WT1-related Syndromes

What are WT1-related syndromes?

WT1-related 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 and eyes, and sometimes problems 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

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

People with a WT1-related syndrome 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 is different depending on the presence or absence of other health problems.

**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 also have a higher risk of developing a cancerous tumor in the ovaries and testes, called gonadoblastoma. Because Denys-Drash syndrome is very rare, the exact level of risk for gonadoblastoma is not known.

**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 level of risk is not known.

Most boys with Frasier syndrome have abnormal gonads (testes) that do not function. The gonads may develop cancerous tumors called gonadoblastomas. Girls with Frasier syndrome usually have normal gonads (ovaries) and do not usually develop gonadoblastomas.

**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. Often the gonads (testes) of boys with WAGR syndrome are undescended. This means the testes are located in the pelvis, abdomen or groin instead of the scrotum. Girls with the syndrome often have normal reproductive organs. Some girls may not have ovaries that work correctly and they will be unable to get pregnant. Girls may also have a heart-shaped (bicornate) 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 boys. Some boys are genetically male but have external reproductive organs (genitals) that do not look clearly male or clearly female, called ambiguous genitalia. Sometimes the external genitals of boys appear completely female. Often the gonads (testes) of boys with Denys-Drash syndrome are undescended. This means the testes are located in the pelvis,
abdomen or groin instead of the scrotum. Girls with Denys-Drash or Frasier syndrome usually have normal reproductive organs.

- 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.

**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 females and testes in males). 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 can help determine if the patient has WAGR, Denys-Drash or Frasier syndrome or has a WT1-related syndrome that does not fit into one of these three syndromes.

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 doctor 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 doctor who is familiar with WT1-related syndromes.
- **Ultrasound exams** of the abdomen and kidneys to screen for Wilms tumor. These should be started at diagnosis and repeated every three months until 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.

It is possible that recommended screenings may change over time as doctors learn more about \textit{WT1}-related syndromes. Parents should discuss all screening options for their child with a doctor who works regularly with \textit{WT1}-related syndromes. Because \textit{WT1}-related syndromes are complex conditions, it is important that parents seek out an experienced doctor for their child.

**How is genetic testing for \textit{WT1}-related syndromes done?**

The doctor may suspect a \textit{WT1}-related syndrome after looking at a person’s medical or family history. In most cases, a doctor or genetic counselor will ask questions about a person’s health and the health of other family members. Any boy who has both Wilms tumor and abnormal genitals (such as undescended testes) should be tested for a \textit{WT1}-related syndrome.

The genetic counselor or doctor 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. Doctors 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 \textit{WT1}-related syndromes, and
• If the people with cancer had other physical or health features related to a \textit{WT1}-related syndrome.

If a \textit{WT1}-related syndrome is suspected in a child or other family members, the doctor or genetic counselor will likely recommend genetic testing of the \textit{WT1} gene.

**Diagnostic genetic testing**

If the doctor or genetic counselor suspects that a person has a \textit{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 \textit{WT1} gene are checked for possible changes. A genetic specialist compares the two copies of the person’s gene to a normal \textit{WT1} gene. If there are differences, the specialist decides if they might cause a certain condition such as a \textit{WT1}-related syndrome.
• If a \textit{WT1} mutation is found, the genetic counselor will work with the family in the following ways:
  o To help the family understand the cancer risks of \textit{WT1}-related syndrome
  o To find out if other family members should consider testing
  o To help with decisions about prenatal genetic testing.
If WAGR syndrome is suspected, genetic tests called chromosome studies may be done. These tests 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 the pregnancy is affected with a known *WT1* mutation in the family. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of the testing. 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 diagnosis (PGD). This special type of genetic testing is done along with in vitro fertilization (IVF). PGD 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 (first three months)
- **Amniocentesis**—during the second trimester or later (last six months)

Collected tissue can be checked 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 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 testing is done. If they choose testing, they should review the test results with the doctor 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 an *WT1* mutation could have trouble getting disability coverage, life insurance or long-term care insurance in some states. 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 doctors. 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 healthful 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 healthful diet with lots of fruits and vegetables
• Get regular exercise
• Avoid smoking or using tobacco products
• Avoid secondhand smoke

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](http://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:
- Gene Ed (geneed.nlm.nih.gov)

Sources:
1. Children’s Hospital of Philadelphia – WTI-Related Wilms Tumor Syndromes  
   www.chop.edu/conditions-diseases/WTI-related-wilms-tumor-wt-syndromes#.VQwzy2d0vtU
   ghr.nlm.nih.gov/condition/denys-drash-syndrome
4. Genetics Home Reference – Frasier Syndrome  
   ghr.nlm.nih.gov/condition/frasier-syndrome
5. Gene Reviews - Wilms Tumor Overview  
   www.ncbi.nlm.nih.gov/books/NBK1294/