

PRECISELY
YOU



Not an actual patient.

BIOMARKER TESTING

in Advanced and Metastatic Melanoma



Overview

Getting Tested

Using Test Results

Learn More

Introduction

If you are hearing about biomarkers for the first time, you may wonder how biomarkers affect your care and what to do next. Here is some background information to help you get started.

Why Are Biomarkers Important?

Biomarkers provide clues about how your cancer works, including its strengths and weaknesses. Testing for biomarkers can help your doctors¹⁻⁶:



Predict how your cancer may behave



Understand how likely (or unlikely) it is that a specific treatment might work for you



Monitor your response to a specific treatment



Determine if members of your family are at a greater risk of developing melanoma or other cancers, like pancreatic cancer

What Is a Biomarker?



- A biomarker is a substance found in blood or tissues that signals a normal or abnormal process, or a condition or disease^{3,4}
- A biomarker can be a change in DNA (mutations), RNA, or protein⁴



To learn more about biomarkers, please go to **page 6**

Which Biomarkers Should I Be Tested for?

- Patients with advanced or metastatic melanoma should be tested for biomarkers²
- The specific biomarkers that you should be tested for will vary based on the stage of your melanoma and your medical history^{2,7,8}



To learn more about additional biomarker testing, please go to **page 8**

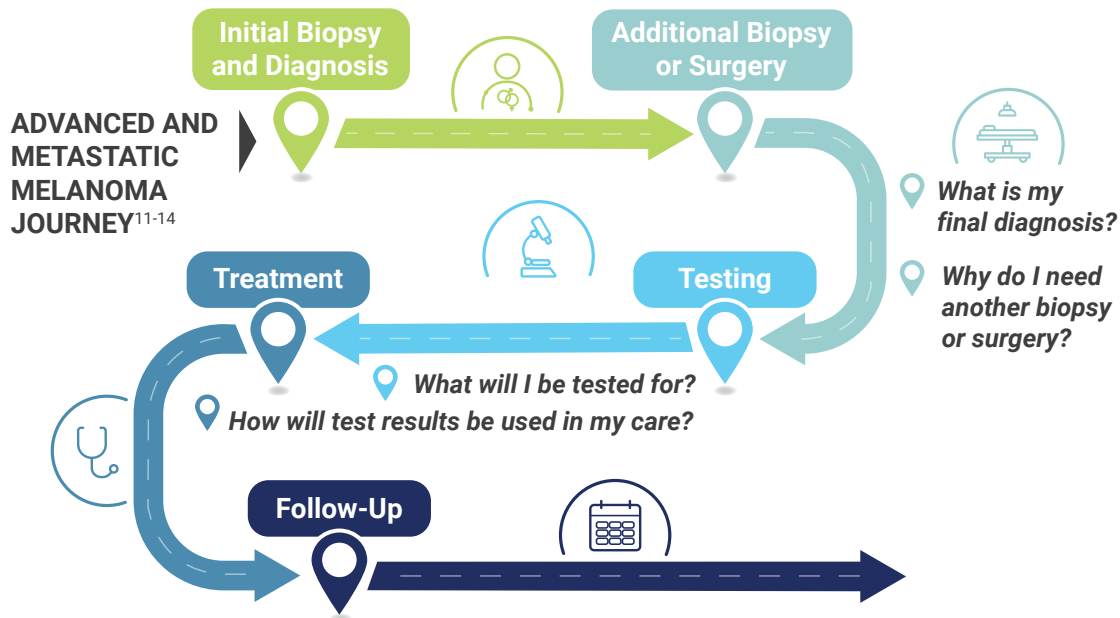


No two melanomas are the same. Biomarker testing helps your care team get key information to make treatment decisions precisely for you^{2,7-10}

When Will I Be Tested for Biomarkers?

Patients with advanced or metastatic melanoma have unique experiences, but many will go through similar steps. All patients will be tested to determine their prognosis or how their disease might act.^{1,2,11}

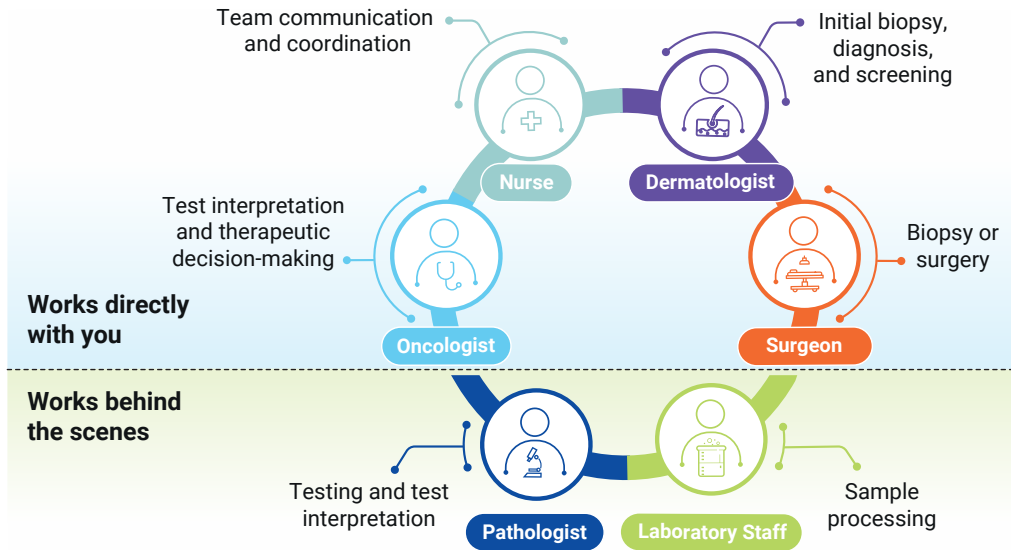
- If you are diagnosed with advanced or metastatic melanoma, additional biomarker testing may help determine the best treatment for you^{1,2,11}



Who Is Involved in Biomarker Testing?

Biomarker testing requires input from different specialties, so your care team includes a multidisciplinary team made up of professionals who specialize in different areas. These experts work together to get you the best care, even if you never meet them all.¹¹⁻¹⁴

Some Members of Your Care Team That Help You Get Biomarker Testing¹¹⁻¹⁴



Questions for Your Care Team

If I have questions about biomarker testing, whom should I ask?

Are there resources that can help support me, like financial assistance programs or financial counselors to help me understand my insurance coverage?

What Types of Biomarkers Are Important in Melanoma?

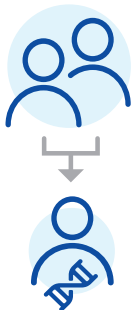
There are 4 types of biomarkers commonly used to help guide treatment decisions and optimize your care.

- **Risk** or **susceptibility biomarkers** provide information on the likelihood of developing melanoma or other cancers⁵
- **Prognostic biomarkers** provide information about expected health outcomes⁵
- **Predictive biomarkers** provide information on the expected treatment response⁵

Why Is Biomarker Testing Important?

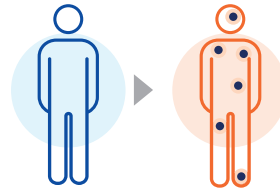
The goal of biomarker testing is for you to get the best possible treatment. It helps your health care team know if your melanoma has a biomarker for which there is a specific treatment and how likely it is that a specific treatment might work for you.²

What Else Do I Need to Know About Risk Biomarkers?



Risk or susceptibility biomarkers are typically inherited mutations. If you are positive for an **inherited mutation**, it means that members of your family may also have these mutations and may be at a higher risk for developing melanoma or other cancers.^{2,5,6,15,16}

Because inherited risk mutations are rare, most mutations linked with cancer are not inherited. Being positive for a mutation does not always mean that your family is at risk for melanoma.^{17,18}



How Will I Know if I Have a Risk Biomarker? Does My Family Need to Be Tested?

If you have a family history of melanoma, pancreatic cancer, renal cancer, breast cancer, mesothelioma, and/or astrocytoma (a type of brain cancer), your doctor may recommend genetic testing for an inherited mutation. If you are positive for an inherited mutation, your doctor may recommend that your family be tested.^{2,19}

What Do I Need to Know About Prognostic Biomarkers?

- Prognostic biomarkers provide information on the disease course. These biomarkers can be used to predict how likely it is that your cancer will come back or **recur**⁵
- Some biomarkers can be both predictive and prognostic^{2,15,20-22}

Biomarker Testing in Melanoma

Who Should Have Biomarker Testing?

Everyone with advanced or metastatic melanoma should have biomarker testing.²

- National professional guidelines summarize the evidence that supports biomarker testing and provide recommendations to improve care for patients like you²
- The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) are updated on a continual basis to include testing recommendations for biomarkers associated with FDA-approved therapies²



The National Comprehensive Cancer Network[®] (NCCN[®]) recommends that all patients with advanced or metastatic melanoma receive biomarker testing²

FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.
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What Biomarkers Should I Be Tested for? How Will the Results Be Used in My Care?

Depending on the stage of your cancer, you may be tested for risk, prognostic, predictive, or monitoring biomarkers.²



Risk Biomarkers

Patients with a family history of melanoma and/or other cancers may be tested for the following biomarkers²:

CDKN2A

CDK4

MCR1

TERF

MITF

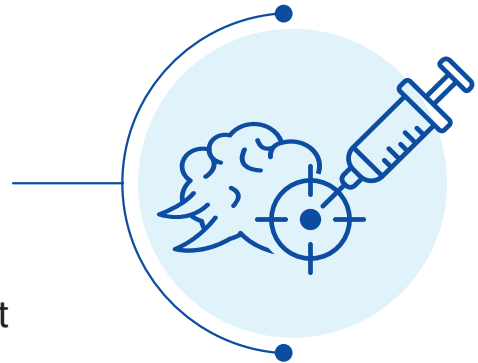
PTEN mutations

CDKN2A is the most common inherited risk biomarker. It occurs in **20% to 40%** of familial melanomas⁶

CDKN2A mutation is present in **10%** of all melanoma patients²³

What Is the First Step in Biomarker Testing?

- Biomarker testing starts with a biopsy to extract tumor tissue or blood from your body^{7,24}
- After the initial biopsy by your dermatologist, you may have an additional surgery, called a **wide excisional surgery**, to confirm that all melanoma cells were removed during the first biopsy⁷
- In other situations, you may have a procedure called a **sentinel lymph node biopsy**. This procedure gets tissue from your lymph nodes to determine if the cancer has spread there. Sentinel lymph node biopsies are important to accurately stage advanced melanomas⁷⁻⁹
- Even if you received biomarker testing at initial diagnosis, you may receive a **rebiopsy** after your cancer progresses for additional biomarker testing, which may provide new information for treatment planning^{2,7,24}



What if I Can't Get a Tissue Biopsy?

While tissue biopsy is optimal for biomarker testing, a liquid biopsy may be a viable alternative in some scenarios.^{25,26}

- Liquid biopsy may be used when the patient is not in good enough health for tissue biopsy or for monitoring disease progression or recurrence later on
- Liquid biopsies measure tumor cells and tumor DNA in the blood

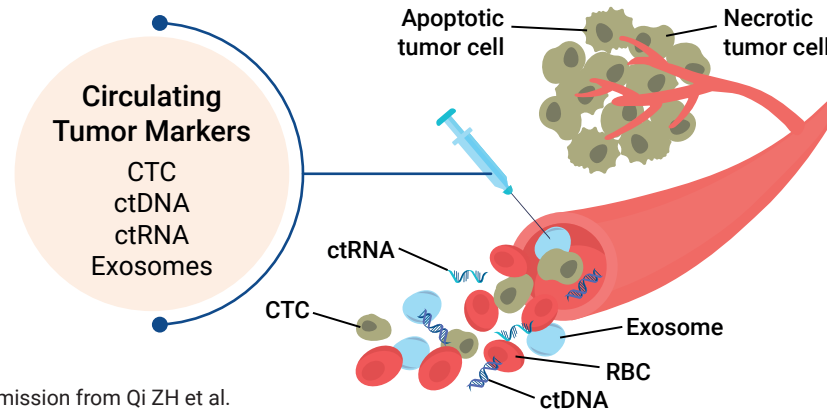


Image adapted with permission from Qi ZH et al. *J Cancer*. 2018;9(18):3417-3426.²⁷

Key Considerations of Liquid Biopsy^{25,26}

Advantages

Minimally invasive and a shorter time to get results

Disadvantages

Prone to “false negatives” (failing to detect existing biomarkers)

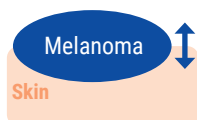


If you get a negative result from a liquid biopsy, ask your doctor if tissue testing is right for you

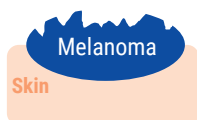
ctDNA, circulating tumor DNA.

Prognostic Biomarkers

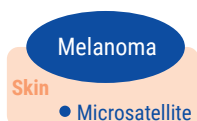
In melanoma, prognosis is based on biomarkers and clinical features based on the characteristics of the primary melanoma itself and how far it has spread in the body. These include⁹:



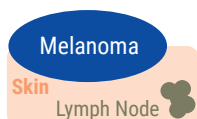
Breslow depth, or how thick the melanoma is and how deep it goes into the skin



Ulceration, or if the top layer of the skin is not intact when looking under a microscope



Microsatellites, or the presence of a small number of melanoma cells near (but not touching) the primary tumor



Sentinel lymph node disease burden, or the presence of melanoma cells in neighboring lymph nodes



LDH serum, or the amount of the LDH protein in the blood stream



Metastatic sites,¹⁰ or the distant location(s) of melanoma in the body



A pathologist will measure these characteristics and use them to determine the stage of your disease and your prognosis⁷⁻⁹

LDH, lactate dehydrogenase.

Predictive Biomarkers

In melanoma, NCCN recommends testing for specific driver alterations. Importantly, NCCN recommendations are specific to cancer stage.²

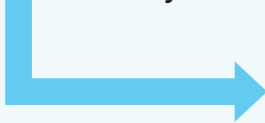
- NCCN recommends testing for *BRAF* V600 mutations in patients with Stage III melanoma
- In patients with Stage IV disease, NCCN recommends testing for *BRAF* V600 mutations and *KIT* mutations

Driver Alterations

c-KIT Mutations



KIT mutations are rare driver alterations found in only 2% to 5% of patients with melanoma^{2,8,22,28}



KIT mutations are more common in some melanoma subtypes^{2,8,22,28}



Patients with a *KIT* mutation may have additional personalized treatment options²

BRAF V600 Mutations



Nearly 1 out of every 2 patients is positive for a *BRAF* V600 mutation. *BRAF* V600 mutations are driver alterations that are not inherited^{15,20-22,28}



BRAF V600 mutations are linked with a poor prognosis^{15,20-22,28}



Patients with *BRAF* V600 mutations may have personalized treatment options, including targeted therapies²

Predictive Biomarkers for Immunotherapy

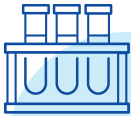
- NCCN does **not** recommend testing for PD-L1 or TMB²
- You may be eligible for treatment with an immunotherapy without biomarker testing²



Every patient with advanced and metastatic melanoma should be tested for *BRAF* V600 mutations. Patients with metastatic melanoma should also be tested for *c-KIT* mutations²

Monitoring Biomarkers

Monitoring biomarkers can be used to monitor for disease progression or recurrence or to look at response to treatment. If you have metastatic melanoma, your doctor may also look at changes in LDH level in addition to radiographic scans.^{7,9}



Biomarker testing is an important part of your cancer care. It helps your doctor understand more about your cancer and may open the door to personalized treatment options



- **Any decision to test for biomarkers and which tests to use should be made together by you and your health care team**
- **Biomarker testing decisions depend on several factors, including the type and stage of your cancer, availability of tissue, your current treatment plan, and your overall health²**

What Happens After Biomarker Testing?

Your care team will be there to support you after biomarker testing.

- Your **oncologist** may discuss test results with you and use biomarker test results to make treatment decisions^{11,13,14}
- A **pharmacist** will assist with providing prescription medications ordered by your oncologist²⁹
- A radiation **oncologist** will administer radiation therapy, if part of your treatment plan^{2,30,31}
- Your **oncologist** and **nurse** will oversee your overall treatment progress, help monitor symptoms and side effects, and adjust your treatment plan as needed¹³



- Treatment decisions should be made together by you and your health care team
- Treatment decisions depend on several factors, including the type and stage of your cancer, your biomarker status, your overall health, and your treatment goals²

Checklists can help you remember what to ask your health care team. The checklist below shows all biomarkers that are recommended by the professional society, NCCN, by stage.²




Stage III	Stage IV
<input type="checkbox"/> <i>CDKN2A</i> ^a	<input type="checkbox"/> <i>BRAF V600</i>
<input type="checkbox"/> <i>BRAF V600</i> ^b	<input type="checkbox"/> <i>KIT</i>
<input type="checkbox"/> <i>NRAS</i>	<input type="checkbox"/> <i>NRAS</i>



- These biomarkers can be prognostic and/or actionable so it's important to have all the information your health care team may need up front before making treatment decisions²
- Make sure your care matches the guidelines! Ask your care team about biomarker testing for these biomarkers²

^aConsider genetic counseling referral for *p16/CDKN2A* mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family. Multigene panel testing that includes *CDKN2A* is recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer. ^b*BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future *BRAF*-directed therapy may be an option.

What to Bring to Your Appointment

-  Scans at initial diagnosis, initial biopsy report, and any additional imaging results, if applicable
-  Treatment recommendations from current and previous treatment teams
-  Prior biomarker testing results, if applicable



Call the office ahead of time if you're not sure what to bring

Questions for Your Care Team

At Appointment

Why do I need biomarker tests? Are there tests that will inform me of my prognosis?

What biomarkers are you testing for?



How are the tests performed? Who will perform these tests?

When will I learn my biomarker test results, and how will they be communicated to me?

What are the limitations of the biomarker test I'm getting, if any?

How much will the tests costs? Is there financial assistance if needed?

After Appointment

What are the results of my biomarker tests? What do these results mean?

Should I speak to a genetic counselor?

How will the biomarker test results affect my treatment plan, if at all?

In what situations might I need additional biomarker testing later?

How can I get a copy of the report with my biomarker testing results?



Are There Any Additional Resources I Should Know About?

There are multiple online resources full of information and support for patients like you. Some resources are listed below.

If you are looking for more resources about melanoma, including patient support programs, please visit the Melanoma Research Foundation at <https://melanoma.org/>

If you'd like to connect with other patients with cancer who may have the same biomarker status as you, join a biomarker group at <https://biomarkercollaborative.org/>

This list of resources is not exhaustive. The above websites are independently operated and not managed by Novartis Pharmaceuticals Corporation. Novartis assumes no responsibility for the content on the sites.



NOTES



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Glossary

Biomarker: A substance or process found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker can be a change in DNA (mutations), RNA, or protein. Biomarkers may be helpful for understanding the nature of disease, predicting health outcomes, and planning treatments³⁰

Biomarker testing: One or more tests using various techniques to identify the presence or absence of biomarkers³⁰

Chemotherapy: A type of treatment using drugs that kill cancer cells³⁰

Clinical stage: Refers to how advanced your cancer is based on the size of your tumor and whether it has spread to other locations (metastasized). Cancer staging will help your oncologist determine your chance of survival and the best course of treatment³⁰

Clinical trial: A type of research study that tests the effectiveness of new medical approaches in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease³⁰

Driver alteration: A change to your genes that may promote the growth or survival of cancer cells in your body^{17,32}

Exon skipping: Refers to missing parts of a gene that may be important for tumor growth or treatment response³³

Gene amplifications: Increases in the number of copies of a gene, which may cause cancer cell growth or resistance to certain drugs³⁰

Gene fusion: The joining of parts of two separate genes that may lead to the development of certain types of cancer³⁰

Gene mutations: Changes in the DNA sequences of a cell, which may be inherited or caused by environmental factors³⁰

Histology: The study of tissues and cells under a microscope³⁰

Imaging tests: Initial evaluations (eg, CT scans, MRIs, X-rays, mammography) to determine the presence of tumors³⁰

Immunotherapy: A type of cancer therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases³⁰

Interventional radiologist: A medical doctor who is specially trained to use minimally invasive, image-guided procedures to diagnose and treat diseases³⁴

Liquid biopsy: Use of blood, saliva, or urine to investigate the presence of tumor cells or DNA shed from the primary tumor³⁰

Malignancy: Tissue cells obtained from biopsy that grow in an uncontrolled way (indicating cancer)³⁰

Metastatic cancer: Cancer cells that have spread from the original tumor location through the blood or lymph system to other locations in the body³⁰

Multigene panel: A biomarker test that examines multiple genetic biomarkers at the same time (may also be referred to as “comprehensive genomic profiling,” “comprehensive biomarker tests,” or “next-generation sequencing”)³⁰

Oncologist: A medical practitioner qualified to diagnose and treat cancer³⁰

Pathologist: A doctor who identifies diseases and/or the presence of biomarkers by studying cells and tissues under a microscope or with other equipment³⁰

Pathology report: The description of cells and tissues made by a pathologist based on what is seen under a microscope³⁰

Primary tumor: The original or first group of cancer cells in the body³⁰

Prognosis: The likely outcome or course of a disease; the chance of recovery or recurrence³⁰

Radiation therapy: The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors³⁰

Recurrent cancer: The return of cancer after a period of it not being detectable³⁰

Refractory cancer: Cancer that fails to respond to treatment³⁰

Remission: The signs and symptoms of cancer are partially or completely reduced³⁰

Resection: The removal of the entire tumor through surgery as part of the treatment plan³⁰

Targeted therapy: A type of treatment that uses drugs to attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth of cancer cells³⁰

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Summary



As we've seen, biomarker testing is a complex process that requires several steps and input from many different medical experts



Understanding the purpose of biomarker testing and knowing the right questions to ask may help you and your care team achieve the best possible health outcomes