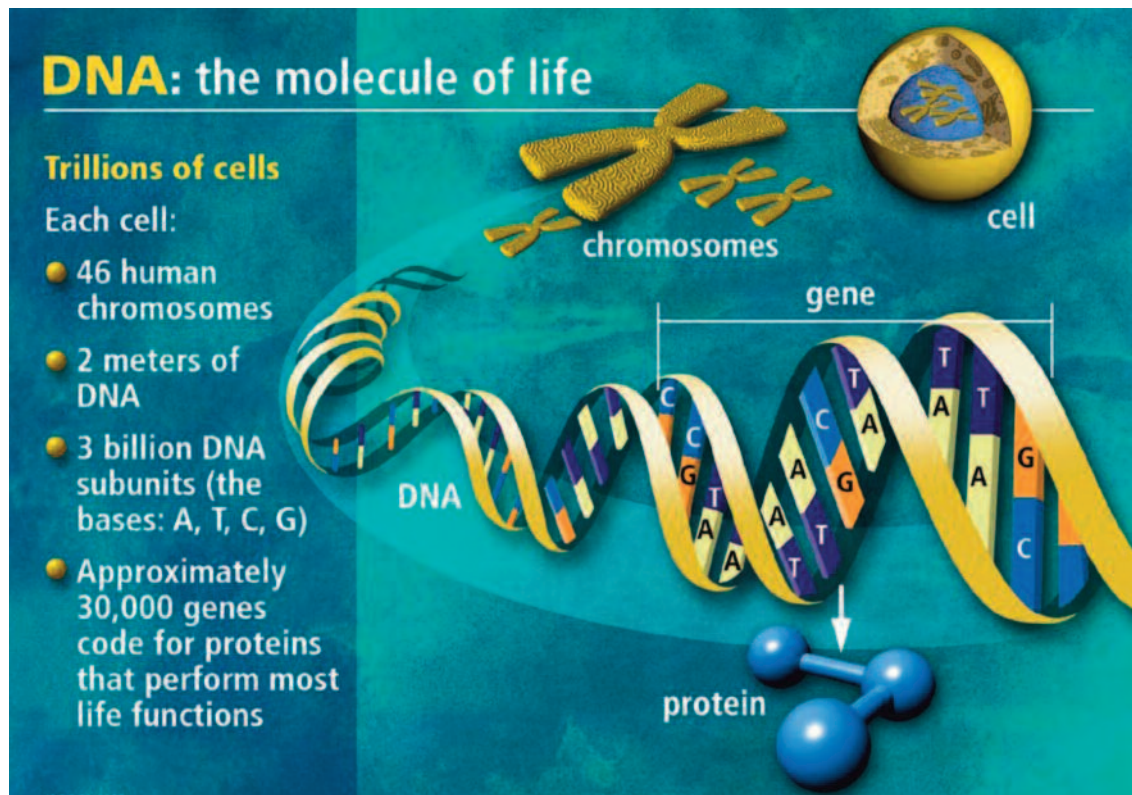


Image courtesy of U.S. Department of Energy Human Genome Program, <http://www.ornl.gov/hgmis>.

## What Types of Genes Are Commonly Involved in the Development of Cancer?

Several different types of gene mutations are particularly associated with the development of cancer. These kinds of mutated genes (oncogenes, tumor suppressor genes, and DNA repair genes) can be biomarkers for cancer.

Oncogenes are variations of normal genes that control cell growth and reproduction. Oncogenes accelerate this process abnormally, causing the development of cancer. An example of an oncogene is *HER2/neu* (human epidermal growth factor receptor 2), which accelerates the growth of some breast cancers. Think of oncogenes like the accelerator pedal on your car: They can speed up cancer.

Tumor suppressor genes regulate the growth and reproduction of cells. When these cells are mutated, cell growth is uncontrolled, and cancer can result. *PTEN* is a tumor suppressor gene that is involved in the development of many kinds of cancers, including brain tumors, melanoma, and cancers of the prostate, endometrium, kidney, and lungs. Tumor suppressor genes are like a car's brake pedal: When they work right, they stop or slow cancer.

DNA repair genes fix errors that occur when cells replicate or are exposed to something that can trigger a mutation. Some examples of these genes are *MLH1*, *MSH2*, *MSH6*. Mutations in these genes have been implicated in the development of a particular type of colon cancer. DNA repair genes are like auto mechanics: They keep things running smoothly.

Other genes, known as susceptibility genes, increase the likelihood that a carrier will develop cancer, but do not directly cause cancer. *BRCA1* and *BRCA2* are examples of susceptibility genes.

## How Is DNA Tested?

Many different laboratory techniques are used to study DNA. Some of these are described in the table that follows:

### LABORATORY TECHNIQUES FOR DNA ANALYSIS

Technique	Application
Karyotyping	Separating individual chromosomes and arranging them systematically for examination
Fluorescence in situ hybridization (FISH)	Checking a specific chromosomal region for deletions or rearrangements
PCR (polymerase chain reaction)	Increasing the amount of DNA in the sample
Gel electrophoresis	Visualizing DNA that has undergone PCR
Array comparative genomic hybridization (aCGH)	Checking the whole genome for large deletions or duplications (copy number variation)
Quantitative fluorescence - polymerase chain (QF-PCR) reaction (QF-PCR)	Controlled PCR that allows the number of copies of a chromosome region to be assessed. This is used in the rapid prenatal test for common chromosomal trisomies such as Down syndrome
Multiplex Ligation-dependent Probe Amplification (MLPA)	Detecting deletions or duplications of part of a gene
DNA sequencing (Sanger)	Checking for alterations in the order of bases in the genetic code
Next generation sequencing (NGS)	Large-scale DNA sequencing producing vast amounts of data in a single test.

Source: National Genetics and Genomics Education Centre. What Happens in the Laboratory? <http://www.geneticseducation.nhs.uk/laboratory-process-and-testing-techniques>. Accessed March 8, 2016.

Sequencing is a common type of gene-based testing performed in labs. Briefly, these are the steps in sequencing:

- A sample of body tissue is collected from the patient. Often, this is a sample of blood, but it could also be skin, saliva, amniotic fluid, or tumor cells obtained during a biopsy.
- The sample is sent to a lab, and part or all of the DNA is put into a DNA sequencer. This machine reads DNA and collects the data in short fragments known as “reads.”
- Computers compile the “reads” in order, a process that is similar to putting the pages of a book in order. Then the patient’s DNA is compared with the human reference genome to find variants.
- Finally, a computer-generated report lists the variants detected and the health care team analyzes the findings.

### Gene-Based Testing and Its Role in Precision Oncology

In recent decades, genomic research has rapidly increased the number of gene-based tests available. There are hundreds of tests that can reveal valuable information about a particular patient and his or her cancer. For example, gene-based tests can tell us about a patient’s risk of developing particular cancers, help to diagnose cancer or determine which subtype of a particular cancer a patient has, optimize treatment, and evaluate response to treatment or recurrence of disease. A comprehensive discussion of gene-based tests used for precision oncology is beyond the scope of this tutorial, but the following table highlights some of the more widely used and well-known gene-based tests for various types of cancer.

#### EXAMPLES OF SOME GENE-BASED TESTS

Gene or Marker Name	Type of Cancer	Relationship of Gene or Marker to Cancer
<i>BRCA1</i> and <i>BRCA2</i>	Breast	Changes in these genes increase the risk of cancer
<i>BCR-ABL</i>	Leukemia	Genetic material is exchanged between two chromosomes, causing two genes to come together that are not supposed to. These genes are called the BCR and ABL genes. These genes spell out the chemical letter code for a hybrid protein that leads to uncontrolled growth of some blood cells, leading to leukemia
<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , and <i>PMS2</i>	Hereditary nonpolyposis colorectal cancer	These genes are part of the system that corrects errors in DNA. When they do not have the correct chemical letters, errors in DNA may go unchecked and lead to cancer
<i>HER2/neu</i> (human epidermal growth factor receptor 2)	Breast	A gene that helps control how cells grow, divide, and repair. Cancers with too many copies of the <i>HER2</i> gene have too many <i>HER2</i> receptors and tend to grow fast





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## Chapter 3: Clinical Trial Designs for Precision Medicine

Before we begin a discussion of how clinical trials are designed to advance precision medicine, it may be useful to review the design of clinical trials generally.

Clinical trials are conducted in a series of steps, called phases. Each phase is designed to answer a separate research question.

**Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

**Phase II:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

**Phase III:** The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

**Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

The trials we will discuss in this chapter are mainly Phase III trials, intended to compare how large groups of patients with and without particular biomarkers do on standard treatments vs. newer, targeted treatments.

The gold standard in clinical research has long been the randomized controlled trial. The purpose of these trials is to establish causality between an intervention (for example, a new targeted treatment) and the outcome (for example, longer survival). To accomplish this, researchers take steps to ensure that the experimental arm (that is, patients receiving the new treatment) and the control arms (patients receiving the standard treatment) are similar in every way except the interventions. Three techniques for achieving this are randomization, blinding, and stratification.

**1) Randomization** assigns patients to treatment arms by chance, avoiding any systematic imbalance in characteristics between patients who will receive the experimental versus the control intervention. Usually patients are assigned equally to all arms, although this need not be the case. With a simple two-arm trial (one experimental and one control) randomization can be accomplished with a flip of a coin. When there are more than two arms, or unequal numbers of patients are to be assigned to different arms, computer algorithms can be used to ensure random assignment.

**2) Blinding** is ensuring that neither patients, healthcare providers, nor researchers know to which group specific patients are assigned. Trials are said to be single, double, or triple blinded, depending upon how many of the relevant participants in the trial are unaware of patient assignment. The purpose of blinding is to minimize patients receiving different care, or having their data interpreted differently, based on the intervention to which they are assigned.

### Randomized Clinical Trials: The "Gold Standard" for Medical Research

- Equal number of patients randomly assigned to two or more treatment arms
- Double blinded (patients, healthcare providers, and researchers are all unaware of which patients are assigned to which arm of the study), if possible
- Single primary endpoint
- May require many trials to answer complicated questions

**3) Stratification** prior to randomization can be used to ensure that the numbers of patients assigned to the experimental and control arms are balanced with respect to important attributes, also known as stratification variables. Examples of stratification variables are gender and disease stage.

### What Are the Objectives of Clinical Trials in Precision Medicine?

According to Dr. Barbara Conley of the National Cancer Institute, precision oncology clinical trials have several possible purposes:

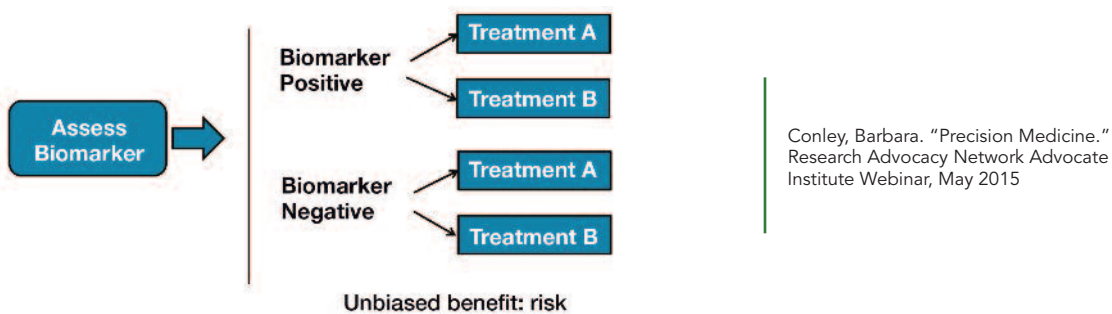
- To evaluate an assay for a biomarker.
- To assess whether a biomarker is useful.
- To evaluate a biomarker that is known to be or believed to be useful.
- To evaluate the effect of a treatment in patients who have a particular biomarker.

### What Designs Are Used for Clinical Trials in Precision Medicine?

#### Stratified Trial Design:

An ideal approach to assessing whether a biomarker and its associated treatment are useful is to stratify a group of patients into 2 groups: those who have the biomarker and those who don't. After patients are grouped according to the presence or absence of the biomarker, they are randomly assigned to either the standard treatment for their cancer or an experimental treatment that targets the biomarker being studied.

#### BIOMARKER STRATIFIED



Clinical trials designed this way allow researchers to answer several important questions in an unbiased way:

- What is the "cutpoint" for the biomarker in question? Some biomarkers are either present or absent whereas other biomarkers are quantitative and can present at varying levels. For these quantitative biomarkers, well-designed clinical trials can help determine to which degree a biomarker needs to be present for it to affect their treatment outcome?
- How does the prognosis differ for patients who have the biomarker compared with those who don't?
- How do patients with and without the biomarker fare when they are assigned to the standard treatment for their cancer?
- Does the targeted treatment lead to better outcomes for patients who have the biomarker?

#### Enriched Trial Designs

When researchers determine that a particular treatment is in fact helpful for a group of patients with a particular biomarker, they change the way they conduct trials and use a different trial design. This type of clinical trial uses what is known as an enriched design. Enriched design clinical trials exclude patients who do **not** have the biomarker and focus only on patients with the biomarker. The main reason for using an enriched design is that it would be unethical to give patients without the biomarker a targeted treatment that we know will most likely not help them.

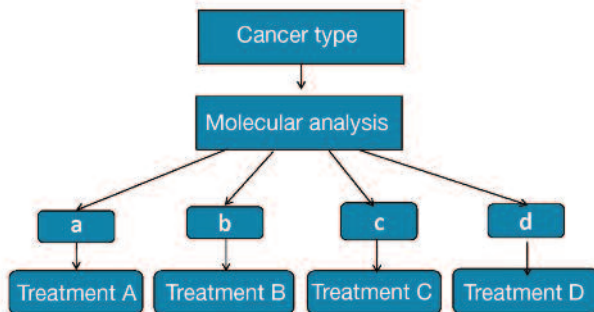
#### Umbrella Protocols

A variation of the enriched clinical trial design used for precision oncology is the umbrella protocol. This protocol involves molecular analysis of patients with a particular type of cancer and focuses on multiple biomarkers, rather than a single biomarker. Patients with different biomarkers

are then stratified to receive different drugs targeted to their biomarker. Because this type of trial evaluates multiple biomarkers and multiple drugs, umbrella protocols can be much more efficient than trials that focus on one single biomarker and one targeted therapy for that biomarker.

**MASTER PROTOCOLS: DESIGNS**

- ▶ Umbrella Protocol:
  - One cancer type
  - Separate treatments for different molecular profiles



Conley, Barbara. "Precision Medicine." Research Advocacy Network Advocate Institute Webinar, May 2015

An example of an ongoing clinical trial that is using an umbrella protocol is the Lung-MAP trial. (Lung-MAP is short for "lung cancer master protocol.") This nationwide trial is focused on patients who have advanced squamous cell cancers of the lung and who have already received standard treatment. In this trial, patients' lung tumors are being tested to see whether they have certain biomarkers, and patients are then matched with targeted treatments based on their test results.

Five targeted treatments will be studied as part of the Lung-MAP trial. Additional targeted therapies can be added to the trial as they become available, and therapies can be dropped from the study if results indicate that a drug is not effective. This flexible approach increases the likelihood that patients will receive a drug that effectively targets their tumor's profile, and helps researchers figure out which biomarkers will not work, and spare patients unneeded toxicity from drugs that will likely not provide benefit.

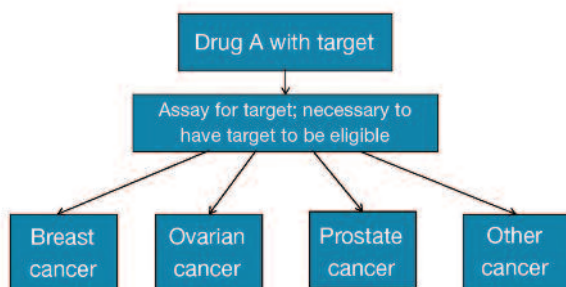
Interested in learning more about the Lung-MAP trial or know someone who might want to enroll in the study? Visit <https://clinicaltrials.gov/ct2/show/study/NCT02154490#locn>. Click on "Show Study Locations" to find an investigator in your area who is currently recruiting participants.

**Basket Protocols**

So-called "basket" clinical trials focus on a drug treatment that is known to target a particular biomarker and might be effective for patients with different types of cancer who all have the biomarker targeted by that drug. Basket trials can involve patients with different kinds of cancers who receive the same targeted therapy. The aim of basket trials is to find out which kind or kinds of cancer the drug works best for. So, for instance, patients with colon, breast, and lung cancer might all be enrolled in a basket trial designed to examine the effectiveness of a drug that targets a mutation of the *BRAF* gene.

**BASKET PROTOCOL**

- One or a few drugs, different tumor types with same molecular feature



Conley, Barbara. "Precision Medicine." Research Advocacy Network Advocate Institute Webinar, May 2015



Basket trials can involve several arms, meaning that one trial may evaluate multiple biomarkers and multiple drugs that are being studied for treatment of multiple cancers. One such trial is the National Cancer Institute (NCI) MATCH (Molecular Analysis for Therapy Choice) Trial. Patients who enroll in this trial will have their tumors tested for a variety of genetic mutations that are thought to respond to a particular drug. The table below shows the molecular targets for the MATCH trial and their corresponding drug treatments as of March, 2016. For current status of the MATCH trial, please refer to the MATCH web site at: <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>. Ultimately, more than 20 drugs or drug combinations targeted at specific genetic mutations will be included in the MATCH trial.

Drug(s)	Molecular Target(s)	Estimated Mutation Prevalence
Crizotinib	ALK rearrangement	4%
Crizotinib	ROS1 translocations	5%
Dabrafenib and Trametinib	BRAF V600E or V600K mutations	7%
Trametinib	BRAF Fusions/ Non-V600E/ Non-V600K BRAF mutations	2.8%
Afatinib	EGFR activating mutations	1-4%
Afatinib	HER2 activating mutations	2-5%
AZD9291	EGFR T790M mutations and rare EGFR activating mutations	1-2%
Ado-trastuzumab emtansine	HER2 amplification	5%
VS6063	NF2 loss	2%
Sunitinib	cKIT mutations	4%

Source: NCI MATCH Trial. <http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>. Accessed March 6, 2016.

If a patient has one of the mutations being studied, he or she may be eligible to receive the drug matched to that biomarker. All of the drugs being investigated are either approved for another type of cancer or have shown promise in other trials for treating cancers with the associated biomarker. One of the goals of the MATCH trial is to enroll patients with a wide variety of cancers, including both common and rare types. Researchers plan to screen about 3,000 cancer patients and enroll about 1,000 in the trial.

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NCI-MATCH is a unique, groundbreaking trial," explained Doug Lowy, M.D., acting director of the National Cancer Institute. "It is the first study in oncology that incorporates all of the tenets of precision medicine. There are no other cancer clinical trials of this size and scope that truly bring the promise of targeted treatment to patients whose cancers have specific genetic abnormalities. It holds the potential to transform cancer care."

# Chapter 4: Targeted Therapies and Precision Medicine

## Traditional vs. Targeted Treatment for Cancer

For most of the past 50 years or so, cancer treatment has relied on traditional therapies such as radiation therapy and chemotherapy. Chemotherapy is drug treatment that can kill cancer cells, but also has the potential to harm normal, healthy cells. Likewise, radiation therapy using x-rays, gamma rays, neutrons, or protons can kill cancer cells and shrink tumors, but even when carefully directed at a tumor inevitably harms some normal cells as well.

Targeted therapies are different. These therapies are drugs or other substances that block the growth and spread of cancer by interfering with the molecules that are specifically involved in cancer cell growth and progression, rather than normal cell activity. The goal of targeted therapies is to rid the body of cancerous cells while leaving normal cells unharmed.

You might think of the distinction between traditional and targeted therapies this way: Traditional cancer therapies are similar to fishing with a net. When you cast a net on the water, you may catch lots of the fish you want to catch (the cancerous cells), but you're also likely catch at least some fish you don't want to catch (normal cells), and you may hurt or kill them in the process. Targeted therapies are more like fishing with a hook that's baited with something only the fish you want to catch will bite at. Other fish ignore the bait and swim away unharmed. In this chapter, we'll look at two main types of targeted therapy for cancer patients: monoclonal antibodies and small molecule inhibitors.

## Monoclonal Antibodies: What They Are and How They Work

An antibody is a protein produced by certain blood cells in response to the presence of antigens. Antigens are foreign substances, such as a viruses, bacteria, and toxins, that trigger the production of antibodies. When an antibody finds the antigen it was made to fight, the antibody binds to the antigen, like a key fitting into a lock. The antibody then recruits the immune system to attack and destroy the antigen.

Antibodies are an important part of the body's immune system and can be directed against cancer cells. However, as with other types of cancer treatment, it's important to target just the cancer cells and avoid normal, healthy cells. That's where monoclonal antibodies come in. A monoclonal antibody is a protein produced in a laboratory that's designed to bind tightly and specifically to one substance—such as a protein on the surface of a cancer cell—and to work potently against it.

The process of creating monoclonal antibodies in the lab is a fascinating and fairly complicated undertaking that involves fusing animal spleen cells with cells from human myeloma, a type of cancer that affects the blood and bones. The details are beyond the scope of this tutorial, but readers who are interested to learn more about how monoclonal antibodies are produced can refer to the tutorial titled *Targeted Therapies*, available for download on the Research Advocacy Network website.

Monoclonal antibodies (also known as mAbs) are administered to patients intravenously (through a vein) and work to defeat cancer cells in several different ways. For example, mAbs have been designed to:

- Make cancer cells more obvious to the body's immune system.
- Block signals that trigger cells to grow.
- Stop angiogenesis (the formation of new blood vessels), which is necessary for the growth of cancerous tumors.
- Deliver radiation directly to a cancer cell when combined with a radioactive particle.
- Deliver a chemotherapy drug or toxin directly to a cancer cell.

Monoclonal antibodies that are combined with another substance to fight cancer cells, such as a radioactive particle or chemotherapy drug, are called "conjugated monoclonal antibodies." These types of mAbs are sometimes also referred to as tagged, loaded, or labeled. In contrast, mAbs that work by themselves against cancer are known as "naked" or unconjugated monoclonal antibodies.

### Small Molecules: What Are They, and How Do They Differ from mAbs?

Like mAbs, small molecules are also a primary type of targeted therapy. And like mAbs, small molecules are drugs that interfere with essential processes in cancer cells. But whereas mAbs attach to the outside of cancer cells, small molecules can penetrate inside cells to perform their work. Small molecules are, as their name implies, much tinier than monoclonal antibodies.

Small molecule inhibitors work by interfering with or inhibiting cell processes such as growth, proliferation, movement, and new blood vessel formation. Many of the small molecule inhibitors available today inhibit proteins known as kinases, or more specifically, tyrosine kinases. Kinases are enzymes that transfer chemical groups called phosphate groups from one place in the cell to another. The transfer of phosphate groups within cells acts as a cellular switch, turning off or on a variety of cellular functions.

In addition to their sizes and their location outside vs. inside the cell, there are a number of other key differences between mAbs and small molecules. For example:

- Small molecule inhibitors are manufactured by combining chemicals in a laboratory, whereas monoclonal antibodies are produced using bioengineering techniques. mAbs are expensive and technically difficult to produce; small molecule inhibitors are easier and less costly.
- Small molecule inhibitors are usually taken orally, whereas monoclonal antibodies are usually administered intravenously. If monoclonal antibodies were taken orally, their structure would change in the stomach and intestines and they would not work because their structure is critical to their activity.
- Monoclonal antibodies last in the body for days to weeks and therefore only need to be administered on a weekly or monthly basis. In contrast, small molecule inhibitors last only hours in the body and therefore need to be taken every day.
- Monoclonal antibodies are not broken down by the liver, so they do not interact with many other types of drugs. In contrast, most small molecule inhibitors are broken down in the liver by enzymes that also break down other drugs. If multiple drugs compete for the same enzyme, this can lead to drug interactions, which may be harmful to patients.
- Because the specificity of interactions between antibodies and antigens, mAbs are highly specific for their targets. In contrast, small molecule inhibitors tend to be less specific, with some of them targeting more than one molecule.

The names of monoclonal antibodies end in "mab" (for monoclonal antibody), whereas the names of small molecule inhibitors generally end in "ib" (for inhibitor), but may have other endings such as "imus" for immune system inhibitors (immunosuppressants).

### A Small Molecule Success Story

In 1960, two researchers at the University of Pennsylvania School of Medicine made a discovery that would eventually lead to one of the first and most successful targeted cancer therapies. They found a strange-looking chromosome in the white blood cells of patients with chronic myelogenous leukemia that was not present in cells of people who did not have that type of cancer. This mutated chromosome was named the Philadelphia chromosome, after the city where it was discovered.

Eventually, researchers determined that the Philadelphia chromosome arises when there is a translocation of DNA between two normal chromosomes, chromosome 9 and chromosome 22. Translocation means changing places, and in this case a section of chromosome 9 migrates to chromosome 22. As a result of the translocation, an abnormal gene is created on chromosome 22. The *BCR-ABL* gene, as it is known, provides instructions for making an abnormal protein that causes leukemia.

More research led to the discovery a small molecule inhibitor called imatinib that inhibits overproduction of the protein responsible for the cancer. Imatinib (trade name: Gleevec) is an extremely effective therapy. In 98% of patients with chronic myelogenous leukemia, treatment with imatinib leads to a complete response.

#### THE PHILADELPHIA CHROMOSOME AND *BCR-ABL* GENE

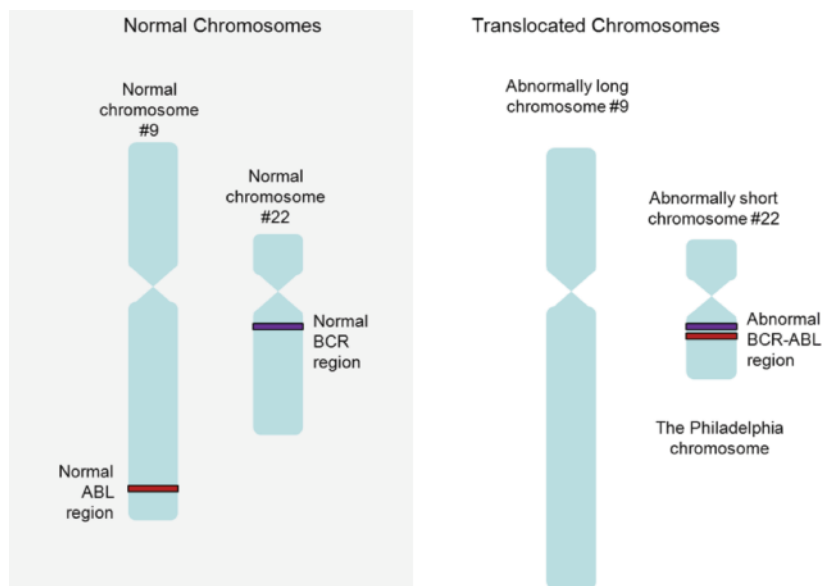


Illustration of chromosomes 9 and 22 in their normal, noncancerous state (left) and after the cancer-causing translocation of chromosomes 9 and 22 seen in patients with chronic myelogenous leukemia (right). This translocation causes an abnormally long chromosome #9 and an abnormally short chromosome #22, known as the Philadelphia chromosome. The Philadelphia chromosome contains the aberrant *BCR-ABL* region that provides the instructions for a cancer-causing protein.



## Which Targeted Therapies Are Currently Approved by the Food and Drug Administration?

The FDA has approved many targeted treatments for solid malignancies. ***Please find a listing of the FDA approved treatments as of March 2016 in the pocket of this tutorial.***

As mentioned previously, monoclonal antibodies can be distinguished from small molecules based on their nonproprietary (or generic) names. The generic names for mAbs end in the stem “-mab,” whereas the generic names of small molecules end with the stem “-ib” or “-imus.” The proprietary (or trade) names are listed after the generic name in the table.

## What Are Some Challenges Associated With Targeted Cancer Therapies?

As promising and exciting as targeted therapies for treating cancer are, they also are associated with many challenges. Research advocates should be aware of the following roadblocks to successful treatment with targeted therapies:

**Cost.** Compared with traditional cancer therapies, targeted therapies can be extremely expensive. For example, an 8-week course of a common chemotherapy drug might cost as little as \$100, while an 8-week course of treatment with a targeted therapy could top \$30,000. Many factors contribute to the prohibitively high cost of targeted therapies, including the costs of discovering and developing new drugs, clinical trials, biotechnology required to produce mAbs, insurance and reimbursement issues, and the need for pharmaceutical companies to make a profit. Fortunately, as patents expire on targeted therapies, less-expensive biosimilar drugs may become available, easing the burden on payers.

**Medication adherence.** Studies have shown that cancer patients may only take 50% to 90% of the medication prescribed for them if they are not participating in a clinical trial. This is particularly a problem for small molecule inhibitor therapies, which are taken daily in pill form for months or years. Reasons for the failure to take a medication as prescribed can include the drug's cost, as well as lack of understanding about how and why to take the drug correctly. In any case, not taking a therapy as prescribed reduces its effectiveness.

**Acquired resistance.** In some cases, a targeted therapy works well initially, but then loses effectiveness because the tumor evolves and develops resistance to the treatment. Researchers are working to understand this complex phenomenon better, but in some circumstances we do not yet know why or how resistance develops. However, we do know that sometimes targeted therapies work better when used in combination, rather than singly.

**Uncertainty about optimal dosing.** Unlike traditional cancer therapies, which may shrink tumors and are also associated with significant side effects, targeted therapies may merely hold the growth of a tumor in check and are not necessarily associated with toxic side effects. Determining optimal dosing is easier with traditional therapies: Clinicians seek maximal shrinkage of the tumor and minimal (or at least tolerable) side effects. In comparison, determining the optimal dose for targeted therapies can be less clear cut, and clinicians remain uncertain in some circumstances about whether the patient is receiving optimized treatment.

**Unpredictable response to treatment.** Curiously, just because a patient has the marker for a particular treatment does not mean that patient will necessarily respond to the targeted therapy. This situation is known as primary resistance. Conversely, some patients who do not have the marker sometimes respond to the associated therapy. This situation can make it difficult to successfully match patients with therapies.

**Time.** Some oncologists report that they simply lack the time to order molecular diagnostic tests, await results, and analyze reports to determine whether a targeted treatment might be appropriate for a particular patient. This may be especially true of physicians in busy community practices, as opposed to those at research centers. Because of heavy patient caseloads and limited time, the one-size-fits-all or empiric approach may seem more efficient.

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# Chapter 5: Molecular Diagnostics and Precision Medicine

## What are Molecular Diagnostics?

Molecular diagnostics are tests that detect genetic material, proteins, or related molecules that provide information about health or disease. These tests are most commonly run on samples of blood, saliva, or tumor tissue. Depending on the type of test, a molecular diagnostic may also be referred to as a gene panel, a gene signature panel, a gene signature test, or a gene expression panel. However, molecular diagnostics is the broader term encompassing many different types of tests that examine DNA and related molecules. The table below lists some common examples of molecular diagnostic tests used for cancer.

### EXAMPLES OF MOLECULAR DIAGNOSTICS IN CANCER\*

Test	Associated Health Condition(s)
Human papilloma virus (HPV)	Cervical cancer
<i>BRCA1</i> and <i>BRCA2</i> genes	Breast, ovarian and cervical cancers
CA125 protein	Ovarian cancer
Prostate Specific Antigen (PSA)	Prostate cancer
<i>HER2/neu</i> gene	Breast cancer
DNA mismatch repair genes ( <i>MSH2</i> , <i>MLH1</i> , <i>MSH6</i> , <i>PSM2</i> )	Lynch syndrome (colon cancer)
<i>KIT</i> gene	Acute myelogenous leukemia and GIST tumors of the gastrointestinal tract
EGFR, ALK, and KRAS genes	Lung cancer
Estrogen receptor/Progesterone receptor (ER/PR)	Breast cancer

## How Are Molecular Diagnostic Tests Used?

Molecular diagnostic tests are used for several different purposes, and a single molecular diagnostic may have more than one use.

### Risk assessment

Molecular diagnostics can be used to determine whether a person is at risk for a certain type of cancer. When used this way, the tests may also be referred to as molecular profiling or molecular risk assessment. These tests help a person determine how likely he or she is to develop cancer. They can also be used to help decide whether a person should undergo more intensive screening or take preventive measures.

### Differential Diagnosis

Molecular diagnostics can help differentiate cancer from benign tumors (i.e., growths that are not harmful) and can further help identify the type of tissue in which the cancer originated (breast, lung, skin, etc.). Molecular diagnostics can even help classify different cancer subtypes that affect the same tissue. These analyses may help estimate the aggressiveness of the cancer. For example, there are many different types of blood cancers, and molecular diagnostics are widely used to determine blood cancer subtypes. The cancer's molecular subtype may have implications for treatment.

### Prognosis

Prognosis refers to the natural course of disease in the absence of treatment or a predicted outcome of the results from medical treatment. Some cancers are naturally more aggressive than others and knowing this may help patients and physicians determine which treatment to select. An example is the gene known as *FLT3*. Alterations in this gene indicate an aggressive cancer in people diagnosed with AML.

Molecular diagnostics can also be used to evaluate the likelihood that cancer will recur after treatment—another aspect of prognosis. Several molecular diagnostics are available to predict the likelihood of breast cancer recurrence in women with specific types of invasive breast cancer who will be treated with hormone therapy. These tests examine multiple genes in cells obtained from a sample of the breast tumor.

### Predicting Treatment Response

As just described, molecular diagnostics can also help predict whether patients will respond to cancer treatments. An example is the test for *HER2/neu* gene overexpression in breast cancer tumor tissue. The *HER2/neu* gene directs cells to make a protein known as human epidermal growth factor receptor 2 (*HER2*). Approximately one-fourth of all breast cancers have too many copies of this gene, which cause too much of the protein to be produced. The extra protein makes cells grow and divide rapidly. Trastuzumab inhibits the activity of the *HER2* protein and may be used to treat breast cancers with overexpression of *HER2/neu*.

### Assessing Pharmacokinetics

When you swallow a pill, the medication must be absorbed and distributed throughout the body so that it can reach its intended site of action—in this case, the cancerous tissue. After a period of time, the body breaks down and eliminates the medication, leading to a need for more medication. The process of absorption, distribution, metabolism (break down), and elimination of drugs is called pharmacokinetics. The rate at which these processes occur depends on a variety of factors, including genetics. Because of genetic differences, some people metabolize drugs faster than others, which has major implications for certain cancer therapies. An example of this is a medication known as irinotecan, used for the treatment of colon cancer. Individuals with a genetic pattern known as *UGT1A1\*28* metabolize irinotecan more slowly than those without this pattern. To prevent the medication from accumulating in the body, these individuals must be given a lower dose than normal.

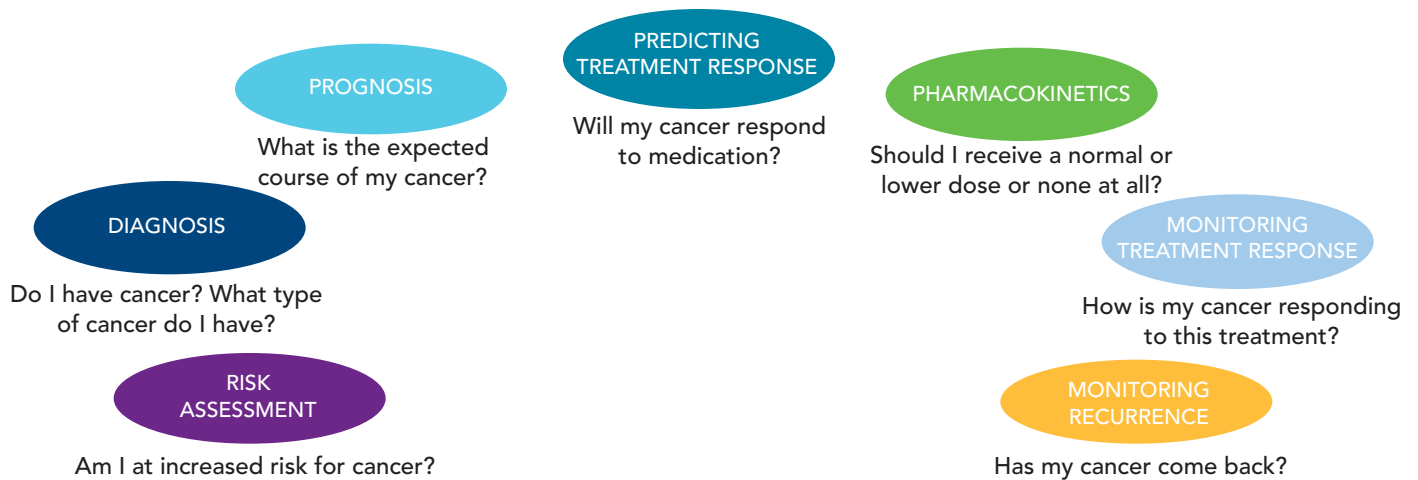
### Monitoring Treatment Response

Naturally, patients and physicians want to know as soon as possible whether a treatment is working. Some cancers can develop resistance to medications, as in the case of chronic myelogenous leukemia—a type of blood cancer. This cancer is often treated with a medication known as imatinib, which inhibits a protein made by an abnormal combination of genes. People with chronic myelogenous leukemia may need to take imatinib for years, and in some people, the sequence of genetic material can change over time. This change may lead to reduced medication effectiveness. Consequently, patients who no longer respond to imatinib may undergo molecular diagnostic testing to determine whether the gene has changed.

### Monitoring Recurrence in Patients Without Symptoms of Cancer

Patients whose cancer has been successfully treated are typically monitored at regular intervals for signs of recurrence. For some cancers, molecular diagnostics can aid in determining whether a cancer has recurred. For breast, prostate, and ovarian cancers, the use of molecular diagnostics to monitor recurrence in patients without symptoms of cancer is controversial. However, in the future, scientists are likely to develop better molecular diagnostics that can more accurately monitor recurrence in patients whose disease has been successfully treated.

## CLINICAL USES OF MOLECULAR DIAGNOSTICS



Molecular diagnostics and precision medicine are changing the face of medicine, although we are still at an early stage in the game. Undoubtedly, molecular diagnostics will continue to play an ever-increasing role in cancer management for the foreseeable future.

## What Are the Steps in Molecular Diagnostic Testing?

### Tissue Sampling

The first step in molecular diagnostics is to obtain tissue, often referred to as a specimen, for testing. Tissue samples are collected by different methods depending on the purpose and the type of test. Blood samples are often drawn from veins in the arm. Urine can be studied, as can saliva obtained from the mouth. Samples may be taken from the skin following administration of a local anesthetic.

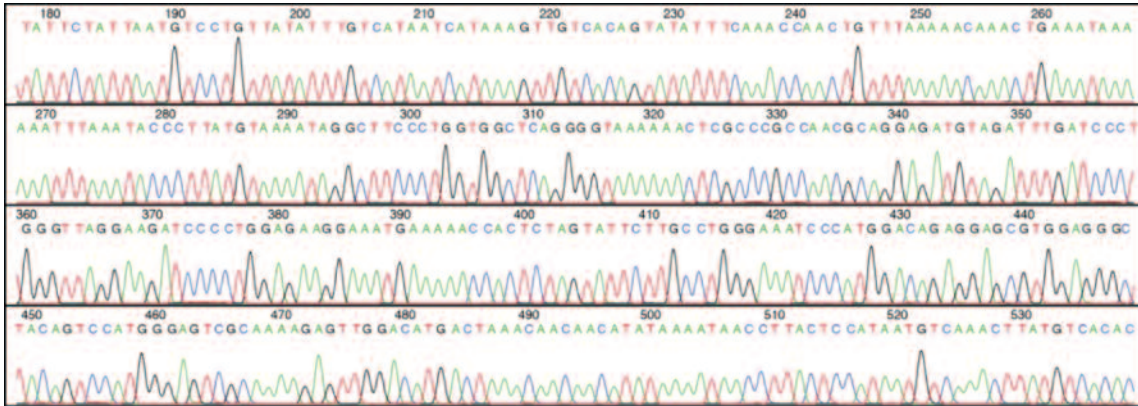
When samples need to be obtained from a solid tissue abnormality or tumor, the simplest and least invasive option is a fine-needle biopsy, in which a fine needle is inserted into the tissue and cells are aspirated. If a larger amount of tissue is needed, a core-needle biopsy may be used to remove cells and a small amount of surrounding tissue. Surgical procedures may also be used when the removal of an even larger amount of tissue is needed; an incisional biopsy removes a portion of the abnormality and an excisional biopsy removes the entire abnormality or tumor. Cells can also be obtained by scraping tissues that naturally open to the environment, such as the cheek and cervix. Another method involves the use of a flexible, lighted instrument called an endoscope that is inserted into one of the body's natural openings. The endoscope allows the physician to see abnormal areas on the lining of organs and pinch off tiny bits of tissue.

## Methods Used To Detect DNA

### DNA Sequencing

One method used to detect DNA is to directly determine the nucleotide bases it contains. The first person to develop this method was Fred Sanger, and the method is sometimes known as the Sanger method. With the Sanger method, the DNA is first separated into two strands. Next, one strand is copied multiple times using chemicals that stop the copying process at different places along the DNA strand. This process results in numerous smaller DNA strands of different lengths. The researchers know which nucleotide is on the end of each fragment because of the chemicals they used to stop the copying process. This allows them to assemble the pieces of DNA like a jigsaw puzzle to reveal the sequence of the original DNA strand.





DNA Sequence Data From an Automated Sequencing Machine

Image credit: Darryl Leja, National Human Genome Research Institute

Today, methods are available that sequence DNA much more quickly and inexpensively. The most popular method used currently is called next generation sequencing, or NGS. In this method, up to 500 million separate sequencing reactions are run at the same time on a slide the size of a Band-Aid. This slide is put into a machine that analyzes each reaction separately and stores the DNA sequences in a computer. The reaction is a copying procedure similar to the one described for the Sanger method, but does not require the use of altered nucleotide bases.

### DNA Microarrays

DNA microarrays were developed to detect thousands of genes at once—a feature that is integral to the field of genomics. In DNA microarrays, DNA probes containing selected DNA sequences are “arrayed” or spotted in a grid pattern on a very small glass surface. The DNA microarray actually looks like thousands of tiny dots arranged in precise rows and columns. Each dot contains a single DNA probe like the one just described that is designed to hybridize with the complementary DNA sequence in the tissue sample. Because there are many spots for probes, many different DNA sequences can be detected at the same time. This allows so-called “high throughput,” or the analysis of many DNA sequences in parallel.

After the DNA probes are placed in the microarray, a sample containing the person’s DNA is prepared for analysis. The double-stranded DNA in the sample is denatured or separated into two complementary single strands. The strands are then cut into smaller fragments and attached to fluorescent dye. The labeled DNA in the sample is placed into the chip and allowed to hybridize with the DNA probes. The microarray is then washed; DNA that has hybridized will not wash off, but DNA that has not hybridized will wash off. Bound and unbound DNA is then detected as fluorescence. If the DNA in the sample has hybridized with the DNA probe, that spot on the array will light up. Computers contain information about which spot corresponds to which DNA sequence and can identify the presence or absence of that sequence in the sample. Depending on the type of technology, the array may use between one and four colors in the detection scheme.

DNA microarrays are also called genome chip, GeneChip® (trade name of a specific product), and gene array. Microarrays can be placed on other surfaces besides glass—bead arrays, capillary arrays, and well arrays all work the same way. That is, DNA probes (whose sequence is, of course, known because you put them in) are attached to the array surface, allowing thousands of genes or even the whole genome to be examined in a single experiment. Some microarray analyses detect different variations of the same gene. For example, more than 800 mutations have been found in the *BRCA1* gene. A single microarray can be used to detect all of these variations.

## How Good Are Molecular Diagnostics? Determining Validity, Reliability, and Clinical Utility

Since 1986, the prostate specific antigen (PSA) test has been used along with a digital rectal exam to screen for prostate cancer in men 50 years of age and older. However, in 2012, the U.S. Preventive Services Task Force released a statement recommending against using the PSA test to screen for prostate cancer. Other organizations are also reconsidering their recommendations in light of findings from two large studies in which annual PSA screening combined with digital rectal exams did not save lives. Men who underwent annual screenings were just as likely to die from prostate cancer as men who did not undergo annual screenings.

This example illustrates a major problem with molecular diagnostics: they are not always useful. The PSA test, which measures levels of PSA in the blood, suffers from at least two important flaws: It is not specific, and it often leads to overdiagnosis and overtreatment. In this section, we discuss concepts used to determine the usefulness of molecular diagnostics.

### Analytical Validity

Molecular diagnostics must show two types of validity to be considered useful: analytical validity and clinical validity. Analytical validity refers to how well a test measures what it is supposed to measure. For example, a test designed to detect a mutation associated with melanoma should not give a positive result for an unrelated mutation associated with diabetes.

Analytical validity is a measure of how well the test measures what it claims to measure.

### Specificity

Good tests demonstrate two different aspects of validity: specificity and sensitivity, which are really two sides of the same coin. These concepts can apply to the analytical validity of the molecular diagnostic test as well as to the clinical validity of the biomarker. Let's consider specificity first.

Specificity is the test's ability to correctly identify patients who do not have the biomarker or condition. Said another way, a specific test is one that gives a positive result only when the biomarker or condition is present. Returning to our PSA example, approximately 80% of men who have a positive PSA test do not have prostate cancer. This is because high levels of PSA are not specific for prostate cancer; they are also associated with inflammation of the prostate and benign prostatic hypertrophy (enlargement of the prostate)—relatively common health conditions in older men. Thus, one of the problems with the PSA test as a screening tool for prostate cancer is that it has poor specificity.

Specificity is the ability of the test to correctly identify patients without the condition. Stated another way, a test is specific if it gives a positive result only when the condition is present. For instance, a specific test for a cancer mutation would give a negative result for everyone who does not have the mutation and only give a positive result if someone does have the mutation.

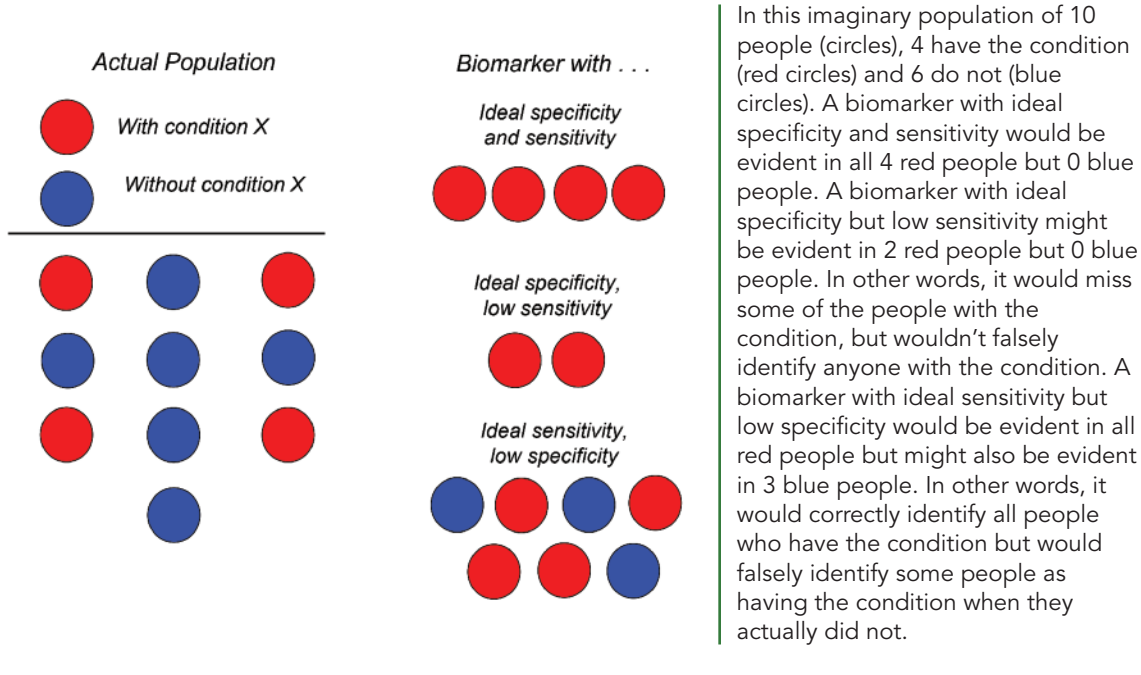
A lack of specificity is problematic because it can cause emotional distress and result in unnecessary follow-up procedures and treatments that are associated with risks. For example, men with high levels of PSA or abnormal findings on a digital rectal exam may elect to undergo a needle biopsy. Such biopsies can cause stress and anxiety and may be associated with financial costs. Although prostate needle biopsies are relatively safe, they can cause severe bleeding or infection of the prostate gland or urinary tract in 1% of patients, in addition to erectile dysfunction and incontinence.

**Sensitivity**

Sensitivity can be considered the opposite of specificity. Sensitivity is the test’s ability to correctly identify patients with the biomarker or condition; in other words, it should correctly identify everyone who has the biomarker or condition. With a sensitive test, you can be relatively certain that, if you have the biomarker or condition, you will get a positive result on the test.

**Sensitivity is the ability of the test to correctly identify those patients with the biomarker or condition.**

**SPECIFICITY AND SENSITIVITY**



**True and False Positives and Negatives**

Results of molecular diagnostics (or any tests, for that matter) can be classified as correct or incorrect. When a test correctly identifies a person with a given biomarker or condition, the result is said to be a true positive. When a test correctly determines that a person does not have a given biomarker or condition, the result is said to be a true negative. This is the ideal situation. However, when a test is incorrect, the results are said to be false. If the test incorrectly identifies a person as having a biomarker or condition, the result is a false positive. If the test incorrectly identifies a person as not having the biomarker or condition, the result is a false negative.

Does the person actually have the biomarker or condition being tested for?	Test Result	
	Positive (yes)	Negative (no)
Yes	True positive	False negative
No	False positive	True negative

Accurate and useful tests have high true positive and true negative rates and low false positive and false negative rates. In the ideal case, the test would identify only those people with the biomarker or condition, but would also identify everyone with the biomarker or condition. In real life, very few molecular diagnostics come close to this ideal.

In molecular diagnostic testing, these terms are often called the positive and negative predictive values (PPV and NPV). A highly specific test will have a high positive predictive value; that is, if it is positive in a patient, it is very likely that patient has the condition. A highly sensitive test will have a high negative predictive value; that is, if the test is negative in a patient, it is very unlikely that the patient has the condition. However, no test is perfect. Depending on the condition, it may be better to have a higher positive predictive value or negative predictive value.

For example, let's presume that 100,000 people undergo cancer screening and 200 of them have a certain cancer. Let's apply a test with high sensitivity, say 90%. In this case, 180 of the 200 patients who actually have the cancer will be identified. Let's also give this test what appears to be a high specificity, say 90%. In this case, 10%, or 10,000, of the screened patients will have a false positive test, leading them to worry needlessly and undergo additional screenings and procedures even though they are not necessary. So, in this case, the positive predictive value is only approximately 2%; that is, of the 10,180 positive tests, only 2% were true positives.

The positive and negative predictive values depend on three issues:

- The prevalence of the condition in the population
- The sensitivity of the test
- The specificity of the test

In the example above, if the prevalence were much higher, let's say 50% or occurring in half of the 100,000 people, then we would have detected 45,000 true positives, but would still have had 10,000 false positives. In this case, 45,000 of the 55,000 positives were true positives, and therefore the positive predictive value would have been 82%!

These considerations highlight how important the use context and analytical validity are for a given molecular diagnostic.

### Test Reliability

Another aspect of analytical validity is test reliability. Test reliability means that the results of the test are repeatable. If a molecular diagnostic performed on Monday indicates that a cancer is positive for a certain gene, it should also give the same result when conducted on Tuesday. Clearly, unreliable tests are not useful in making diagnoses or treatment decisions.

### Clinical Validity

Clinical validity refers to a test's ability to provide clinically relevant information. Clinical validity depends on close association of the biomarker with a clinically important outcome, such as response to a medication or aggressiveness of the cancer.

Clinical validity is the measure of a test's ability to provide clinically relevant information.

Many experts, including a committee of the Institute of Medicine, consider clinical validity a measure of whether the assay reliably divides one population into two or more with different biological or clinical characteristics or outcomes. However, if this difference is not large enough to justify treating the two groups differently, OR if knowing the difference does not result in a different treatment for one of the groups that improves clinical outcomes, then the test lacks clinical utility.

### How Are Molecular Diagnostics Clinically Validated?

Molecular diagnostics are clinically validated by conducting studies that document the relationship of the test's outcome with an important medical or clinical outcome. For instance, if the molecular diagnostic purports to detect response to therapy, then test results would need to show a relationship with reduced tumor growth, patient survival, or another important variable in a clinical study. Such studies provide scientific proof of the molecular diagnostic's accuracy. Without validation in a clinical study, the test's accuracy must be considered unproven.

### Clinical Utility

Clinical utility refers to the overall usefulness of a molecular diagnostic in clinical practice. This is determined by weighing its benefits and drawbacks. As discussed earlier, molecular diagnostics must provide some clinically useful information in order to be clinically valid. This information should aid in diagnosis or clinical decision making. A test that could reliably detect 20 common genes associated with a tumor may not be clinically useful if those genes don't predict anything of value for the patient or physician.

Clinical utility is the overall usefulness of a molecular diagnostic test in clinical practice determined by weighing its benefits and drawbacks. This definition is still evolving, with some experts equating clinical validity and clinical utility.

In addition to being valid and reliable, a molecular diagnostic should also be practical. For example, a test that is extremely difficult to perform or requires rare technical equipment may not have clinical utility in routine hospital use, even if it provides clinically useful information. Practical concerns are an important part of the equation, although not all experts consider them an aspect of "clinical utility." Instead, some experts limit the definition of clinical utility to mean providing clinically useful information. Regardless of whether you consider practical concerns and drawbacks as part of clinical utility, they are important determinants of how useful molecular diagnostics are.

### Possible Reasons for a Lack of Clinical Utility in Molecular Diagnostics

- The test doesn't really work.
- The test works but doesn't distinguish one group of patients from another with sufficient magnitude that they would receive different treatments or procedures.
- The test works and distinguishes patient groups adequately, but no better treatments are available for either group.
- There is insufficient evidence that the test reliably distinguishes one group of patients from another.

### Standardizing Molecular Diagnostics

Ideally, molecular diagnostics would be standardized, meaning that they would be performed exactly the same way on the same equipment with the same chemicals each time. However, this is often not the case. Because many molecular diagnostics require precise measurements, complicated equipment, and/or different mixtures of chemicals, reliability can be difficult to achieve.

One feature that can contribute to the variability of results from a molecular diagnostic test is the way tissue samples are collected, processed, and stored—so-called pre-analytic factors. These factors can substantially alter the consistency of the tissue and its molecular composition. Consequently, the same tissue sample evaluated in the same molecular diagnostic may give different results depending on how it is collected, processed, and stored. Differences in pre-analytic factors can also contribute to variability in scientific studies that incorporate molecular diagnostics.

Ideally, the pre-analytic factors would be standardized, but at the very least, it is important that they are consistently reported. In 2011, experts published recommendations on Biospecimen Reporting for Improved Study Quality (BRISQ). These guidelines describe the pre-analytic details that must be reported anytime human biospecimens are used; this information is designed to help evaluate, interpret, compare, and reproduce the experimental results. To combat the lack of reliability of molecular diagnostics, ASCO-CAP recommends that laboratories adhere to strict tissue sample handling procedures, among other things. These guidelines also recommend that new tests for *HER-2* should show 95% agreement with a reference test for *HER-2* that has been clinically validated (i.e., the reference test predicts clinical outcome). Stringent laboratory accreditation standards are recommended, along with proficiency testing and competency assessments. Standardization is important not only so that an individual undergoing pathology testing can be confident that his or her results are accurate, but also so that results from different patients and laboratories can be compared.



Sometimes tests that are sold by the manufacturer as kits include an internal standard—a test sample that contains a known amount of the biomarker being detected. This standard can then be used to calibrate the test. For example, a test kit might contain an internal standard that consists of 100 micrograms of a protein. When that standard sample is run in different laboratories, they should also find that it contains 100 micrograms. In this way, laboratories can make sure that their test is giving the correct results and that they are comparable to those of other laboratories.

Standardization in laboratory tests may be achieved by requiring laboratories to undergo proficiency testing. For example, blood samples may be sent to participating laboratories to determine the substance of interest. The results from all participating laboratories are sent to a central facility where they are evaluated and the laboratory is either certified or not based on its ability to obtain accurate results.

To overcome the problem of reliability, some companies have designed molecular diagnostics that require tissue samples be sent to the company's own laboratory. In this case, the test can be performed the same way each time and the company has control over the reliability of the results. This is the case for *Oncotype*<sup>®</sup> DX, a test that helps predict the likelihood of benefit from add-on (adjuvant) chemotherapy and of breast cancer recurrence. For this test, healthcare professionals obtain samples of breast tumors and then send them to the company's laboratory for analysis.

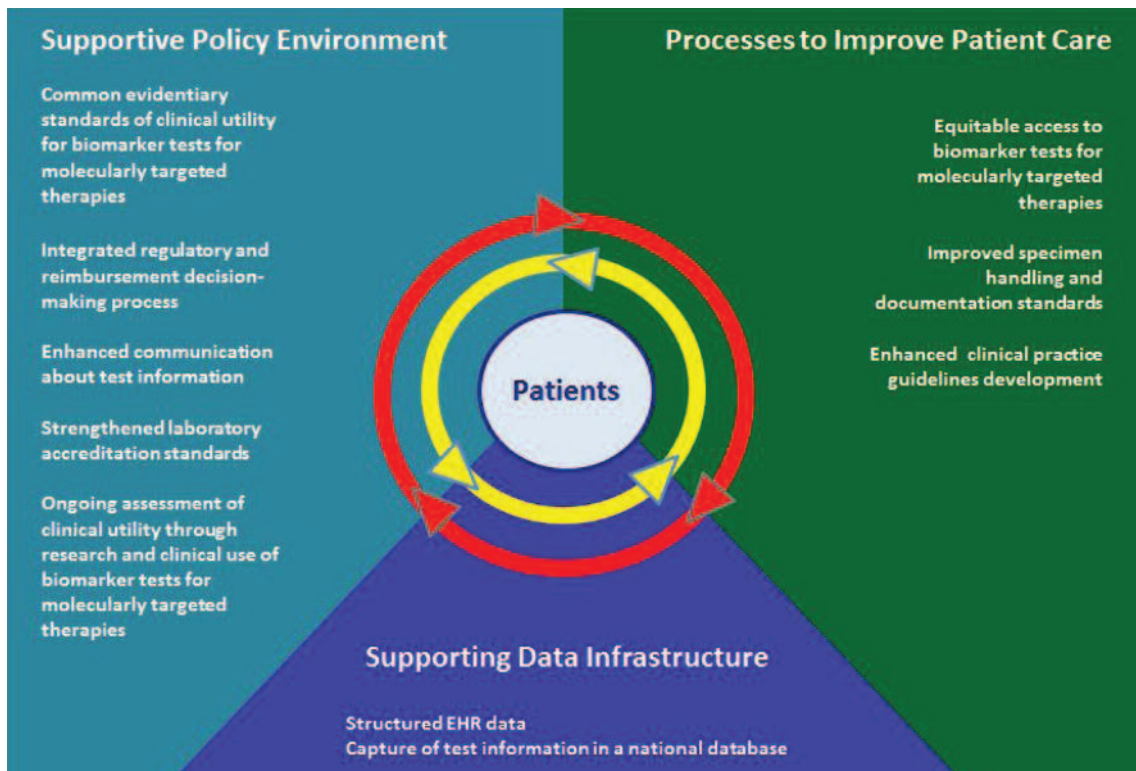
### The Institute of Medicine's New Goals for Biomarker Tests

In March 2016, The Institute of Medicine identified 10 goals to further advance the development and appropriate clinical use of biomarker tests for molecularly targeted therapies.

The goals are as follows:

- 1) Establish common evidentiary standards of clinical utility—using evidence generated both within and outside the context of clinical trials— across all stakeholders. Currently, lack of such standards is a significant limiting factor for patients, health care providers, test developers, regulators, and payers.
- 2) Establish a more coordinated and transparent federal process for regulatory and reimbursement decisions for biomarker tests for molecularly targeted therapies. Processes for making regulatory and reimbursement decisions regarding biomarker tests used in clinical care are misaligned, creating inefficiencies. The Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS) should work closely together to enable effective coordination of these decision-making processes.
- 3) Enhance communication to patients and providers about the performance characteristics and evidence for use of specific biomarker tests for molecularly targeted therapies. Health care providers and patients both lack adequate information about biomarker tests for molecularly targeted therapies.
- 4) Update and strengthen oversight and accreditation of laboratories providing biomarker tests for molecularly targeted therapies.
- 5) Ensure ongoing assessment of the clinical utility of biomarker tests for molecularly targeted therapies. The generation of evidence of the clinical utility of any biomarker test should be viewed as a continuous process.
- 6) Ensure development and use of electronic health records and related biomedical informatics tools and assessments that support the effective clinical use of biomarker tests for molecularly targeted therapies.
- 7) Develop and maintain a sustainable national database for biomarker tests for molecularly targeted therapies through biomedical informatics technology to promote rapid learning for the improvement of patient care. Currently, a tremendous learning opportunity is lost because biomarker test data are maintained in separate siloes at individual institutions. A national repository for such data needs to be developed, and incentives should be used to encourage all health care systems and providers to submit their data to the repository.

- 8) Promote equity in access to biomarker tests for molecularly targeted therapies and the expertise for effective use of the results in clinical decision making. Patients of particular economic, ethnic, and cultural backgrounds and geographic locations may face challenges in obtaining access to biomarker tests and associated therapies. Research should identify existing barriers to equitable access and develop approaches to address them.
- 9) Enhance specimen handling and documentation to ensure patient safety and the accuracy of biomarker test results. Professional organizations and health care institutions should develop and implement standards for obtaining adequate specimens.
- 10) Improve the processes for developing and updating clinical practice guidelines for the effective use of biomarker tests for molecularly targeted therapies. Increasingly, a broader base of interdisciplinary expertise is needed to generate trustworthy clinical practice guidelines for biomarker tests.



Biomarker tests for molecularly targeted therapies represent a crucial area of focus for achieving the full potential of precision medicine. Appropriate regulatory oversight of these tests is needed to ensure they are accurate, reliable, properly validated, and appropriately implemented in clinical practice. To enhance patient care and clinical outcomes, a rapid learning system is needed that can integrate research with clinical practice. This would enable health care providers to continuously collect and assess real-world patient data for continuous learning and rapidly apply new knowledge to a wide variety of clinical practice settings, while also enabling regulators and payers to make more informed decisions.

Source: Biomarker Tests for Molecularly Targeted Therapies: Key to Unlocking Precision Medicine. Institute of Medicine Report in Brief. March 2016. Retrieved from <https://iom.nationalacademies.org/~media/Files/Report%20Files/2016/Biomarkers/Biomarkers-RiB.pdf>

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## Chapter 6: How Research Advocates Can Use This Information

Advocates need a solid understanding of precision medicine because of its growing importance in cancer prevention, diagnosis, treatment, and monitoring. The information in this tutorial is intended to give advocates a broad introduction and basic working knowledge of precision medicine and its role in oncology so that they can more easily communicate with clinicians and researchers. Familiarity with the principles of precision medicine gives advocates additional credibility for their viewpoints and enables them to stay up to date with new developments in this fast-advancing field.

The ultimate goals of the learning and communication fostered by this tutorial are to advance the science of oncology, improve care for people with cancer, and prevent or, eventually, eliminate cancer. This chapter introduces a few of the issues in precision medicine that advocates might be interested in pursuing.

### Encouraging Participation in Research Studies

Only a small percentage of people who might be willing to participate in cancer research studies actually do. The National Cancer Institute reported that one reason for this is that healthcare providers sometimes fail to inform patients about studies.

The future of precision oncology, including finding new biomarkers, new ways to test for biomarkers, and new targeted therapies for patients with cancer, depends on research. And effective research requires sufficient numbers of people willing to participate in studies. Advocates can help with this in several ways. They can encourage physicians to talk with their patients about research studies, provide educational materials about ongoing studies, and communicate the urgency of research from the advocate's point of view. Advocates can also play a role in helping researchers develop effective study protocols. Research advocates are in a unique position to help ensure that patients understand research studies, are willing to do what's needed by the trial, and will stay in the study.

### Promoting Donation of Tissue Specimens

Identifying new biomarkers for cancer requires the use of tissue specimens, such as blood samples or samples of tumor tissue, for research and testing. Because many studies are being conducted both in the United States and worldwide, the need for tissue samples is continuous. Unfortunately, many areas of cancer research do not have enough tissue samples, and this has become a barrier to developing new diagnostic tests.

Research advocates can play an important role in helping patients and the public at large understand the critical need for body tissues in biomedical research. Many advocates have themselves donated tissue. In addition, advocates have the motivation and contacts to assist with designing and implementing tissue collection programs. Some advocates have even formed their own tissue banks to protect donors' rights and ensure they have a say in what is done with that tissue. Other advocates are working with the National Cancer Institute to develop best practice standards for tissue banks.

For more information on tissue banks, see the Research Advocacy Network's booklet titled *Understanding Pathology and Tissue Research*, which is available on RAN's website, [www.researchadvocacy.org](http://www.researchadvocacy.org).

## Finding Better Ways to Communicate Test Results

Often, the results of molecular diagnostic tests are presented to patients so that they can participate in health-related decisions. In such cases, it is critically important that patients understand this information because their health outcomes can depend on how the information is presented. Some people have difficulty understanding numeric values and may benefit from a picture showing the amount of cancer risk accounted for by a given mutation. The same can be said for test results that help determine risk of cancer recurrence or monitoring: Patients may not know whether the results put them in a high, medium, or low risk category.

Advocates can address this situation in many ways, such as:

- Helping healthcare providers find ways to present the results of molecular diagnostics in ways that patients can understand. Often, simpler is better (see *Understanding Cancer Risk*: <http://researchadvocacy.org/general-resources>).
- Working with the developers of molecular diagnostics to ensure that the results are presented in an understandable format.
- Developing materials that clearly explain different risk values and what they mean for patients.

## Protecting the Privacy of Genomic Information

Although whole-genome sequencing is not a routine part of today's cancer treatment, it is certainly on the horizon. Allowing others to decode our entire genome raises many concerns about possible ethical issues. For example, do we want our cancer treatment team to know that we are at increased risk for Alzheimer's disease? Do we even want to know that ourselves, considering that no preventive measures are currently available? How can we be sure that insurance companies and employers won't use such information against us? Patients need to be thoroughly informed about all of the potential advantages and drawbacks of genomic sequencing.

Two of Research Advocacy Network's publications delve deeper into the ethical issues surrounding genomic testing. Readers may want to refer to *Genomics in Cancer — An Advocate's Guide and Training Manual* and *Biomarkers in Cancer — An Introductory Guide for Advocates* to gain a better understanding of the issues.

## Helping Patients Choose the Course That's Best for Them

Ideally, the results of molecular diagnostics would tell us what steps we should take to optimize our health. In reality, few tests give such clear-cut information. But, for many molecular diagnostics, the results may or may not be actionable depending on whom you ask. Experts often disagree about whether a given molecular diagnostic results warrants any action and/or what that action should be. Physicians in different specialty areas have different perspectives and may disagree based on their experience. Moreover, patients may disagree based on personal beliefs, experiences, and a host of other factors.

Advocates can take a variety of actions to ensure that patients are aware of different preventive treatment options and different views about what actions should be taken when faced with the results of molecular diagnostics for cancer. It sometimes helps patients to know that there is no one right way and that, in consultation with their doctor, they should choose the path that seems best for them.

### Ensuring That Patients Receive Only Information They Want to Have

Genomic knowledge and molecular diagnostic techniques have advanced rapidly over the past few decades. It is now possible to sequence a person's entire genome, and some experts believe that this practice will become affordable and commonplace in the foreseeable future. Today, it is possible for molecular diagnostics to evaluate biomarkers for multiple conditions at once, which has the potential to turn up unexpected findings. For example, a person undergoing a screening test for colon cancer-related mutations may be found to have a mutation related to Alzheimer's disease. This is called an incidental finding.

Incidental findings are not new in medicine—most people have probably heard at least one story about a patient who went in to the doctor for one medical problem and was found to have another, entirely unrelated problem. However, as whole genome screenings become more common, incidental findings will increase. Advocates can be an important part of the conversation about incidental findings, ensuring that patients receive all of the information they want and none of the information that they don't, and raising awareness of the need for genomic counseling.

### Encouraging Treatment Follow-Through

In many cases, patients do not adhere to prescribed treatment regimens. This may be particularly true of small molecule inhibitor therapies, which patients must take daily for long periods of time. Advocates may be able to help encourage patients to continue with life-saving therapies, such as by assisting with development of patient education materials that explain why and how patients should complete their treatment.

### Advancing Clinical Validation of Molecular Diagnostics

Many advocates are interested in this issue and want to make sure that, if patients undergo molecular diagnostic tests, the information will be useful to them. Advocates can help ensure that the molecular diagnostics used in clinical practice are clinically valid by supporting and encouraging policies that require clinical validation studies. Advocates may also help by encouraging patients to participate in clinical validation studies.

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# Glossary of Terms

**Analytical validation** Establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures).

**Antibody** A protein made by plasma cells (a type of white blood cell) in response to an antigen.

**Antigen** A substance that causes the immune system to develop antibodies; a substance to which antibodies bind.

**Arm** Any of the treatment groups in a clinical trial. Many randomized trials have two arms—one experimental and one control—but some have three or more “arms.” Some phase II trials have only one arm.

**BCR-ABL fusion gene** A gene formed when pieces of chromosomes 9 and 22 break off and trade places. The ABL gene from chromosome 9 joins to the BCR gene on chromosome 22 to form the BCR-ABL fusion gene. The changed chromosome 22 with the fusion gene on it is called the Philadelphia chromosome. The BCR-ABL fusion gene is found in most patients with chronic myelogenous leukemia and in some patients with acute lymphoblastic leukemia or acute myelogenous leukemia.

**Biomarker** A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

**Chemotherapy** Treatment with drugs that kill cancer cells.

**Chromosomes** Compacted structures of long strands of DNA located inside almost all of our cells.

**Clinical trial** A type of research study that assesses medical questions in people. These studies often test new methods of screening, prevention, diagnosis, or treatment of a disease.

**Clinical validation** Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

**Clinical utility** The overall usefulness of a molecular diagnostic test in clinical practice.

**Clinical validity** The measure of a test’s ability to provide clinically relevant information.

**DNA** Deoxyribonucleic acid, the material that makes up genes. DNA is a series of chemical letters (base pairs) that spell out the instructions for constructing our bodies and making them work.

**Endpoint** In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. For example, a clinical trial studying a new cancer drug might use death as an endpoint to determine if people getting the drug lived longer than those who did not get the drug.

**Experimental Design** The general plan of an experiment, including the method of assigning research participants or patients to treatment conditions, controlling extraneous variables, manipulating the independent variable, and measuring the dependent variable or outcome.

**Gene** A section of the DNA on a chromosome. A gene carries a particular set of instructions to produce a specific chemical product, usually a protein.

**Genetics** A branch of biology that deals with the heredity and variation of organisms. Today, the term genetics is often used to refer to the study of single genes.

**Genome** All of an organism’s DNA.

**Genomics** The study of multiple genes, their functions, and their interactions or all of our genes acting together.

**Intervention** The act or instance of intervening. In a clinical trial, an experimental or investigational intervention is compared to a comparison or control intervention. The interventions are often different treatment drugs, but may simply entail different schedules of drug administration, supportive therapies, etc.

**Kinase** An enzyme that transfers phosphate groups from one place in the cell to another.

**Molecule** The smallest particle of a substance that has all of the physical and chemical properties of the substance.

**Monoclonal antibodies** Antibodies that are identical because they are produced by one type of immune cell, all clones of a single parent cell.

**Mutation** A change in the nucleotide base sequence of our DNA that occurs in less than 1% of the population. It is generally used to refer to a change that has deleterious effects on the organism.

**Nucleotide bases** The 4 chemical letters in DNA that spell out the instructions for building and running our bodies. The 4 letters are A (adenine), T (thymine), C (cytosine), and G (guanine). Often called bases for short.

**Personalized medicine** An older and now less preferred term for precision medicine.

**Pharmacokinetics** The process of drug absorption, distribution, metabolism (break down), and elimination by the body.

**Phase I Trial** The first step in testing a new treatment in humans. These studies test the best way to give a new treatment (for example, by mouth, intravenous infusion, or injection) and the highest tolerable dose. The dose is usually increased a little at a time in order to find the highest dose that does not cause harmful side effects. Because little is known about the possible risks and benefits of the treatments being tested, Phase I trials usually include only a small number of patients who have not been helped by other treatments without a comparison group.

**Phase II Trial** A study to test whether an experimental intervention has an anticancer effect (for example, whether it shrinks a tumor or improves blood test results) and whether it works against a certain type of cancer.

**Phase III Trial** A study to compare the results of people taking an experimental intervention with the results of people taking the standard of care (for example, which group has better survival rates or fewer side effects). In most cases, studies move into phase III only after an intervention seems to work in phases I and II. Phase III trials may include hundreds of people and always includes a control group.

**Phase IV** Trial A study conducted after a treatment has been approved and is being marketed to evaluate side effects that were not apparent in the phase III trial. Thousands of people are involved in a phase IV trial.

**Precision medicine** An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

**Protocol** An action plan for a clinical trial. The plan states what the study will do, how, and why. It explains how many people will be in it, who is eligible to participate, what study agents or other interventions they will be given, what tests they will receive and how often, and what information will be gathered.

**Radiation therapy** The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors.

**Randomization** The process by which patients are assigned by chance to separate groups that compare different treatments or other interventions. Randomization can use equal weighting (i.e., 50:50) or not (e.g., 75:25)

**Randomized controlled trial** A research design used for testing the effectiveness of a drug, or any other type of experimental intervention, in which research participants are assigned randomly to experimental and control or groups and the differences in outcomes are compared.

**Sensitivity** The ability of the test to correctly identify those patients with the biomarker or condition.

**Specificity** The ability of the test to correctly identify those patients without the condition.

**Translocations** Movement of chromosomal material, such as a section of DNA from one chromosome that switches places with a section on another chromosome.

# About Research Advocacy Network

The Research Advocacy Network (RAN) was formed in 2003 to bring together participants in the research process with the focus on educating, supporting, and connecting patient advocates with the medical research community. While there are many organizations addressing the needs of patients with specific diseases, political advocacy, cancer education and fundraising, no organization has focused on advancing research through advocacy. Research Advocacy Network is committed to improving patient care through research. Our goals are to get results of research studies (new treatments) to patients more quickly, to give those touched by the disease an opportunity to give back and to help the medical community improve the design of its research to be more attractive to potential participants.

To provide those touched by the disease an opportunity to give back, RAN created the Advocate Institute™. This virtual learning center provides advocates with multiple methods of learning to improve their effectiveness in interactions with the research “world.” The Institute uses an innovative curriculum, on-site presentations and online learning opportunities. RAN has used the latest technology to reach a larger audience of advocates through Focus on Research™. This is a system of preparatory conference calls, virtual classrooms (webinars), learning materials and mentoring to prepare advocates to attend research-oriented meetings.

RAN applies best practices from the world of market research to inform research design. Using the models of focus groups and structured interviews, RAN was able to inform the design of the PACCT-1 (now renamed as TAILORx) clinical trial. Patient advocacy in research has many opportunities for all kinds of people to make a contribution. RAN has training and educational programs, publications and tools for advocates on our Web site, and experience in effectively working with researchers in cancer centers. RAN works with advocates and organizations to effectively integrate advocates into research activities. Please learn more about us at our Web site at [www.researchadvocacy.org](http://www.researchadvocacy.org) or contact us about our work by e-mailing us at [info@researchadvocacy.org](mailto:info@researchadvocacy.org) or by FAX at 888-466-8803. We look forward to hearing from you!

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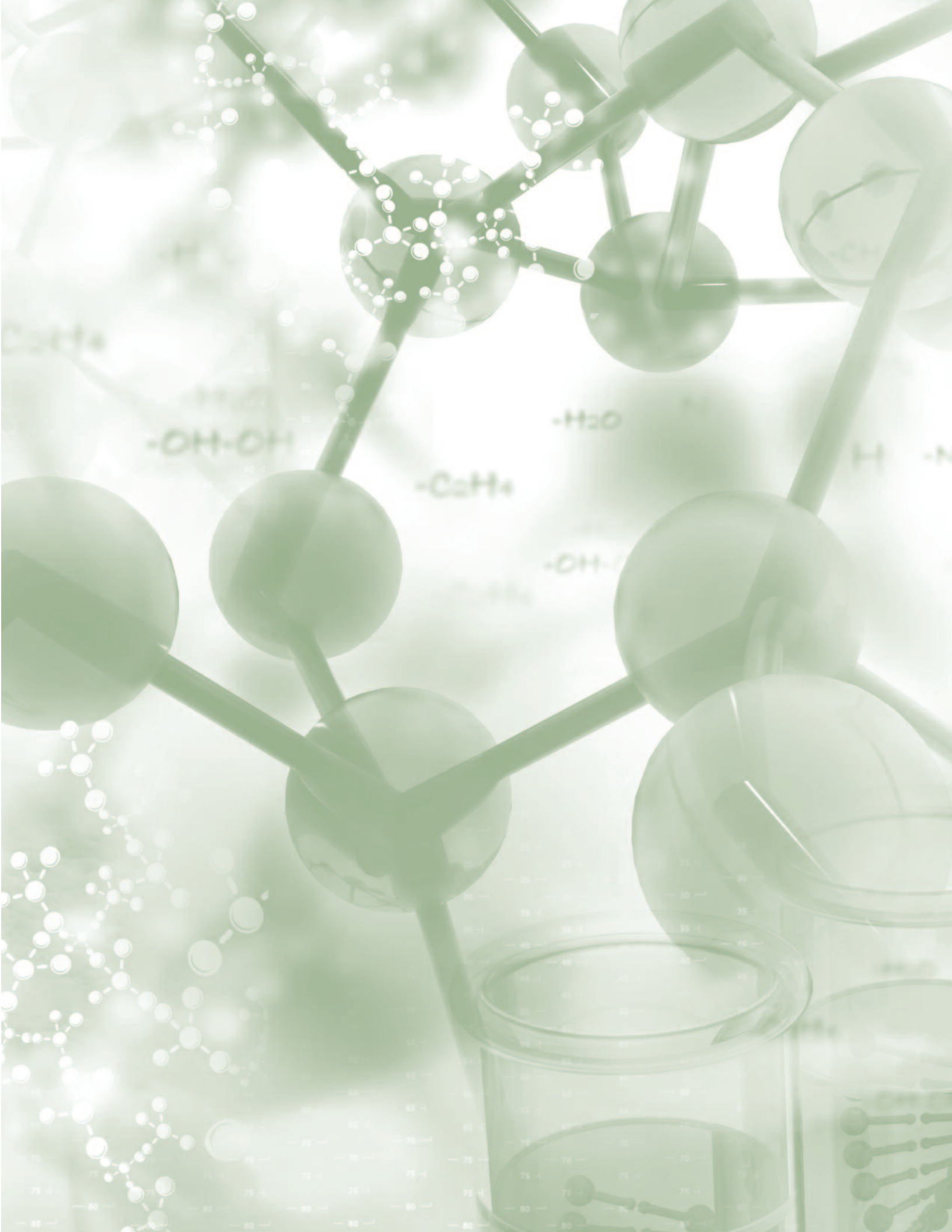
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