Inheritest℠
CARRIER SCREEN

What is Zellweger Syndrome Spectrum?
Zellweger syndrome spectrum (ZSS) is a group of inherited diseases that includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). While initially thought to be distinct disorders, these conditions are now known to be part of the same disease spectrum and share similar symptoms but vary in severity. Zellweger syndrome spectrum is characterized by progressive neurological disease, liver and kidney disease, and hearing and vision loss.[1] The symptoms of ZSS are due to a defect in the body's ability to produce peroxisomes. Peroxisomes are structures found in almost every cell of the body and are essential for normal brain and nervous system development as well as normal eye, liver, kidney, and bone functions.[2]

What are the Symptoms of Zellweger Syndrome Spectrum and What Treatment is Available?
Zellweger syndrome is the most severe of the three conditions and is typically characterized by onset at birth, with death generally occurring within the first year of life. Neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD) usually have onset in late infancy or early childhood. Children with NALD often survive to childhood, while children with IRD may live to their teens or possibly to adulthood. In rare cases, symptoms are very mild with developmental delay in childhood and vision and hearing problems beginning in adulthood.[3]

Zellweger syndrome symptoms usually include:[3]

- Profound hypotonia (low muscle tone)
- Feeding problems
- Profound mental retardation
- Seizures
- Hearing and vision loss
- Distinctive facial features (flattened face, broad nasal bridge, high forehead)
- Liver and kidney disease
- Chondroplasia punctata (x-ray findings of scattered calcification at the end of the long bones and knee)

Children with neonatal adrenoleukodystrophy and infantile Refsum disease have many of the same features seen in Zellweger syndrome but with slower progression. Symptoms may include:[1,3]

- Hypotonia (low muscle tone)
- Intellectual disability
- Liver and kidney disease
- Seizures
- Hearing and vision loss
- Hemorrhage (severe bleeding episodes) including intracranial bleeds (bleeding within the brain)
- Regression (loss of previously acquired skills)

There is no cure for the Zellweger syndrome spectrum. Treatment includes supportive care for symptoms.[1]

How is *PEX1*-related Zellweger Syndrome Spectrum Inherited?
ZSS is a group of autosomal recessive diseases caused by mutations in 12 different genes. Integrated Genetics' Inheritest looks for mutations in the *PEX1* gene, which account for the majority (70%) of cases of Zellweger syndrome spectrum.[3] An individual who inherits one copy of a *PEX1* gene mutation is a "carrier"

and is not expected to have related health problems. An individual who inherits two mutations in the *PEX1* gene, one from each parent, is expected to be affected with ZSS.

If both members of a couple are carriers, the risk for an affected child is 25% in each pregnancy; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

Who is at Risk for Zellweger Syndrome Spectrum?
ZSS can occur in individuals of all races and ethnicities, although some variation in frequency has been observed. ZSS is estimated to have an overall incidence of 1/50,000 with a calculated *PEX1* carrier rate of 1 in 134.[3]

Having a relative who is a carrier or is affected can also increase an individual's risk of being a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

What Does a Positive Test Result Mean?
If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

What Does a Negative Test Result Mean?
A negative result reduces, but does not eliminate, the possibility that an individual carries a *PEX1* gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results. There are 12 genes associated with Zellweger syndrome spectrum. InheriTest looks for mutations in the most common ZSS-related gene, *PEX1*, but does not assess a person's risk for being a carrier of the other less common ZSS-related genes.

Where Can I Get More Information?
- National Institute of Neurological Disorders and Stroke (NINDS) Zellweger Spectrum Information Page http://www.ninds.nih.gov/disorders/zellweger/zellweger.htm
- United Leukodystrophy Foundation www.ULF.org

References
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2. NINDS Zellweger Syndrome Information Page. http://www.ninds.nih.gov/disorders/zellweger/zellweger.htm Accessed March 19, 2012.
3. Zellweger spectrum. http://ghr.nlm.nih.gov/condition/zellweger-spectrum Accessed March 19, 2012.