

A publication of  
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# GENETICS Update

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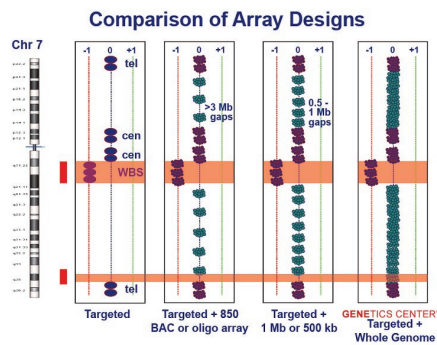
Genetics Center provides a full range of genetic services, including clinical genetics, genetic counseling, laboratory services, and fluorescence in situ hybridization (FISH). We have CAP accredited on-site cytogenetics and molecular genetics laboratories. Genetics Center is a state-approved and contracted comprehensive prenatal diagnosis center. Genetics Center is recognized by the Children’s Oncology Group (COG) as an approved laboratory. We publish this periodic newsletter, *Genetics Update*, as a service to our referring physicians, the healthcare community at large, and our patients. We appreciate your association and inquiries.

## Genetics Center’s 180k Array CGH: Postnatal, Prenatal, Products of Conception Detecting Chromosome Imbalances Beyond What Conventional Techniques Are Able to Detect.

Genetics Center is pleased to offer the latest in array-based comparative genomic hybridization (array CGH) testing. Our high-resolution array containing 180,000 oligonucleotide clones is based on the International Standards for Cytogenomic Arrays (ISCA) Consortium chip design.

Array CGH has the ability to test for a broad range of microscopic and submicroscopic chromosomal abnormalities through *one test*. The advantage of this technology over existing ones (such as chromosome analysis and/or FISH) is that array CGH allows the simultaneous detection of many conditions in a single test and for certain cases is more cost effective than sequential testing with more traditional techniques. The detection rate with array CGH is higher than traditional chromosomal analysis.

The American College of Medical Genetics (ACMG) has recommended the use of array CGH as a first-tier test in the initial postnatal evaluation of an individual with developmental delay/intellectual disability, autism spectrum disorder, or multiple con-



genital anomalies that are not part of a recognizable syndrome. Also, the American College of Obstetricians and Gynecologists (ACOG) recommends that array CGH be offered as an adjunct tool in prenatal cases with abnormal anatomical findings on ultrasound and a normal conventional karyotype.

Since many abnormal phenotypes are associated with chromosomal imbalances (subtle gains or losses of genetic material), the identification of specific abnormalities is helpful to accurately diagnose and refine the medical management of a patient. Abnormalities detected by array CGH include:

chromosomal aneuploidies, such as Down syndrome and trisomy 18; microdeletion and duplication syndromes, such as Prader-Willi syndrome and Angelman syndrome; gains or losses at the ends of chromosomes; and gains or losses in some chromosomal regions associated with autism. Other chromosome abnormalities that currently have unclear clinical significance may also be detected, which makes genetic counseling more challenging. Array CGH cannot detect certain chromosome rearrangements, such as balanced translocations or inversions (since no DNA is gained or lost) as well as some polyploidies (such as triploidy). It also cannot detect changes in DNA sequences caused by intragenic mutations.

For more information on postnatal testing (pediatric and adult), prenatal testing, products of conception testing, retesting at higher resolution, pre- and post-test genetic counseling, or a list of our targeted regions, please feel free to contact us.

# Spinal Muscular Atrophy

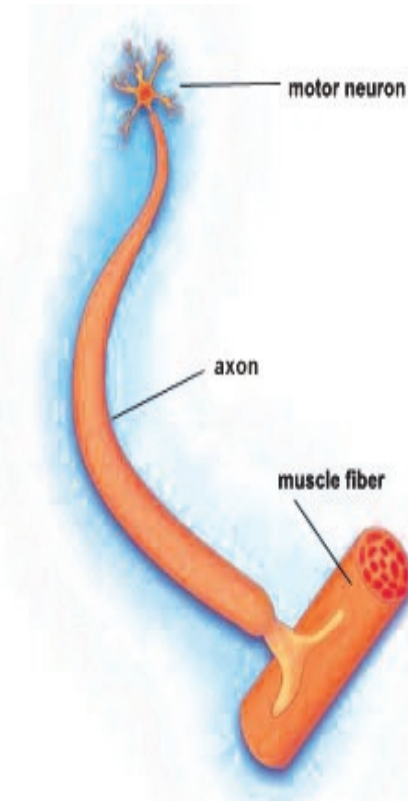
American College of Medical Genetics recommends carrier screening be made available to all couples

Spinal muscular atrophy (SMA) is a disease characterized by progressive muscle weakness resulting from degeneration of motor neurons. Signals are normally transmitted from motor neurons in the spinal cord to muscle via the motor neuron's axon. For individuals with SMA, muscle fibers lose this connection from the spinal cord that communicates when to contract. The clinical spectrum of SMA ranges from early infant death to normal adult life with only mild weakness.

The severity of SMA is closely related to the age of onset. SMA I (also called Werdnig-Hoffman syndrome) is the most common and severe type. Onset occurs before the age of six months and death usually results from respiratory failure before age two. Type II has onset between six and twelve months with survival up to 70% by the age of 25. Lifespan is normal for those with SMA III, occurring after twelve months of age, and SMA IV, which occurs in adulthood.

A diagnosis of SMA can be confirmed by molecular genetic testing. The two genes associated with SMA are SMN1 and SMN2, which are adjacent to each other on chromosome #5. SMN1 is the primary disease-causing gene, and about 95-98% of individuals with SMA are homozygous for the absence of exons 7 and 8 of SMN1. 2-5% of individuals with SMA are compound heterozygous for a deletion of exon 7 and an intragenic mutation of SMN1. Moreover, the presence of three or more copies of SMN2 is correlated with a milder phenotype of SMA. All forms of SMA result from faulty genes providing insufficient supply of the SMN protein, the lack of which causes motor neurons to die off and muscles depending on the motor neurons to atrophy and waste away.

The most promising treatment



**Degeneration of motor neurons causes muscle weakness in individuals with SMA. Normally, signals from the motor neuron cause the muscle to contract via the motor neuron's axon.**

available for individuals with SMA relies on the fact that, even though the SMN1 gene is affected, the SMN2 gene continues to produce limited quantities of the SMN protein. Many promising therapies are intended to upregulate, or increase the expression of, the SMN2 gene. Since severity of the disease corresponds to levels of SMN protein, upregulation of SMN2 should mitigate the effects of the disease.

Other approaches to treatment include gene therapy (replacing the SMN1 gene), protein therapy (injecting the SMN protein), finding a drug that can substitute for the SMN protein, and treating the symptoms of SMA directly. Certain drugs may allow motor neurons to have less susceptibility to SMN

depletion or enhance their ability to sprout extra connection to muscle fibers. Furthermore, assistive technology such as ventilators are important, since infants with SMA frequently succumb to respiratory disease due to weakness of the muscles that support breathing.

SMA is an autosomal recessive genetic disease, meaning that 98% of parents of an affected child are carriers of an abnormal SMN1 gene. It is estimated that between 1 in 40 to 1 in 60 individuals carry an abnormal SMN1 gene, making it the second most common recessive disease after cystic fibrosis.

The American College of Medical Genetics (ACMG) recommends that carrier screening for SMA be made available to all couples as part of their family planning process. Genetics Center provides an accurate test for detecting 91-94% of carriers of the SMN1 gene deletion that causes SMA. Without such screening, there is no way to identify couples at risk of having children with SMA. Genetics Center can also provide genetic counseling for prospective parents to discuss the values and limitations of SMA screening. Like other genetic diseases, differences in the frequency of SMA carriers are significant among several ethnic groups (see Hendrickson et al 2009, <http://jmg.bmj.com/content/46/9/641.full>).

The ACMG also stipulates that genetic counseling be made available to anyone requesting SMA carrier testing. It is important for individuals to understand that carriers are not at risk of developing the disease, but have the risk of passing the gene mutation to his or her offspring. Couples with positive carrier screening will also be provided with information regarding the risks to current or future pregnancies and potential treatment options. Please feel free to contact us for further information.

# Paternity/Identity Testing - Prenatal or Postpartum

Genetics Center offers accurate and confidential legal paternity/identity testing for peace of mind

Genetics Center offers confidential DNA-based identity and paternity testing for peace of mind or for evidence in a court of law. This testing has many benefits including high accuracy, ease of specimen collection, and the inexpensive nature of the tests. Additionally, Genetics Center has the ability to perform paternity testing prenatally (during pregnancy) as well as postpartum (after birth).

Both identity and paternity testing are based on the fact that each individual has a unique genetic blueprint known as DNA. One-half of an individual's DNA comes from their mother and one-half from their father. DNA is found in virtually every cell in the body, so testing can be performed on many different specimen types.

Identity testing is extremely beneficial to patients who have recently undergone bone marrow transplantation. By analyzing the DNA in the patient's bone marrow after transplantation, it is possible to quantify the ratio of patient to donor DNA in the sample of bone marrow. This information is a direct measure of the success of a bone marrow transplant and can be used as a prognostic tool for relapse. Another use of this test is the identification of twin zygosity. In determining twin zygosity, identity testing is based on the fact that monozygotic twins have exactly the same genetic makeup, while dizygotic twins do not.

Prenatal testing is performed using cultured amniotic cells or chorionic villi. Alternatively, paternity can be determined after birth by obtaining blood samples from the child, the alleged father, and the mother. The volume of blood required for testing is quite small,



so this specimen type can be safely collected from newborns and children.

Paternity and identity testing rely on a series of markers scattered throughout the genome. These markers are called short tandem repeats (STRs). DNA is made up of 4 types of molecules (bases), called A, C, T and G. These bases are strung together in long chains to make molecules of DNA. It is the order of the bases that determines our unique genetic makeup. By looking at how the base pairs are ordered at each STR site, a genetic profile can be built that can be used to

compare with other people's DNA.

At the Genetics Center, DNA is first isolated from the specimen. A PCR is run, which makes millions and millions of copies of each STR site. The products of the PCR are then put into a genetic sequencer, which can determine the order of the bases at each STR site. Finally, the genetic profiles are made from the sequencing information, and paternity or identity can be determined by comparing the genetic profiles using advanced statistical population algorithms.

The result of a paternity test can be used in a court of law for child support, inheritance, immigration, or adoption purposes. Maternity testing is also offered in cases where the biological mother is unclear. For example, an adopted child may wish to reconnect with his or her biological parents, or during in vitro fertilization an unrelated embryo may be mistakenly implanted into the mother.

For a paternity test to hold up in court against allegations of tampering, our legal paternity testing has the required *chain of custody*. In these cases, a neutral third party laboratory staff member identifies the individuals being tested, collects their blood samples, and the specimen handling is tracked and documented throughout the entire process. For non-legal testing (for peace of mind), this chain of custody is not required or performed.

Genetics Center is a CLIA approved and CAP accredited laboratory. For further information, please feel free to contact us.

# CHRONOLOGY

of selected milestones in genetics / and our Genetics Center's history

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| <p>1980: The Human Genome Project is proposed.</p> <p>1986: Genetics Center opens its doors offering clinical genetics, cytogenetics, genetic counseling, and amniocentesis.</p> <p>1987: Genetics Center is approved by the State of California as a Comprehensive Prenatal Diagnosis Center (PDC).</p> <p>1988: Genetics Center is the first in Orange County to offer chorionic villus sampling (CVS) for first trimester prenatal diagnosis.</p> <p>1989: The gene for cystic fibrosis is identified by researchers at Toronto's Hospital for Sick Children and University of Michigan.</p> <p>1993: Discovery of the gene for Huntington disease, an adult onset neurological disease.</p> <p>1994: Genetics Center laboratory begins performing amniotic fluid AFP analysis.</p> <p>1995: Genes that account for the majority of hereditary breast cancers are identified.<br/>Genetics Center offers fluorescence in situ hybridization (FISH).</p> <p>1998: Genetics Center establishes a molecular genetics laboratory.</p> <p>2000: Working draft of the entire human genome sequence is announced in June 2000, with analyses published in February 2001.</p> <p>2001: Genetics Center moves into our new facilities at 211 S. Main St. in Orange.<br/>Genetics Center receives Outstanding Orange Business award.<br/>FDA approves Gleevec®/imatinib, a genetics-based drug to treat CML.</p> <p>2002: Genetics Center continues to grow with additional services offered such as:<br/>- ACOG recommended cystic fibrosis testing<br/>- Factor V Leiden testing<br/>Genetics Center upgrades its computer facility to a web-based computer system and integrated electronic karyotyped documentation.</p> | <p>2003: Genetics Center starts offering Connexin 26 testing for detecting a form of genetic deafness.<br/>Completion of the Human Genome Project.</p> <p>2004: Genetics Center starts offering a Thrombotic Panel test for venous thrombosis and other various risk factors.<br/>Genetics Center is approved by the California DHS-LFS as a training program for clinical cytogeneticist scientists.</p> <p>2005: Genetics Center is recognized by Childrens Oncology Group (COG) as an approved laboratory.<br/>Completion of HapMap Project; a database of human variation useful for identification of genes associated with common diseases such as diabetes.<br/>Genetics Center starts offering prenatal aneuploidy FISH analysis for trisomies 13, 18, 21, and sex chromosome aneuploidy.</p> <p>2006: National Cancer Institute and National Institutes of Health starts The Cancer Genome Atlas Project to identify the genes associated with various forms of cancer.</p> <p>2007: Genetics Center starts offering JAK2 testing for diagnosing myeloproliferative disorders.</p> <p>2008: The Genetic Information Nondisclosure Act (GINA), designed to prohibit improper use of genetic information in health insurance and employment, is signed into federal law.</p> <p>2009: The State of California launches its new Prenatal Screening Program, which includes 1st trimester screening.<br/>Genetics Center becomes a CAP accredited laboratory.</p> <p>2010: Discovery of a gene associated with Kabuki syndrome, a congenital cognitive impairment syndrome.<br/>Genetics Center starts offering 180k Array CGH (microarray) testing for postnatal, prenatal, and products of conception.<br/>Genetics Center is approved by the California DHS-LFS as a training program for clinical genetic molecular biologist scientist.</p> |
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**THANK YOU**

*We are grateful to all of the people who have supported us and have made our 25th year as a provider of a full-range of genetics services possible.*



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