MESSAGE FROM THE CHAIR

Because of the hard work representing the last 4½ years, GMI has recently been privileged to input to national policy relevant to genetics and genomic medicine in healthcare. I have now been a member of the DHHS’ Secretary’s Advisory Committee on Genetics, Health and Society (SACGHS) for approximately 6 months, and was asked to co-chair an informational workshop on whole genome sequencing (WGS) related to clinical application that was presented at the June 15-16, 2010 meeting. Because of the cutting edge clinical care and translational research GMI has been doing, workshop speakers Rich Sharp and Emily Edelman were able to tell SACGHS at the informational workshop of the Cleveland Clinic experience in the educational survey surrounding the direct-to-consumer genomic screening continuing medical education sessions last year and the creation of genomic counseling.

WGS will be an everyday clinical reality in the near future as the price point reaches affordability, ie, the $1,000 genome. Many predict this could occur within a year or two. So that this technology and derived information are used wisely and appropriately to personalize healthcare, SACGHS has formed a Task Force, of which I am co-chair. This task force will examine multidisciplinary information, challenges and potential solutions of WGS for clinical application so that SACGHS may advise Secretary Sebelius after the period of study.

Every decade, DHHS releases public health-directed goals for the general population. The immediate past set of national goals set in 2000, Healthy People 2010, included eating a balanced meal comprising all the food groups and regular exercise. Never before has genetics or family health histories played a role in these goals. Two of the proposed goals for Healthy People 2020 are the identification of as many people as possible who are at genetic risk of breast or colorectal cancer, so that they can be directed to proper care including genetic counseling, appropriate clinical surveillance and personalized prevention strategies.

Differentiating us from other academic medical centers, we have already reached far into identifying individuals at genetic risk for colorectal cancer. Thanks to Brandie Leach, GMI has successfully led multidisciplinary efforts involving many clinical institutes to ensure that every colorectal cancer that has been surgically resected at the Cleveland Clinic undergoes a rapid, cost-efficient screen for Lynch syndrome, the most common adult-onset genetic colon cancer syndrome. Importantly, 80% of individuals who test positive come to CPGH. This type of screen can be offered because of genetics translational research performed over the last dozen years.

Stay tuned for other GMI efforts that contribute towards national health objectives such as the EMR-compatible electronic family health history tool, MyFamilyHealthHistory; the importance of genetics and genomic medicine education for all healthcare providers; and the importance of primary care physicians and nurses as our clinical integration partners.

To continue to effectively contribute our expertise to our national health, GMI must have a great work environment. Therefore, I am reiterating my strongest support for our department’s continuing hard work on making GMI a great place to work, which would facilitate us attaining all those goals so that we may continue to lead in the pioneering field of genomic medicine and personalized healthcare on the tripartite fronts of translational research, clinical care and education.

Charis Eng, MD, PhD

Dr. Eng in the News....

- named an American Cancer Society (ACS) Clinical Research Professor, which includes a 5-year, $400,000 grant award
- co-chaired an exploratory workshop at HHS’ Advisory Committee on Genetics, Health and Society (SACGHS) on Whole Genome Sequencing (WGS) for Clinical Application. From this workshop, a Task Force has been created to address medical issues brought on by the incorporation of WGS into clinical care.
- participated in a Think-Tank Workshop on Resulting Research Results from Biospecimen Resource-based Research at the National Cancer Institute, July, 2010.

Upcoming Events:
GMI Summer Picnic
July 31st at 12:00-6:00 PM

Integrative Genomic Medicine Seminar Series
August 9th at 12:00PM in NC1-202
Stephen Baylin, M.D
Dissecting the Cancer Epigenome – Its Constitution, Origins, and Translational Implications

Candidate Seminar
August 10th at 1:30PM in NC1-202
Lisa Guay-Woodford
Autosomal Recessive Polycystic Kidney Disease: Complexities from the Clinic to the Cilium
The Center for Personalized Genetic Healthcare (CPGH) redesigned its website. The new website was migrated to “my.clevelandclinic.org.” GMI worked closely with Hileman Enterprises and Cleveland Clinic’s Interactive Internet Marketing Department to re-design the previous website. Internal stakeholder interviews were conducted with patients and physicians to develop CPGH’s persona. The persona helped to determine layout, features, color palette and needed content. “This was a very comprehensive and enlightening process. Our internal website committee learned a great deal about the backend work needed to successfully design a clinical website.”

The primary goal for migrating CPGH’s website to the main Cleveland Clinic portal is to increase visibility and align CPGH with the other CC Institutes and clinical areas. We also want to promote CPGH as being among the nation’s leading authorities in Genetic and Genomic Medicine and patient-oriented clinical research. In addition, this website will serve as an outlet to educate patients and physicians about CPGH comprehensive genetic services, the clinical team and locations. This newly designed website will help prospective patients understand the genetic evaluation process and the importance of knowing your family health history.

To learn more about CPGH’s genetic services and locations, please visit us at www.my.clevelandclinic.org/genomics-genetics

GMI’s new clinical website highlights a topic which seems to be synonymous with genetic health care: Genetic Testing. The web site guides potential patients through the four stages of effective testing: Assess, Consult, Test, Manage. The new website points out that once a comprehensive risk assessment is completed, the genetic counselors and clinical geneticists do a great deal of education and counseling, explaining basic genetics and possible testing options. Of special note for patients visiting our web site is the fact that genetic testing is not for everyone, nor is it a stand alone solution. It should be part of a carefully devised, personalized process. If a test result shows the presence of a genetic mutation, our staff assist the patient with the creation of a management plan which is then shared with their referring health care provider. Advances that impact genetic testing are happening every day. The best advice to those individuals seeking some type of genetic assessment is don’t go it alone. Your doctor and genetic counselors are best equipped to guide you in the direction of good health.
**Under the Scope:**
Genetic studies of Pulmonary Arterial Hypertension

by Micheala Aldred, Ph.D.

Pulmonary arterial hypertension (PAH) is a rare but serious lung disease characterized by progressive narrowing of the small pulmonary arteries and the formation of obliterative vascular lesions, leading to elevated pulmonary artery pressure that potentially causes right heart failure. Treatments are improving, but PAH significantly impacts the patients' quality of life and lung transplantation may be required where other treatments fail. A small proportion of cases are inherited, caused by mutations in genes of the bone morphogenetic protein signaling pathway. But the cause of most other cases is unknown and even within the families, not everyone who inherits a genetic mutation will actually develop the disease, suggesting that additional genetic or environmental factors contribute to the etiology of PAH.

In collaboration with colleagues at the University of Colorado, Denver and in the Department of Pathobiology here at the Cleveland Clinic, we have recently uncovered evidence of genomic instability within the proliferative lung lesions (Aldred et al., Am. J. Resp. Crit. Care Med. in press), suggesting that PAH may result from a series of cancer-like genetic changes localized within the lung. Drugs originally used to treat certain cancers are already being trialed in PAH and early results are promising. Our grant awarded by the National Heart Blood and Lung Institute will extend these findings, testing the hypothesis that genetic or epigenetic changes are present in PAH lung tissues and contribute to the development or progression of PAH through abnormal cell proliferation and signaling. The aims of the study are to fully characterize the extent of genetic mutations and alterations in the methylation status of gene promoters in PAH lungs and to investigate the mechanisms that could predispose to genomic instability, with the overall goal of better understanding the causes of PAH. Our studies utilize cells and tissue from the lungs of consenting patients who undergo lung transplantation.

This unique resource has been established by the Pulmonary Hypertension Breakthrough Initiative, a nationwide collaboration between transplant centers including Cleveland Clinic, and is transforming PAH research by enabling genetic investigations that were previously impossible on archival lung specimens. We hope that a better understanding of the genetic changes that underlie PAH could lead to improved targeting of existing drugs and ultimately to the development of novel therapeutic strategies.

**NEW GRANTS**
($>$100,000)

- Since 11/2009

Charis Eng, MD, PhD, National Stimulus Act. “Next Generation Sequencer”; $500,000 equipment grant, residing in the Lerner Research Institute’s Genomics Core.

- Ephraim Sehayek, PhD, National Heart, Lung and Blood Institute/NIH RO1. “Cholesterol Fat Absorption”; $250,000 ADC (2010-2014)

- Micheala Aldred, PhD, National Heart, Lung and Blood Institute/NIH RO1. “Germline and Somatic Genetic Changes in Pulmonary Hypertension”; $250,000 ADC (2010-2014)

Charis Eng, MD, PhD, National Stimulus Act Administrative Supplement, National Cancer Institute P01 “Succinate Dehydrogenase Genes as Novel Mediators of Breast and Thyroid Cancer Susceptibility” $65,000 ADC (+thermal cycler x 1)

Charis Eng, MD, PhD, National Geographic Explorers’ Grant, “Ancient DNA” $7000

**PUBLICATIONS (in print)**


**SCIENTIFIC PRESENTATIONS:**

Charis Eng, MD, PhD. “Cancer Predisposition: I say genomics, you say genetics, but are we there yet?”, American Association for Cancer Research’s (AACR) Frontiers in Cancer Prevention Research Conference plenary talk, December 2009


Ephraim Sehayek, PhD. “Enterohepatic recycling of bile acids is a modifier of reverse cholesterol transport from peripheral tissue macrophages” at the Arteriosclerosis Thrombosis and Vascular Biology Annual Meeting, San Francisco, CA, April, 2010.

Charis Eng, MD, PhD. “Genetics of SDH in Pheochromocytoma and Paraganglioma … and Beyond”, Glaxo-Smith-Kline Oncology Seminar, April 2010.

Charis Eng, MD, PhD. “Cancer predisposition: Gene-informed personalized management” Grand Rounds, Massachusetts General Hospital, Partners Health, Boston, March, 2010.

Micheala Aldred, PhD. “microRNA processing is dysregulated by mutations associated with PAH” at the Aspen Lung Conference, Aspen, CO, June, 2010.

Micheala Aldred, PhD. “Genetic analysis of Pulmonary Hypertension lung tissues” at the Pulmonary Hypertension Association 9th International Conference, Garden Grove, CA, June, 2010.
Educational and Community Outreach Efforts

Charis Eng, MD, PhD “PTEN – A smart gene that AKTs against cancer: Of mice and men” to benefit Scott Hamilton CARES, Taussig Cancer Institute. Cleveland Skating Club, Shaker Heights, April, 2010

Charis Eng, MD, PhD “Genetics & Genomics: How 21st Century Technology Affects Individuals & Society”, Tucker Ellis & West LLP

GMI Genetic Counselors participated in Cleveland Clinic’s Education Fair, with the goal of better educating both Cleveland Clinic Staff and patients about the important role family history and genetics play in personalizing healthcare provision. The fair was held in multiple locations throughout the Cleveland Clinic System on various dates. Participants included: Christina Rigelsky, MS, CGC, Diane Clements, MS, CGC, Patricia Arscott, MS, CGC, Brandie Leach, MS, CGC, Allison Schrieber, MS, CGC, Kate Lynch, MS, CGC, Marissa Smith, MS, Megan Doerr, MS, CGC, Shanna Gustafson, MS, MPH, CGC, Jessica Mester, MS, CGC and Amy Shealy, MS, CGC.

Rocio Moran, MD, presented at the January 4, 2010, Nephrology Grand Rounds and the January 22, 2010, Pediatrics Grand Rounds. Dr. Moran educated the attendees about the genetic services available at the Cleveland Clinic and increased provider knowledge regarding indications for referral.

Jessica Mester, MS, CGC, Genetic Counselor in GMI’s Center for Personalized Genetic Healthcare (CPGH), presented at the Endocrine Surgery Symposium.

Jessica Moline, MS, CGC, presented at the Gynecology/Oncology Fellows Didactic on February 6, 2010, in efforts to further educate Cleveland Clinic healthcare providers about Hereditary Cancer Syndromes.

The Genomic Medicine Institute, in collaboration with the Wellness Institute, hosted Genomics Week at the 360-5 Wellness Store in March. Megan Doerr, MS, Jessica Mester, MS, CGC, Amy Shealy, MS, CGC, and Allison Schreiber, MS, CGC, Genetic Counselors from the Genomic Medicine Institute’s Center for Personalized Genetic Healthcare, educated employees about the importance of their family history and addressed questions about genetics and how to personalize wellness related to the environment, cancer, cardiovascular issues, prenatal/preconception and children’s health.

Amy Shealy, MS, CGC, and Jessica Moline, MS, CGC, Genetic Counselors from the Genomic Medicine Institute’s Center for Personalized Genetic Healthcare, gave a presentation titled “Genetics in Your Practice: Overview of Common Prenatal Screening Tests and Hereditary Cancer” at the OB/GYN & Women’s Health Institute’s Grand Rounds in March, 2010.

Allison Schreiber, MS, CGC gave a presentation titled “Clinical Genetics” at the March, 2010, Molecular Genetics Class.

Jessica Moline, MS, CGC gave a talk titled “Genetic Screening in Pheochromocytoma and Paraganglioma” at the Endocrinology Symposium’s Update on the Management of Adrenal Diseases and Lesions meeting in April, 2010.

Charis Eng, MD, PhD, gave a presentation titled “PTEN – How a cancer gene helps autism research” as the invited speaker at the Autism Speaks Cleveland Walk Kick-Off Event in May, 2010.

Jessica Moline, MS, CGC, gave a talk titled “Knowing Your Family History of Colon Cancer Can Save Your Life” at Cleveland Clinic Westlake as part of the Cleveland Clinic’s Health Talk series.

Allison Schreiber, MS, CGC, gave a talk titled “The New Genetics of NF1” as part of the Cleveland Clinic’s Neurofibromatosis Day.

Micheala Aldred, PhD, participated and presented a talk titled “Progress in molecular studies of 2q37 deletions” at a unique study weekend on 2q37 deletions, held in Oxford UK, in June.
New: High-throughput Sequencing Services in the Genomics Core

The Cleveland Clinic Genomics Core currently provides Capillary Sequencing services (plasmids and PCR products) using an Applied Biosystems 3730xl DNA analyzer and Micro-array services (Whole Genome Gene Expression, SNP genotyping and methylation) using an Illumina micro-array scanner. The capillary sequencer and micro-array scanner are Genomics Core equipment because they are expensive pieces of equipment that require well-trained personnel to operate them, which is not reasonable for individual labs. Since its inception in 2006, the Genomics Core has grown by 20% annually, a tribute to the instrument choices that were made and the quality of the data produced.

The Genomics Core has identified a new technique in Genomics Research that requires an instrument of similar expense and value to scientific discovery: High-throughput Sequencing (HTS) also known as DEEP sequencing, next generation sequencing, massively parallel sequencing, second generation sequencing or now generation sequencing. In essence HTS uses instruments that can currently generate 16 billion base-pairs of sequence in a week. This equals a human genome at 5x coverage. While these instruments are being heavily used by Genome Centers in Human Genome Sequencing Projects the High-throughput Sequencing techniques have also been found very useful for research purposes needed by the labs at the Cleveland Clinic:

**Coming 3rd Quarter, 2010: a High-Throughput Sequencing Instrument**

A $500k shared instrumentation grant was awarded in March 2010 (PI = Dr. C. Eng with contributions from Drs. Colmenares, Serre and Faber) The sequencer has been ordered and is expected later in the year. The Genomics Core will focus on operating the new instrument, but services will also include the preparation of sequencing libraries/samples. With regards to data output the Genomics Core will provide Core clients access to Illumina’s Genomestudio software, which allows for some basic data analysis on a standard PC. For additional data analysis clients can enlist the services of the newly formed LRI Bio-informatics Core or statisticians in the Department of Quantitative Health Services.

Until the new sequencer is on site, the Genomics Core will continue to offer High-throughput Sequencing services that include: library preparation, off-site sequencing analysis and data transfer in a GenomeStudio format.

If you are interested in running a High-throughput Sequencing experiment in any of the applications mentioned above contact the Genomics Core (faberp@ccf.org) for more information or to set up an appointment.

**APPLICATION EXAMPLES:**

1) **Targeted Re-Sequencing of the Genome:** Up to 5 Mb of genomic sequence can be isolated and DEEP sequenced at a 100 fold coverage.

2) **mRNA-SEQ:** A full-length cDNA library can be generated from a total RNA sample and sequenced to completion. The generated data is as quantitative as a micro-array but also provides information about structural variation, sequence variants, for any transcript present in the RNA sample, not just those represented on the array.

3) **CHIP-SEQ:** Following a chromatin immuno-precipitation experiment the precipitated DNA can be sequenced at more than a 100 fold coverage. The resulting data has been shown to be more precise in locating peaks than CHIP-CHIP experiment where background hybridization can cause problems.

4) **Methylation-SEQ:** DNA samples can be enriched for methylated regions of the genome and the enriched samples can subsequently be sequenced to obtain epigenetic information about the sample(s) of interest.

The examples given above represent only a subset of applications in which High-throughput Sequencing can provide scientific data that better the data that could previously be obtained for similar research experiments in quality, price or timing. See http://www.illumina.com/applications/sequencing.ilmn for additional applications as well as recent high profile research papers using Illumina High-throughput Sequencing technology.
New Personnel (since November 2009)
Thad Meese (Senior Business Analyst)
Ricky Chan (Postdoc, Serre lab)
Menggui Huang (Postdoc, Sehayek lab)
Min-Han Tan (Research Scholar, Eng lab)
Martie Gabel (Administrative Assistant, Dr. Eng)
Nicole Achkar (Research Technician, GMB)

New Students
Emily Pontzer (Graduate Student, Eng lab)
Amanda Tilot (Graduate Student, Eng lab)

Farewells & All the Best
Kate Lynch
Shanna Gustafson
Janice Blount
Jun Peng
Angela Marko

New Arrivals
Nicole Catherine Zygmunt
born on February 15th to proud parents Deb and Jonathan Zygmunt
Evan Moran
born on February 17th to proud parents Rocio and Tim Moran.
Landon Casey Leach
born on April 10th to proud parents Brandie and Dan Leach.
Hannah Faith Meese
born on April 28th to proud parents Thad and Beth Meese.
Leland Yilin Fan
born on May 26th to proud parents Ying Ni and Wei Fan.
Sean Michael Hobert
born on June 2 to proud parents Judith and Mike Hobert.

Promotions
Kathleen Babb  (Research Administrative Manager)
Petra Platzer  (Director, Integrative Development)

Congratulations for a job well done!
Christina Rigelsky, for contributing role as a member of the National Coalition for Health Professional Education in Genetics’ (NCHPEG) Genetic Public Policy Center Advisory Panel to create documents to better educate health professionals about the Genetic Information Nondiscrimination Act (GINA) and its implications on their clinical practice.

Drs. Eng and Moran for having been named to the 2010 Best Doctors List by Cleveland Magazine in the categories of Medical Genetics and Medical Oncology & Hematology (Dr. Eng) and Pediatric Medical Genetics (Dr. Moran).

Dr. Rocio Moran was awarded “2010 The Center for Child Neurology Merit Award” from Pediatric Neurology given “in recognition of her outstanding contributions in furthering the mission of the department and improving care of children with neurologic disorders.”

Dr. Charis Eng named to the 2010 Castle Connolly Medical Ltd Top Doctors list for Clinical Cancer Genetics and Medical Oncology, for the fourth year in a row.

Min-Han Tan, research scholar in the Eng lab and Cancer Genomic Medicine Clinical Fellow, for garnering a Lee Foundation (Singapore) Fellowship for training in clinical cancer genetics.

Yu Wang, postdoctoral fellow in the Eng lab, for winning a Susan G. Komen Post-doctoral Fellowship with his proposal entitled, “Androgen receptor regulates PTEN expression in breast cancer”

Ying Ni, pre-doctoral student in Dr. Eng’s lab, for receiving a DOD Breast Cancer Research Program pre-doctoral fellowship for her application entitled “Succinate Dehydrogenase Genes as Novel Susceptibility and Modifier Factors for PTEN-related Heritable Breast Cancer.”

Kylie Drake, a postdoc in Dr. Aldred’s lab, for winning the Third Annual American Thoracic Society Jane Morse Memorial Award for her work on microRNA processing in Pulmonary Arterial Hypertension. She was also awarded a Travel Award for this abstract.

Ying Ni, pre-doctoral student in Dr. Eng’s lab, for winning the Outstanding Translational Research Award at the Department of Molecular Medicine’s first retreat.

Bau Gopalan, Manager of the Bioinformatics Core, for her hard work and dedication as the LRI Diversity Council Coordinator for her term over the last 2 years.

Kylie Drake for being selected as the next Coordinator of the LRI Diversity Council beginning June 2010.

Chun Lei Zheng, postdoc in Dr. Zhang’s lab, on winning an AHA Postdoctoral Fellowship for his proposal titled “A common pathway mediating the intracellular trafficking of both factor V and factor VIII”.

Peter Balint for making a creative video piece for the State of the LRI telling how LRI personnel have an impact on patient care.

Dr. Charis Eng for being named Editor-in-Chief of the journal, Endocrine Related Cancer.

GMI’s Employee of the Quarter Recipients
Quarter 4, 2009: Phyllis Harbor
Quarter 1, 2010: Kathleen Babb & Nichole Prescott
Quarter 2, 2010: Monika Hanus & Jen Wilcox

Gloria Hunter received special recognition from Cleveland Clinic after completing twenty years of outstanding service.