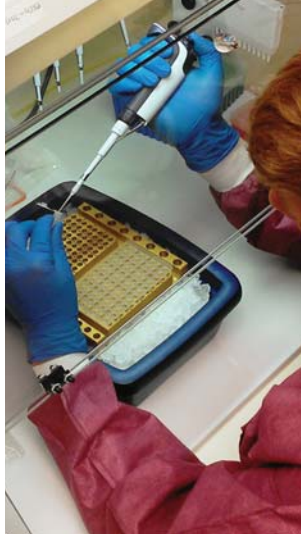


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HATTIE B. MUNROE PAVILION

Newsletter

for health care providers

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HGL introduces improved microarray platform for detection of constitutional abnormalities.

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Cell sorting technology increases FISH panel sensitivity in patients with multiple myeloma.

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New autism and cardiomyopathy testing

NGS testing now includes expanded autism panel and new cardiomyopathy panel.

Laboratory services include preauthorization

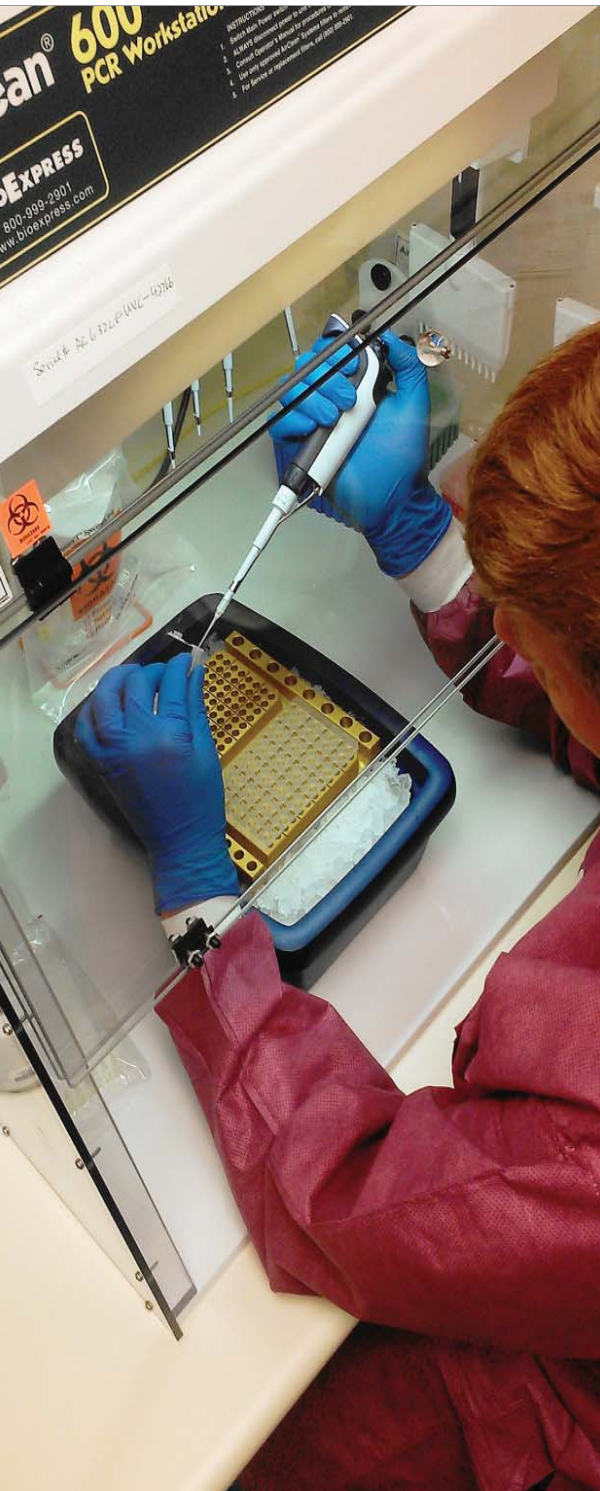
HGL responds to client and patient preauthorization needs.



UNMC Human Genetics Laboratory

NEWSLETTER

for health care providers



SNP SNP Array!

Diane Pickering, MS, CG(ASCP)^{CM}

The SNP (Single Nucleotide Polymorphism) Array is here.

The Human Genetics Laboratory recently introduced the Postnatal High-Density SNP Array, representing one of the most comprehensive microarray tests to date for constitutional abnormalities.

For more complete and detailed genotyping, the Affymetrix Cytoscan HD™ SNP array utilizes 1.9 million non-polymorphic SNP markers for deletion/duplication detection and 750,000 polymorphic SNP markers to identify uniparental disomy (UPD). There are two types of UPD: uniparental isodisomy and uniparental heterodisomy; the SNP array is

specific for uniparental isodisomy. When uniparental heterodisomy is suspected, chromosome-specific methylation studies are warranted for patients that have clinical findings consistent with a known UPD syndrome. In addition to the added detection of uniparental isodisomy, this SNP array provides improved breakpoint delineation and enhanced detection of mosaicism and triploidy. The SNP array complements next-generation sequencing testing with marker coverage every 1-2Kb for detection of small intragenic deletions and duplications. Our laboratory is moving toward streamlining the SNP array workflow across applications because of improved performance on DNA from saliva, buccal swab, needle biopsy, and formalin-fixed paraffin-embedded tissue (FFPE) specimens.

HUMAN GENETICS LAB PASSES CAP INSPECTION WITH NO DEFICIENCIES

The UNMC Human Genetics Laboratory had an unannounced routine inspection by the College of American Pathologists (CAP) on June 7, 2013. The laboratory inspection was performed by three doctoral level CAP inspectors in the following areas: Team Leader, Laboratory General, Cytogenetics, and Molecular Pathology. An independent inspector employed by CAP also did a separate inspection of the process. During this inspection, no deficiencies were identified. In addition, the Inspector's Summation Report stated, "This laboratory has done extremely well in terms of quality work following the guidelines of CAP." This inspection accredits the Human Genetics Laboratory for another two years. The Human Genetics Laboratory has been continually accredited by CAP since 1974. The Human Genetics Laboratory is also accredited by CLIA (Clinical Laboratory Improvement Amendments).

From the director



Newsletter | Summer 2013

This Newsletter is produced by the Human Genetics Laboratory, part of Munroe-Meyer Institute at the University of Nebraska Medical Center.

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COVER PHOTO

Jadd Stevens, BA, BS, MB(ASCP)^{CMCGCM},
Cytogenetic Technologist II,
performing the pre-PCR steps of the
Postnatal High Density SNP Microarray

Genetic diagnostic testing technologies continue to evolve to include new and often complex approaches. In order to most accurately classify the genetic changes identified using these technologies as benign or as disease-causing, clinical correlation is necessary. To this end, our department has integrated our clinical genetics group with our genetic laboratory function. This integration of laboratory and clinical expertise ensures that we provide the highest quality diagnostic testing and result interpretation to our referring medical professionals and their patients.

Our primary objective is to provide accurate genetic testing and interpretation for the patients you serve. As part of this goal, our department is continually expanding our test menu to meet the needs and requests of our medical colleagues. In the realm of molecular cytogenetics, we continue to develop custom probes for fluorescence *in situ* hybridization (FISH) studies. In the molecular genetic testing arena, we have recently expanded the gene lists for a number of our next generation sequencing panels. In addition, we launched a next generation sequencing panel for cardiomyopathy this summer. The details of these next generation sequencing developments are included in this newsletter and are also available on our laboratory website.

We welcome and appreciate your suggestions and feedback on our test menu, as this input helps drive our research and development efforts. Please communicate with me or a member of our laboratory team should you have a need that our laboratory services do not currently meet.

Finally, we are pleased to announce the arrival of a new Associate Director for our laboratory. Dr. Tanner Hagelstrom has completed fellowships both in clinical cytogenetics and molecular genetics and is ABMG board eligible in these two genetic specialties. He will join our staff as the second Associate Director of our laboratory, along with Dr. Bhavana Davé. Dr. Hagelstrom's addition will allow for development of new tests which are desired by the medical community.

A handwritten signature in black ink that reads "W. Sanger".

Warren G. Sanger, PhD

Director of Cytogenetics and Human Genetics Laboratory
Director of Genetic Medicine
Munroe-Meyer Institute
University of Nebraska Medical Center

FACULTY HIGHLIGHTS



Bhavana J. Davé, PhD, FACMG

Bhavana Davé is Professor of Pediatrics and Munroe-Meyer Institute for Genetics and Rehabilitation at UNMC and Associate Director of the Human Genetics Laboratory. She is board certified in Clinical Cytogenetics by the American Board of Medical Genetics.

Dr. Davé is involved in patient care by providing clinical cytogenetics services utilizing state-of-the-art genetic technologies.

She has authored/co-authored over 100 journal articles/reviews/book chapters. She serves as a reviewer and is on the editorial board of Medical Genetics and Cancer Biology related journals.

Dr. Davé's research involves in-depth genetic characterization of lymphomas and leukemias and delineation of the basic mechanisms of genetic abnormalities. Her research studies impact the prognosis and management of cancer, developmental, and prenatal disorders.

Which chromosome do you feel best describes you, and why?

“ My ‘karyotype’ best describes me; each and every chromosome represents me in some way! As a cytogeneticist I appreciate the ‘uniqueness’ of each chromosome which make them identifiable. ”



Ann Haskins Olney, MD

Ann Haskins Olney is a Clinical Geneticist, Professor of Pediatrics and Munroe-Meyer Institute for Genetics and Rehabilitation at UNMC, and Director of the Medical Genetics Fellowship. She is board certified in Clinical Genetics by the American Board of Medical Genetics.

Dr. Olney is involved in patient care by providing clinical genetics services to infants, children, and adults.

Dr. Olney's clinical interests include dysmorphism, multiple congenital anomaly syndromes, overgrowth syndromes, and syndrome delineation.

She is actively involved in research collaborations studying the molecular etiology of syndromes.

Which chromosome do you feel best describes you, and why?

“ I like every chromosome, so this is a tough question. Maybe chromosome 1, because I really love phenotypes. And the deletion 1p36 phenotype is so distinctly recognizable that once in awhile I can “beat” the cytogenetics lab to the diagnosis! ”



Richard E. Lutz, MD

Richard Lutz is Associate Professor of Pediatrics at UNMC and works as a Clinical Geneticist and Pediatric Endocrinologist at the Munroe-Meyer Institute. He is board certified in Clinical Genetics by the American Board of Medical Genetics, and Pediatrics/Pediatric Endocrinology by the American Board of Pediatrics.

Dr. Lutz is involved in patient care by providing consultations and clinical care in Clinical Genetics. The endocrine and metabolic problems of genetic disease are a particular focus.

His clinical interests include birth defects, intellectual disabilities and autism, biochemical and hormonal newborn screening and therapy, enzyme replacement therapy (ERT), clinical genetic informatics, and medical education. He has published papers and book chapters on these subjects and is primary investigator for a Phase 2 clinical trial of ERT for infantile hypophosphatasia.

Which chromosome do you feel best describes you, and why?

“ Chromosome 14... Fairly big without a central constriction (no waistline) and not much on top. Lots of information (trivia) on 14 but nothing especially noteworthy. ”

Is the Male Infertility Panel Right for Your Patient?

Julie M. Carstens, MS, MB(ASCP)^{CM}CG^{CM}

According to the Male Infertility Best Practice Policy Committee of the American Urological Association and the Practice Committee of the American Society for Reproductive Medicine, comprehensive genetic screening should be offered to men who exhibit non-obstructive azoospermia or severe oligospermia (<5-10 million sperm/ml). This screening includes both cytogenetic analysis and Y-chromosome microdeletion (YCMD) testing.

Approximately 10-15% of men with azoospermia and ~5% of men with severe oligospermia have been found to carry cytogenetic abnormalities, including sex chromosomes aneuploidies, translocations (Robertsonian & reciprocal), and inversions.

An additional 10-15% of men with azoospermia and severe oligospermia carry a microdeletion in the azoospermia factor region (AZF) of the Y chromosome which is not detectable by cytogenetics¹. This AZF region can be divided into 3 sub-regions (AZFa, AZFb & AZFc) with 5 recurrent interstitial Y-deletion

patterns identified (AZFa, AZFb, 2 different AZFb+c patterns & AZFc). The Human Genetic Laboratory tests for microdeletions along the entire length of the AZF region to determine not only whether a patient carries a microdeletion, but also the class of deletion the patient might have.

A "normal" or "negative" result indicates that a chromosome or molecular abnormality is likely not the cause of the patient's infertility.

An "abnormal" or "deleted" result indicates that chromosome or molecular studies detected a possible cause for

¹ American Society for Reproductive Medicine, *Fertil Steril* 2008;90:S74-7.

Automated Cell Separation Increases Abnormality Detection Rate For Patients With Multiple Myeloma

Pamela Althof, MS, CG(ASCP)^{CM}

In December of 2012, the Human Genetics Laboratory began using the RoboSep™ automated system from Stemcell Technologies to perform immunomagnetic cell sorting on diagnosis-specific specimens.

The first clinical application for this new technology was the use of CD138 positive cell selection on cases with a suspected diagnosis of multiple myeloma or a related indication, such as monoclonal gammopathy of undetermined significance, for fluorescence in situ hybridization (FISH)

TABLE 1. Comparison of Abnormality Rates in Cases Submitted for Multiple Myeloma FISH Testing Pre- and Post-CD138+ Cell Sorting

	Number of Samples Received	Number of Abnormal Cases	Percentage of Abnormal Cases
1/15/2012 - 5/14/2012 (whole specimen)	207	62	30.0%
1/15/2013 - 5/14/2013 (CD138+ fraction)	198	100	50.5%

the patient's infertility. Patients who exhibit YCMD should be offered genetic counseling due to reproductive implications associated with the diagnosis. Genetic counseling can be scheduled by calling our laboratory.

Ordering both cytogenetic analysis and YCMD testing is the most comprehensive approach in determining a possible genetic cause of male infertility.

Results are generally available in 10-14 days, and the required sample type is 3-5ml whole blood per tube in both a sodium heparin and EDTA tube. Collection kits are available at no cost to our clients.

analysis. Since the initiation of this testing, the abnormality detection rate for these indications has increased by 20.5% (see Table 1). In addition, abnormal results have been obtained from samples with low plasma cell content (less than 1%) that might have otherwise been below the limits of detection due to dilution of plasma cells in a whole bone marrow/peripheral blood specimen. Research and validation of additional FISH and molecular applications for this technology are currently in progress.

Community Involvement

Hustle for Hunger

is a campus walk/run to commemorate the start of our annual drive to collect food for the Food Bank of the Heartland. Runners tackled a 3-mile course around campus while walkers trekked 1.5 miles. Human Genetics Laboratory staff joined the campaign and kicked off UNMC's annual food drive in October 2012.



Hustle for Hunger Team HGL

Back Row: Chestnut Livermore, Kendra Coufal, Kim Wiechman, Chris Semler, Zephyr VanDyke, Rachel Utter, Chris Higgins **Middle Row:** Lisa Winkler, Denae Golden, Jenni Grove, Marilu Nelson, Francie Reboloso **Front Row:** Bunnita Washington

Omaha with Lights: Owl Ride

owlride.org

A NIGHTTIME URBAN CYCLING ADVENTURE!

Launched in Omaha in 2010, the Owl Ride has been a huge benefit for the Meyer Foundation for Disabilities (MFD), while providing a much anticipated date on the calendar for cyclists. MFD is dedicated to serving adults with developmental/intellectual disabilities in the Omaha metropolitan area by providing programs that improve their quality of life and promote inclusion in the community. Human Genetics Laboratory staff are regular Owl Ride participants, and thanks to proceeds from this event, MFD in recent years has been able to significantly expand available programming, including sponsorship of regular social outings, dances, cooking classes, and a reading club. Many of the programs are offered through the professional staff of the University of Nebraska Medical Center's Munroe-Meyer Institute, a renowned service provider in our area.

Just over 1,000 riders participated in the first Owl Ride and the goal for 2013 is 3,000!



HGL Owl Riders

Back Row: Lisa Winkler, Jeff Pinnt, Tom Hempel, Kristen Jackson, Michele Wiggins, Chris Semler, Rebecca Stroebel **Front Row:** Kendra Coufal and her bike

New Autism Multidisciplinary Diagnostic Clinic at Children's Hospital and Medical Center OPEN June, 2013

This clinic provides a multidisciplinary evaluation and diagnosis of children suspected of having an Autism Spectrum Disorder. The evaluation includes behavioral assessments, genetics, developmental pediatrics, and also offers a speech evaluation. After the completion of clinical examination, a diagnosis is made and further medical testing may be recommended. Resources are provided to help families navigate follow-up care and community services.

Medical Director: Lois J Starr, MD, FAAP

Clinical Staff: Howard Needelman, MD, FAAP
Candice M Lake, PhD, BCBA-D

Family Advocate: Jennifer Schrage, PLMHP

**Physician Referred Appointments Available
by calling 402-955-6570**



Cardiomyopathy Panel: Newest Addition to NGS

Jennifer N. Sanmann, PhD, MB(ASCP)^{CM}CG^{CM}

The Human Genetics Laboratory is excited to announce the release of its newest next generation sequencing (NGS) panel: cardiomyopathy.

Like other NGS panels, this assay allows for the interrogation of many genes in a more time- and cost-efficient manner than traditional sequencing methodologies. The NGS Cardiomyopathy Panel detects sequence-based mutations in a total of 70 genes associated with the following disorders:

- Dilated cardiomyopathy (DCM)
- Hypertrophic cardiomyopathy (HCM)
- Restrictive cardiomyopathy (RCM)
- Left ventricular non-compaction (LVNC)
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Long QT syndrome
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)

In addition to offering the large-scale NGS Cardiomyopathy Panel for individuals with significant clinical findings and/or family history, our laboratory also offers targeted mutation analysis for a known familial mutation. This targeted analysis

provides an economical means for family members of an individual with an identified disease-causing (pathogenic) genetic change to be studied for that particular genetic abnormality.

The results (positive or negative) of these targeted familial studies helps future surveillance and medical management of tested individuals.

Our laboratory genetic counselors are collaborating with UNMC Heart Center cardiologists to provide pre- and post-test genetic counseling to patients who may have inherited cardiac disease.

NGS Autism/ID/Multiple Anomalies Gene Panel Update

Lois J. Starr, MD, FAAP

The Autism/Intellectual Disability/Multiple Anomalies Next Generation Sequencing Panel (NGS) was released for clinical use in the fall of 2012. This panel was designed to detect disease-causing (pathogenic) sequencing mutations in genes known to be associated with a range of related clinical indications and genetic syndromes (see table).

Since the launch of this NGS panel, a stunning number of genes linked to autism spectrum disorders have been identified. We have accordingly added the well-proven genes to our Autism/Intellectual Disability/Multiple Anomaly NGS Panel, making this panel ideal for patients on the autism spectrum with or without dysmorphic features whose families and physicians are looking for the underlying genetic cause. This updated Autism/Intellectual Disability/Multiple Anomalies NGS Panel also includes additional genes associated with a number of suspected genetic syndromes. For a complete gene list for this or any of the Human Genetics Laboratory's NGS panels, please visit our laboratory website or contact the laboratory genetic counselor (402-559-5070).

Clinical Indications	Suspected Syndromes		
<ul style="list-style-type: none"> • autism spectrum disorders <ul style="list-style-type: none"> • dysmorphic • nondysmorphic • congenital heart defects • other congenital anomalies • certain dermatologic findings • developmental delays • dysmorphic features • intellectual disabilities • macro- or microcephaly • seizure disorders • structural brain anomalies 	<ul style="list-style-type: none"> ✓ Aarskog (Faciogenital dysplasia) ✓ Angelman ✓ Bardet Biedl ✓ Cardiofaciocutaneous ✓ CHARGE ✓ Cockayne ✓ Coffin Lowry ✓ Cohen ✓ Cornelia de Lange (CdLS) ✓ Costello ✓ DMD/BMD ✓ Dravet ✓ FG 	<ul style="list-style-type: none"> ✓ Gorlin ✓ Joubert ✓ Kabuki ✓ Kleefstra ✓ Legius or SPRED1 ✓ LEOPARD ✓ Lesch-Nyhan ✓ Mowat-Wilson ✓ Neurofibromatosis ✓ Noonan ✓ Opitz ✓ Pitt-Hopkins ✓ Pitt-Hopkins-like ✓ PTEN 	<ul style="list-style-type: none"> ✓ Rett ✓ Rubeinstein-Taybi ✓ Smith-Lemli-Opitz ✓ Smith-Magenis ✓ Sotos ✓ Tuberous sclerosis ✓ several genes involving: <ul style="list-style-type: none"> ▪ autism-neurosynaptic pathway ▪ lissencephaly and hydrocephalus ▪ seizure disorder

The NGS Cardiomyopathy Panel is most commonly performed on DNA isolated from a peripheral blood specimen. For this purpose, our laboratory requests 3-5 ml of peripheral blood in an EDTA (purple top) tube. Results for this test are typically available within 6-10 weeks.

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



Tips & Tools:

Preauthorization of Genetic Testing

Due to the rapid advancements in genetics, a growing number of practitioners are utilizing genetic testing for the diagnosis and medical management of their patients. Pre-authorization for genetic testing has become increasingly required by insurance providers **prior to or at the time of specimen collection**. In order to aid practitioners in this pre-authorization process, our laboratory has developed specimen- and diagnosis-specific forms that query the information required for the determination of coverage and preauthorization.

The following preauthorization forms are available on the Human Genetics Laboratory website:

- hematology/oncology
- postnatal (peripheral blood)
- prenatal
- pregnancy loss

Upon request, our laboratory will obtain preauthorization for your patient's genetic studies. Please contact our billing team with any questions or concerns related to this process. **402.559.5699**