Test Kits Simplify Specimen Collection and Transport

**Question.** What do you do when answers are needed for the following questions.

- What tube do I need for genetic testing?
- How much specimen should I collect?
- Which request form do I need to fill out?
- Argh! Why is this so complicated?

**Answer.** Most will call and speak to helpful lab staff, and along they go. Mostly painless, right?

But, what if, you could grab a box off the shelf? What if that box was a Human Genetics Laboratory test kit, and inside were collection instructions, the correct tubes, the correct request form, and if you need them - FedEx® supplies which cover shipping costs? What if such kits were offered to you at no charge? What if every time you used a test kit, your day at work became a little less complicated?

The introduction of test kits to our laboratory services has made a positive impact on the evolving needs of our clients.

Use of kits is not obligatory - they are provided for client convenience.

**AVAILABLE TEST KITS:**

- Hematology/Oncology
- Male Infertility
- Postnatal Blood
- Pregnancy Loss Microarray

PLEASE NOTE: Not all sample types accepted by our laboratory can be transported with a kit.

**ONLINE TOOLS**  www.unmc.edu/geneticslab

- test catalog
- specimen requirements and turn-around-times
- CPT codes
- prior authorization forms
- shipping information
- test request forms
  - including adobe interactive
- provider fact sheets
- patient fact sheets
- patient brochures
- client satisfaction survey
The Human Genetics Laboratory offers a two-year fellowship training program in clinical cytogenetics, which prepares individuals holding an M.D. or a Ph.D. for the American Board of Medical Genetics examination in Clinical Cytogenetics.

Cytogenetic fellows participate in all aspects of sample preparation, analysis, and reporting.

Our laboratory is pleased to announce that Dr. Lois Starr and Dr. Jennifer Sanmann began two-year clinical cytogenetic fellowships in the laboratory in July 2012.

As fellows, Drs. Starr and Sanmann serve as excellent resources for both general testing questions and patient-specific inquiries.

Lois J. Starr, M.D.
Jennifer N. Sanmann, Ph.D.

Human Genetics Laboratory Newsletter | Fall 2012
Cancer Microarray

**Design**
- 105,000 Oligonucleotide probes
- 75,000 SNPs 1
- CCMC 2 design for cancer applications

**Detection**
- Custom design targets all known genes implicated in cancer at 10K and provides 25k backbone coverage throughout the genome
- Targets over 1,200 cancer-related genes based on curated cancer gene lists
- SNP probes identify copy neutral loss of heterozygosity (cnLOH) in tumor-suppressor gene regions

**Benefits**
- Does not require mitosing cells
- High resolution whole genome scan (10-25K)
- Not limited to available FISH probes
- Detects prognostically important deletions in ALL (IKZF1 and CDKN2A) and will identify doubling of a hypodiploid clone
- Can be performed on FFPE

**Limitations**
- Unable to detect balanced translocations, or the location of duplicated or rearranged segments
- Need additional 0.5-1.0 ml of specimen
- Increased resolution may identify uncertain clinical findings or unexpected abnormalities unrelated to malignancy (constitutional, consanguinity)

**Recommended Indications for Testing**
- **Diagnostic Studies**
  - ALL - upon receipt in conjunction with cytogenetic analysis and FISH
  - AML - reflex to microarray when cytogenetic analysis is normal or identifies a sole abnormality
  - CLL, CML, and NHL - reflex to microarray when cytogenetic analysis is normal
- **Follow-Up Studies**
  - Helpful for detecting additional abnormalities associated with disease progression when chromosome and/or FISH studies are unexpectedly normal

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1 SNP = Single Nucleotide Polymorphisms  
2 CCMC = Cancer Cytogentic Microarray Consortium

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Cancer Microarray: A Complementary Technology to Traditional Genetic Analysis

Jennifer N. Sanmann, PhD, MB(ASCP)CG

**Cancer Microarray** is the newest of several microarray platforms offered at the Human Genetics Laboratory (HGL). The current Cancer Microarray is a Cancer Cytogentic Microarray Consortium (CCMC) design utilizing a combination of 180,000 oligonucleotide/SNP probes that target over 1,200 cancer-related genes in addition to high-resolution whole genome coverage. This microarray is designed to identify two types of genetic changes associated with neoplasms: copy number changes associated with chromosomal deletions and duplications and copy neutral loss of heterozygosity (LOH) associated with loss of genetic variation in the absence of a net loss of genetic material. Detection of LOH is particularly useful in regions of the genome that contain oncogenes and tumor suppressor genes.

Cancer microarray testing is available for all hematologic malignancies. It can provide both diagnostic and prognostic information, even in cases with low mitotic indexes. This testing circumvents one of the limitations of routine cytogenetics and of selective FISH panel analyses by interrogating known and novel disease-associated regions of the entire genome at a higher resolution than is possible with the traditional testing methodologies. In addition, the cancer microarray assay is unique in its ability to detect loss of heterozygosity (LOH), which is of significant interest in tumor suppressor gene regions.

At this time, we are recommending a diagnosis-specific approach to testing, either as an initial test upon receipt of the specimen in the laboratory or as a reflex assay in the absence of cytogenetic and/or FISH abnormalities (see above table for specifics).

This assay is most commonly performed on fresh specimens, and typically results are available within 1 week of receipt. Additionally, results are generally available 2-3 weeks after receipt when performed on paraffin-embedded specimens.

Please contact the laboratory with any questions regarding the applications for and the utility of this assay for your patients.

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Laboratory Offers Automated Cell Separation for Multiple Myeloma and CLL

Pamela Althof, MS, CG(ASCP)CM

Immunomagnetic cell sorting combines the specificity of monoclonal antibodies with a simple column-free magnetic system that allows for cell purification and enrichment of selected cell populations through positive and negative cell selection. In December 2012, the Human Genetics Laboratory began using the RoboSep™ automated system from Stemcell Technologies to perform cell sorting on diagnosis-specific specimens. This sorting will be incorporated into the laboratory’s internal workflow and will not modify the specimen requirements for any genetic testing offered by our laboratory.

The first application for this technology in our laboratory is that of enriching the multiple myeloma cells through CD138 cell sorting for FISH analysis. The sorted cell population (CD138+ cells) increases detection of prognostically significant genetic abnormalities in patients with multiple myeloma and decreases false negative results caused by plasma cell dilution in whole bone marrow/blood specimens. Because this sorting will increase the percentage of abnormal cells as compared to analysis on the whole (non-sorted) specimen, our reports will be modified to reflect targeted analysis on the CD138+ cells when applicable. Moving forward, we will utilize cell separation technology for purification of cells for additional diagnoses (e.g., CLL, AML) and for cancer microarray and gene sequencing technologies.

Rachel Utter, BS, CG(ASCP)CM, Cytogenetic Technologist II, loading bone marrow specimens into the RoboSep™ for cell marker separation.
Next Generation Sequencing (NGS) Developments

Historically, genes have been sequenced individually (e.g., using Sanger sequencing) to identify the underlying genetic causes for many disorders. However, because various genetic conditions exhibit overlap in clinical presentation, interrogation of each disorder-specific gene is often merited for accurate diagnosis. Similarly, a single diagnosis can be associated with aberrations in any one of many genes, requiring analysis of several genes for comprehensive genetic testing. Using traditional sequencing methodologies, this multiple-gene testing is difficult to perform in a time- and cost-efficient manner. Next generation sequencing (NGS) is an emerging technology which addresses these historical challenges.

Specifically, NGS enables one to sequence many genes simultaneously, allowing for rapid analysis of a panel of potentially causative genes.

Our laboratory currently offers NGS for a variety of clinical indications:

- Autism/Intellectual Disability/Multiple Anomalies
  - See table (right) outlining the clinical indications for this panel. Please Note: this panel includes all genes in the Rett/Atypical Rett/Angelman Syndromes and the Noonan/RAASopathy Disorders Panels PLUS additional genes of clinical significance.
  - Rett/Atypical Rett/Angelman Syndromes
  - Noonan/RAASopathy Disorders
  - Craniosynostosis
  - Duchenne Muscular Dystrophy (DMD)
  - Connective tissue disorders – coming soon
  - Amyotrophic lateral sclerosis (ALS) – coming soon

We intend to add to the gene content of each NGS panel as new, supportive literature becomes available to maximize the panel’s diagnostic utility. Thus, for the most up-to-date gene list for each of these panels we encourage you to visit our website.

www.unmc.edu/geneticslab

Additionally, we will update our laboratory website when the NGS panels currently in development are validated for clinical use. Please contact us directly with any questions about the availability and the utility of these sequencing panels for your patients.

The Clinical Genetics Team Welcomes Drs. Rush and Starr!

Eric Rush, M.D. is board-certified in Pediatrics and in Internal Medicine and is board-eligible in Clinical Genetics. Dr. Rush was named Assistant Professor of Pediatrics and Associate Program Director for the Clinical Genetics Fellowship at UNMC in July 2012.

Due to his previous training in Internal Medicine, Dr. Eric Rush has had the privilege of starting a dedicated adult genetics clinic with Amber Carter, one of nine certified Genetic Counselors, at the Munroe-Meyer Institute. In this clinic, Dr. Rush sees patients with a wide range of diagnoses, but disorders such as Ehlers-Danlos syndrome and Marfan syndrome are very common. He also sees a number of patients who either have or are at risk for development of neurodegenerative disorders or cancer. Dr. Rush has also had the opportunity to assume the role of geneticist in the Metabolic Bone and Osteogenesis Imperfecta (OI) Clinic at Children’s Hospital and Medical Center where he sees patients with OI and other metabolic bone disorders such as hypophosphatasia, hypophosphatasia, rickets, and juvenile osteoporosis. Additionally, Dr. Rush is a member of the team which provides genetics services to several outreach clinics in greater Nebraska.

Lois Starr, M.D. is a board-certified Pediatrician and a board-eligible Clinical Geneticist. Following her Clinical Genetics fellowship, Dr. Starr accepted a position at UNMC as an Assistant Professor of Pediatrics and began a second, complimentary fellowship in Clinical Cytogenetics.

Dr. Starr holds weekly general genetics clinics where she sees patients with indications including dysmorphic features, autism, stature anomalies, symptoms of connective tissue or neurocutaneous disorders, and many others. She also shares the responsibility of being the genetics physician with Dr. Bruce Buehler in the Complex Craniofacial Clinic at Children’s Hospital and Medical Center where she follows patients with variable craniofacial anomalies. Dr. Starr is one of a team of geneticists who travels to greater Nebraska to provide genetics services to these communities in well-established, outreach clinics. In addition, Dr. Starr has a passion for finding the underlying genetic cause for families with children with autism and is very excited to be part of the Multidisciplinary Autism Diagnostic Clinic at the Children’s Hospital and Medical Center (in cooperation with Munroe-Meyer Institute) which is currently in planning stages.

<table>
<thead>
<tr>
<th>Autism/Intellectual Disability/Multiple Anomalies Panel</th>
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<tbody>
<tr>
<td>- dysmorphic features</td>
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<tr>
<td>- intellectual disabilities</td>
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<tr>
<td>- macro- or microcephaly</td>
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<td>- congenital heart defects</td>
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<td>- other congenital anomalies</td>
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<th>Suspected Syndromes</th>
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<tr>
<td>Aarskog (facioscapulohumeral dysplasia)</td>
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<td>Angelman</td>
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<td>Joubert</td>
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<td>Kabuki</td>
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<td>Legius or SPRED1</td>
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<td>Mowat-Wilson</td>
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<td>Neuromyelomalacia</td>
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<td>Sotos</td>
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<td>Tuberculous sclerosis</td>
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Test Kits Simplify Specimen Collection and Transport

We have introduced four primary test kits designed to aid in the collection and transport of samples being sent to our laboratory.

Cancer Microarray Utility

Available for all hematologic malignancies, this array platform provides both diagnostic and prognostic information - even in cases with low mitotic indexes.

Next Generation Sequencing (NGS). It’s here!

One panel, multiple genes... Too good to be true? No. Say Hello to NGS. This new technology identifies underlying causes for many disorders in one test.