LEUKEMIA & LYMPHOMA SOCIETY®

Cancer Molecular Profiling

No. 31 in a series providing the latest information for patients, caregivers and healthcare professionals.

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There is a list of definitions on page 4. These words are italicized at first mention throughout the text.

Highlights

- *Molecular profiling* uses various technologies to identify cancer *biomarkers*; the findings inform doctors of the probability that cancers will be sensitive or resistant to treatment.
- A cancer biomarker is associated with the presence of cancer in the body. A biomarker can be produced by the tumor itself, or it may be a specific response by the body to the presence of cancer.
- Examples of molecular profiling technologies include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), next-generation sequencing (NGS) and quantitative polymerase chain reaction (qPCR).
- *Precision medicine*, also called "personalized medicine," uses information about a person's lifestyle, environment and biology to prevent, diagnose and treat diseases.
- The goal of precision medicine is to understand the relevant characteristics related to a particular disease and then to tailor therapy to that disease.

Introduction

Cancer is a result of an uncontrolled growth of abnormal cells, driven by genetic (molecular) changes that are either acquired or inherited from our parents. Each cancer has a unique set of molecular changes in the cancer cells. Technological developments have made a molecular profiling analysis possible; this allows doctors to distinguish the molecular differences between cancer cells and healthy cells.

Molecular test findings provide doctors with the information they need to review what genes have been changed (mutated). By identifying these mutations, your doctor can figure out if one treatment may work better than another for you.

It is now possible to identify unique combinations of tumor-specific biomarkers that can help in the diagnosis, prognosis (likely outcome) and treatment of cancer. The type and number of mutations may predict how a patient will respond to a specific drug. The ultimate goal of molecular profiling is the development of individualized, highly targeted and effective therapies that can improve patient outcomes.

Molecular Profiling

Molecular profiling involves the use of various technologies to understand the underlying characteristics that are found in cancer cells. Biomarkers are molecules that show either normal or abnormal signs or processes in the body; abnormal signs could indicate disease. Molecular profiling can be used to identify specific cancer biomarkers that are associated with response, resistance or lack of response to certain treatment approaches. This information can lead to the development of targeted therapies which are designed to be more effective for a specific tumor profile (a "profile" is information about the genes within cancer cells).

How Molecular Profiling Works. Molecular profiling identifies the specific DNA (deoxyribonucleic acid), RNA (ribonucleic acid), or protein molecule that is associated with a disorder. First, a biopsy procedure obtains a patient's sample from a tumor tissue; bone marrow; lymph node (for some blood cancers); or peripheral blood, in cases where tumor cells are circulating. The sample is sent to a laboratory, where it undergoes various molecular profiling tests to identify the unique biomarkers that correspond to the patient's cancer. These are some methods currently used for tumor profiling.

Immunohistochemistry (IHC)—This lab test uses *antibodies* to detect certain *antigens* (markers) in a tissue sample acquired from a biopsy. When the antibodies bind to the antigen in the tissue sample, fluorescent dyes or enzymes linked to the antibodies are activated and the antigen can be seen under a microscope. Immunohistochemistry provides information that helps doctors to diagnose diseases such as cancer. It may also be used to distinguish between different types of cancer. A test called "flow cytometry" uses the same principles, except that it is performed on a suspension of cells in a liquid, rather than on cells embedded in a tissue sample.

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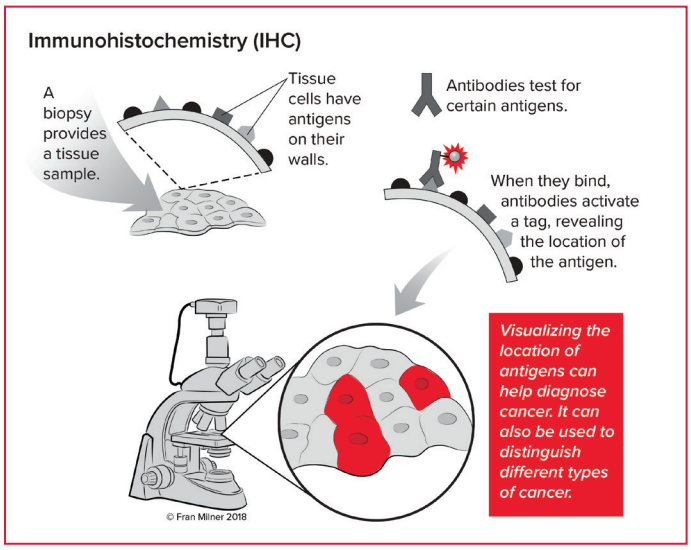
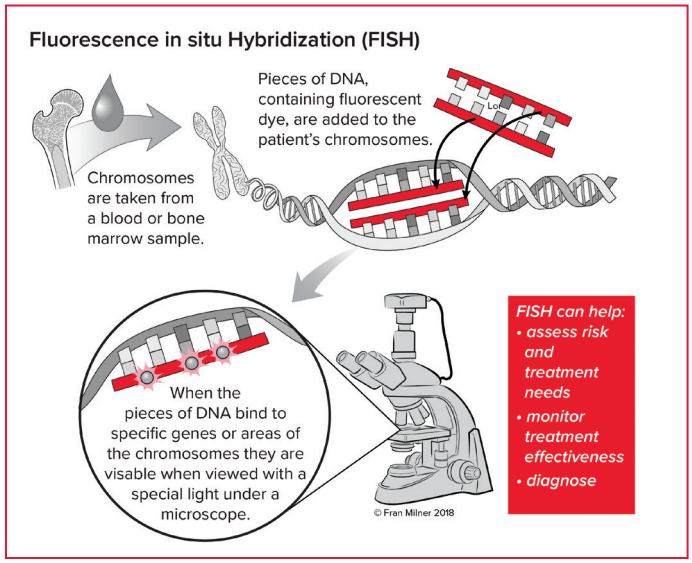
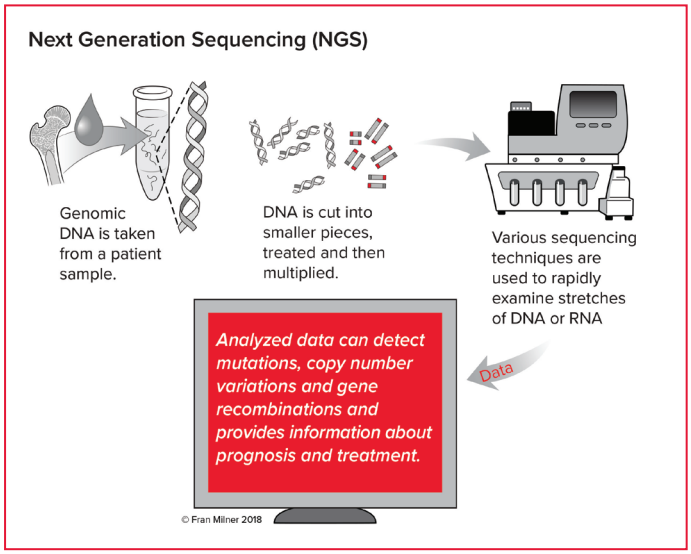


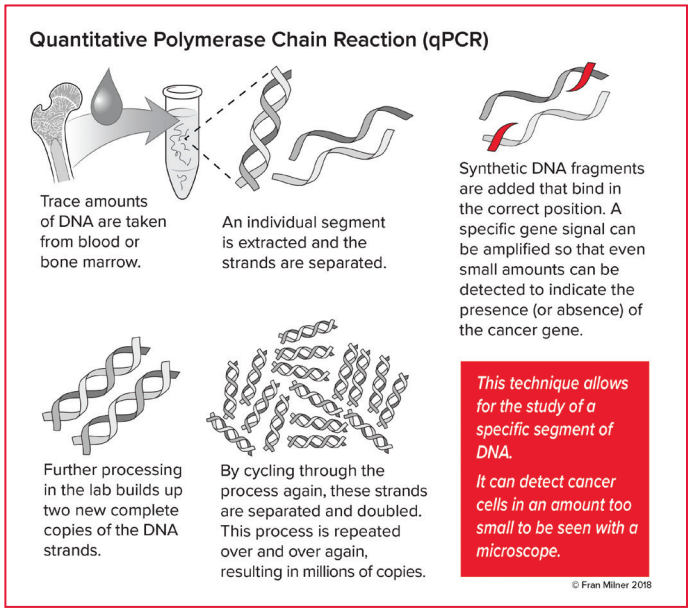
Fluorescence in situ Hybridization (FISH)—This laboratory technique is used to evaluate genes and/or *DNA sequences* on chromosomes. Cells and tissue are removed using blood or marrow tests. In the laboratory, a fluorescent dye is added to segments of the DNA; the modified DNA is added to cells or tissues on a glass slide. When these pieces of DNA bind to specific genes or areas of chromosomes on the slide, they "glow" when viewed under a microscope that has a special light. In this way, portions of chromosomes that are either increased or decreased in number, or are rearranged, can be identified. FISH can be helpful in diagnosing, assessing risk and treatment needs, as well as for monitoring treatment effectiveness.



Next-Generation Sequencing (NGS)—This term describes a number of different sequencing technologies. NGS tests rapidly examine stretches of DNA or RNA. They detect DNA mutations, *copy number variations* and gene fusions across the *genome* and provide information about prognosis and treatment.



Quantitative Polymerase Chain Reaction (qPCR)— This is a technique that expands trace amounts of DNA so that a specific segment of DNA can be studied. This technique has become useful in detecting a very low concentration of blood cancer cells, too few to be seen using a microscope. A test using qPCR can detect the presence of a single blood cancer cell among 100,000 to 1,000,000 healthy blood cells. A patient's blood or bone marrow is used for this test.



Cancer Biomarkers. Biomarkers are molecules that indicate either a normal or an abnormal process in the body; abnormal signs, substances, or processes may indicate an underlying disease or condition. Several types of molecules—including DNA, proteins, or RNA—can be used as biomarkers. Biomarkers are produced by the cancer tissue itself or by other cells in the body that may be responding to cancer. Biomarkers may be found in the blood, urine, stool, and cancer tissue, as well as in other tissues and bodily fluids. Biomarkers are not limited to indicating cancer. There are biomarkers for other conditions, such as heart disease, multiple sclerosis and many other diseases. (Biomarkers are also known as "molecular markers.")

There are many types of cancer biomarkers. Depending on the particular characteristics of the molecule, biomarkers can have different functions and can react in specific ways to certain treatments. Biomarkers can be

- **Diagnostic markers—**A large group of molecular tests can provide information that helps in the diagnosis or classification of a particular disease. An example of a diagnostic marker is the presence of the "Philadelphia chromosome" in chronic myeloid leukemia.
- **Prognostic markers—**These biomarkers help the doctor determine likely patient outcomes, such as overall survival. An example of a prognostic marker is the presence of *TP53* mutations (the most commonly mutated gene in people who have cancer). The presence of a *TP53* mutation identifies patients who are likely to have a more aggressive disease course, regardless of the treatment used in most cases.
- **Predictive markers—**These biomarkers are used to help doctors tailor treatment decisions to a particular patient. They can predict the activity of a specific type of therapy. They indicate the potential benefit of a specific treatment for the intended patient. An example is the effectiveness of lenalidomide (Revlimid®) in patients with myelodysplastic syndromes (MDSs) who have the del(5q) mutation. Patients with the del(5q) mutation have shown improved outcomes when treated with lenalidomide.

Implications for Targeted Therapy: Precision Medicine

Precision medicine, also known as "personalized medicine," is defined by the National Cancer Institute as "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose and treat disease." Precision medicine emerged within the last 20 years as a result of the development and refinement of molecular

Biomarkers Significant for Study and Treatment of Hematologic Cancers

Chromosome and Gene Abbreviations	Associated Cancer	Treatment Correlation
Philadelphia chromosome t(9;22) (translocation between chromosomes 9+22)	Chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL)	Responds to imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®)
IDH2 *(R140 or R172)*	Acute myeloid leukemia (AML)	Responds to enasidenib (Idhifa®)
JAK2 V617F	Myeloproliferative neoplasms (MPNs): polycythemia vera (PV), myelofibrosis (MF), essential thrombocythemia (ET)**	Responds to ruxolitinib (Jakafi®)
PML-RARA	Acute promyelocytic leukemia (APL)	Responds to all-*trans* retinoic acid (ATRA), arsenic trioxide (Trisenox®)
FLT3-ITD	Acute myeloid leukemia (AML)	Responds to midostaurin (Rydapt®)
ALK rearrangement	Anaplastic large-cell lymphoma (ALCL)	Responds to crizotinib (Xalkori®)*
BRAF V600E	Hairy cell leukemia	Responds to vemurafenib (Zelboraf®)*

*This drug is not FDA approved for this indication.

**Use of ruxolitinib for this diagnosis has not been FDA approved.

Table 1. This table lists some of the biomarkers that are currently known to be significant for the study and treatment of hematologic cancers.

techniques. While *cytotoxic* agents (drugs that are toxic to cells) destroy rapidly dividing cells by disrupting DNA and mechanisms of cell division, molecularly-targeted therapies control the function of specific molecular targets in the signaling, proliferation, metabolism and death of cells.

Most tumors have multiple mutations, rather than just the one or two mutations originally suspected. This is an important discovery in recent years and it explains why therapies designed to target a single mutation may not be fully effective. Now, the challenge for researchers and doctors is to utilize the information that molecular profiling provides, and determine its implications for targeted therapy. Targeted therapies can be more effective, cause fewer side effects, and have a better chance to cure, or at least effectively manage, a disease.

Current research strategies aim to

- Match the individual genetic profile of tumor cells (and patients) with therapies that have been designed to address this complexity
- Include several molecularly targeted agents in the same protocol. Patients are assigned to a specific agent based on the molecular abnormalities identified in their tumors.

In some cancers, molecular profiling has been instrumental in identifying factors that have led to noteworthy improvements in survival rates. They include

- A current understanding of the molecular features of tumors
- The development of diagnostic technologies that identify patient biomarkers
- Modern drug development that enables targeting of either specific biomarkers or cellular mechanisms.

The Cancer Genome Atlas (TCGA). This project, established by the National Institutes of Health (NIH), is designed to generate comprehensive maps of essential genomic changes in the major types and subtypes of cancer. The Cancer Genome Atlas was designed to be a resource for groundbreaking research aimed at developing better strategies for preventing, diagnosing and treating cancer. The Cancer Genome Atlas also serves as a model for other genome mapping projects.

Questions for Your Treatment Team

Molecular profiling may be neither applicable nor available to every patient or for every cancer diagnosis. Patients should discuss with the members of their treatment team whether or not molecular profiling is a good option for their particular case. When you have this conversation with your healthcare provider(s), the following questions may be useful.

Questions to ask about molecular profiling:

- Is my tumor/cancer eligible for molecular profiling?
- Can I have molecular profiling if I have already received treatment?
- What are the benefits of molecular profiling for my specific cancer?
- What biomarkers are generally associated with my cancer?
- What could molecular profiling or biomarker analysis tell me about my specific cancer?
- Will I need any additional testing? If so, what type of tests?
- How costly is molecular profiling? Will the testing be covered by my insurance provider? Is there financial assistance available?
- Who will perform my molecular profiling analysis? Where will it be performed?
- How long will it take to get results?
- How will you use the results of my molecular profiling analysis?
- How likely is it that molecular profiling could identify a targeted treatment for my type of cancer?
- What happens if molecular profiling identifies a prescription drug that would be considered “off-label” use, but that may be an effective treatment for me?
- Will I ever need to get another molecular profile done for this diagnosis? What if I develop a different form of cancer?

Definitions

Antibody. A type of protein created by plasma cells (white blood cells) when they encounter bacteria, viruses, or other triggers called “antigens” that the body senses as foreign. Antibodies help the body fight against invaders that make people sick. Antibodies can also be made in a lab.

Antigen. A substance that creates a response when it encounters cells of the immune system. Examples of antigens are bacteria, viruses, toxins (poisons), chemicals and allergens. Body tissues and cells, including cancer cells, also carry antigens that can cause an immune response. Antigens stimulate T cells to respond, and plasma cells to produce antibodies.

Biomarker. A molecule found in blood or tissues that is a sign of either a normal or an abnormal process, or of

a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Copy number variations. Sections of the genome that are repeated. The number of times they are repeated varies from person to person as well as between some tumor cells and normal cells.

Cytotoxic. Toxic (harmful or poisonous) to living cells.

DNA sequencing. The process of determining the precise order of nucleotides (which form the basic structural unit of DNA) within a DNA molecule.

Genetic markers. A gene or short sequence of DNA used to identify a chromosome, or to locate other genes on a genetic map.

Genome. The complete set of either genes or genetic material present in a cell or an organism (an "organism" could be a person).

Molecular diagnosis. The process of identifying a disease by studying molecules, such as proteins, DNA and RNA, in a tissue or fluid.

Molecular profiling. Various technologies used to identify cancer biomarkers associated with either the response or the resistance to certain treatments. The information gathered is used to identify and create targeted therapies designed to work better for a specific cancer or tumor profile.

Overexpression. Too many copies of a protein or other substance are being made.

Precision medicine (personalized medicine). This type of treatment uses information about a person's lifestyle, environment, and biology to prevent, diagnose and treat diseases.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our Web site at www.LLS.org/chapterfind or contact

The Leukemia & Lymphoma Society
3 International Drive, Suite 200
Rye Brook, NY 10573

Contact an Information Specialist at (800) 955-4572
Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, from 9 am to 9 pm EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationspecialists
- Visit: www.LLS.org/informationspecialists.

Free Information Booklets. LLS offers free education and support booklets that can either be read online or ordered. For more information, please visit www.LLS.org/booklets.

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. To join, visit www.LLS.org/community.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients to reach out and share information. To join, please visit www.LLS.org/chat.

LLS Chapters. LLS offers support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Clinical Trials (Research Studies). New treatments for patients are ongoing. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialist who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Resources

My Cancer
www.mycancer.com

My cancer is an educational resource for cancer patients and their caregivers. The site is sponsored by the biotechnology company Caris Life Sciences® and is designed to provide information about molecular profiling, cancer biomarkers and the transformation of cancer treatment through ongoing research.

PubMed
www.pubmed.gov

PubMed is a service of the National Library of Medicine that enables searches for science-based information. It includes more than 21 million citations for biomedical literature from MEDLINE, life science journals, and online books.

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