
GREENWOOD GENETIC CENTER
DIRECTORY OF LABORATORY SERVICES

Today's laboratory technology helps in the evaluation, treatment and prevention of many human genetic disorders. The diagnostic laboratories of the Greenwood Genetic Center offer comprehensive and state-of-the-art genetic testing in:

- **Cytogenetics**
- **Biochemistry**
- **Molecular Genetics**
- **Prenatal Screening**

Laboratory faculty and staff work closely with their clinical counterparts to ensure health care providers and families receive counseling, support and professional consultation, emphasizing care in every sense of the word.

The Greenwood Genetic Center is a nonprofit institute organized to provide clinical genetic services and laboratory testing, to develop educational programs and materials, and to conduct research in the field of medical genetics.

This manual is intended to provide information about laboratory diagnostic studies available through the Greenwood Genetic Center. We hope you find it helpful and welcome your questions and comments.

The Greenwood Genetic Center Diagnostic Laboratories are CLIA certified and actively participate in CAP proficiency surveys.

Additional information may be obtained by telephoning the Greenwood Genetic Center Diagnostic Laboratory toll free at:

1(800) 473-9411

www.ggc.org

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Chromosome Analysis

Chromosome analysis is an important component in the diagnosis and evaluation of genetic disorders. Chromosome abnormalities in which there is too much or too little genetic material can result in congenital malformations, mental retardation, or aberrant sexual differentiation.

Chromosome disorders occur in approximately 1 in 150 liveborns and are a significant cause of mental retardation and dysmorphic features. In addition, over 50% of first trimester spontaneous abortions are due to a fetal chromosome abnormality.

Individuals with

- suspected classic chromosomal syndrome
- ambiguous genitalia
- pubertal failure
- mental retardation of undetermined etiology
- dysmorphic features
- abnormalities of sexual development
- certain types of malignancies
- abnormalities of growth
- multiple congenital abnormalities

Couples with

- two or more spontaneous abortions
- infertility

Family members

- both parents of a child with a structural chromosome rearrangement, deletion, or duplication
- all family members at risk of having chromosome rearrangement

Pregnancy products

- abortuses (including blighted ova and missed abortions)
- malformed stillborns
- stillborns of undetermined etiology

Chromosome analysis can be performed on blood, solid tissue, bone marrow, amniotic fluid cells, and chorionic villi. The following sections describe the samples needed for specific types of chromosome studies.

Routine Cytogenetic Analysis of Peripheral Blood

Specimen requirements: 5 - 10 ml peripheral blood in a *sodium heparin* (green top) VacutainerTM tube. In newborn infants, 1 to 2 ml of blood may be sufficient. Certain anticoagulants, such as lithium heparin and ammonium heparin, may be toxic to lymphocytes; therefore sodium heparin is the anticoagulant of choice. Certain types of blood collection tubes have also been associated with reduced cell growth, therefore VacutainerTM tubes, as opposed to VenojectTM tubes, are preferred for specimen collection.

Transport: Specimen should be kept at room temperature; *do not freeze or refrigerate*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 20 cells are counted and 5 cells are analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are available in 14 to 21 days. For STAT samples, results are available in 2 to 4 days.

CPT Codes: 88230, 88262, 88291

High resolution Analysis of Peripheral Blood

High resolution chromosome analysis requires the use of elongation methods to obtain a high percentage of prophase and prometaphase spreads. The chromosomes are less condensed than in routine metaphase analysis and the number of identifiable bands is expanded, allowing a more sensitive analysis of the karyotype. Because special culture conditions are required, *high resolution studies must be specifically requested*. For sample requirements, see above.

This study is required for the detection of subtle chromosome rearrangements and is considered an important component in the diagnosis of microdeletion syndromes such as Prader-Willi syndrome, Angelman syndrome, Smith-Magenis syndrome, and Miller-Dieker syndrome.

Transport: Specimen should be kept at room temperature; *do not freeze or refrigerate*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 20 cells are counted and 5 cells are analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are available in 14 to 21 days. For STAT samples, results are available in 2 to 4 days.

CPT codes: 88230, 88262, 88289, 88291

Special Stains

(may be added to any chromosome study)

R-banding procedures produce the reverse or opposite banding pattern as G-banding and Q-banding and denotes the GC-rich euchromatic regions. R-bands are important for detecting minor inversions, for comparing length of homologs, for examining the ends of chromosomes, and for identifying subtle deletions or rearrangements that may go undetected using G- or Q-bands.

Q-banding methods produce fluorescent bands after staining chromosome preparations with quinacrine. These bands represent the AT-rich regions of the chromosome and are analogous to the bands produced by G-banding. Q-banding is particularly useful in identifying polymorphisms on the satellites of the acrocentric chromosomes and of the Y chromosome, and in confirming translocations involving the Y.

C-banding is a procedure which stains the constitutive heterochromatin that is localized in the pericentromeric regions of all chromosomes and on the distal long arm of the Y. C-banding is useful in confirming pericentric inversions and in identifying polymorphisms of the centromeric regions of chromosomes 1, 9, and 16 and the heterochromatic region of the Y, and in confirming translocations involving the Y.

NOR staining is a silver staining procedure which stains the nucleolus organizer regions (NORs) of satellited chromosomes. It is particularly useful in studying variations in the size of the stalks and satellites of the acrocentric chromosomes.

DAPI staining produces bright fluorescence of the heterochromatic regions of chromosomes 1, 9, 16, Y, and the centromeric region of 15. It is particularly helpful in identifying the origin of small bisatellited marker chromosomes and in confirming translocations involving the heterochromatic region of Y.

CPT codes: Special Stains (each): 88283 plus appropriate codes for tissue type studied.

Chromosome Breakage

Certain conditions, such as Fanconi anemia, show an increased frequency of spontaneous chromosome breakage. In these cases, chromosome breakage studies are performed by treating cultured cells with mitomycin-C or diepoxybutane (DEB) to induce breakage. Chromosome breakage studies are not performed at the Greenwood Genetic Center, however we can provide information about where to send samples for these special studies.

Sister Chromatid Exchange (SCE)

A sister chromatid exchange represents the interchange of homologous segments between two chromatids of one chromosome. SCEs can be detected by growing cells under special culture conditions to produce differential staining of sister chromatids. SCE analysis aids in the diagnosis of inherited conditions such as Bloom syndrome, which shows an increased rate of SCE compared to controls. Because special culture conditions are required, chromosome breakage studies must be specifically requested.

Fragile X

Recent advances in molecular genetics have led to a highly accurate and dependable DNA test that can diagnose fragile X syndrome in both affected and carrier states. The molecular testing, rather than chromosome testing, is now recommended in cases where fragile X syndrome is suspected. See DNA Diagnostic Section for test information and sample requirements (page 32).

Buccal Smear for Barr Body Analysis

Historically, Barr body analysis has been used as a quick screen in individuals, particularly infants, with ambiguous genitalia. Disadvantages of Barr body analysis are that structural abnormalities of the sex chromosomes will not be detected and that mosaicism for sex chromosome aneuploidy can be missed. With recent developments in fluorescence in situ hybridization [FISH], sex chromosomes can be rapidly and reliably identified in interphase cells. FISH analysis for sex chromosome constitution is now preferred over buccal smear analysis. See page 7 for sample requirements. It is recommended that FISH analysis be followed by a G-banded chromosome study to confirm the results and to look for changes in chromosome structure that may go undetected by FISH.

Fluorescence In Situ Hybridization

[FISH]

Fluorescence in situ hybridization is a molecular cytogenetic technique in which fluorescently labeled DNA probes are hybridized to metaphase spreads or interphase nuclei. Applications include identification of structurally abnormal chromosomes, including several of the cancer translocations, such as BCR/ABL and TEL/AML1 translocations; identification of marker chromosomes; detection of very small deletions (microdeletions); and rapid detection of Down syndrome and other numerical chromosome abnormalities; and the rapid detection of sex chromosomes and the SRY gene. FISH should be used in conjunction with G-banded chromosome analysis.

FISH is performed upon request when a specific numerical or structural abnormality or microdeletion is suspected. FISH is also utilized to confirm microdeletions identified during high resolution chromosome analysis and to aid in identification of abnormal chromosomes. Interphase FISH is especially useful in bone marrow / cancer analyses when there is poor or no growth of the specimen.

Specimen requirements: FISH can be performed on any tissue that can be cultured for chromosome analysis and interphase FISH can be performed on any cytogenetic sample. Follow collection and transport guidelines specific for each tissue type. Studies requested should be indicated at the time of sample submission.

Analysis: The standard of analysis varies depending on the probe used. Hard copies of at least 2 cells are digitally archived for documentation.

Report: Results are come as a separate report for most studies, and should be available within one week of culturing.

CPT codes: Vary according to specific purpose.

FISH 3-5 metaphase cells = 88272, 88271*
FISH 10-30 metaphase cells = 88273, 88271*
FISH 25-99 interphase cells = 88274, 88271*
FISH 100-300 interphase cells = 88275, 88271*

* for each probe – so, a dual-probe assay would be 88271 X 2

FISH probes are available for:

(New probes are always being developed, please call concerning other conditions)

Microdeletion Syndromes

A number of genetic syndromes are caused by the deletion of a small region of a particular chromosome. Often these deletions are too small to be picked up by standard or high resolution chromosome analysis, in which case, microdeletion syndrome probes must be used to elucidate the chromosome abnormality. These probes are pieces of DNA specific for the region deleted in the specified syndrome, and usually include a control probe which identifies the chromosome of interest.

Wolf-Hirschhorn (4p-)

Cri-du-chat (5p-)

Williams syndrome (7q11.23)

Prader-Willi syndrome (15q11.2-q13)

Angelman syndrome (15q11.2-q13)

Miller-Dieker syndrome (17p13.3)

Smith-Magenis syndrome (17p11.2)

DiGeorge and Velo-cardio-facial syndromes (22q11.2)

Kallman syndrome (Xp22.3)

 Steroid Sulfatase Deficiency (STS) (Xp22.3)

 X-Linked Ichthiosis (Xp22.3)

Retinoblastoma (13q14)

Trisomy Detection and Sex Determination

Probes for chromosomes 13, 18, 21, X, Y and SRY. These probes are used to screen interphase (uncultured) cells for trisomy 13, trisomy 18, trisomy 21, chromosome number for sex chromosomes (X and Y) and for the presence of the male determining gene SRY. FISH can be performed as an initial screening test in certain high risk situations where trisomy is suspected, such as in amniocytes from a pregnancy with an abnormal ultrasound or uncultured lymphocytes from an infant with ambiguous genitalia.

Results may be obtained 24 hours after receipt of the sample.

Oncology

FISH analysis is available to rule out certain common oncology related translocations, deletions and amplifications. This analysis is particularly useful when a specific hematologic disease is highly suspected (i.e. Philadelphia chromosome in chronic myelogenous leukemia) and/or cells fail to grow in culture. FISH can be used to look for minimal residual disease in patients undergoing treatment or in patients thought to be going into or coming out of remission. It can be used to detect unusual variants of the Philadelphia chromosome translocation, and to follow bone marrow transplants in certain patients. Since most of these oncology probes are used on interphase cells, standard cytogenetics is still necessary to look for other chromosomal aberrations and to detect clonal evolution of disease, an important prognostic indicator.

Single Gene Probes (deletion or amplification)

P58 CLK-1 Locus (1p36)

D7S486 (7q31)

Retinoblastoma (13q14)

p53 (17p13.1)

Her-2/neu (17q11.2-q12)

Enumeration probes for all chromosomes

Dual Color Translocation Probes

bcr/abl translocation t(9;22)(q34;q11.2) (both major and minor breakpoints)

M-bcr/abl translocation t(9;22)(q34;q11.2) (major breakpoint)

IGH/CCND1 translocation t(11;14)(q13;q32)

PML/RARA translocation t(15;17)(q22;q21.1)

TEL/AML1 translocation t(12;21)(p13;q22)

Amniotic Fluid

Aneuploid detection by FISH for chromosomes 13, 18, 21, X and Y may be indicated in situations where there is a risk of a numerical chromosome abnormality. This risk is usually based on abnormal ultrasound findings. FISH may also be indicated in cases of late gestational age when a rapid result is required. *FISH should be followed by a complete karyotype analysis and no clinical action should be taken based solely upon FISH results.* FISH is best performed prior to 22 weeks gestation. After 22 weeks, considerable cellular debris is present and may lead to inconclusive results. **This test must be requested at the time the sample is received so that 3 – 5 mls of amniotic fluid can be separated for use with this test.**

Results are available 24 – 48 hours after receipt.

Newborn Screening

FISH can be performed on peripheral blood or cord blood from newborns at risk for trisomy 13, 18, 21 or abnormalities of sex chromosome number. Blood must be collected in a sodium heparin (green top) tube. Please call to advise when samples are being sent for this screening.

Results are obtainable within 24 hours of receipt.

Telomere Alteration Testing

This test will identify alterations in 7% to 10% of cases with moderate/severe mental retardation (MR) and cases with multiple congenital anomalies (MCA) with MR. The analysis involves the detection of deletions or duplications or cryptic translocations using subtelomere FISH probes for each chromosome.

Samples should be collected as for high resolution chromosomes in sodium heparin tubes. Please make sure to clearly indicate telomere analysis. If chromosome analysis has not been done previously by GGC, please call the laboratory before requesting.

Results are currently taking 3 to 4 weeks, as the test is very labor intensive.

Cytogenetic Analysis Of Leukemia

Cytogenetic analysis in malignant disease involves the study of the dividing tumor cells. In leukemia, a bone marrow aspirate is usually obtained for study. Alternatively, in patients with a high white blood cell count (>10,000) a sample of peripheral blood may be cultured without addition of mitogen (i.e., unstimulated cultures). Mitogens stimulate the division of normal lymphoid cells and may interfere with the study of spontaneously dividing malignant cells. It is very important that the laboratory be informed that the peripheral blood sample is for a leukemic study so that the cells will be established in unstimulated cultures. When a consistent chromosome abnormality is detected in unstimulated peripheral blood, it may be necessary to study cells from stimulated blood to verify that the chromosome abnormality reflects the tumor cell population rather than the constitutional karyotype. Whenever a blood sample is received for an unstimulated analysis, a stimulated culture is also prepared in the event that it is necessary to determine the constitutional karyotype.

In addition to routine chromosome analysis on bone marrow and unstimulated blood, fluorescence in situ hybridization studies are also available.

The study of chromosome abnormalities in leukemia serves two functions: first, to assist in a more accurate diagnosis and second, to provide prognostic information. In leukemia, specific chromosome abnormalities often correlate with particular subtypes of disease. Serial samples from the patient permits the study of cytogenetic patterns during the various stages of a patient's clinical course.

Clinical information provided with the patient sample can aid the cytogenetics laboratory in selecting the appropriate culture method and can alert them to the potential presence of specific abnormalities. Information that should be included with a bone marrow or unstimulated blood specimen include patient name, age, sex, referring diagnosis, clinical status (diagnosis, residual disease, remission, relapse, exposure history), presenting CBC, percent circulating immature cells, bone marrow cellularity, and percent blasts.

Bone Marrow

Specimen requirements: 1 to 5 ml of bone marrow should be aspirated in a sterile syringe coated with 0.1 ml of sodium heparin. The specimen can be transferred to a sterile tube for transport. Alternatively, the needle can be removed from the syringe, the syringe capped, and the specimen transported in the original syringe. Patient information including WBC count and suspected diagnosis should accompany the specimen.

Transport: Specimen should be kept at room temperature; *do not freeze or refrigerate*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 20 cells are counted and analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are called to the referring physician's office in about 3 to 5 days. Final reports are mailed to the physician's office.

CPT codes: 88237, 88264, 88291, and possibly 88280

Unstimulated Leukemic Blood

Specimen requirements: 5 to 10 ml of peripheral blood in a sodium heparin Vacutainer™ tube. Patient information including WBC count should accompany the specimen.

Transport: Specimen should be kept at room temperature; *do not freeze or refrigerate*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 20 cells are counted and analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are called to the referring physician's office in about 3 to 5 days. Final reports are mailed to the physician's office.

CPT codes: 88237, 88264, 88291, and possibly 88280

Cytogenetic Analysis Of Solid Tissue

Although peripheral blood is the most easily obtainable tissue for chromosome analysis, it is sometimes necessary to study solid tissue. Indications for obtaining chromosome analysis on solid tissue include the following:

- suspicion of chromosome mosaicism - mosaicism may be suspected based on previous blood chromosomes or due to phenotypic features.
- blood is not available on the patient, but solid tissue is available - this may be the case when studying products of conception and abortus tissue, or when solid tissue is obtained from surgical or post-mortem procedures.

Skin Biopsy

Specimen requirements: Using sterile technique, obtain a 5 mm biopsy of tissue and place in a sterile tube containing transport media. If tissue culture media is not available, sterile solutions such as balanced salt solution may be used. *Do not allow the specimen to come into contact with formalin or other fixatives as fixed tissue will not grow.*

Transport: Specimen should be kept at room temperature. If specimen is not being immediately transported to the laboratory, it may be refrigerated; *do not freeze*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 15 cells are counted and 5 cells are analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are available in about 10 to 20 days. The final report is mailed to the referring physician's office.

CPT codes: 88233, 88262, 88291

Products of Conception

Specimen requirements: Products of conception should be placed in a sterile container for transport. The specimen must be kept moist - there is usually sufficient fluid present to ensure moisture. However, if it is necessary to add a sterile solution; add tissue culture media or sterile saline, by aseptic technique. *Do not allow the specimen to come into contact with formalin or other fixatives as fixed tissue will not grow.*

Transport: Specimen should be kept at room temperature if it will be transported immediately. If specimen is not being immediately transported to the laboratory, it may be refrigerated; *do not freeze*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 15 cells are counted and 5 cells are analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Reports: Results are available in 10 to 20 days. A report will be mailed. Results may also be faxed, upon request.

CPT Codes: 88233, 88262, 88291

Abortus tissue

Specimen requirements: Using sterile technique, obtain a 5 mm biopsy of unmacerated fetal tissue and place in tube containing transport media. If tissue culture media is not available, sterile solutions such as balanced salt solution may be used. If fetus is macerated, fetal tissue may not grow in culture; however, placental tissue will often be viable beyond the time that fetal tissue can be successfully cultured. The preferred placental tissues are fetal membranes or chorionic villi. If fetal samples are obtained at autopsy, lung, gonad, or thymus are preferred for chromosome study. *Do not allow the specimen to come into contact with formalin or other fixatives as fixed tissue will not grow.*

Transport: Specimen should be kept at room temperature if it will be transported immediately. If specimen is not being immediately transported to the laboratory, it may be refrigerated; *do not freeze*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 15 cells are counted and 5 cells are analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are available in about 10 to 20 days. The final report is mailed to the referring physician's office.

CPT Codes: 88233, 88262, 88291

Prenatal Chromosome Analysis

Prenatal chromosome analysis is indicated in the following cases:

- Couples at increased risk of having infants with abnormal chromosomes
- advanced maternal age - 35 years or older
- previous child with a chromosome disorder such as Down syndrome
- one member of the couple is known to carry a chromosome rearrangement
- in certain cases, relatives of a child with a chromosome disorder
- multiple (two or more) spontaneous abortions
- Couples at risk for having children with X-linked disorders for which molecular testing may not be available.
- Pregnancies at increased risk of chromosome defects due to finding of fetal defects on ultrasound.
- Pregnancies identified by prenatal serum screening to be at increased risk for neural tube defects or chromosome defects.

Amniotic Fluid for Prenatal Chromosome Analysis

Specimen requirements: 20 to 30 ml amniotic fluid collected in 2 to 3 sterile tubes. The first few mls of fluid should be discarded as they increase the likelihood of maternal cell contamination. The following information should accompany the specimen: patient's name, physician's name, date collected, EGA by ultrasound, LMP (if available), maternal age, and indication for study. *Sterile tubes and mailers are available from the Greenwood Genetic Center.*

Transport: Specimen should be kept at room temperature; *do not freeze or refrigerate.* Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: A minimum of 15 cells representing at least 10 distinct colonies are counted and 5 cells are analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are called to the referring physician in 7 to 10 days. The final report is faxed and mailed to the physician's office. Patient consultation is available.

CPT Codes: 88235, 88269, 88280, 88291

Chorionic Villus Sampling for Prenatal Chromosome Analysis

Chorionic villus sampling is a method for first trimester prenatal diagnosis of chromosome disorders. Chromosome analysis is performed on a villus biopsy by harvest following a short-term culture. CVS is performed earlier in pregnancy than amniocentesis. However, in about 3% of cases, an ambiguous result may be obtained from CVS, which necessitates follow-up amniocentesis for confirmation or clarification. While CVS has the advantage of providing an earlier result to the mother, the CVS procedure does not permit analysis of alpha-fetoprotein. Therefore, if the indication for study is increased risk of a neural tube defect, the amniocentesis rather than CVS would be recommended.

Specimen requirements: 5-10 mg of chorionic villi obtained in 10 ml of transport media. The following information should accompany the specimen: patient's name, physician's name, date collected, EGA by ultrasound, LMP (if available), maternal age, and indication for study. *Sterile tubes, transport media, and mailers are available from the Greenwood Genetic Center.*

Transport: Specimen should be kept at room temperature; *do not freeze or refrigerate*. Specimen should be sent by courier or overnight mail to arrive at the laboratory within 24 hours.

Analysis: At least 15 cells representing at least 10 distinct colonies are counted and 5 cells are completely analyzed from G-banded preparations. Hard copies of two karyotypes and 3 chromosome spreads are retained for documentation.

Report: Results are called to the referring physician in 7 to 10 days. The final report is faxed and mailed to the physician's office. Patient consultation is available.

CPT Codes: 88235, 88267, 88280, 88285, 88291

Metabolic Disorders/ Biochemical Assays

In general, infants and children with metabolic disturbances do not have birth defects or dysmorphic features common in other genetic conditions such as chromosomal abnormalities. There are disorders, however, which have dysmorphic features and have a metabolic cause, i.e. Smith-Lemli-Opitz syndrome and Zellweger syndrome; therefore, dysmorphic features should not necessarily rule out a metabolic disorder. Clues to the presence of a metabolic defect may be largely limited to abnormalities of growth, development, or organ function. Inborn errors of metabolism (metabolic disorders) should be suspected and metabolic studies are warranted in patients with the following clinical symptoms:

- Failure to grow, poor feeding, vomiting, diarrhea
- Lethargy or coma, hypotonia, respiratory distress
- Hepatomegaly, abnormal odor, abnormal eye findings
- Hypoglycemia, metabolic acidosis, ketosis, hyperammonemia

Metabolic tests usually require blood, urine or biopsy specimens.

The following analyses are performed at the Greenwood Genetic Center and are the most often requested. Please contact the Center for assays not listed or questions regarding specific biochemical or metabolic disorders.

- Urine Metabolic Screen
- Amino Acids
- Organic Acids
- Lysosomal Enzymes
- Sugars
- Mucopolysaccharides (Glycosaminoglycans)
- Oligosaccharides
- Sialic Acid
- Orotic Acid
- CDG (Congenital Disorders of Glycosylation)

Urine Metabolic Screen

A metabolic screen is a battery of simple tests that is performed on urine specimens to detect the possibility of a metabolic disorder. These tests are not specific and are used only as screening tests. The metabolic screen includes the following:

- Benedict's Test (reducing sugars)
- Dinitrophenylhydrazine test (keto acids)
- Toluidine blue spot test (mucopolysaccharides)
- Nitroprusside test (cystine, homocystine)
- Nitrosonaphthol test (tyrosine metabolites)
- Ferric chloride test (phenylalanine and histidine metabolites)

Specimen required: Urine (at least 10 ml)

Transport: Frozen on dry ice by 24-hour delivery. The sample may be transported at ambient temperature if it is delivered to the lab on the same day it is collected.

Standard of Analysis: Six screening tests are employed: ferric chloride, nitrosonaphthol, nitroprusside, Benedict's test, dinitrophenylhydrazine test, and toluidine blue spot test. These are screening tests and do not necessarily confirm or exclude a particular diagnosis. Results are compared to negative and positive controls run concurrently.

Time required: Analysis is usually completed the day after receiving specimen.

Reports: Written reports with interpretation are mailed to the referring physician, and when an abnormality is detected, the report will also be telephoned to the referring physician.

Special requests: Other tests for metabolic disorders are available, and may be appropriate following the screening test. Special requests or questions should be directed to the laboratory.

CPT Code: 84999

Amino Acids

Amino acids are components of all of the body's proteins, both enzymatic and nonenzymatic. An abnormality in the metabolism of amino acids may lead to mental retardation or other problems. In some of the amino acid disorders, treatment may prevent mental retardation or other handicaps.

Amino acid analysis is usually performed on plasma (serum) or urine. In certain circumstances, it may be performed on cerebrospinal fluid or other tissues.

Disturbances of amino acid metabolism may be suspected in infants or children who have:

- feeding abnormalities
- growth failure
- development failure
- seizures
- unexplained acidosis (uncommon)
- elevated blood ammonia.

Specimen requirements: Amino acid analysis may be performed on any fluid in the body (urine, plasma or serum, spinal fluid, amniotic fluid). For metabolic studies, urine (at least 10 ml of a random catch; 24-hour collection preferred) and plasma (at least 1 ml) are usually analyzed. Plasma is the preferred tissue for amino acid quantitation. Because urine amino acid values are based on creatinine concentration and the concentration of urine varies greatly, values can be falsely elevated or lowered. Unless there is the suspicion of a transport defect, i.e. cystinuria, *plasma is the preferred specimen.*

Transport: Samples (plasma, serum, or urine) must be frozen, preferably on dry ice. Samples must be received within 24 hours by overnight delivery services or courier. *Do not freeze whole blood.*

Standard of analysis: Quantitative analysis will be done by ion-exchange high performance liquid chromatography (Beckman 6300 system).

Time required: Analysis is usually complete within three days.

Special requests: Any type of special request, including STAT assays, must be made directly with the laboratory at the time the specimen is submitted.

Report: Written reports will be mailed, and when abnormalities exist, a report will be given by telephone. Elevations of any amino acid level will be noted and compared to normal levels with interpretation. Reports may be sent by FAX or email if requested.

CPT Code: 82139

Organic Acids

Organic acids are involved in many of the cells' metabolic processes. With certain genetic disorders, there may be abnormal concentrations of organic acids that are present in blood or other body fluids. Organic acid analysis is usually carried out on urine since many of the abnormal compounds will not be observed in other tissues. However, analysis may be carried out on other fluids such as plasma or serum, amniotic fluid, or cerebrospinal fluid.

Disturbances of organic acid metabolism may be suspected in infants or children who have:

- feeding abnormalities
- unexplained acidosis
- failure to grow
- failure to develop
- seizures
- unusual body odor
- hypotonia
- hyperammonemia

Specimen requirements: Urine (at least 10 ml of random catch) is usually used for organic acid analysis.

Transport: Samples must be frozen, preferably on dry ice. Samples must be sent frozen by overnight delivery services or courier. If the sample can be delivered the same day, it may be sent cold or at room temperature.

Standard of analysis: Analysis will be done by gas-liquid chromatography/mass spectroscopy (GC/MS) with identification of elevated and/or abnormal organic acids. For some organic acids quantitation is offered.

Time required: Analysis will usually be complete within three days.

Special requests: Any type of special request must be made directly with the laboratory at the time the specimen is submitted.

Report: Written reports with interpretation will be mailed, and when abnormalities exist, the report will be made by telephone. Results may be sent by FAX or by email when requested.

CPT Code: 83919

Lysosomal Enzymes

Lysosomal enzymes are those enzymes (acid hydrolases) which are responsible for breaking down complex chemicals within a cell which have expended their useful life. The breakdown products are then eliminated from the cell or reused. A deficiency of any one of these enzymes will lead to a "storage disease" which is usually associated with developmental regression. Examples of such diseases include the mucopolysaccharidoses, Tay-Sachs disease, and metachromatic leukodystrophy.

These tests may be done on special preparations of white blood cells, or from cells cultured from skin or other biopsy material including amniotic fluid and chorionic villi. Since several different storage diseases may have similar clinical features, it may be necessary to measure a number of different enzyme activities prior to finding the one deficient in the particular patient. Lysosomal storage disease should be suspected in infants or children who:

- fail to grow
- regress in development
- have clouding of the corneas or lenses
- have hepato- and/or splenomegaly
- have coarsening of facial features
- have certain abnormalities of the skeletal system

Specimen requirements: Lysosomal enzymes may be measured in cultured skin fibroblasts, cultured amniocytes, cultured chorionic villi, leukocytes, plasma, serum, and most solid tissues. Not all enzymes can be measured in every tissue, however; therefore, the lab should be contacted for guidance if needed.

Transport: Please contact the laboratory before transporting tissue for enzyme assay. The laboratory will separate leukocytes for assay if a blood sample is sent. Send a green top tube (7-10 ml) by courier or 24 hour delivery - *not frozen*. Insure that the specimen will not freeze or get above room temperature during shipment. Fresh tissue for culture (skin biopsy, chorionic villi, or amniotic fluid) should be sent by courier or 24-hour delivery.

Standard of analysis: Assays for lysosomal enzymes will usually employ the appropriate paranitrophenyl- or 4-methylumbelliferyl-substrate and will be quantitated per mg protein (tissue) or per ml (serum, plasma).

Time required: Most assays will be complete in one week. Assays of cultured cells will usually take 3-4 weeks.

Special requests: Any type of special request must be made directly with the laboratory.

Report: The report will contain specific activities of enzymes assayed, comparison to control values, and interpretation. Abnormal results will be called by telephone. Results may be sent by FAX or email if requested.

CPT Code: 84999

Sugars

Sugars or combinations of sugar subunits (disaccharides, glycogen, carbohydrates) are involved in many metabolic processes in the body. Any abnormality in the genes that control carbohydrate metabolism may lead to disturbances in growth and mental function.

Sugar analyses are usually performed on urine.

Dysfunction of carbohydrate or sugar metabolism should be considered in patients with:

- cataracts
- hepatosplenomegaly
- jaundice
- feeding difficulties
- growth failure
- unexplained acidosis, developmental failure, seizures (less common)

Specimen requirements: At least 10 ml of a random catch sample of urine is needed for sugar analysis. The laboratory should be contacted for assays involving other specimens or involving galactosemia or glycogen storage diseases.

Transport: Urine samples must be frozen, preferably on dry ice. Samples must be sent frozen by overnight delivery services or courier.

Standard of analysis: Qualitative analysis of sugars will be made by thin-layer chromatography with positive and negative controls run concurrently.

Time required: Sugar analysis will usually be completed within one week.

Special requests: Any type of special request must be made directly with the laboratory at the time the specimen is submitted.

Report: A written report will be sent, and when abnormalities exist, a report will be made by telephone. Results may be sent by FAX or email when requested.

CPT Code: 82489

Congenital Disorders of Glycosylation

(Transferrin isoforms analysis)

Congenital disorders of glycosylation, (CDG), also known as carbohydrate deficient glycoprotein syndromes, are a collection of disorders in which many glycoproteins are deficient or have reduced carbohydrate side chains. Many subtypes of congenital disorders of glycosylation have been described based on the isoelectric focusing patterns of transferrin and on clinical features. Enzyme deficiencies have been reported in at least four of the subtypes: Type Ia, phosphomannomutase; Type Ib, phosphomannose isomerase; Type Ic, glucosyltransferase; Type II, glucosamine-transferase; Type IV, mannosyltransferase. Sialic acid is the terminal sugar residue of the two carbohydrate side chains of transferrin. Any block in the synthesis of these side chains will result in an undersialylated transferrin molecule. Because it is a major serum protein and is easily detectable, transferrin is utilized as a marker in screening for congenital disorders of glycosylation. Although many congenital disorders of glycosylation are yet to be described, CDG may be suspected in patients with one or more of the following:

- Failure to thrive
- Hyptonia
- Inverted nipples
- Unusual fat deposits
- Mental and psychomotor retardation
- Stroke-like episodes
- Protein losing enteropathy
- Hypoglycemia
- Generalized dysmyelinization
- Optic atrophy

Specimen requirements: Transferrin analysis for carbohydrate deficient glycoprotein syndromes is performed on serum. Obtain 1 ml serum from a red top blood collection tube.

Transport: Serum must be frozen and sent on dry ice.

Standard of analysis: Qualitative analysis of transferrin isoforms will be done by capillary electrophoresis.

Time required: Analysis will be complete within one week.

Report: Written reports will be mailed, and when abnormalities exist, a report will be given by telephone. If an abnormal isoform is detected, the percentage of isoforms in relation to tetrasialotransferrin will be reported. Reports may be sent by FAX or email if requested.

CPT Code: 82373

Mucopolysaccharides

(Glycosaminoglycans)

The mucopolysaccharidoses are a group of inherited lysosomal storage disorders of connective tissue each with distinctive phenotypes and a progressive course due to severe deficiency of an enzyme that usually catalyzes a step in the degradation of glycosaminoglycans. In general, excessive quantities of glycosaminoglycans are excreted in urine which can be analyzed. Specific enzyme analyses must be run for a definitive diagnosis.

Mucopolysaccharide analysis is usually performed on urine.

A mucopolysaccharide storage disorder should be considered in patients with:

- coarse facies
- hepatosplenomegaly
- developmental regression
- corneal clouding
- stiff joints
- dysostosis multiplex

Specimen requirements: At least 10 ml of a random catch sample of urine is needed for mucopolysaccharides analysis.

Transport: Urine samples must be frozen, preferably on dry ice. Samples must be sent frozen by overnight delivery services or courier.

Standard of analysis: Qualitative analysis of mucopolysaccharides will be made by electrophoresis with positive and negative controls run concurrently.

Time required: Mucopolysaccharide analysis will usually be completed within one week.

Special requests: Any type of special request must be made directly with the laboratory at the time the specimen is submitted.

Report: A written report will be sent, and when abnormalities exist, a report will be made by telephone. Results may be sent by FAX or email when requested.

CPT Code: 84999

Oligosaccharides

Oligosaccharides analysis is a qualitative screening test to detect various storage diseases of lysosomal origin. The test is performed on urine and is useful in ruling out a number of "storage diseases". More specific enzyme analysis must be carried out (see the section on lysosomal enzyme analysis) when a positive screening test is found.

Specimen requirements: Urine (at least 10 ml).

Transport: Urine should be sent frozen on dry ice by courier or 24 hour delivery. Specimens may be brought by courier at ambient temperature if it can be delivered on the day of collection.

Standard of Analysis: Oligosaccharides are analyzed by thin layer chromatography in conjunction with appropriate controls.

Time Required: Analysis is usually completed within one week.

Reports: The report will indicate if the chromatogram is normal or abnormal, and if abnormal, will suggest additional studies. Abnormal reports will be given by telephone as well. Results may be sent by FAX or by email if requested.

CPT Code: 82489

Sialic Acid

Sialic acid is one of the small chemicals which is a component of a number of more complex chemical structures in the human body. A disturbance in a gene responsible for sialic acid metabolism may lead to an abnormality reflected in sialic acid concentration in blood, urine and solid tissue. The abnormalities of sialic acid metabolism will almost always lead to both physical and mental deterioration.

Sialic acid can be analyzed in cells cultured from solid tissue such as skin, or can be measured in blood or urine.

Abnormalities of sialic acid metabolism may be suspected in infants who:

- fail to grow
- regress in development
- have hepatosplenomegaly
- have coarsening of facial features
- have failure of pigmentation of hair and skin

Specimen requirements: To rule out a sialic acid storage disorder, urine (at least 10 ml) is the usual specimen. However, sialic acid may be measured in other specimens (serum, cultured cells, tissue samples).

Transport: Urine should be sent frozen on dry ice by courier or 24 hour delivery service. Tissue specimens or cultured cells should be sent at ambient temperature by courier or overnight delivery.

Standard of Analysis: Total and free sialic acid is measured by the barbituric acid method and results are compared with controls run concurrently.

Time Required: Assays will be completed in one week.

Report: A report will include the total and free sialic acid calculated in nanomoles sialic acid per mg creatinine (for urine) and compared to control values with interpretation. Results may be sent by FAX or email when requested.

CPT Code: 84275

Orotic Acid

Orotic acid is a chemical overproduced in an alternative pathway when there is a block in the urea cycle. Excessive amounts of orotic acid are usually found in OTC (ornithine transcarbamylase) deficiency, citrullinemia, and oftentimes in argininosuccinic aciduria. Orotic acid determination is useful in delineating the cause of hyperammonemia.

Specimen requirements: For orotic acid analysis, at least 10 ml urine is needed.

Transport: Urine should be sent frozen on dry ice by courier or 24 hour delivery service.

Standard of Analysis: Orotic acid is measured by capillary electrophoresis, and results are compared with controls run concurrently.

Time Required: Assays will be completed in one week.

Report: A report will include the level of orotic acid in micromol per mmol creatinine and compared to control values with interpretation. Results may be sent by FAX or email when requested.

CPT Code: 84999

Additional Tests

The following are a group of individual chemical tests that may be performed when looking for a specific metabolic abnormality. These tests can be done on urine or blood or on extracts from cultured cells. These chemical tests, among others, include:

- phenylalanine analysis
- tyrosine analysis
- other individual amino acid analysis
- orotic acid quantitation
- aspartylglucosamine

The laboratory staff will assist you with requests for other metabolic tests which have not been outlined in the preceding sections. Please call the laboratory (see front cover) to discuss your special needs. In some cases, we can arrange for certain tests through other laboratories.

Molecular Diagnostic Services

Molecular analysis of gene mutations is the standard practice for diagnosis of many genetic disorders. In contrast to molecular genetic studies of the past, which could only detect mutations indirectly via linkage, specific alterations at the DNA level are now discernible. Mutations in disease genes are detectable using a variety of molecular diagnostic techniques. The identification of a specific mutation in a proband allows rapid and accurate testing of other family members for the same mutation. This information plays a crucial role in genetic counseling and determination of recurrence risk. With the current growth of genetic knowledge from the Human Genome Project, molecular diagnosis of additional disorders will become possible in the near future.

The Molecular Diagnostic Laboratory at the Greenwood Genetic Center currently performs testing for the following genetic disorders:

- Aarskog Syndrome
- Achondroplasia
- Alpha-thalassemia X-Linked Mental Retardation (ATR-X)
- Angelman: Methylation analysis; UBE3A sequencing; Uniparental Disomy studies
- Apert syndrome
- ARX-Related Spectrum of X-Linked Mental Retardation
- Beare-Stevenson with cutis gyrate
- Coffin-Lowry Syndrome
- Congenital Disorders of Glycosylation type 1a (PMM2)
- Connexin-26
- Craniosynostosis – non-syndromic
- Crouzon syndrome
- Cystic Fibrosis
- Duchenne and Becker muscular dystrophy
- Dykeratosis Congenita
- Edrodactyly-Ectodermal Dysplasia-Clefting Syndrome, Hay-Wells Syndrome and Isolated Split-Hand/Foot Malformation
- Fibroblast Growth Factor Receptor gene (FGFR) –associated syndromes
- Fragile X syndrome
- FRAXE syndrome
- Hemochromatosis
- Hunter syndrome
- Hypochondroplasia
- Jackson-Weiss syndrome
- Myotonic dystrophy
- Medium chain acyl-CoA dehydrogenase (MCAD)
- Noonan (PTPN11)
- Prader-Willi: Methylation analysis; Uniparental Disomy studies
- Rett syndrome
- Rett Syndrome Deletion/Duplication
- Russell-Silver syndrome
- Saethre-Chotzen syndrome (TWIST gene mutation analysis)
- Sanfilippo A
- Smith-Lemli-Opitz
- Sotos Syndrome (NSD1)
- Thanatophoric dysplasia types I and II
- Thrombosis panel
 - Factor V Leiden
 - Prothrombin 20210A mutation
 - MTHFR
- Uniparental Disomy Studies: Chromosomes 7 (Russell-Silver), 14, 15 (Prader-Willi/Angelman)
- X-inactivation
- X-Linked Hydrcephalus (L1CAM)

Analysis in the Molecular Diagnostic Laboratory is typically performed on nucleic acids isolated from peripheral blood, buccal swabs, cultured amniocytes, or cultured chorionic villi samples. Culturing services for prenatal samples are also available. Please contact the Molecular Diagnostics Laboratory for details.

Aarskog Syndrome

Aarskog syndrome is due to mutations in the FGD1 gene, a Rho/Rac guanine exchange factor localized to Xp11.21. Males present with short stature, hypertelorism, shawl scrotum and joint hyperextensibility. Carrier females tend to be shorter than non-carriers and usually have subtle facial features. Males can have mild cognitive impairment.

Sample requirements: FGD1 testing offered in this laboratory uses DNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband (male):

CPT codes: 83890, 83894 (x7), 83898 (x10), 83904 (x7), 83912,

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

ARX-Related Spectrum of X-Linked Mental Retardation

Mutations in the ARX gene cause nonsyndromic XLMR as well as West, Partington and Proud syndromes and X-linked hydrocephalus with ambiguous genitalia (XLAG). The gene is localized to Xp21.1. Two mutations, a 24bp duplication and a 21bp insertion, in exon 2 of ARX account for a significant proportion of the alterations within the gene. Carrier females have no phenotype.

Sample requirements: ARX testing offered in this laboratory uses DNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband (male):

CPT codes: 83890, 83894 (x7), 83898 (x10), 83904 (x7), 83912

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912

Alpha-thalassemia X-linked Mental Retardation (ATR-X)

Alpha-thalassemia X-linked mental retardation (ATR-X) is an XLMR condition caused by mutations in the ATRX/XNP gene localized to Xq13. Males usually present with moderate mental retardation and characteristic hypotonic facies, consisting of small head size, depressed nasal bridge, large open mouth, large prominent lips and an inverted upper lip. Carrier females exhibit no features, a result of highly skewed X-inactivation. Males can sometimes exhibit hemoglobin H inclusion bodies but this clinical test is unreliable for diagnosis purposes.

Sample requirements: ATRX testing offered in this laboratory uses RNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in a Qiagen PAXgene Blood RNA tube. The PAXgene tube contains approximately 7 milliliters of RNA-stabilizing solution. During collection, the tube is designed to stop filling beyond the 2-3 milliliters of blood required for analysis. As these specialized tubes are not normally available in most clinical settings, please contact the Molecular Diagnostic Laboratory to request a PAXgene Blood RNA tube with enclosed instructions for drawing. **(Please note: for optimal results, the specimen must be collected directly into the PAXgene tube. Blood should not be transferred from other Vacutainer tubes into a PAXgene tube.) Another three to five milliliters of whole blood should also be collected in an EDTA Vacutainer (lavender top).**

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband (male):

CPT codes: 83890, 83894 (x7), 83898 (x10), 83904 (x7), 83912,

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (X2), 83904, 83912,

Coffin-Lowry Syndrome

Coffin-Lowry syndrome is an X-linked mental retardation condition caused by mutations in the protein kinase gene, RSK2, localized to Xp22. Males present with moderate to severe developmental delay, coarse facies, large soft hands with short tapering fingers, hypotonia, joint hyperextensibility and skeletal changes. Carrier females have mild mental impairment and short stature, coarse face, prominent lips, soft fleshy hands with thick tapering fingers. Decreased levels of RSK2 activity can be observed in white cells but usually only after establishing a cell line.

Sample requirements: RSK2 testing offered in this laboratory uses RNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in a Qiagen PAXgene Blood RNA tube. The PAXgene tube contains approximately 7 milliliters of RNA-stabilizing solution. During collection, the tube is designed to stop filling beyond the 2-3 milliliters of blood required for analysis. As these specialized tubes are not normally available in most clinical settings, please contact the Molecular Diagnostic Laboratory to request a PAXgene Blood RNA tube with enclosed instructions for drawing. (**Please note: for optimal results, the specimen must be collected directly into the PAXgene tube. Blood should not be transferred from other Vacutainer tubes into a PAXgene tube.**) Another three to five milliliters of whole blood should also be collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband (male):

CPT codes: 83890, 83894 (x7), 83898 (x10), 83904 (x7), 83912,

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

Congenital Disorders of Glycosylation type 1A

Congenital disorders of glycosylation (CDG) type 1a is an autosomal recessive disorder caused by a deficiency of phosphomannomutase. This enzyme normally catalyzes the conversion of mannose-6-phosphate to mannose-1-phosphate. This step is required for the addition of N-linked sugars to proteins.

Mutational analysis of the phosphomannomutase gene (PMM2) detects over 95% of the causative mutations in CDG1a patients. Identification of the causative mutation/s in the proband can facilitate carrier detection in interested family members.

Prenatal analysis can be performed provided the mutations in the family are known. CVS samples will not be accepted.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavendar top) Vacutainer tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 30 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes (unknown mutation): 83890, 83898 (x8), 83904 (x10), 83912
(known mutation): 83890, 83898 (x2), 83904, 83912

Connexin-26

The frequency of childhood deafness is estimated to be 1/500. Half of this hearing loss is genetic and approximately 80% of genetic hearing loss is nonsyndromic and inherited in an autosomal recessive manner. Approximately 50% of childhood nonsyndromic recessive hearing loss is caused by mutations in the connexin 26 (Cx26) gene (GJB2/DFNB1), making it the most common form of autosomal recessive nonsyndromic hearing loss with a carrier rate estimated to be as high as 1 in 36 (2.8%). One mutation, 35delG, accounts for about 75-80% of mutations in this gene.

Complete DNA sequencing of the Cx26 gene is also available at the Greenwood Genetic Center. Sequencing is recommended in all individuals found to be heterozygous for the 35delG mutation and may also be requested on samples found to be normal for the 35delG mutation.

Newborns with confirmed hearing loss should have Cx26 testing. Cx26 testing will help define a group in which approximately 60% will have profound or severe-profound hearing loss requiring aggressive language intervention.

Specimen requirements: 5ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 10 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83898, 83904, 83912

CPT Codes (complete sequence): 83898, 83904 (x2), 83912

Creatine transporter deficiency

Creatine transporter deficiency is due to mutations in the creatine transporter gene (SLC6A8; CTR1) localized to Xq28. Males can present with speech and developmental delay, seizures and hypotonia. Carrier females can have a mild mental impairment and problems with social skills. Males show a significant elevation in urinary creatine excretion and may have a mild elevation of plasma creatine. Creatine uptake studies or molecular analyses are recommended to confirm positive biochemical findings.

Sample requirements: SLC6A8 testing offered in this laboratory uses RNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in a Qiagen PAXgene Blood RNA tube. The PAXgene tube contains approximately 7 milliliters of RNA-stabilizing solution. During collection, the tube is designed to stop filling beyond the 2-3 milliliters of blood required for analysis. As these specialized tubes are not normally available in most clinical settings, please contact the Molecular Diagnostic Laboratory to request a PAXgene Blood RNA tube with enclosed instructions for drawing. (**Please note: for optimal results, the specimen must be collected directly into the PAXgene tube. Blood should not be transferred from other Vacutainer tubes into a PAXgene tube.**) Another three to five milliliters of whole blood should also be collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband (male):

CPT codes: 83890, 83894(x7), 83898(x10), 83904 (x7), 83912

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912,

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912

Cystic Fibrosis

CF is a common autosomal recessive disorder that affects many functions of the body such as respiration, endocrine function, and reproduction. CF worsens with age and affects both males and females. Although great strides in treatment have increased the length and quality of life for CF patients, it is nearly always fatal by the fourth decade of life. Sweat chloride testing remains the gold standard for diagnosis of CF, however DNA analysis is indicated not only for CF patients but also for their extended families. In addition to providing information about the specific mutations that cause CF, molecular testing allows rapid detection of cystic fibrosis carriers and can determine if the patient has a pancreatic sufficient or insufficient type of the disease. This information plays a large role in clinical management of the affected individual. Over 800 mutations have been described in the CF gene. However, screening for the 33 most common mutations detects 80% of the mutant alleles in a population of European ancestry. The carrier rates of the disorder are 1/29 Caucasians, 1/65 African-Americans, 1/46 Hispanics, 1/90 Asians, and 1/29 in the Ashkenazi Jewish population. The results of a NIH Consensus Development Conference on Genetic Testing for Cystic Fibrosis were published in 1999. The expert panel of 14 members representing multiple medical specialties formally recommended DNA testing for CF for the following individuals:

- adults with a positive family history of cystic fibrosis
- partners of people with CF
- couples planning a pregnancy and couples presenting for prenatal care
- males with congenital bilateral absence of the vas deferens

DNA testing for cystic fibrosis at the Greenwood Genetic Center screens for the 33 most common mutations, to detect approximately 80% of mutations causing CF occurring in Caucasians of European descent. 97% of Ashkenazi Jewish CF mutations will be detected by this analysis.

Specimen Requirements: 5ml of peripheral blood in an EDTA (lavender top) Vacutainer™ tube. The minimal amount needed for reliable DNA isolation is 3ml. If necessary, ACD Solution A Vacutainer™ tubes (yellow top) may be substituted. **Prenatal testing is available from amniocytes and CVS material.**

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis Standards: Analysis will be completed within 5 days of sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and interpretation will be mailed and/or faxed following completion of the test. Reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs.

CPT Codes: 83890, 83894, 83898, 83912

Duchenne and Becker Muscular Dystrophy

Both Duchenne and the milder Becker muscular dystrophy are due to mutations in the dystrophin gene located on the X chromosome. The characteristic features of these disorders include pseudohypertrophy of the calf muscle, myofiber degeneration, myopathic EMG changes, and dramatic elevations of serum creatine kinase. Approximately two-thirds of disease causing mutations in the dystrophin gene are due to deletions and duplications. The majority of the remaining dystrophin defects result from point mutations within the gene. Testing for Duchenne and Becker muscular dystrophy at the Greenwood Genetic Center involves multiplex PCR analysis that can detect up to 98% of all deletions and duplications in muscular dystrophy patients and in females that carry the mutation. Linkage analysis is also available for families with unknown mutations in the dystrophin gene. Prenatal testing is available. Please contact the Molecular Diagnostics Laboratory for details.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 7 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be provided upon request.

CPT Codes: 83890, 83894 (x2), 83898 (x2), 83912

Dyskeratosis Congenita

Dyskeratosis congenita is a rare condition which causes bone marrow failure, nail dystrophy, and skin abnormalities, including telangiectases, skin atrophy and reticulated hyper/hypopigmentation. The X-linked form of the condition is associated with mutations in the DKC1 gene localized to Xq28. The majority of mutations are single-nucleotide substitutions, which result in missense mutations.

Sample requirements: DKC1 testing offered in this laboratory uses DNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be provided upon request.

Proband (male):

CPT codes: 83890, 83894(x7), 83898(x10), 83904(x7)

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912

Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome, Hay-Wells Syndrome and Isolated Split-Hand/foot Malformation

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome, Hay-Wells syndrome (also called ankyloblepharon-ectodermal dysplasia-clefting, or AEC, syndrome), and isolated split-hand/foot malformation (SHFM) are variable autosomal dominant disorders that can be caused by mutations in the gene P63 (TP63, TP73L) localized to 3q27. Persons with EEC syndrome have split-hand/foot malformation, ectodermal dysplasia (abnormal hair, teeth, skin, nails, and/or lacrimal ducts), and cleft lip/palate. Persons with AEC syndrome have ectodermal dysplasia, cleft lip/palate, and congenital adhesions between the eyelids. P63 mutations cause most cases of the EEC and AEC syndromes but only a small percentage of isolated SHFM cases.

Sample requirements: P63 (TP63, TP73L) testing offered in this laboratory uses DNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be provided upon request.

Exons 5-8, 13, 14 Proband:

CPT codes: 83890, 83894 (x4), 83898 (x7), 83912 (x4), 83904

Hay-Wells (exons 13, 14 only) Proband:

CPT codes: 83890, 83894, 83898 (x3), 83904, 83912

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83904, 83912

Fibroblast Growth Factor Receptor Genes (FGFR)

Mutations within Fibroblast Growth Factor Receptor (FGFR) genes have been associated with several common skeletal dysplasias and a number of craniosynostosis syndromes. FGFR analysis depends on the clinical diagnosis as listed below. Consult with the laboratory director for more information regarding FGFR analysis.

Gene	Syndrome	CPT codes
FGFR1 & FGFR2	Pfeiffer syndrome	83890, 83898 (X2), 83904(X4), 83912
FGFR2	Apert syndrome Crouzon syndrome Jackson-Weiss syndrome Beare-Stevenson with cutis gyrata	83890, 83898 (X2), 83904 (X4), 83912
FGFR3	Thanatophoric dysplasia type I	83890, 83898 (X2), 83904 (X4), 83912
FGFR3 *****	Thanatophoric dysplasia types II Achondroplasia Hypochondroplasia Non-syndromic craniosynostosis (NSC)	83890, 83892, 83894, 83898, 83912

Note: ***** This group is not a panel. Each condition is ordered and billed separately. *****

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis Standards: Analysis will be complete within 5 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs.

CPT Codes: see list of disorders above

Fragile X Syndrome

Fragile X Syndrome is the most common form of inherited mental retardation. More than 99% of cases are due to the expansion of a polymorphic (CGG) repeat within the FMR1 gene. Approximately 1/1250 males and 1/2500 females are affected by the condition. Some population studies have shown the carrier frequency to be as high as 1/250 individuals. The American College of Medical Genetics policy statement on Fragile X testing recommends consideration of testing under the following circumstances:

- Individuals of either sex with mental retardation(MR), developmental delay, or autism
- Individuals with a family history of Fragile X syndrome or unexplained MR
- Prenatal testing of fetuses of known carrier mothers
- Patients with negative cytogenetic fragile X testing results who have clinical symptoms of Fragile X syndrome

Fragile X testing at the Greenwood Genetic Center involves two independent molecular approaches. Southern blotting and subsequent analysis allows the repeat segment size and methylation status of a sample to be determined. Polymerase chain reaction analysis is utilized to more accurately determine (CGG) repeat numbers in high normal and premutation ranges. Prenatal testing is available, please contact the Molecular Diagnostics Laboratory for details.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FEDEX delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83892 (x2), 83894, 83896 (x2), 83912

FRAXE Syndrome

Expansions of a polymorphic (CCG) repeat in the FMR2 gene have been associated with a phenotype of mild mental handicap and severe language delay. The FRAXE disorder has no distinct dysmorphology, making clinical diagnosis difficult. Females with FMR2 expansions are typically normal, suggesting that this disorder may follow an X-linked pattern of expression. The Greenwood Genetic Center is currently offering analysis for male patients only. Females with a confirmed family history may also be submitted for detecting carrier status.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83894, 83898, 83912

Hemochromatosis

Hemochromatosis is a common inherited disorder of iron metabolism seen in, but not limited to, people of European descent. The recessively inherited disorder has a carrier frequency of 1/8 individuals and affects 1/250. Premature death may be caused by complications of chronic liver disease, hepatocellular carcinoma, or heart failure if the disease goes untreated. Early detection and treatment with routine phlebotomy can prevent these severe complications. For this reason, testing for hemochromatosis is recommended in individuals with abnormal iron studies. Elevations in serum iron levels, transferrin saturation, and ferritin are often noted in patients with hemochromatosis.

The molecular diagnosis of hemochromatosis involves an assay to detect two mutations within the Hfe (HLA-H) gene. Both the C282Y and H63D mutations have been associated with the clinical diagnosis of hemochromatosis, but the C282Y genotype appears to be more penetrant. The polymerase chain reaction followed by restriction endonuclease digestion is utilized to detect these DNA alterations.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Buccal swabs for DNA isolation may be accepted in some cases. Please contact the laboratory for more information regarding this service.

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 7 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83894, 83898, 83912

Hunter Syndrome

Hunter syndrome is an X-linked lysosomal storage disorder caused by a deficiency of iduronate-2-sulfatase (IDS). Typically, the disorder is diagnosed by enzymatic assay, however, the determination of carrier status using enzyme assay has proved problematic. Sequencing of the IDS gene has been shown to detect 80-90% of causative mutations in Hunter syndrome patients. This information can be used to determine the carrier status for interested family members.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavendar top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Buccal swabs for DNA isolation may be accepted in some cases. Please contact the laboratory for more information regarding this service.

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes (unknown mutation): 83890, 83898(X8), 83904(X8), 83912

CPT Codes (known mutation): 83890, 83894, 83898, 83904 (x2), 83912

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common defect in mitochondrial β -oxidation in humans. It is estimated that in the Caucasian population 1 in 50 individuals is a carrier and 1 in 10,000 live births will be affected. The disease shows an autosomal recessive pattern of inheritance and is characterized by a wide spectrum of clinical features including developmental delay, behavioral problems, fasting intolerance, and vomiting. Patients demonstrate hypoglycemia and medium chain dicarboxylic aciduria. If untreated the disease can lead to coma and premature death.

Molecular analysis of MCAD gene has shown that one mutation, K304E, accounts for approximately 90% of the total mutant alleles among Caucasian individuals. The polymerase chain reaction followed by restriction endonuclease digestion is utilized to test for the presence of the K304E mutation.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 10-14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83898, 83912

Myotonic Dystrophy

Myotonic dystrophy is the most common form of adult onset muscular dystrophy and has an incidence of 1/8000 individuals. The genetic defect in the disorder is the expansion of a (CTG) trinucleotide repeat in the DM gene. This autosomal dominant disorder is characterized by myotonia, muscle wasting, frontal balding, hypogonadism, and ocular and ECG abnormalities. Genetic anticipation is commonly seen in families with myotonic dystrophy. In these families, extreme amplification can occur during mother to child transmission of the abnormal allele leading to a congenital form of the disease. Congenital myotonic dystrophy can be associated with a very severe disease state including generalized hypotonia and mental retardation. Molecular diagnosis of myotonic dystrophy at the Greenwood Genetic Center involves a combination of Southern blotting tests and direct PCR analysis to determine the (CTG) repeat number. Prenatal testing is available via material from amniocentesis.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83892 (x2), 83894, 83896(x2), 83912

Noonan Syndrome

Noonan Syndrome (NS) is an autosomal dominant condition characterized by short stature, webbing of the neck, pectus excavatum/ carinatum, cryptorchidism, characteristic facies, and cardiac defects including pulmonic stenosis and hypertrophic cardiomyopathy. It has recently been reported that approximately 50% of NS cases may be due to mutations in the PTPN11 gene that encodes the non-receptor protein tyrosine phosphatase SHP-2. We currently offer genomic sequencing for exons 2, 3, 4, 7, 8, 13. Testing these exons will identify greater than 95% of the mutations identified in PTPN 11 in patients with Noonan Syndrome. Sequential testing is available. Analysis of exons 3, 8, and 13 will detect approximately 80% of PTPN11 mutations. Sequencing exons 2, 4, and 7 will detect an additional 15 %.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 7 to 10 days from sample receipt. The laboratory director assesses the quality and interpretation of test results. Technical staff independently assesses the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: (Unknown Mutation Step 1: Exons 3, 8, 13) 83890, 83898 (x 3), 83904 (x 7), 83912

**(Unknown Mutation Step 2: Exons 2, 4, 7) 83898 (x 3), 83904 (x 4), 83912
(Known Mutation) 83890, 83894, 83898, 83904 (x2), 83912**

Prader-Willi/Angelman Methylation Studies

Prader-Willi (PWS) and Angelman (AS) syndromes are examples of disorders involving imprinted genes. Imprinted genes are only expressed from either the maternally or paternally derived member of a homologous chromosome pair. PWS results from the loss of genes that are expressed only from the paternally derived chromosome 15, either through a deletion on the paternally derived chromosome 15 or a maternal uniparental disomy for the chromosome 15 pair. AS results from the loss of genes that are expressed only from the maternally derived chromosome 15 via a deletion on the maternally derived chromosome 15 or a paternal uniparental disomy for the chromosome 15 pair. This differential gene expression is thought to be controlled by methylation of the DNA on the maternally versus the paternally derived chromosome 15. Southern blot analysis using methylation sensitive restriction enzymes illustrates whether the patient has both maternally derived and paternally derived material in the critical region of chromosome 15. The molecular diagnosis of Prader-Willi and Angelman syndromes is part of a comprehensive package of services recommended for referred individuals. High resolution cytogenetic analysis, FISH deletion analysis, UPD analysis, and/or UBE3A analysis for Angelman syndrome complete the recommended diagnostic work-up. All of these services are offered at the Greenwood Genetic Center. Prenatal testing is available via material from amniocentesis. Amniocentesis is recommended for methylation studies due to hypomethylation observed in CVS material.

Specimen requirements: 5 to 10 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing cultured CVS material or amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83892(x2), 83894, 83896(x2), 83912

Rett Syndrome

A neurodevelopmental disorder that affects females, Rett syndrome is associated with cortical atrophy, stereotypical hand movements and severe mental deficiency. With an incidence of 1 in 10,000 – 15,000, it is one of the most common causes of mental retardation in females. Rett syndrome is characterized by loss of acquired skills after a period of normal development in infancy. Mutations in X-linked methyl-CpG binding protein 2 (MECP2) which cause Rett syndrome include both nonsense, missense, and other frameshift mutations.

Genetic analysis for Rett Syndrome at the Greenwood Genetic Center includes complete sequencing of the entire coding region of the MECP2 gene.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 14 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes (unknown mutation): 83890, 83894(x3), 83898(x3), 83904 (x7), 83912

CPT Codes (known mutation): 83890, 83894, 83898, 83904 (x2), 83912

Rett Syndrome Deletion/Duplication Detection

Rett syndrome is a neurodevelopmental disorder that affects mostly females. The condition is associated with cortical atrophy, stereotypical hand movements and severe mental retardation. With an incidence of 1 in 10,000 - 15,000, it is one of the most common causes of mental retardation in females. Rett syndrome is characterized by loss of acquired skills after a period of normal development in infancy. Mutations in the X-linked methyl CpG binding protein 2 (MECP2) gene cause Rett syndrome and include nonsense, missense, and frameshift alterations.

Approximately 80% of individuals with a classic Rett syndrome phenotype will have a detectable mutation by sequencing the MECP2 gene. Further testing is available for individuals who test negative via sequencing but continue to carry a clinical diagnosis of Rett syndrome. Large MECP2 deletions and duplications that are not detectable by sequencing can be detected using multiplex ligation-dependant probe amplification (MLPA) analysis. Approximately 15% of females with Rett syndrome and a normal sequencing result will have an abnormal MLPA result for the MECP2 gene.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. If the sequencing analysis was performed at the Greenwood Genetic Center, an additional blood sample may not be needed. Please contact JoAnne Babb or Kristy Lee to determine whether an additional blood sample is necessary (1-800-473-9411).

Transport: The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available. Please contact JoAnne Babb or Kristy Lee for any additional questions or concerns regarding shipping requirements.

Analysis standards: Analysis will be completed within 14 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83892, 83894, 83896 (x2), 83898 (x2), 83912

Saethre-Chotzen Syndrome (TWIST Gene)

Saethre-Chotzen Syndrome is one of the most common autosomal dominant disorders of craniosynostosis, affecting approximately 1/2000 newborn infants. It is characterized by craniofacial and limb anomalies. Mutations in the TWIST gene, which maps to chromosome 7p21-p22 are found in a majority of individuals with Saethre-Chotzen Syndrome. Nonsense, missense, insertion, and deletion mutations of the TWIST gene have been found in studies of patients with Saethre-Chotzen syndrome.

Analysis of patients with Saethre-Chotzen Syndrome in the Greenwood Genetic Center laboratory includes complete sequencing of the entire coding region of the TWIST gene.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 14 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83898 (X2), 83904 (X4)

Sanfilippo Syndrome Type A

Sanfilippo syndrome type A (mucopolysaccharidosis IIIA) is an autosomal recessive lysosomal storage disease caused by a deficiency of heparin sulfamidase. This enzyme is required for the normal catabolism of heparan sulfate. The storage of partially heparan sulfate in the patient's cells is believed to result in the clinical phenotype.

Mutational analysis of the heparan sulfamidase gene (SGSH) detects between 80-90% of the causative mutations in enzymatically diagnosed patients. Identification of the causative mutation/s in the proband can facilitate carrier detection in interested family members.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube if preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer tubes™ (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 14 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes (unknown mutation): 83890, 83898(X6), 83904(X6), 83912

CPT Codes (known mutation): 83890, 83898, 83904, 83912

Smith-Lemli-Opitz

Smith-Lemli-Opitz (SLO) is an autosomal recessive disorder involving cholesterol metabolism. The disease results from a deficiency of 7-dehydrocholesterol reductase, the enzyme catalyzing the final step in cholesterol synthesis. SLO patients demonstrate low serum cholesterol and elevated 7-dehydrocholesterol.

Mutational analysis of the 7-dehydrocholesterol reductase gene (DHCR7) has shown that one mutation, IVS8-1G>C, is present in over 60% of SLO patients in the United States (Yu et al. 2000). Population studies have shown that this change is present in approximately 1% of the general population. The discordance between the frequency of the mutation and the prevalence of SLO has led some authors to suggest that homozygosity for IVS8-1G>C is incompatible with life.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavendar top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 5 – 7 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: 83898, 83912

CPT Codes (sequence):83898 (x6), 83904 (x6), 83912

Sotos Syndrome (NSD1)

Sotos syndrome is an autosomal dominant overgrowth condition due to mutations in the NSD1 gene, which has been localized to 5q35. Individuals present with a typical facial appearance, including a long narrow face and prominent narrow jaw, down-slanting palpebral fissures, frontal bossing, malar flushing and a sparsity of hair in the frontotemporal region. Developmental delay is also a common feature.

Sample requirements: NSD1 testing offered in this laboratory uses DNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband:

CPT codes: 83890, 83894 (x10), 83898 (x13), 83912, 83904 (x10)

Known mutation:

CPT codes: 83890, 83898 (x2), 83912, 83904

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83912, 83904

Thrombosis panel

Recent research has discovered two mutations within genes in the blood coagulation pathway that have been implicated as significant factors for thrombotic risk. These two defects, factor V Leiden and prothrombin 20210A, are responsible for over 60% of all cases of inherited thrombophilia. In addition to being significant risk factors for hypercoagulation, the mutations are frequently found in, but are not limited to, people of European descent. Population studies indicate that 2-7% of the Caucasian population carries the Leiden mutation and up to 3% carry the prothrombin mutation. Carriers of the Leiden R506Q mutation have an 8 fold increased risk for venous thrombosis and homozygotes have a 91 fold increased risk. Specific acquired or environmental factors may dramatically increase this baseline risk. Mutations in a third gene, MTHFR, or methylenetetrahydrofolate reductase, can also increase the risk of thrombosis and other vascular diseases as a result of elevated serum homocysteine. Two mutations of the MTHFR gene, designated "677C-T" and "1298A-C" are examined. About 35% of the population is heterozygous (carriers) for the 677C-T mutation. About 33% of the population carries the 1298A-C mutation. Although the 1298 mutation alone does not cause elevated homocysteine levels, it can when it coexists with the 677 mutation. If an individual has two copies of the 677 mutation (homozygote)[12% of the population], or has one copy of 677 and one copy of 1298 (compound heterozygote)[20% of the population], he/she will have significantly higher mean plasma homocysteine concentrations, and the associated higher risk of vascular disease. The molecular diagnosis of these mutations is done with the polymerase chain reaction and restriction endonuclease digestion or allele specific oligonucleotide amplification.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Please contact the laboratory for more information regarding this service.

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. Do not freeze the specimen. Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 7 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: panel: 83896, 83898, 83912
Factor V Leiden alone: 83898, 83912
Prothrombin 20210A alone: 83898, 83912
MTHFR C677T and A1298C alone: 83898, 83912

UBE3A

Angelman syndrome is characterized by severe motor and intellectual retardation, absence of speech, ataxia and a characteristic open-mouthed face. Other features such as hypotonia, epilepsy and excessive laughter help in the diagnosis of the condition. Mutations in the ubiquitin-protein ligase E3A gene (UBE3A) located on chromosome 15 are known to be associated with a subset of Angelman syndrome cases. UBE3A is specifically imprinted in the brain where it is only expressed from the maternal allele. In individuals that retain the clinical diagnosis of Angelman syndrome following normal methylation studies, UBE3A sequencing studies should be given strong consideration. In cases where UBE3A mutation studies identify an alteration, extended family studies may be pursued and prenatal testing offered.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Prenatal analysis can be performed provided the mutations in the family are known. CVS samples will not be accepted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 14 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: (unknown mutation) 83890, 83894(x5), 83898(x12), 83904(x5), 83912

(known mutation) 83890, 83894, 83898, 83904(x2), 83912

Uniparental Disomy Studies

- Chromosome 7 (Russell-Silver Syndrome)
- Chromosome 14
- Chromosome 15 (Prader-Willi / Angelman Syndrome)

Uniparental disomy describes the abnormal assortment of chromosomes from parent to child. Normally, one-half of the genetic material is derived from each parent. In uniparental disomy, the chromosome number is correct, but both members of a chromosome pair or segments of a chromosome pair are inherited from the same parent. The detection of uniparental disomy involves PCR analysis of genetic material from the affected child and both parents. Genetic conditions that are often associated with uniparental disomy include Prader-Willi syndrome, Angelman syndrome, Russell-Silver syndrome and various other malformation syndromes.

Specimen requirements: 5 to 10 ml of peripheral blood (from both parents and the proband) collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be substituted. Prenatal studies require two confluent T-25 flasks containing cultured CVS material or amniocytes. *A maternal blood sample is also requested for prenatal analysis.*

Transport: Please contact JoAnne Babb (1-800-473-9411), the Molecular Diagnostic Laboratory coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx delivery is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on a Friday can be safely designated for Monday delivery. However, Saturday delivery is available.

Analysis standards: Analysis will be completed within 21 days from sample receipt. The quality and interpretation of test results are assessed by the laboratory director. Technical staff independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results and their interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director is available and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83894, 83898(X3), 83912

X-inactivation

Determination of maternal and paternal X chromosome activation status is useful in the diagnostic analysis of nonrandom patterns. Skewed patterns of inactivation in female carriers of a number of X-linked recessive disorders and asymptomatic female carriers of some X-linked dominant diseases have been observed. X-inactivation studies are useful in diagnosing such disorders and determining carrier status of family members.

By using the methylation-sensitive restriction enzyme *HpaII* and the polymerase chain reaction, the methylation status of both the maternal and paternal X chromosome is determined. Methylation of the *HpaII* restriction endonuclease site in the human androgen-receptor gene, HUMARA, correlates with X-inactivation.

Specimen requirements: 5 ml of peripheral blood collected in an EDTA (lavender top) Vacutainer™ tube is preferred. The minimal blood needed for reliable DNA isolation is 3 ml. If necessary, ACD solution A Vacutainer™ tubes (yellow top) may be submitted. Please contact the laboratory for more information.

Transport: Please contact JoAnne Babb (1-800-473-9411), the molecular diagnostic lab coordinator, for shipping information. The specimen should be kept at room temperature and delivered via overnight shipping. FedEx is preferred. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. *Do not freeze the specimen.* Samples collected on Friday can be safely designated for Monday delivery. However, our lab does accept specimens on Saturdays.

Analysis standards: Analysis will be complete within 5 days of sample receipt. The lab director assesses the quality and interpretation of results. Technical staff members independently assess the quality and interpretation of the test. The Greenwood Genetic Center Molecular Diagnostic Laboratory is CLIA certified and actively participates in CAP proficiency surveys.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

CPT Codes: 83890, 83894, 83898, 83912

X-Linked Hydrocephalus (L1CAM)

L1CAM is associated with a phenotype spectrum including X-linked hydrocephalus, MASA (mental retardation, aphasia, spastic paraplegia and adducted thumbs), X-linked complicated hereditary spastic paraplegia type 1 (SPG1) and X-linked agenesis of the corpus callosum. The gene encodes for neuronal L1 cell adhesion molecules in the central and peripheral nervous systems, and has been localized to Xq28.

Sample requirements: L1CAM testing offered in this laboratory uses DNA as the starting nucleic acid for analysis. This requires a peripheral blood sample collected in an EDTA Vacutainer (lavender top).

Transport: All samples should be shipped at room temperature and delivered via overnight courier. (FedEx is preferred.) **Do not freeze the specimen prior to transport.** Though Saturday receiving is available, it is preferable to ship samples early in the week for delivery Monday through Friday. Please contact Kristy Lee, Jo Anne Babb or Mike Friez (1-800-473-9411) in the Molecular Diagnostic Laboratory for details regarding transport.

Analysis standards: Testing will be completed within six weeks of sample receipt. The referring party will be contacted should delays arise. Technical staff members assess the quality and interpretation of all test results. Following an independent analysis of results by the Director of the Laboratory, a hard copy report will be issued. Verbal reports with consultation are available upon request by the referring party.

Reporting of Test Results: Test results with interpretation will be mailed and/or faxed following completion of the test. Verbal reports will be telephoned to the person(s) requesting the test when an abnormal test result occurs. Consultation with the laboratory director and explanations of testing protocols will be supplied upon request.

Proband (male):

CPT codes: 83890, 83894 (x8), 83898 (x11), 83912, 83904 (x8)

Carrier for known mutation:

CPT codes: 83890, 83898 (x2), 83912, 83904

Prenatal Analysis for known mutation:

CPT codes: 83890, 83898 (x2), 83912, 83904

Prenatal Maternal Serum Screening

Prenatal maternal serum screening consists of measuring three chemical markers present in the mother's blood during pregnancy: alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and dimeric inhibin A (DIA). Abnormal levels of these chemicals may indicate increased risk for certain birth defects and genetic diseases. Approximately 5% of all pregnancies tested will have an abnormal screening test requiring additional diagnostic testing. Only a small number of these pregnancies are affected with a birth defect or genetic disease. Inaccurate pregnancy dating (gestational age) and the presence of twins or other multiples can cause an abnormal screening result. Pregnancy dating by ultrasound will ensure the most accurate test result. Estimation of gestational age by ultrasound using biparietal diameter is optimal because it reduces the initial screen positive rate and increases detection of neural tube defects. Use of fetal femoral length dating potentially decreases the detection of Down syndrome. Genetic counseling and prenatal diagnostic testing should be considered with any positive maternal serum screening result.

Alpha-fetoprotein (AFP) is a protein produced by the fetal liver and yolk sac. The function of AFP during fetal development has not been clearly defined. AFP is present in high concentration in fetal blood and declines rapidly in newborn serum after birth. AFP is present in lower concentration in fetal urine and is detectable in amniotic fluid. During pregnancy, there are detectable levels of AFP in maternal serum. Open neural tube defects and other open fetal malformations with exposed membranes and blood vessel surfaces allow excessive AFP to transudate into amniotic fluid. In the presence of open fetal defects, increased levels of AFP in maternal serum may result from increased levels of AFP in amniotic fluid.

Human chorionic gonadotropin (hCG) is a glycoprotein hormone synthesized by the placenta and is necessary for early pregnancy maintenance. HCG appears in maternal serum about 6-8 days after conception and reaches a peak around 10 weeks. During the second trimester, hCG declines progressively to a fairly constant level at 18-20 weeks.

Unconjugated estriol (uE3) is a steroid hormone produced in the placenta using precursor steroids from the fetus and mother. The hormonal functions of uE3, a relatively weak estrogen, are not well understood. During pregnancy, estrogens are thought to maintain proper functioning of the uterus, soften cervix and aid lactation. Maternal serum uE3 levels rise above non-pregnancy levels by 7-9 weeks gestation and continue to increase throughout pregnancy. Low levels of maternal uE3 in the third trimester have been reported in newborns with low birth weight and have been found to indicate fetal distress.

Dimeric inhibin A (DIA) is a glycoprotein hormone synthesized by the corpus luteum and placenta in pregnancy. The specific role of DIA during pregnancy has not been determined. Maternal serum DIA levels increase during the first trimester, then decline after 10 weeks and remain stable between 15-25 weeks. DIA levels rise again after 25 weeks to reach a peak at term.

	AFP	hCG	UE3	DIA	Risk Cutoff	Detection
NTD	High	----	----	----	>2.0 MOM	85%
Down Syndrome	Low	High	Low	High	>1/270	70%
Trisomy 18	Low	Low	Low	----	>1/100	60%

Neural Tube Defect Screening: Elevated Maternal serum AFP levels indicate an increased risk for open spina bifida and anencephaly. Other risk factors include family history of neural tube defects, certain maternal drug exposures, and maternal insulin-dependent diabetes. More definitive tests such as high-resolution ultrasound,

amniotic fluid AFP, and acetylcholinesterase are recommended when there is an increase risk for an open neural tube defect. Adverse pregnancy outcomes associated with elevated maternal serum AFP are prematurity, growth retardation, low birth weight, and fetal demise.

Down Syndrome Screening: Maternal serum screening for Down syndrome utilizes the maternal age specific risk and second trimester levels of AFP, hCG, uE3, and DIA to calculate a risk estimate for each pregnancy. A positive screen for Down syndrome is reported when the risk is greater than or equal to 1:270. Risks less than 1:270 are reported as a negative screen.

Trisomy 18 Screening: The estimated trisomy 18 risk for each pregnancy is calculated based on the maternal age risk and the levels of AFP, hCG, and uE3. A positive screen for trisomy 18 is reported when the risk is greater than or equal to 1:100.

Specimen Requirements: Obtain 2 ml of serum from a **red top vacutainer tube** (no anticoagulant) between 15 and 20 weeks gestation. For optimal detection of neural tube defect samples should be collected at 16-18 weeks gestation.

Hemolytic and lipemic serum samples do not interfere with assays but icteric samples may cause a decrease in estriol concentrations. Plasma samples cannot be used.

Note: *Always collect serum samples prior to amniocentesis.* The amniocentesis procedure may introduce significant amounts of AFP into the maternal serum, resulting in a transient increase in AFP.

Transport: Transport samples at room temperature by first-class mail or overnight courier on the day the sample is obtained. Protect from extreme temperatures when necessary. If shipment is delayed, serum sample may be stored up to 6 days refrigerated at 2°-8° C. For longer periods, store at -20° C. Repeated freezing and thawing should be avoided. Prepaid mailers are provided by the Greenwood Genetic Center upon request.

Information required: The *Maternal Serum Screening* patient registration card should be completed, signed and enclosed with each sample. If no registration card is available, please include the following information with the sample:

- Patient name, address, telephone number and date of birth
- Social security number
- Race
- Patient's current weight
- Date of sample collection
- Gestational age in weeks and days on date of sample collection
- LMP
- EDC
- Is this a twin or other multiple gestation?
- Does the patient have insulin dependent diabetes?
- Family history of neural tube defects with relationship to patient or father of baby
- Family history of Down syndrome with relationship to patient or father of baby
- Is the patient on medication for seizures? If so, list medications.
- Does the patient smoke cigarettes? If so, include amount per day.
- Name of referring physician
- Billing and insurance information

- Signed informed consent

This information is necessary for interpretation of screening results. If information is omitted, interpretation and reporting of results will be delayed.

NOTE: *Maternal serum screening interpretations for neural tube defects and Down syndrome are dependent on **accurate gestational dating**. Estimation of gestational age by ultrasound using biparietal diameter (BPD) is optimal because it reduces the initial screen positive rate and increases detection of neural tube defects. Use of fetal femoral length dating potentially decreases the detection of Down syndrome.*

Standard of Analysis: Available upon request

Time required: 2 days from receipt of sample.

Report: A **normal** screening report is mailed to the referring physician, clinic, or laboratory. An **abnormal** screening report is telephoned and/or sent by FAX to the referring physician, clinic, or laboratory followed by a mailed written report.

CPT Codes: 82105, 84702, 82677, 86336

Contact: Kim Stewart (864) 941-8131 or (800) 473-9411 toll free

Amniotic Fluid Alpha-Fetoprotein Assay (AF-AFP)

Alpha-fetoprotein (AFP) is a protein produced by the fetal liver. The function of the protein is unknown. It is present in high concentration in fetal blood and in lower concentration in fetal urine. AFP is present in amniotic fluid which is composed primarily of fetal urine. Amniotic fluid AFP (AFAFP) may be elevated in open fetal body wall defects, most commonly open neural tube defects (NTD) and open ventral wall defects, due to transudation from exposed fetal vessels and tissue. AFAFP is elevated in congenital nephrosis from increased glomerular filtration of this relatively small protein. In cases with elevated AFAFP, the risk for an open NTD or other fetal abnormality depends on the degree of elevation in the AFAFP MoM (multiple of the median), the results of amniotic fluid acetylcholinesterase testing and other significant risk factors.

Specimen requirements: Amniotic fluid, 2-5 ml, obtained at 14-24 weeks gestation.

Transport: Transport amniotic fluid samples at ambient temperature by same day or overnight courier. In high temperatures, the specimen should be packed with a refrigerant and shipped at 2°-8°C. If shipment is delayed, freeze the sample at -20°C and transport on dry ice. This is necessary to prevent the degradation of alpha-fetoprotein. Elevated temperatures and aging of the sample accelerate the degradation of the protein. Amniotic fluid samples for chromosome analysis should not be frozen.

Standard of Analysis: Amniotic fluid alpha-fetoprotein is measured in micrograms/ml ($\mu\text{g/ml}$) by a solid phase, two-site fluoroimmunoassay on the Wallac AutoDELFI system. In normal pregnancies, the AFP concentration in amniotic fluid decreases by about 10% with each gestational week during the second trimester. Conversion of the AFP concentration to multiple of the median (MoM) allows use of a single cut off level for all gestational weeks. AFAFP values greater than or equal to 2.0 MoM are considered elevated.

Time required: Approximately one to two days is required for AFAFP analysis.

Report: A written report is mailed to the referring physician. Results for any samples with elevated AFAFP MoM, increased risk for NTD or other fetal abnormalities are telephoned and/or sent by FAX to the physician's office followed by a written report. In addition, results may be sent by email if requested.

Special Requests: Special requests may be made directly to the laboratory.

CPT Code: 82106

Amniotic Fluid Acetylcholinesterase Assay (AChE)

Acetylcholinesterase (AChE) is a neural enzyme present in cerebral spinal fluid and fetal blood. AChE is not present in maternal blood and is not normally detectable in amniotic fluid. The abnormal presence of acetylcholinesterase in amniotic fluid is suggestive of an open fetal defect. When AChE is detected, the ratio of AChE to pseudocholinesterase (PChE), a non-specific cholinesterase normally found in amniotic fluid, may help distinguish open neural tube defects from open ventral wall defects or fetal blood contaminated fluid.

Specimen requirements: Amniotic fluid, 2-5 ml, obtained from 14 - 24 weeks gestation. The gel electrophoresis may be performed on specimens obtained prior to 14 weeks or after 24, but results are less reliable.

Transport: Transport amniotic fluid samples at ambient temperature by same day or overnight courier. In high temperatures, the specimen should be packed with a refrigerant and shipped at 2°-8°C. If shipment is delayed, freeze the sample at -20°C and transport on dry ice. Amniotic fluid samples for chromosome analysis should not be frozen.

Standard of analysis: Acetylcholinesterase is assayed in all amniotic fluid samples for which there is an increased risk of a neural tube defect or other fetal abnormality. Amniotic fluid is examined for the presence of acetylcholinesterase and pseudocholinesterase by using slab gel electrophoresis. When acetylcholinesterase is detected, the ratio of acetylcholinesterase to pseudocholinesterase may help distinguish an open neural tube defect from an open ventral wall defect or fetal blood contaminated fluid.

Time required: Approximately one week is required for the AChE assay.

Report: Results from any samples with detectable AChE will be telephoned and/or sent by FAX to the physician's office. Written reports will be mailed to the physician.

Special Requests: Special requests should be made directly to the laboratory.

CPT Code: 82013

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Shipping Information

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For the Upstate region, including Greenville, Spartanburg, Anderson and Greenwood, call

1-864-801-2720

For the central portion of the state and the Pee Dee region, including Columbia and Florence, call

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Contact person: Angela

If courier service is not available in your area or if you have difficulty with a shipment, please call us at the number below. Federal Express overnight service or United Parcel Service overnight may be used.

Please call us at 1-800-473-9411

If samples are being shipped on Friday, please make sure that the package is clearly labeled for **Saturday Delivery**. Also, we would appreciate a call to let us know a sample is going to be delivered on Saturday.

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