Neuroblastoma Early Detection, Diagnosis, and Staging

Learn about the signs and symptoms of neuroblastoma. Find out how neuroblastoma is tested for, diagnosed, and staged.

Detection and Diagnosis

Catching cancer early often allows for more treatment options. Some early cancers may have signs and symptoms that can be noticed, but that is not always the case.

- Can Neuroblastoma Be Found Early?
- Signs and Symptoms of Neuroblastoma
- Tests for Neuroblastoma

Stages, Risk Groups, and Outlook (Prognosis)

After a diagnosis of neuroblastoma, the stage and risk group of the cancer provide important information about the anticipated response to treatment.

- Neuroblastoma Stages and Prognostic Markers
- Neuroblastoma Risk Groups
- Neuroblastoma Survival Rates by Risk Group

Questions to Ask About Neuroblastoma

Here are some questions you can ask your child's cancer care team to help you better understand your child's diagnosis and treatment options.

- Questions to Ask the Health Care Team About Neuroblastoma

Can Neuroblastoma Be Found Early?

- Screening for neuroblastoma

Screening for neuroblastoma could have downsides as well. For example, finding tumors that would never cause serious problems might still needlessly frighten parents and lead to unnecessary tests and surgery in some children.

For these reasons, **most experts do not recommend screening for neuroblastoma in infants who are not at increased risk of the disease**.

Screening might be recommended for infants who *are* at increased risk, such as those with a family history of neuroblastoma. Along with a urine test, this might also include genetic testing[2] to look for changes in the *ALK*

Sometimes, a tumor in the abdomen or pelvis can affect other parts of the body. For example, tumors that press against or grow into the blood and lymph vessels in the abdomen or pelvis can stop fluids from getting back to the heart. This can sometimes lead to swelling in the legs and, in boys, the scrotum.

In some cases, the pressure from a growing tumor can affect the child's bladder or bowel, which can cause problems urinating or having bowel movements.

Tumors in the chest or neck: Tumors in the neck can often be seen or felt as a hard, painless lump.

complain of bone pain. The pain may be so bad that the child limps or refuses to walk. If it spreads to the bones in the spine, tumors can press on the spinal cord and cause weakness, numbness, or paralysis in the arms or legs.

Spread to the bones around the eyes is common and can lead to bruising around the eyes or cause an eyeball to stick out slightly. The cancer might also spread to other bones in the skull, causing bumps under the scalp.

Spread to bone marrow: If the cancer spreads to the bone marrow (the inner part of certain bones, where new blood cells are made), the child may not have enough red blood cells, white blood cells, or blood platelets. These shortages of blood cells can result in tiredness, irritability, weakness, frequent infections, and excess bruising or bleeding from small cuts or scrapes.

Bleeding problems: Rarely, large tumors can start to break down, leading to a loss of clotting factors in the blood. This can result in a high risk of serious bleeding, which is known as a **consumption coagulopathy** and can be life threatening.

Stage 4S (MS) neuroblastoma: A special widespread form of neuroblastoma (known as stage 4S or stage MS) sometimes occurs, usually during the first few months of life. In this special form, the neuroblastoma has spread to the liver, to the skin, and/or to the bone marrow (in small amounts). Blue or purple bumps that look like small blueberries may be a sign of spread to the skin. The liver can become very large and can be felt as a mass on the right side of the belly. Sometimes it can grow large enough to push up on the lungs, which can make it hard for the child to breathe. While stage 4S neuroblastoma is already widespread when it is found, it is very treatable, and it often shrinks or goes away on its own. Almost all children with this form of neuroblastoma can be cured.

Signs or symptoms caused by hormones from the tumor

Neuroblastoma cells sometimes release hormones that can cause problems with tissues and organs in other parts of the body, even though the cancer has not spread to those tissues or organs. These problems are called **paraneoplastic syndromes**.

Signs and symptoms of paraneoplastic syndromes can include:

- Constant watery diarrhea
- Fever
- High blood pressure (causing irritability)
- Rapid heartbeat

- Reddening (flushing) of the skin
- Sweating

An uncommon set of symptoms is called the **opsoclonus-myoclonus-ataxia syndrome** or opsoclonus myoclonus ataxia (OMA). This is thought to result from the body's immune system attacking the normal nerve tissue. A child with this syndrome typically has irregular, rapid eye movements (opsoclonus) and twitch-like muscle spasms (myoclonus), and appears uncoordinated when standing or walking (ataxia). They might also have trouble speaking. Children who have this syndrome tend to have a better outlook when it comes to the neuroblastoma itself, although some children might have long-term nervous system problems, even after the neuroblastoma has been treated. (For more on this, see Late and Long-Term Effects of Neuroblastoma and Its Treatment[2].)

Hyperlinks

1. www.cancer.org/cancer/diagnosis-staging/lymph-nodes-and-cancer.html
2. www.cancer.org/cancer/types/neuroblastoma/after-treatment/long-term-effects.html

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Dome JS, Rodriguez-Galindo C, Spunt SL, Santana VM. Chapter 92: Pediatric solid tumors. In: Neiderhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 6th ed. Philadelphia, PA. Elsevier; 2020.

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Last Revised: April 28, 2021

Tests for Neuroblastoma

These tests are important because many of the symptoms and signs of neuroblastoma can also be caused by other diseases, such as infections, or even other types of cancer.

Blood and urine catecholamine tests

Cells in the body make many different types of hormones. For example, sympathetic nerve cells normally release hormones called **catecholamines**, such as epinephrine (adrenaline) and norepinephrine, which enter the blood and eventually break down into smaller pieces, called **metabolites**. The metabolites normally pass out of the body in urine. When epinephrine and norepinephrine are broken down by the body, the two most common metabolites made are:

- Homovanillic acid (HVA)
- Vanillylmandelic acid (VMA)

Neuroblastoma cells also often make these catecholamines, so these same metabolites can be detected in blood and urine. If the neuroblastoma cells are making catecholamines, the amount of HVA and VMA in urine or blood will be higher than expected.

If a child does have neuroblastoma, levels of HVA and VMA can also be followed during treatment to get an idea of how well it is working.

Other blood and urine tests: If neuroblastoma is suspected or has been found, your child's doctor will probably order blood tests[2] to check blood cell counts, liver and kidney function, and the balance of salts (electrolytes) in the body. A urinalysis (urine test) may also be done to help check kidney function.

Imaging tests

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive substances to create pictures of the inside of the body. Imaging tests can be done for a number of reasons, including:

- To help find out if a suspicious area might be cancer
- To learn how far cancer has spread
- To help determine if treatment is working

Most children who have or might have neuroblastoma will get one or more of these tests, but they might not need all of them.

Children with neuroblastoma are often very young, so it can be hard to do some of these tests because the child might need to hold very still. Depending on the child's age and the imaging test being done, they might get medicines to make them drowsy (or

the tumor tests that are needed.

MIBG scan

This test is often an important part of finding out how far a child's neuroblastoma has spread. It is often done after a CT scan or MRI has been done.

For this test, a form of the chemical meta-iodobenzylguanidine (MIBG) that contains a small amount of radioactive iodine is injected into the blood. MIBG is similar to norepinephrine, a hormone made by sympathetic nerve cells, and in most patients it will attach to neuroblastoma cells anywhere in the body. Between 1 and 3 days later, the body is scanned with a special camera to look for areas that picked up the radioactivity. This helps doctors know where the neuroblastoma is and if it has spread to the bones and/or other parts of the body.

MIBG scans can be repeated after treatment to see if the tumors are responding well. It is also good to know if the tumor takes up the MIBG because in some cases, this radioactive molecule can be used at higher doses to treat the neuroblastoma (see Radiation Therapy for Neuroblastoma[6]).

The thyroid gland can also absorb MIBG, so a medicine containing iodine is sometimes given before, during, and after the test to protect the thyroid.

Bone scan

A bone scan[7] can help show if a cancer has spread to the bones, and can provide a picture of the entire skeleton at once. Neuroblastoma often causes bone damage, which can be seen on a bone scan. This test isn't often needed for neuroblastoma, because an MIBG scan can usually detect cancer spread to the bone. But if the MIBG scan doesn't find cancer in the bone and the doctor still suspects it might have spread there, a bone scan might be helpful.

For this test, a small amount of low-level radioactive material (technetium-99) is injected into a vein. (The amount of radioactivity used is very low and will pass out of the body within a day or so.) The substance settles in areas of damaged bone throughout the skeleton over the course of a couple of hours. Your child then lies on a table for about 30 minutes while a special camera detects the radioactivity and creates a picture of the skeleton. Younger children may be given medicine to help keep them calm or even asleep during the test.

Areas of active bone changes attract the radioactivity and appear as "hot spots" on the

skeleton. These areas may suggest cancer, but other bone diseases can also cause the same pattern. To help tell these apart, other imaging tests such as plain x-rays or MRI scans, or even a bone biopsy might be needed.

Positron emission tomography (PET) scan

For a PET scan[8], a radioactive substance (usually a type of sugar called FDG) is injected into the blood. The amount of radioactivity used is very low and will pass out of the body within a day or so. Because cancer cells are growing quickly, they absorb large amounts of the radioactive sugar. After about an hour, your child will be moved onto a table in the PET scanner. They will lie on the table for about 30 minutes while a special camera creates a picture of areas of radioactivity in the body. Younger children may be given medicine to help keep them calm or even asleep during the test.

PET scans usually aren't needed if an MIBG scan has been done. But a PET scan might be useful for some neuroblastomas, especially if the neuroblastoma cells do not absorb MIBG.

X-rays

X-rays[9] can be used to look at the bones, although they aren't as good at showing other structures in the body.

The doctor may order an x-ray of part of the body as an early test if a child is having symptoms and it's not clear what might be causing them. But the pictures might not be good enough to spot tumors.

In children with neuroblastoma, an MIBG, PET, or bone scan is usually better than an x-ray for looking at the bones in the rest of the body and to see if neuroblastoma has spread to the bones, but an x-ray test might still be helpful in some situations.

Biopsies

During a biopsy, a doctor removes one or more pieces (samples) from the tumor for testing.

Exams and imaging tests might strongly suggest a child has neuroblastoma, but a biopsy is usually needed to be sure. (Some very young infants with small adrenal tumors seen on an imaging test might not need a biopsy. Instead, the tumor might be watched closely with further imaging tests, as these tumors often mature or go away on their own.)

during the procedure.

For a bone marrow **aspiration**, a thin, hollow needle is inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow.

For a bone marrow **biopsy**, a small piece of bone and marrow is removed with a slightly larger needle that is pushed down into the bone. Once the biopsy is done, pressure is applied to the site to help stop any bleeding.

Samples from the bone marrow are sent to a lab, where they are looked at and tested for the presence of cancer cells. You can read more about testing tissue samples in Testing Biopsy and Cytology Specimens for Cancer[11].

Hyperlinks

1. www.cancer.org/cancer/types/neuroblastoma/causes-risks-prevention/risk-factors.html
2. www.cancer.org/cancer/diagnosis-staging/tests/understanding-your-lab-test-results.html
3. www.cancer.org/cancer/diagnosis-staging/tests/imaging-tests/ultrasound-for-cancer.html
4. www.cancer.org/cancer/diagnosis-staging/tests/imaging-tests/mri-for-cancer.html
5. www.cancer.org/cancer/diagnosis-staging/tests/imaging-tests/ct-scan-for-cancer.html
6. www.cancer.org/cancer/types/neuroblastoma/treating/radiation-therapy.html
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9. www.cancer.org/cancer/diagnosis-staging/tests/imaging-tests/x-rays-and-other-radiographic-tests.html
10. www.cancer.org/cancer/types/neuroblastoma/treating/surgery.html
11. www.cancer.org/cancer/diagnosis-staging/tests/biopsy-and-cytology-tests.html

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Last Revised: April 28, 2021

Neuroblastoma Stages and Prognostic Markers

If someone is diagnosed with neuroblastoma, doctors will try to figure out if it has spread, and if so, how far. This process is called staging. The **stage** of a neuroblastoma describes how much cancer is in the body.

(For neuroblastoma, several other factors are looked at along with a child's stage to decide what **risk group** a child falls into. Risk groups give an overall picture of how a neuroblastoma is likely to respond to treatment and, it helps doctors choose the treatments that might work best. Doctors also use neuroblastoma risk groups when talking about survival statistics. For more information, see Neuroblastoma Risk Groups.)

There are two systems used for neuroblastoma staging. The main difference between them is whether the staging system can be used to help determine a child's risk group *before* treatment has started.

- The **International Neuroblastoma Risk Group Staging System (INRGSS)** uses results from imaging tests (such as CT or MRI and MIBG scans) to help decide the

MS: Metastatic disease in children younger than 18 months, with cancer spread only to skin, liver, and/or bone marrow.

International Neuroblastoma Staging System (INSS)

The INSS takes into account the results of surgery to remove the tumor. It cannot help doctors determine a stage before any treatment has started, so it doesn't work as well for children who don't need or can't have surgery. In simplified form, the stages are:

Stage 1: The cancer is still in the area where it started. It is on one side of the body (right or left). All visible tumor has been removed completely by surgery (although looking at the tumor's edges under the microscope after surgery may show some cancer cells). Lymph nodes near the tumor are free of cancer (although nodes enclosed within the tumor may contain neuroblastoma cells).

Stage 2A: The cancer is still in the area where it started and on one side of the body, but not all of the visible tumor could be removed by surgery. Lymph nodes near the tumor are free of cancer (although nodes enclosed within the tumor may contain neuroblastoma cells).

Stage 2B: The cancer is on one side of the body, and it may or may not have been removed completely by surgery. Nearby lymph nodes outside the tumor contain neuroblastoma cells, but the cancer has not spread to lymph nodes on the other side of the body or elsewhere.

Stage 3: The cancer has not spread to distant parts of the body, but one of the following is true:

- The cancer can't be removed completely by surgery, and it has crossed the midline (defined as the spine) to the other side of the body. It may or may not have spread to nearby lymph nodes.
- The cancer is still in the area where it started and is on one side of the body. It has spread to lymph nodes that are relatively nearby but on the other side of the body.
- The cancer is in the middle of the body and is growing toward both sides (either directly or by spreading to nearby lymph nodes).

Stage 4: The cancer has spread to distant parts of the body such as distant lymph nodes, bones, liver, skin, bone marrow, or other organs (but the child does not meet the criteria for stage 4S).

Stage 4S (also called “special” neuroblastoma): The child is younger than 1 year old. The cancer is on one side of the body. It might have spread to lymph nodes on the same side of the body but not to nodes on the other side. The neuroblastoma has spread to the liver, skin, and/or the bone marrow. However, no more than 10% of marrow cells are cancer cells, and imaging tests such as an MIBG scan do not show cancer in the bone marrow.

Recurrent: While not a formal part of the staging system, this term is used to describe cancer that has come back (recurred) after it has been treated. The cancer might come back in the area where it first started or in another part of the body.

Prognostic markers

Prognostic markers are features that help predict whether the child’s prognosis (outlook for cure) is better or worse than would be predicted by the stage alone. Many of these prognostic markers are used along with a child's stage to assign their risk group:

- **Age:** Younger children (under 12-18 months) are more likely to have a better outcome than older children.
- **Tumor histology:** Tumor histology is how the neuroblastoma cells look under the microscope. Tumors that contain more normal-looking cells and tissues tend to have a better prognosis and are said to have a **favorable histology**. Tumors whose cells and tissues look more abnormal under a microscope tend to have a poorer prognosis and are said to have an **unfavorable histology**.
- **DNA ploidy:** The amount of DNA in each cell, known as ploidy or the **DNA index**, can be measured using special lab tests. Neuroblastoma cells with about the same amount of DNA as normal cells (a DNA index of 1) are classified as **diploid**. Cells with increased amounts of DNA (a DNA index higher than 1) are termed **hyperdiploid**. Neuroblastoma cells with more DNA are associated with a better prognosis, particularly for children under 2 years of age. DNA ploidy is not as useful for understanding a prognosis in older children.
  ***MYCN gene amplifications*:** *MYCN* is a gene that normally helps regulate cell growth. Changes in the *MYCN* gene can turn it into an **oncogene**, which can make cells grow and divide too quickly, as with cancer cells. Neuroblastomas with too, which can make

linked with a worse prognosis. Understanding the importance of chromosome deletions/gains is an active area of neuroblastoma research. For more information, see What's New In Neuroblastoma Research?[2]

- **Neurotrophin (nerve growth factor) receptors:** These are substances on the surface of normal nerve cells and on some neuroblastoma cells. They normally allow the cells to recognize neurotrophins, which are hormone-like chemicals that help the nerve cells mature. Neuroblastomas that have more of certain neurotrophin receptors, especially the nerve growth factor receptor TrkA, may have a better prognosis.

Serum (blood) levels of certain substances can also be used to help predict prognosis.

- Neuroblastoma cells release **ferritin**, a chemical that is an important part of the body's normal iron metabolism, into the blood. Patients with high ferritin levels tend to have a worse prognosis.
- Increased levels of **lactate dehydrogenase (LDH)** in the blood is also linked with a worse outlook in children with neuroblastoma.

Hyperlinks

1. www.cancer.org/cancer/types/neuroblastoma/treating/surgery.html
2. www.cancer.org/cancer/types/neuroblastoma/about/new-research.html

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Neuroblastoma Risk Groups

- Low risk
- Intermediate risk
- High risk

These risk groups are based on what is known about neuroblastoma and how it is treated. As new research provides more information, the risk groups may change over time. For example, in recent treatment recommendations the age cut-off for some of these categories has been revised from up to 12 months to up to 18 months.

International Neuroblastoma Risk Group (INRG) classification

The International Neuroblastoma Risk Group (INRG) classification is a newer system that is now being used to help researchers in different countries compare results and work together to find the best treatments. This system is based on the INRGSS staging system, which includes the image-defined risk factors (IDRFs), as well as many of the prognostic factors listed in Neuroblastoma Stages and Prognostic Markers, such as:

- The child's age
- Tumor histology (how the tumor looks under the microscope)
- The presence or absence of *MYCN* gene amplification in tumor cells

What is a 5-year survival rate?

The 5-year survival rate refers to the percentage of children who live **at least**5 years after their cancer is diagnosed. Of course, many children live much longer than 5 years (and many are cured).

To get 5-year survival rates, doctors have to look at children who were treated at least 5 years ago. Improvements in treatment since then may result in a better outlook for children now being diagnosed with neuroblastoma.

Survival rates are based on previous outcomes of large numbers of people who had the disease, but they can't predict what will happen in any particular child's case.

The survival rates below are based on the risk group of the child's cancer. The risk group, in turn, is based on the stage (extent) of the cancer, as well as other prognostic factors (such as the child's age). But other factors can also affect a child's outlook, such as the location of the tumor and how well the cancer responds to treatment. Your child's doctor can tell you how the numbers below might apply to your child, as they know your situation best.

Survival by Children's Oncology Group (COG) risk group

- **Low-risk group:** Children in the low-risk group have a 5-year survival rate that is higher than 95%.
- **Intermediate-risk group:** Children in the intermediate-risk group have a 5-year survival rate of around 90% to 95%.
- **High-risk group:** Children in the high-risk group have a 5-year survival rate of around 50%.

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Questions to Ask the Health Care Team About Neuroblastoma

It's important to have open, honest discussions with your child's cancer care team. Ask any question, no matter how minor it might seem. Among the questions you might want to ask are:

If a neuroblastoma has been diagnosed

- What is the stage (extent) of the neuroblastoma? What does this mean?
- Which risk group does my child's cancer fall into? What does this mean?
- What else can you tell about the cancer based on the tests that have been done?
- Do we need to have any other tests before we discuss treatment options?
- How much experience do you have treating this type of cancer?
- Do we need to see any other types of doctors?
- Who else will be on the treatment team, and what do they do?

When deciding on a treatment plan

- Does the neuroblastoma need to be treated? Why or why not?
- What are our treatment[1] options?
- Does one type of treatment increase the chance of cure more than another?
- Are there any clinical trials[2] we should consider?
- Which treatment do you recommend? Why?
- Should we get a second opinion[3]? How do we do that? Can you recommend a doctor or cancer center?
- How soon do we need to start treatment?
- What should we do to be ready for treatment?
- How long will treatment last? What will it be like? Where will it be done?
- How will treatment affect our daily lives?
- How long will it take my child to recover from treatment?

- What are the possible side effects[4] from treatment? What can be done for them?
- Which side effects start shortly after treatment and which ones might develop later on?
- How might treatment affect my child's ability to learn, grow, and develop?
- Will treatment affect my child's ability to have children someday? Can we do anything about this?
- Will my child have a higher long-term risk of other cancers?

During and after treatment

Once treatment begins, you'll need to know what to expect and what to look for. Not all of these questions may apply, but getting answers to the ones that do may be helpful.

- How will we know if the treatment is working?
- Is there anything we can do to help manage side effects?
- What symptoms or side effects should we tell you about right away?
- How can we reach you or someone on your team on nights, weekends, or holidays?
- Who can we talk to if we have questions about costs, insurance coverage, or social support?
- What are the chances that the cancer will come back[5] after treatment? What would we do if this happens?
- What type of follow-up will my child need after treatment?
- Do you know of any local or online support groups where we can talk to other families who are coping with neuroblastoma or childhood cancer?

Along with these sample questions, be sure to write down some of your own. For instance, you might want more information about recovery times so that you can plan your work or school schedules.

Keep in mind, too, that doctors aren't the only ones who can give you information. Other members of your health care team, such as nurses and social workers, can answer some of your questions. To find more about speaking with your health care team, see The Doctor-Patient Relationship[6].

Hyperlinks

1. www.cancer.org/cancer/types/neuroblastoma/treating.html
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Last Revised: April 28, 2021

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