

TESTING SERVICES:

? Chromosome analysis

Specimen: 10 ml whole blood in a green top
Na Heparin tube

Specimen: 10 ml whole blood in a green top
EDTA tube

Results available: 7 days

? Y-Chromosome Microdeletion Testing

Specimen: 10 ml whole blood in a lavender top
EDTA tube

Results Available: 2-3 weeks

? Cystic Fibrosis Gene Testing

Specimen: 10 ml whole blood in a lavender
top EDTA tube

Results Available: 1 week

HOW CAN TESTING BE ARRANGED?

Physicians or healthcare providers may contact one of our Centers for consultations. Blood specimens may be sent by a physician or healthcare provider or drawn at GeneCare if testing is recommended.

Couples experiencing male factor infertility who are interested in pursuing assisted reproduction are encouraged to discuss genetic testing with their physicians or healthcare providers and to consider having genetic counseling .

SPECIMEN COLLECTION:

- Call GeneCare at (800) 277- 4363 to discuss clinical indications, current testing, informed consent, fees, and payment method.
- Complete Consent Forms and Laboratory Request. Enclose family history.
- Label each specimen tube with patient name, birth date, and collection date.

SPECIMEN TRANSPORT:

? **SHIP AT ROOM TEMPERATURE** in our kit.

? **DHL/Airborne** (800) 247-2676 **priority overnight** (or by our courier) to reach GeneCare Monday-Thursday. Delivery required within 24 hours.

? Enclose Laboratory Request / Consent Forms.

? Call GeneCare with the DHL/Airborne airbill/ tracking number.

REFERENCES:

Johnson, M. D. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. *Fertility and Sterility* 1998; 70: 397-411.

Kim, E. D., Bischoff, F. Z., Lipshultz, L. I., and Lamb, D. J. Genetic concerns for the subfertile male in the era of ICSI. *Prenat. Diagn.* 1998; 18: 1349-1365.

Meschede, D., and Horst, J. Genetic counseling for infertile male patients. *Int. J. of Andrology* 1997; 20(3): 20-30.

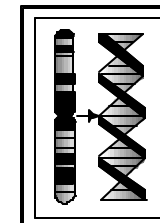
Schlegel, P. N. and Girardi, S. K. Clinical review 87: In vitro fertilization for male factor infertility. *J Clin Endocrinol Metab* 1997; 82(3): 709-16.

MALE INFERTILITY GENETIC TESTING

CHROMOSOME ANALYSIS with Y-DNA MICRODELETION ANALYSIS

CYSTIC FIBROSIS PANEL for CONGENITAL ABSENCE of the VAS DEFERENS

Information for Healthcare Providers



GeneCare[®]
Medical Genetics Center

www.genecare.com

GeneCare Medical Genetics Center
201 Sage Road, Suite 300
Chapel Hill, NC 27514
(800) 277-4363 ? (919) 942-0021
Fax (919) 967-9519

The development of assisted reproductive technologies, specifically intracytoplasmic sperm injection (ICSI), now enables many infertile men to have children. Before undergoing ICSI, it is important to discover the cause of infertility. A significant proportion of men with infertility may have a genetic alteration causing their infertility. This fact is significant because these men are at increased risk for having recurrent miscarriages with their partner, children with birth defects and learning disabilities, and male offspring with infertility. Three main genetic causes for male infertility characterized by severe oligospermia (low sperm production) or azoospermia (no sperm production) are:

1. chromosome abnormalities,
2. Y-chromosome microdeletions, or
3. mutations (changes) within the cystic fibrosis gene.

1. CHROMOSOME ABNORMALITIES.

Approximately 5-10% of men with oligospermia and 10-15% of men with azoospermia carry a chromosome abnormality, most commonly of the sex chromosomes. Chromosomes are units of genetic information in the cells of the body. Each cell should contain 46 chromosomes, arranged into 23 pairs. The last pair of chromosomes is the sex chromosomes, X and Y. Males should have an X and a Y (46,XY), while females should have two Xs (46,XX).

The most common chromosome abnormality associated with male infertility is Klinefelter syndrome, in which males carry an extra X chromosome (47,XXY). Klinefelter syndrome is characterized by an increased chance for learning disabilities, minor physical differences, and infertility. Most men with Klinefelter syndrome go undetected until experiencing difficulty with their partner concerning children, and an evaluation for infertility is performed. With the assistance of ICSI, men with Klinefelter syndrome are often able to have children. Although these men can have healthy children, there is also an increased chance to have a child with a sex chromosome abnormality.

Other chromosome abnormalities may also cause infertility in the otherwise healthy male. An example of a structural chromosome abnormality is a translocation, in which pieces of chromosomes from two different pairs are switched. Men carrying these types of chromosome abnormalities are at an increased risk for their partner having miscarriages and children born with birth defects and mental retardation. Carriers can also have healthy offspring with normal chromosome or a normal offspring that are carriers like the parent.

A chromosome analysis should be routinely offered to all men with infertility before proceeding with ICSI.

2. Y-CHROMOSOME MICRODELETIONS

Y chromosome microdeletion of the AZFa, AZFb, AZFa (azoospermia factors) regions or certain other regions (AMELY, SRY, ZFY) of their Y chromosomes are found in ~35% of men with idiopathic azoospermia, 20-25% with severe oligospermia, and 7% of unselected infertility patients. Several genes on the Y chromosome are required for normal spermatogenesis (the process of making the sperm). The absence of one or more of these genes causes infertility. Men with Y microdeletions who undergo ICSI are at risk for producing sons who may carry the same deletions and be infertile.

Y chromosome microdeletion analysis should routinely be offered to all men with severe oligospermia or azoospermia.

CYSTIC FIBROSIS GENE MUTATIONS

Cystic Fibrosis (CF) is a genetic disorder typically characterized by complications of the lung and pancreas. CF is inherited as an autosomal recessive disorder. Autosomal means the abnormal gene is not on a sex chromosome. Recessive means the effect of the gene would only be seen when a baby inherits an abnormal recessive gene from both parents.

Certain mutations within the cystic fibrosis gene are known to cause congenital bilateral absence of the vas deferens (CBAVD); congenital unilateral absence of the vas deferens (CUAVD), without manifestations in the lung or pancreas; or obstructed vas deferens. Abnormalities of the vas deferens cause oligospermia and azoospermia, which consequently results in infertility in men carrying the associated mutations. Approximately 40% of men with CUAVD and 50-80% of men with CBAVD have at least one mutation within the CF gene. A common CF mutation associated with CBAVD is called the 5T variant. Men with CBAVD or CUAVD in addition to unilateral renal agenesis (absence of a kidney) are **not** at increased risk for carrying CF mutations.

Men with CBAVD or CUAVD who carry CF mutation(s) are at an increased risk for having children with infertility, or classical Cystic Fibrosis if the mother is also a carrier of a CF mutation. All men with CBAVD and CUAVD should routinely be offered CF testing before undergoing ICSI.

WHO SHOULD BE OFFERED CHROMOSOME ANALYSIS, Y-CHROMOSOME MICRODELETION TESTING, and/or CF GENE TESTING?

All males with severe oligospermia and/or azoospermia should be offered chromosome analysis and DNA analysis for Y chromosome microdeletions before proceeding with ICSI. Men with CBAVD, CUAVD, or obstructive azoospermia should routinely be offered CF testing as well.