C-B3-02:

Association of FTO, INSIG2, MC4R, and PCSK1 Obesity SNPs With Binge Eating in Morbidly Obese Patients

Glenn S Gerhard, MD, *Weis Center for Research*; Christopher D Still, DO, *Geisinger Health System*; G Craig Wood, MS, *Geisinger Center for Health Research*; Xin Chu, PhD, *Weis Center for Research*; Robert Erdman, BS, *Weis Center for Research*; Meghan Susek, *Weis Center for Research*; Heather Gerst, DO, *Geisinger Health System*; Kim Derr, BS, *Weis Center for Research*; Mouna AlAgha, MD, *Weis Center for Research*; Christina Hartman, BS, *Geisinger Health System*; David Carey, PhD, *Weis Center for Research*; Peter Benotti, MD, *Geisinger Health System*

Background/Aims: Obesity has a strong genetic component. Recent genome-wide association studies have identified single nucleotide polymorphisms (SNPs) in or near over a dozen genes that are related to body mass index (BMI). Despite the association of these SNPs with BMI, the mechanism by which they influence the determination of body weight is not yet known. Recently, the fat-mass and obesity-associated (FTO) obesity SNP was related to energy intake and preference for foods of high caloric density in children. FTO genotype was not associated with resting energy expenditure. We have extended this type of analysis to eating behaviors in the morbidly obese. **Methods:** DNA was obtained from approximately 900 morbidly obese (BMI > 40 kg/m²) patients and used to genotype obesity SNPs in or near the FTO, INSIG2, MC4R, and PCSK1 genes. Binge eating status (normal, episodic overeating, or any binge eating) was determined using the validated Questionnaire on Eating and Weight Patterns (QEWP). Binge eating status was correlated with each individual genotype, the combined obesity allele burden, and the combined homozygous obesity gene burden. **Results:** Binge eating data was obtained from 640 patients who had completed the QEWP. Of these 640, 116 (18%) were classified as manifesting binge eating behavior. No association was present between heterozygous or homozygous FTO ($P=0.59$), MC4R ($P=0.30$), or PSK1 ($P=0.77$) obesity SNPs. However, 29% of those who were homozygous for the INSIG2 obesity SNP were classified as binge eaters, versus 17% of heterozygous or homozygous normal patients ($P=0.006$). Association was also found with binge eating status and the presence of 2 or more homozygous obesity genotypes (28% versus 17%, $P=0.041$), likely due to the INSIG2 gene. Cumulative obesity allele burden (0–8 alleles for the 4 genes) was not associated with binge eating status ($P=0.42$). **Conclusions:** The INSIG2 obesity SNP appears to influence binge eating behavior in morbidly obese adults. The FTO obesity SNP appears to influence eating behavior in children suggesting that different genes may influence obesity at different ages. For both genes, excess caloric intake appears to be the major mechanism influencing BMI. How other obesity genes influence body weight regulation has not yet been determined.

C-B3-03:

Association of Epidemiologic and Genetic Factors With Abdominal Aortic Aneurysm (AAA)

Diane T Smelser, PhD, *Geisinger Center for Health Research*; Alicia Golden, BS, *Geisinger Health System*; Katherine Masker, BS, *Geisinger Health System*; James R Elmore, MD, *Geisinger Health System*; David J Carey, PhD, *Weis Center for Research*

Background: Abdominal Aortic Aneurysm (AAA) rupture is the thirteenth leading cause of death in the U.S. and a major cause of death in the elderly. Since most AAAs are asymptomatic, mortality could be greatly reduced by determining which patients are at risk, then screening those patients prior to a rupture. Our aim was to determine which clinical and genetic risk factors are associated with AAA. **Methods:** This was a case-control study of patients from the Geisinger Vascular Clinic and the Geisinger MyCode Project (a biobanking project of Geisinger Clinic patients who volunteered to participate in genetic research projects). Clinical and environmental risk factor data was obtained from patient electronic medical records (EMR) and analyzed by multivariate logistic regression. In a subset of participants, we also analyzed three promising genetic polymorphisms, two from a prior genome-wide association study in this population (rs12039875, 1q41; rs7635818, 3p12.3) and one from the recent literature (rs10757278, 9p21). The genetic data was combined with the clinical data using multivariate logistic regression. **Results:** In the clinical analysis the number of Vascular Clinic and MyCode AAA cases totaled 722, with 11,761 controls. Adjusted

OR showed a significant AAA risk for age, gender, smoking, intermittent claudication and peripheral artery disease, while body mass index (BMI) and diabetes were surprisingly protective. The genetic analysis consisted of 502 AAA cases and 295 controls from the Vascular Clinic. The GC genotype of rs7635818 showed an increased risk, but the rs12039875 AA genotype showed a significant protective effect when controlling for the clinical variables. This SNP is located in KCNK2, a gene in the potassium channel protein family. Although this gene has not previously been linked with AAA, our laboratory showed that this gene is expressed in vascular tissue. **Conclusions:** Our study indicates a significant elevated risk of AAA for individuals who are older, male, ever smoked, have peripheral artery disease and a GC genotype of rs7635818. Higher BMI, diabetes and the AA genotype of rs12039875 in the KCNK2 gene significantly lower AAA risk. This is one of the first studies to utilize the MyCode population in a research study and establish this population source as a valuable and convenient asset of Geisinger Health System for clinical research.

C-B3-04:

Media Analysis of Genetic Testing Information for Common Disease Presented to the Public

Alanna Kulchak Rahm, MS, *Kaiser Permanente Colorado*

Background/Aims: With the advent of personalized medicine, consumers are routinely exposed to information and direct-to-consumer (DTC) advertising of various genetic tests. Specifically, 2007–2008 saw a return of the DTC advertisement for BRACAnalysis® in the eastern US, and the advent of three new companies offering DTC genetic screening for under \$1000. This abstract presents the results of a media analysis for information presented to the general public on genetic testing for common diseases, such as cancer or heart disease, or for full genome scans for disease risk in general. **Methods:** Lexis Nexis search was conducted using the broad term genetic testing. The search was limited to all major world publications, news wire services, TV and radio transcripts, blogs, and web publications between the dates of September 1, 2007 and September 30, 2008. The purpose was to assess information presented to the lay public; therefore, scientific literature was not searched. These media reports were examined for number of reports, report type (print, television, online), target audience, polarity of information (positive for genetic testing or negative against genetic testing), and test type. **Results:** One-thousand articles were retrieved from the initial search. Immediately excluded were articles about ancestry testing, diagnostic testing, psychiatric testing, food safety, forensic testing, cloning, and pre-marital genetic testing due to ethnicity or consanguinity. Additional exclusions were made for all areas surrounding prenatal genetic testing, including pre-implantation diagnosis and paternity testing. Stock announcements, hearing testimonies, and reports on non-U.S. companies or from non-U.S. sources were also excluded. This resulted in a total of 173 media reports over the one year time period to which the lay public was exposed. These 173 reports were analyzed further for specific information presented. **Conclusions:** Over a one year period, consumers are routinely exposed to information about genetics through the media. These reports span all methods of media delivery and vary in polarity.

PS2-08:

Development and Implementation of a Genetic Fingerprinting Assay for the Personalized Medicine Research Project

Deanna S Cross, PhD, *Marshfield Clinic Research Foundation*; Lynn C Ivacic, *Marshfield Clinic Research Foundation*; Elisha L Stefanski, *Marshfield Clinic Research Foundation*; Catherine McCarty, PhD MPH, *Marshfield Clinic Research Foundation*

Background: For any biorepository, it is necessary to develop measures that determine sample quality and ensure each sample can be correctly identified. One method of devising this type of quality control measure is to rely on DNA polymorphism panels developed for forensic applications. Although valid for identification, these panels are not useful for other purposes, such as medical research. **Aims:** We developed an identification panel for the Personalized Medicine Research Project (PMRP) that uses medically relevant polymorphisms. This panel not only uniquely identifies samples and tests for sample quality but can also be used by investigators for candidate gene studies. **Methods:** Polymorphism candidates were taken from investigator

requests, PharmGKB (www.pharmgkb.org) and the disease association database (<http://geneticassociationdb.nih.gov/>). To be considered, a polymorphism had to be associated with disease in two independent populations and it had to have a reported minor allele frequency in a Caucasian population of at least 0.20. The final assay was developed on the Sequenom platform and all individuals within the PMRP cohort were analyzed. Probability of identity for the panel was calculated and each polymorphism was tested for Hardy Weinberg equilibrium. The allele frequencies found in our population of 20,000 were compared to reported allele frequencies. The allele frequencies in the PMRP population were compared between males and females and between different age categories. **Results:** From a list of 116 potential polymorphisms we developed a single assay of 36 medically relevant somatic polymorphisms with at least one polymorphism on each chromosome and a single sex marker. The probability of identity for the assay was 6.132×10^{-15} and the sibling probability of identity was 3.077×10^{-8} . Three polymorphisms differed from previously reported allele frequencies by more than 10%. In our population, four polymorphisms were different in males and females and four polymorphisms varied in allele frequencies between age groups. Furthermore, the chosen polymorphisms have been used in two studies and as preliminary data in several other studies. **Conclusions:** We were able to create a DNA panel of 36 medically relevant polymorphisms that successfully tested DNA quality, increased the knowledge of population wide allele frequencies, and is useful to investigators for candidate gene studies.

PS2-13:

Genetic and Environmental Risk Factors for Prescription Opioid Dependence in the Healthcare Setting

Joseph A Boscarino, PhD, MPH, *Geisinger Center for Health Research*; Stuart N Hoffman, DO, *Department of Neurology, Geisinger Health System*; Glenn Gerhard, MD, *Weis Center, Geisinger Health System*; John Han, MD, MS, *Pain Management Center, Geisinger Health System*; Margaret Rukstalis, MD, *Geisinger Center for Health Research*; Porat M Erlich, PhD, *Geisinger Center for Health Research*; Walter F Stewart, PhD, MPH, *Geisinger Center for Health Research*

Background: Research on the genetics of opioid addiction among illicit drug users is difficult given challenges to case ascertainment and selection of an appropriate control group. To address this limitation, we tested a model by studying prescription opioid users. **Methods:** We undertook a case-control, candidate-gene study of opioid-dependent users and nondependent users among Geisinger Clinic outpatients. Electronic health record (EHR) data were reviewed for patients who were prescribed opioids. Patients were selected for a phone interview if they had five or more prescription orders for opioids in the prior 12 months for non-cancer pain. Cases were identified based on the Diagnostic and Statistical Manual of Mental Disorder, Version IV (DSM-IV) criteria for opioid dependence. A modified Composite International Diagnostic Interview (CIDI) was used to obtain data on dependence status and history. Data were also gathered on detailed drug, psychological, and environmental exposures. Altogether, 703 patients completed the CIDI; 512 of these patients (73%) provided DNA for genotyping and completed the NEO Five-factor Personality Inventory. **Findings:** Altogether 37.4% (95% CI = 33.8–41.1) of patients met DSM-IV criteria for lifetime opioid dependence and 30.7% (95% CI = 27.3–34.3) met criteria for current dependence. Significant predictors of opioid dependence included younger age, unemployment, psychotropic medication use, as well as history of PTSD, anxiety, depression, alcohol abuse, anti-social personality, illicit drug use, trauma exposure, and substance abuse treatment (all P -values < 0.001). Preliminary Genetic analyses suggested that opioid dependence was associated with dopamine receptors D2 and D3 and the COMT genes. Gene by environment (G x E) interactions were also detected related to opioid dependence and exposure to mental trauma. **Conclusion:** The prevalence of drug dependence is high among pain patients on long-term opioid therapy in the outpatient setting. This disorder is associated with a history of other mental health conditions, employment status, psychotropic medication use, illicit drug use, and exposure to mental trauma. Genetic analyses suggested associations with genes related to neurocognitive processes associated with impulse control and reward regulation. Several G x E interactions were also detected.

Health Economics

C-C2-01:

Financial Assessment of a Comprehensive Cardiac Care Program for Patients With Occlusive Coronary Artery Disease

Thomas Delate, PhD, MS, *Kaiser Permanente Colorado*; Kari Olson, PharmD, BCPS, *Kaiser Permanente Colorado*; Jon Rasmussen, PharmD, BCPS, *Kaiser Permanente Colorado*; Kara Hutka, PharmD, BCPS, *Kaiser Permanente Colorado*; Brian Sandhoff, PharmD, BCPS, *Kaiser Permanente Colorado*; Roseanne Hornak, PharmD, BCPS, *Kaiser Permanente Colorado*; John Merenich, MD, *Kaiser Permanente Colorado*

Background: While early and aggressive comprehensive cardiac care (CCC) programs in patients with coronary artery disease (CAD) have been associated with improvements in clinical outcomes, information on the financial outcomes of such programs are limited. The purpose of this investigation was to assess the financial impact of a CCC program on total healthcare expenditures after an initial coronary event. **Methods:** This was a matched, retrospective cohort analysis of the Kaiser Permanente Colorado (KPCO), a group model HMO, nurseand pharmacist-managed CCC program that was designed to provide evidence-based lifestyle and medication support at the earliest opportunity after a coronary event. Patients with an incident occlusive CAD event between January 1999 and June 2004 were categorized into intervention and comparator groups, respectively, by enrollment or never enrollment (No CCC) into the CCC. Patients were matched 1:1 on chronic disease score (CDS) and 180-day pre-coronary event (baseline) total healthcare expenditures. Pharmacy and medical utilization events were extracted from electronic administrative and claims databases. Utilization events were collected after the initial coronary event until death, health plan termination, three years, or December 31, 2005, whichever came first (follow up). Expenditure estimates from the KPCO Decision Support System (in 2007 dollars) were applied to utilization events. An intervention cost of \$1/follow-up-day was applied to all CCC patients. Expenditures/day were modeled with adjustment for matching variables, patient characteristics, baseline expenditures, and intra-correlations of matched patients. **Results:** 628 CCC patients were matched to 628 No CCC patients. Patients in the No CCC group were slightly older, more likely to be female, and to have had a myocardial infarction. Mean/median baseline expenditures and CDS were equivalent. During follow-up, 12 and 98 cardiac-related deaths occurred in and mean/median total healthcare expenditures/day were \$57/\$30 and \$159/\$45 for the CCC and No CCC groups, respectively (both $P < 0.001$). After adjustment, CCC patients were associated with -\$103/day lower total healthcare expenditures ($P < 0.001$; adjusted R-square=0.71 with log-transformed expenditures). **Conclusions:** Comprehensive and aggressive implementation of secondary cardiac prevention strategies with close monitoring and follow-up of CAD patients is associated with reduced healthcare expenditures.

C-C2-02:

Validation and Uses of the ACG-DX Predictive Modeling and Risk Adjustment Tool in an Israeli HMO

Isaac Hoch, MD, *Maccabi Healthcare Services*; Anthony D Heymann, MB, MHA, *Maccabi Healthcare Services*; Tomas Karpati, MD, *Maccabi Healthcare Services*; Liora Valinsky, MPH, *Maccabi Healthcare Services*

Background: With an ever increasing population of HMO members with chronic disease and continuing economic pressures to provide good medical care as efficiently as possible, there is a need for methods to stratify populations by health status and their future risk for using limited healthcare resources. **Methods:** We used the ACG-DX program developed at Johns Hopkins University for validation testing on an Israeli PPO population. This program uses same year data to provide a risk adjustment analysis for that year and predict high-users (top 5%) for the following year. The Maccabi Healthcare Services has an extensive demographic and medical database keyed by a unique identifier for each member. We provided age and gender data as well as all diagnoses for year 2006 and total cost for years 2006 and 2007 for each member as input to the ACG-DX program. We truncated total costs over the 99.9% for both pharmacy and total costs. The explanatory value for costs in 2006 (R^2) and positive predictive value for total costs in 2007 were calculated for the entire population of 1.7 million subscribers. The R^2 results were compared to results based on American data and reference values (ref.) generated by the