



Cancer Predisposition Clinic

WT1-related Syndromes

What are the WT1-related syndromes?

WT1-related Wilms tumor susceptibility syndromes are conditions that can affect the kidneys. People with these conditions have a greater risk of developing a cancerous tumor of the kidney known as Wilms tumor, or nephroblastoma. Wilms tumor is the most common type of kidney cancer affecting children. Very rarely, Wilms tumor can occur in adults.

WT1-related syndromes are hereditary, which means they can be passed from parents to their children.

People with WT1-related syndromes may have other medical issues besides an increased risk of developing Wilms tumor. These may include problems with the reproductive organs, eyes, and sometimes with behavior or development. These medical issues may or may not be present, depending on the type of WT1-related syndrome that the person has. WT1-related Wilms tumor can be seen in families without any of these other health problems.

Sometimes people with WT1-related syndromes have a pattern of health problems that can be grouped into one of the following syndromes:

- Wilms tumor-Aniridia-Genitourinary malformation-Retardation (WAGR) syndrome
- Denys-Drash syndrome
- Frasier syndrome
- Genitourinary anomalies and Wilms tumor without renal failure

What is the cancer risk for people with WT1-related syndromes?

People with WT1-related syndromes are at higher risk of developing Wilms tumors. These tumors generally appear during the first three to five years of life. The risk for developing Wilms tumors or for other health problems depends on the specific syndrome that a person has.

WAGR syndrome

People with WAGR syndrome have a 50% (1 in 2) risk of developing Wilms tumor.

Denys-Drash syndrome

People with Denys-Drash syndrome have a more than 90% (9 out of 10) risk of developing Wilms tumor.

People with Denys-Drash syndrome who have the chromosomal (genetic) make up of a male individual (i.e., a 46,XY karyotype) also have a higher risk of developing a cancerous tumor in the reproductive organs, called a gonadoblastoma. Because Denys-Drash syndrome is very rare,

the exact risk for gonadoblastoma is not known. People with Denys-Drash syndrome who have the chromosomal (genetic) make up of a female individual (a 46,XX karyotype) are not thought to be at increased risk for gonadoblastoma.

Frasier syndrome

People with Frasier syndrome have a slightly higher risk of developing Wilms tumor than people without a *WT1*-related syndrome, but the overall risk is still low. Because Frasier syndrome is very rare, the exact risk for Wilms tumor is not known.

People with Frasier syndrome who have the chromosomal (genetic) make up of a male individual (i.e., a 46,XY karyotype) also have a higher risk of developing a cancerous tumor in the reproductive organs, called a gonadoblastoma. People with Frasier syndrome who have the chromosomal (genetic) make up of a female individual (46,XX karyotype) usually have normal gonads (ovaries) and usually do not develop gonadoblastomas.

Genitourinary anomalies and Wilms tumor

The exact risk for Wilms tumor with this condition is uncertain, but thought to be increased over the general population.

What are other physical findings seen in people with *WT1*-related syndromes?

People with *WT1*-related syndromes may have other medical issues besides the increased risk of for cancerous tumors. Not all people with a *WT1*-related syndrome will have all the physical findings listed below. These physical findings vary from person to person.

WAGR syndrome

People with WAGR syndrome may have one or more of these features:

- Loss of part or all of the colored part the eye (iris), a condition called aniridia. This is seen in most people with the syndrome.
- Other eye problems, such as clouding of the lens of the eyes (cataracts), increased pressure in the eyes (glaucoma) and involuntary eye movements (nystagmus).
- Defects in the reproductive organs (genitals) and urinary system.
 - These defects are mostly seen in boys who can have undescended testicles (the testicles fail to move down into the scrotum) or a condition known as hypospadias (the urinary opening is located on the underside of the penis instead of the tip).
 - Girls with this condition usually have normal genitals. Some individuals may also have a heart-shaped (bicornuate) uterus, which makes it hard to carry a pregnancy to term.
- End-stage renal (kidney) disease. Renal failure may develop over time. This feature is generally worse in patients who have been treated for a Wilms tumor.

- Mental and learning disabilities. Most people with WAGR syndrome show some degree of cognitive delay, although the severity varies from person to person.
- Behavior problems, including attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, anxiety, depression and obsessive-compulsive disorder.

Denys-Drash syndrome and Frasier syndrome

The physical issues in people with Denys-Drash syndrome or Frasier syndrome are frequently similar. People with these syndromes may develop the following physical issues:

- Defects in the reproductive organs (genitals) and urinary system. These defects are mostly seen in individuals who have the chromosomal (genetic) make up of a male individual (a 46,XY karyotype).
 - Some may have testicles that are undescended.
 - Some may have genitals that do not look clearly male or clearly female. When this occurs, it is called “ambiguous genitalia”.
 - Others may have genitals that appear completely female.
- End-stage renal (kidney) disease. Renal failure may develop over time. This feature is generally worse in patients who have been treated for a Wilms tumor.

Genitourinary anomalies and Wilms tumor

Boys with this condition may have the following physical issues:

- Defects in the reproductive organs (genitals) and urinary system, such as hypospadias (the urinary opening is located on the underside of the penis instead of the tip) and undescended testes (the testicles fail to move down into the scrotum).

What causes *WT1*-related syndromes?

WT1-related syndromes are caused by changes in a gene known as *WT1*. Genes carry information telling cells within the body how to function. The *WT1* gene is needed to develop the kidneys and the gonads (ovaries in people with the chromosomal (genetic) make up of a female [46,XX karyotype] and testes in people with the chromosomal (genetic) make up of a male [46,XY karyotype]). Within these tissues, the *WT1* gene helps control how and when cells grow, divide and die.

Most people without *WT1*-related syndromes carry two working copies of the *WT1* gene in their cells. One copy is inherited from the mother and one from the father. Cells from people with *WT1*-related syndromes carry one working copy of *WT1* and one copy that is changed. This change causes the gene to not work properly. It is called a *WT1* mutation. The type of *WT1* mutation helps determine which of the *WT1*-related disorders a person has.

Most children with *WT1*-related syndromes have a new *WT1* mutation that did not come from a parent. These children have no history of the syndrome in their family. In these cases, the change either happened in an egg or sperm cell when the child was formed or in one of the child's cells during pregnancy. These children are the first in their families to have a *WT1*-related syndrome. A few children with *WT1*-related syndromes inherited their *WT1* mutation from a parent. No matter how they acquired the *WT1* changes, people with *WT1*-related syndromes who are able to have children have a 50% or 1 in 2 chance of passing it on to their children.

In WAGR syndrome, other genes besides *WT1* are affected. These include *PAX6*, which affects how the eyes develop, and *BDNF*, which is probably involved in managing eating, drinking and body weight. Research is ongoing to look for even more genes that might be affected in people with WAGR syndrome.

How are people with *WT1*-related syndromes screened for tumors?

People with *WT1*-related syndromes should be managed by a health care provider who knows this condition well and who specializes in treating Wilms tumor. Wilms tumor can often be cured with proper treatment. Children with *WT1*-related syndromes should have regular screenings to detect possible Wilms tumor as early as possible. The goal of screening is finding and treating tumors early to allow the best outcome for patients.

Recommended screenings for children with *WT1*-related syndromes include the following:

- **Regular physical exams** by a health care provider who is familiar with *WT1*-related syndromes.
- **Ultrasound exams** of the kidneys to screen for Wilms tumor. These should be started at diagnosis and repeated every three months and stopped at age 8. If a tumor is suspected, more detailed images should be taken using CT or MRI scans. The child should be seen by a pediatric cancer specialist (pediatric oncologist).
- **Yearly check-ups** with the child's regular pediatrician.
- **Evaluation** for undescended testicles and appropriate surgical intervention for people with the chromosomal (genetic) make up of a male individual (46, XY karyotype) and either Denys-Drash or Frasier syndrome.

It is possible that recommended screenings may change over time as health care providers learn more about *WT1*-related syndromes.

How is genetic testing for *WT1*-related syndromes done?

Hereditary cancer syndromes such as *WT1*-related syndrome may be suspected after looking at a person's medical or family history. In most cases, a health care provider or genetic counselor will ask questions about a person's health and the health of other family members. Any person with the chromosomal (genetic) make up of a male individual (46,XY karyotype) who has both Wilms

tumor and abnormal genitals (such as undescended testes or hypospadias) should be tested for the presence of a *WT1*-related syndrome.

The genetic counselor or health care provider will record which family members have developed tumors, what types of tumors and at what ages the tumors occurred. From this information they will create a family tree. Health care providers and genetic counselors will look at the family tree to find out:

- If there are more cancers than normal,
- If cancers occurred at younger-than-expected ages,
- If the types of tumors match up with what might be seen in those with *WT1*-related syndromes, and
- If the people with cancer had other physical or health features related to a *WT1*-related syndrome.

If a *WT1*-related syndrome is suspected in a child or other family members, the health care provider or genetic counselor will likely recommend genetic testing of the *WT1* gene.

Diagnostic genetic testing

If the health care provider or genetic counselor suspects that a person has a *WT1*-related syndrome, diagnostic testing may take place as follows:

- A blood sample is collected.
- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- Both copies of the person's *WT1* gene are checked for possible changes. A genetic specialist compares the two copies of the person's *WT1* gene to a normal *WT1* gene. If there are differences, the specialist decides if they might cause a *WT1*-related syndrome.
- If a *WT1* mutation is found, the genetic counselor will work with the family:
 - To help them understand the cancer and other risks of the *WT1*-related syndrome
 - To find out if other family members should consider testing
 - To help with decisions about prenatal genetic testing and family planning

If WAGR syndrome is suspected, special genetic tests may be completed to look for large areas of genetic change that may affect several genes at once.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if a pregnancy is affected with a known *WT1* mutation in the family.

Testing may take place either before pregnancy occurs or during pregnancy. Those considering prenatal testing should work with a genetic counselor to review the pros and cons of the tests. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy— Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for a known *WT1* mutation before placing them into the uterus.

Testing that occurs during pregnancy—Testing can be used to see if a pregnancy is affected with a known *WT1* mutation. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)**—during the first trimester of the pregnancy
- **Amniocentesis**—during the second trimester of the pregnancy or later

Once the tissue is collected, DNA is isolated and examined for the presence of the *WT1* mutation found in the family.

Both of these tests carry minor risks and should be discussed with an experienced doctor and/or genetic counselor.

Special concerns

Genetic testing for *WT1*-related syndromes is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before undergoing the testing. If they choose testing, they should review the test results with the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes children or adults with *WT1*-related syndromes can feel sad, anxious or angry. Parents who pass on a *WT1* mutation to one or more of their children can feel guilty. Some people with a *WT1* mutation could have trouble getting disability coverage, life insurance or long-term care insurance. More information about genetic discrimination can be found at www.ginahelp.org.

Are there other special health care needs for children with a *WT1*-related syndrome?

Many physical issues can develop in people with *WT1*-related syndromes. For this reason, children may need a care team with different types of health care providers. These may include the following:

- **Pediatric nephrologist:** Manages kidney problems.
- **Pediatric oncologist:** Diagnoses and treats Wilms tumor and gonadoblastoma (tumors of the gonads).
- **Pediatric surgeon and/or urologist:**
 - Manages Wilms tumor.
 - Surgically removes abnormal gonads to prevent gonadoblastoma, if needed.
 - Can lower the testes out of the abdomen.

- Can correct other reproductive and urinary system problems.
- **Pediatric endocrinologist:** Evaluates and manages disorders of sex development.
- **Genetics professional:** Provides genetic counseling and genetic testing.
- **Neurologist and/or developmental pediatrician:** Evaluates cognitive delay and behavior problems.
- **Ophthalmologist:** Manages aniridia and other eye problems.

People of any age with a *WT1*-related syndrome have a higher risk of cancer. They should watch their health and adopt healthy habits throughout life. It is important to continue to have regular physical checkups and screenings. That way, any cancer can be found early at the most treatable stage.

Other ideas to reduce the risk of cancer include the following:

- Eat a healthy diet with lots of fruits and vegetables
- Get regular exercise
- Avoid smoking or using tobacco products
- Avoid secondhand smoke
- Avoid excess sun exposure and always wear sunscreen, hat and protective clothing when out in the sun

People with a *WT1*-related syndrome should watch closely for general signs or symptoms that could signal that a Wilms tumor has developed:

- Swelling or a hard lump in the abdomen (belly)
- Fever
- Nausea
- Loss of appetite
- Shortness of breath
- Constipation
- Blood in the urine

It is important to seek medical help if anything unusual appears.

What other information and resources are there for children with *WT1*-related syndromes and their families?

Resource about *WT1*-related syndromes:

- International WAGR (Wilms tumor-Aniridia-genitourinary malformation-retardation) Syndrome Association (www.wagr.org)

More resources about Wilms tumor:

- Kidney Cancer Association – Wilms Tumor (www.kidneycancer.org/knowledge/learn/wilms-tumor/)



- American Cancer Society – Wilms Tumor (www.cancer.org/cancer/wilmstumor/detailedguide/index)
- National Wilms Tumor Study (www.nwtsg.org)

Resources about genetic testing and hereditary cancer:

- Making Sense of Your Genes: A Guide to Genetic Counseling (www.ncbi.nlm.nih.gov/books/NBK115508/)
- Young People with Cancer: A Parent’s Guide (www.cancer.gov/publications/patient-education/young-people)

Sources:

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