INVITED SPEAKERS

Oncology B

DNA and RNA in Precision Medicine

Dr Noam Shomron

Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Next-generation sequencing (NGS; also known as Deep Sequencing) has probably been the most important tool for genomic research over the past few years. NGS has led to numerous discoveries and scientific breakthroughs in the genetic field. The sequencing technology is shifting from the research laboratory to the clinical diagnostic arena. Multiple NGS protocols are used for reading both DNA and RNA molecules. I will present our integrative view achieved when measuring the levels of both DNA and RNA in a given tissue. This mapping is of actionable relevance for the patient leading to efficient precision medicine.

INVITED SPEAKERS

Obesity, Diabetes B

Epigenetics in Diabetes - New Molecular Targets for Life Style Modifications

Francesco Béguinot & Antonella Desiderio

IEOS URT Genomica del Diabete & DiSMET "Federico II" University of Naples, Italy

The known genetic variability (common DNA polymorphisms) does not account either for the current epidemics of type 2 diabetes or for the family transmission of this disorder. However, clinical, epidemiological and, more recently, experimental evidence indicates that environmental factors have an extraordinary impact on the natural history of type 2 diabetes. Some of these environmental hits are often shared in family groups and proved to be capable to induce epigenetic changes which alter the function of genes affecting major diabetes traits. Thus, epigenetic mechanisms may explain the environmental origin as well as the familial aggregation of type 2 diabetes much easier than common polymorphisms. In the murine model, exposure of parents to environmental hits known to cause epigenetic changes reprogram insulin sensitivity as well as beta cell function in the progeny, indicating that certain epigenetic changes can be transgenerationally transmitted. Studies from different laboratories revealed that, in humans, lifestyle intervention modulates the epigenome and reverts environmentally-induced epigenetic modifications at specific target genes. Finally, specific human epigenotypes have been identified which predict adiposity and type 2 diabetes with much greater power than any polymorphism so far identified. These epigenotypes can be recognized in easily accessible white cells from peripheral blood, indicating that, in the future, epigenetic profiling may enable effective type 2 diabetes prediction and might provide innovative tools for personalized treatment.

INVITED SPEAKERS

Big Data and Arthritis

Strategy for Improving Health Outcomes for People with Arthritis and Related Diseases

Amanda Niskar
Arthritis Foundation

Finding a cure for arthritis is, and always will be, a priority for the Arthritis Foundation. With a track record of major scientific achievements, the Arthritis Foundation is leading a new approach to conquering the more than 100 types of arthritis and related diseases. With the help of evolving technologies and science, we can successfully collaborate with the ultimate goal of finding a path to a cure. From small steps to large breakthroughs, we're always finding ways to improve the quality of life for people with Arthritis. Together, we can have "arthritis on the run" by accelerating the movement of scientific knowledge to a faster cure.

For more information about the Arthritis Foundation's path to a cure, visit: http://www.arthritis.org/arthritis-cure/

For the Arthritis Foundation Scientific Strategy, visit: http://www.arthritis.org/Documents/arthritis-foundation-scientific-strategy.pdf

INVITED SPEAKERS

Big Data and Arthritis

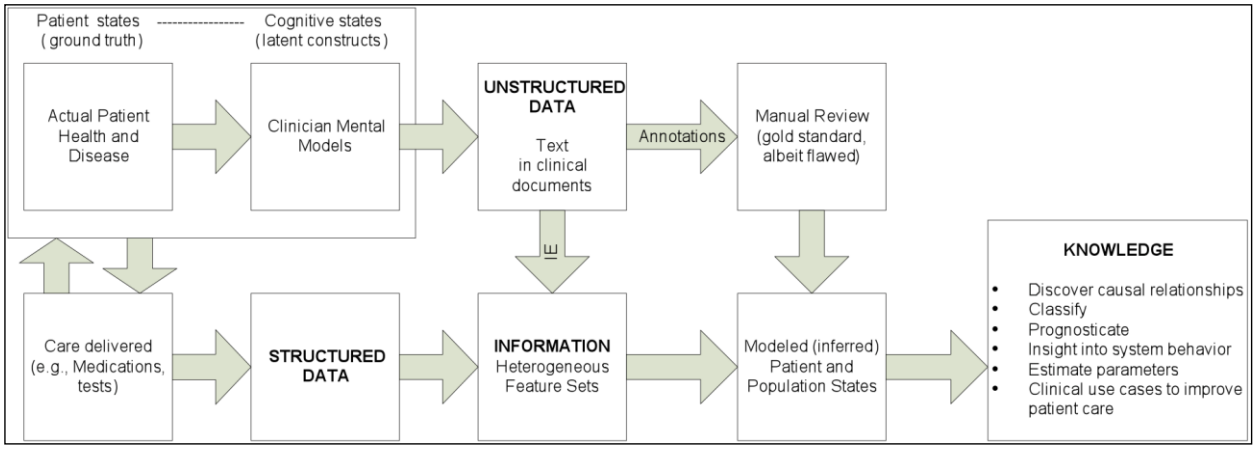
Big Data Analytics – Veterans Affairs Informatics and Computing Infrastructure (VINCI)

By Yelena Yesha, Amanda Niskar, Michael Grasso, Scott DuVall, Naphtali Rishe

U.S. Arthritis Foundation, University of Maryland, University of Utah, NOA Data Science Institute Inc, Florida International University

yelenayesha@gmail.com

We work with clinical data from the Department of Veterans Affairs (VA) to perform Big Data Analytics for Arthritis and other conditions. The VA dataset is one of the largest clinical repositories available, and provides detailed patient information for approximately 25 million patients who have received care at 152 medical centers and more than 800 outpatient clinics across the United States over the past 15 years. The repository includes more than 4 billion progress notes, 2 billion procedure and imaging reports, 1.6 billion medication fills, and 1.5 billion diagnoses. The repository also contains patient demographics, diagnostic codes, outpatient visits, hospital admissions, patient orders, vital signs, laboratory testing, inpatient and outpatient pharmacy data, clinical consults, immunizations, mental health screening, associated physicians, and payment information. This is a large and comprehensive data set, whose size and attributes create analytic and data mining issues that are beyond the capabilities of traditional software tools. The data comes from 163 Hospitals, 800 Clinics, 135 Nursing Homes, 43 Domiciliaries, 180,000 Healthcare Professionals, Hospital sizes vary from 100 to 1000 beds. Outpatient visits vary at the facility from 30,000 to 450,000 visits per year. There are 46.5 million outpatient visits per year, 564,000 inpatient admissions per year, 167 million prescription-months filled. The following diagram depict the knowledge discovery workflow.



This research has been sponsored in part by the Arthritis Foundation.

INVITED SPEAKERS

Big Data and Arthritis

Methods for Moving Towards Pre-Clinical Diagnosis for Rheumatoid Arthritis

Naphtali Rishe PhD, Amanda Niskar PhD, Yelena Yesha PhD, Michael Grasso MD PhD, Tajana Lucic MD
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The Arthritis Foundation is developing new data-driven approaches to improve the care of peoples with arthritis. This research analyzes the comprehensive Electronic Medical Records of the Department of Veterans Affairs (VA). The VA has detailed patient information for roughly 25 million veterans.

Big Data analytics will empower physicians at the point of care to diagnose early arthritis stages, choose treatment approaches, and decide when to refer to a subspecialist.

Preliminary Findings of our research pending validation:

- Defined a cohort of 150,000 people with RA from among the 25 million VA EMR records. Outcome: This large cohort will enable data-driven studies to identify clinically important subsets of RA profiles not otherwise recognized in routine clinical care. Now, there is a basis for performing large-scale studies of specific treatments best suited to any profiles of people with RA.
- Best choice of medication depends on race and age of people as well as on their blood test profile. Outcome: Medications can be customized based on clinical data of the person with arthritis. Optimal treatment choice depends on the presenting signs and symptoms of RA, and is further modified based on patient factors such as age and comorbidities. Future work: customize medications based on both clinical and genetic data of the patient.
- Some groups of people with RA have normal cholesterol level even though they have higher incidence of heart disease. Outcome: Provides guidance to physicians to use factors other than cholesterol in screening for heart disease in people with RA with normal cholesterol level.
- Cardiovascular disease is the leading cause of death among people with RA. The disease risk is double that of the general population of same age and gender. Outcome: Provides guidance to physicians on management of cardiovascular risk factors in people with RA.

This research has been sponsored by the Arthritis Foundation.

ORAL PRESENTATIONS

Identification of the Functional Significance of Mutations using the Novel Precision Cancer Analysis System

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As no two tumors share the same molecular mechanism, each cancer patient presents a unique type of disease. Genomic profiling has armed oncologists with new information leading to major improvements in patient care. The establishment of such tools raised the bar for the next generation of cancer diagnostics to overcome two challenges 1) Identification of the clinical significance of the mutations in tumors and the interplay within them 2) assessing the usefulness of targeted therapeutics to the specific patient's cancer. 20 cancer patients were analyzed by the Precision Cancer Analysis system (PCAS), which quantifies oncogenic activity in the majority of the oncogenic signaling pathways altered by the patients' mutations through a functional assay and does not rely on prior knowledge of the mutations. The system produces a quantitative output enabling grading the different mutants of the same patient, providing prioritization for better drug selection. In 3 tested genes, 16 different mutations were identified- 4 in EGFR, 4 in PIK3CA and 8 in KRAS. Of these 10 were classified as known mutations for which functional annotation exists, and 6 were variants of unknown significance (VOUS). In addition to correctly annotating all known mutations, the PCAS further quantified oncogenic activity in all the VOUS tested. These results clearly demonstrate the value of a functional assay in accurately identifying the optimal course of treatment, particularly by its ability to add actionable information to VOUS. The study produced a comprehensive delineation of the oncogenic activity of each patients' individual mutations using the PCAS method.

Developing a Smart Physician/Patient Decision Support Healthcare System

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Background: Existing clinical decision support systems generally address the problem of diagnosing patients. Today, only 20 percent of the knowledge physicians use to make diagnosis and treatment decisions. The result is that one in five diagnoses are incorrect or incomplete and nearly 1.5 million medication errors are made in the US every year. In this project we are trying to address these problems.

Objectives: Objectives are to develop an innovative cloud-based platform for the smart service system, and novel big data analytics tools. The system will enable medical practitioners to integrate the wide range of data pertaining to their patients and make faster and more accurate diagnoses, and cost effective decisions. The system will be capable of learning, dynamic adaptation, and decision making based upon patient data received and processed.

Methods: Our team is presently developing innovative data mining, machine learning, and data visualization techniques and tools to: determine patient characteristics, risk factors, and disease severity associated with subsequent clinical response to treatment, provide insight into the decision-making process for doctors when making patient treatment plans, and analyze cost models and patient outcomes.

Results: We created software that performs instantaneous analyses and synthesizes of clinical data across the entire network of patients. We present results including visualizing clinical trends, treatments and outcomes to enable data driven decision-making. This provides the forecast of the trend diseases, their outcomes, and efficiency of treatments across a continuum to understand what is working and what is not working.

How to Make an Adherence App Appeal to the Elderly: the Case of "Medication Plan"

Talya Miron-Shatz[1], Stefan Becker[2], Urs-Vito Albrecht[3]

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[2]*Nephrology, Faculty Member, Germany*

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Background: Non-adherence to medication poses a huge challenge to health. Existing technological solutions often ignore the needs of elderly patients, thereby excluding them, and creating a generational digital divide.

Objective: To examine the mobile application "Medication Plan," designed by Dr. Stefan Becker, downloadable for free from the Apple-App-Store 2010-2013

To find correlates associated with regular intake of medication, using "Medication Plan."

Methods: The app-related activities of 1799 users (1708 complete data sets) were recorded. 74% were male, median age 45 years.

Results: The older the patients, the longer they used the app, with users aged 60 and above using it for an average of 103.9 days. There was a significant increase of mean usage duration between the age cohorts < 21 and >60 years ($F = 2.581$; $df = 5$; $p = 0.025$).

"Daily usage intensity" was associated with an increasing number of prescribed medications and increased from an average of 1.87 uses per day and 1 drug per day to an average 3.71 uses per day for users taking over 7 different drugs a day ($p<0.001$). Demographics (sex, age and educational attainment) did not affect usage intensity.

Conclusions: Elderly smartphone users requiring polypharmacy, relied on a mobile application to support drug adherence .The findings strongly suggest mobile applications may be a promising approach to support patients with chronic conditions. No major gamification was applied, thereby indicating that intrinsic motivation – wanting to keep one`s health – is sufficiently powerful. Importantly, patients were helped in installing the app, and with initial usage.

Using the Power of Big Data and Crowdsourcing for Precision Medicine in Amyotrophic Lateral Sclerosis (ALS)

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with significant heterogeneity in its progression. This heterogeneity makes research, clinical care and drug development difficult.

To overcome this challenge, we developed the Pooled Resource Open-access ALS Clinical Trials (PRO-ACT) platform. The PRO-ACT database includes demographics, family history, vital signs, clinical assessment, lab-based, treatment arm, and survival information from 8600 ALS patients. The database was launched open access on December 2012, and since then over 400 researchers from over 40 countries have requested the data. We used this data to launch the DREAM ALS Prediction Prize4Life, a crowdsourcing Challenge seeking the development of more accurate tools for estimating disease progression at the individual patient level.

The DREAM ALS Prediction Prize4Life drew over 1000 registrants that uses three months of clinical data to predict disease progression a year later. In a simulation, the winning algorithms could reduce the number of patients needed for future clinical trials by 20%. The best performing methods also predicted disease progression for a representative subsample of patients consistently better than a group of world leading clinicians. Finally, the algorithms uncovered several novel predictors of disease progressions that can shed light on the mechanisms behind the disease. The algorithms are now being used by several clinical trials and clinics.

These results demonstrate the value of large datasets and DREAM Challenges for developing a better understanding of ALS natural history, prognostic factors and disease variables. We are now working on another crowdsourced Challenge to further these findings.

Mobile GDx - Delivering Genetic and Molecular Diagnositic Test Results

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There has been exponential growth in genetic and molecular diagnostic (GDx) testing and it is quickly and steadily being incorporated into clinical practice guidelines across a wide range of health indications, including cancer, cardiology, infectious diseases, mental health, and primary care. Proper use of genetic tests has the potential to significantly improve health outcomes while decreasing healthcare costs associated with ineffective treatments. Yet, clinical decision support systems to facilitate implementation of genomic medicine have not been developed or integrated into the Electronic Health Record (EHR). Therefore, GDx tests often go unrecorded or tests are recorded inaccurately in the EHR.

Growth in GDx testing has coincided with the US federal government's effort to improve EHRs. One of the core measures of the EHR effort is to provide patients with direct, electronic access to their health information, including laboratory diagnostic test results. Providing patients with this access to their health records also allows clinicians and researchers to gather and validate phenotype data directly from patients .

The Department of Veterans Affairs is building a Mobile GDx App with a patient-facing interface and a provider-facing interface. Through the app, patients will be able to securely access their GDx test results along with educational information and explanations. Care providers will be able to search for a patient and view GDx test results, facilitate the ordering of genetic counselor consultations, and provide decision support to assist providers in ordering GDx tests that are appropriate for a patient`s diagnosis. The app will also allow for patient-provider communication.

Women's Higher Cancer Risk vs. Men's Advantage with High n-6 Fatty Acid Intake, Explained by Direct Estrogen-Fatty Acid Effect on DNA Depurination

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Unexpected low Israeli international health ranking despite adequate diet – but high in n-6 polyunsaturated fatty-acids (PUFA) – with women's much worse status vs. men's advantage, especially for cancer, and lead in the national 'cancer shift' over heart disease mortality, raised questions regarding a 'gender-nutrition paradox' of health dichotomy with the same diet .

The Israeli diet is considered 'good' – close to recommendations – save for n-6 (12%kcal) higher than recommended and 'Mediterranean diet' levels.

Israeli women ranked worse internationally, reflected by all-cancer mortality 15th vs. men's 37th/44 countries and 13th vs. men 2nd-best/22; breast cancer mortality 19.2% above a European 27-country average vs. prostate -30.4% below; and much smaller gender differences, i.e. male-female life expectancy, -31.6% vs. European average and mortality ratios for all-cause, -15.1%, and all-cancer, -27.1%.

Ethnic comparisons revealed consistently higher cancer prevalence in Israeli-Jewish than Israeli-Arab women, but Arabs' recently increased 3.0-fold more rapidly, gradually closing the gap, concurrent with increasing n-6 intake in Arabs, as corn/soy oils replaced traditionally predominant olive. While Jewish n-6 consumption declined (12 to 8.8%kcal [1995-2001]), intake was still 25.5% higher than Arab women`s, with n-6:n-9 monounsaturated fatty-acid ratio 40.4% higher.

Research shows females' greater PUFA conversion, i.e. n-6 linoleic to arachidonic acid and related inflammatory/mutagenic/carcinogenic eicosanoid cascades, and mechanistic/molecular links between estrogen, n-6, and DNA damage, suggesting causal relationships between high n-6 intake and breast cancer. This could exacerbate other risks among Israelis, including genetic (BRCA) and/or sociopolitical stress, emphasizing the importance of gender-nutrition epidemiology in preventive strategies, especially vs. cancer, warranting targeted research.

Testing for BRCA1/BRCA2 in the Department of Veterans Affairs

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Background: Guidelines for BRCA1/BRCA2 testing criteria include offering genetic testing to women diagnosed ≤ age 45, and ≤ age 50 if there is a family history or an additional primary. We sought to assess baseline use of breast cancer genetic testing in an environment that has historically focused on cancers more common in males. Methods: The VA Cancer registry (VACCR) was used to identify Veterans diagnosed with breast cancer aged 50 years or younger for years 2011-2012. Data on patients receiving BRCA testing were provided by Myriad Genetics and linked to the VACCR dataset. We examined patient and clinical characteristics to determine predictors of BRCA testing. Logistic regression was performed to obtain odds ratios and 95% confidence intervals (CIs). Results: 250 Veteran patients aged 50 years or younger were identified from 75 VA facilities. Of those, 66 (26%) received BRCA testing. The mean age of those tested was 42 years (range: 23-50 years). A significant decreased likelihood in testing was shown with every increasing year of age. No statistically significant differences in receiving tests were observed between whites (28%) and blacks (25%). Among those who had family history of any reportable cancer, 30% received BRCA testing compared to 19% who did not have a documented family history; family history was not a significant predictor of testing. Conclusions: In VA, 26% of the patients diagnosed with breast cancer received BRCA1/2 testing. Our findings show no differences in utilization across races. The documentation of family history, another test criterion, varied significantly.

A case study of real–world implementation of IL28B pharmacogenomics testing in the Department of Veterans Affairs

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Background: Hepatitis C (HCV) treatment and its pharmacogenomic testing are rapidly changing. The IL28B test measures likelihood of response to interferon, a common first-line treatment for HCV. Non-interferon direct-acting antiviral agents have been recently approved for HCV treatment. This study evaluates the implementation of pharmacogenomics testing in the context of rapidly evolving treatments and changes in guidelines. We examined regional and site of care variation in IL28B testing, concordance with guidelines, and impact of test results on treatment decisions.

Methods: This was a retrospective observational study. Patient-level test orders and results were obtained from contracted reference laboratories and linked to the VA data. We conducted univariate and bivariate analyses, including t-tests for continuous variables and Pearson's Chi-square for categorical variables, to characterize patient and site of care variations in IL28B testing.

Results: From 2011-2013, IL28B genotyping was performed in 3,529 patients. Of these, 2,988 were linked to VA data. Patient characteristics were: 97% male, age (mean=58.7, SD 6.8), race (Black 42.9%, White 50.3%, Hispanic 3.4%, Other 3.4%). Frequency of favorable genotype was three-fold higher in Whites (541, 36.0%) than in Blacks (151, 12.0%). The timing of testing and treatment was: 566 (18.9%) Veterans were tested post-interferon treatment, 2,373 (79.4%) prior to and 49 (1.6%) concurrent with treatment. Of 630 treatment-naïve Veterans with CC genotype, only 144 (4.8%) initiated interferon treatment after testing.

Conclusions: Only 64.8% of test orders were concordant with guidelines. 35.2% of Veterans were either tested after interferon treatment or results did not influence treatment.

POSTERS

High frequency of the c. 3980 GA (p.W1327X) mutation in AGL gene of Tunisian patients with hepatic presentation of glycogen storage disease type III syndrome

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BACKGROUND: Glycogen storage disease type III (GSD-III) is an inborn error of glycogen metabolism caused by a deficiency of the glycogen debranching enzyme (AGL) .Some of the mutations appear to be population specific, whereas others are found in probands from a variety of different ethnic backgrounds. The recurrent mutation W1327X in exon 31 was identified in the Tunisian population, suggesting a founder effect. In this present study, we report a phenotype-genotype correlation of this frequent mutation.

METHODS: Seven unrelated Tunisian families (from MAHDIA); including 10GSD type III patients were presented with hepatomegaly, progressive severe myopathy and cardiomyopathy. The routine laboratory findings showed an elevated serum aspartate aminotransferase, alanine aminotransferase, creatine kinase and triglyceride levels. The blood lactate and uric acid levels were within normal limits. RESULTS: The biochemical results of ten patients indicated a striking elevation of glycogen content in the erythrocytes after several hours fasting favours type III GSD and completely decrease of debranching enzyme activity was measured in leucocytes. Mutational analysis of the AGL gene showed a homozygous p.W1327X mutation. Study of genotyping method, in 30 families, using four polymorphic microsatellite markers on chromosome arm 1p21, we identified a common haplotype for all patients originated from MAHDIA.

CONCLUSIONS: p.W1327X is the most characteristic mutation for Tunisian patients with GSD IIIa. A common haplotype which shows the existence of a specific effect founder of this population confirmation of GSD-IIIa in Tunisisan (from MAHDIA) patients by clinical and genetic findings.

Erythrocyte Parameters as a Means to Distinguish Stage of Colorectal Cancer

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Objective: The aim of this work was to assess the potential of spectroscopy in association with dielectrophoresis for studying erythrocytes (Er) as a preliminary noninvasive test in colorectal cancer (CRC) staging diagnosing.

Methods: A total of 38 persons (58±7 years old) with CRC in the T1-2 stage (the 1st group) and in T3-4 stage (the 2nd group) were examined. Electric, viscoelastic Er parameters were investigated by dielectrophoresis, membrane structure - by TLC, gas chromatography-mass spectroscopy (GC-MS). Metabolic profiling of macroergic compounds was done by the 31P NMR spectroscopy.

Results: The patients of the 2nd group had marked disturbances of Er deformability, leading to the development of microcirculatory disorders, tissue hypoxia with the expressed deficit of intracellular macroergs. Given in the 2nd group intensities of NMR peaks, reflecting signals of 2,3-DPG, inorganic phosphates were significantly higher and the ones of macroergastic compound resonances (gamma-, alpha-, beta-, Mg-ATP, beta-, alpha-ADP) were lower compared to the 1st group ($p<0,0001$-$0,03$.(

We observed high levels of cholesterol fraction, oleic, stearic, myristic acids, high index of cholesterol/phospholipids (PHL) and low levels of total lipids, easily oxidable PHL, arachidonic acid, polyunsaturated fatty acids (docosahexaenoic, docosapentaenoic, docosatetraenoic), omega-3 index in Er membranes in the 2nd group than those in the 1st one ($p<0,0001$-$0,01$). The change in metabolomic profile was most markedly demonstrated on GC-MS ($P= 4,52\times10$-5.(

Conclusions: In CRC the Er parameters change markedly with stage of the disease. This novel observation may have clinical utility in enhancing staging accuracy and selecting patients for surgical or medical management.

Embedding Pharmacogenomics and Personalized Medicine Education into the Medical School Curriculum

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Background: As the cost of high-throughput DNA sequencing continues to decline, the push to incorporate genomic information into various areas of clinical practice is steadily increasing. Recognizing this, organizations such as the American Association of Medical Colleges have charged medical schools with training new physicians to be competent in genomic medical concepts.

Objective: In response to this, University of Maryland School of Medicine educators incorporated an exercise involving personal genotyping of pharmacogenomic variants and interpretation of results into the medical school curriculum. Anonymous surveys were administered to medical students before and after the exercise to assess knowledge and attitudes towards pharmacogenomic testing, identify the advantages and disadvantages of pharmacogenomic testing, and determine the extent to which the use of one`s own DNA enriched the educational experience.

Methods: Students attended a group information session led by a certified genetic counselor. Students were given the choice to either provide their own DNA sample and receive a personal dataset, or receive a dataset from a de-identified sample. All second-year medical students received a pharmacogenomic dataset generated from the Drug Metabolizing Enzymes and Transporters (DMET) assay.

Results and Conclusion: Eighty-eight percent of students chose to use their own DNA sample for genotyping. Preliminary data indicates the activity was well received by students. We anticipate students will refer to their pharmacogenomic datasets throughout the remainder of their training and that this information will serve as a learning tool to better understand the impact and limitations of pharmacogenomic testing on personalized medicine and improved clinical care.

Genetic Variation in the SVEP1 Gene Impacts On-Clopidogrel Platelet Aggregation in a Sex-Specific Manner

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Introduction: Genetic variation is a significant determinant of on-clopidogrel platelet reactivity and incidence of clinical outcomes. While sex-specific differences in platelet reactivity have been documented, identification of polymorphisms that contribute to gender-specific differences in clopidogrel efficacy has been limited.

Methods: We perform sex-stratified analyses of exome chip data in 442 participants of the PAPI study to identify genetic variants that influence on-clopidogrel platelet aggregation. Phenotype data was collected in all participants pre- and post-clopidogrel exposure (300 mg loading dose followed 75 mg/d for 7 days). Platelet function was assessed using a PAP8E aggregometer after stimulation with ADP (20 μM). Association analyses were performed adjusting for the effects of age, BMI, clopidogrel active metabolite levels, baseline platelet aggregation, and participant relatedness.

Results: A genetic variant in the SVEP1 gene was significantly associated with increased ADP-stimulated platelet aggregation post-clopidogrel exposure in females (rs10980419, P = 5.97 x 10-8) resulting in an approximate doubling of response between homozygote groups (maximal platelet aggregation = 33.8 for CC homozygotes, 45.8 for CT heterozygotes, and 68.0 for TT homozygotes); whereas, no association was observed in men (P = 0.46). A significant SNP x gender interaction was observed (P = 0.002.(

Discussion: We identified a genetic variant in SVEP1 that influences on-clopidogrel platelet aggregation in a sex-specific manner. SVEP1 expression is known to be regulated by 17b-estradiol, strengthening our confidence in these results. However, additional studies are required to replicate our finding and to determine the effects of this variant on recurrent cardiovascular events in women.

The Polymorphisms within FTO Gene and the Metabolic Syndrome Risk in a Kazakh Population

Nurgul Sikhayeva, Zharkyn Dzharmukhanov, Elena Zholdybaeva, Erlan Ramankulov

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Background: This study is aimed to determine the association of single nucleotide polymorphisms (SNPs) within FTO gene and the metabolic syndrome risk in the Kazakh population.

Methods: the study included 683 subjects (191 men and 492 women), aged 18-84 years and living in Almaty. Written informed consent was obtained from the participants. The MS was defined according to the National Cholesterol Education Program-Adult Treatment Panel III. DNA samples were genotyped by the TaqManOpenArray Real-Time PCR Platform. Statistical analysis was performed using R software (version 3.1.2.(

Results: in the studied population, the overall prevalence of the MS was 13.76% according to the NCEP-ATPIII criteria. The influence of gender on MS prevalence was not discovered. For genotyping, 697 samples were selected, and were divided into two groups according to presence (N=208) or absence (N=489) of MS. The risk of developing at least three components of metabolic syndrome was increased by the polymorphisms in FTO (rs3751812: OR=1.49, CI [0.10–2.14], P=0.0284; rs8050136: OR=1.52, CI [0.15–2.21], P=0.0218; rs9939609: OR=1.59, CI [0.11–2.32], p=0.0138.(

Conclusion: Significant associations were found between the SNP rs3751812, rs8050136 and rs9939609 of FTO and the risk of developing at least three components of metabolic syndrome.

Keywords: metabolic syndrome, polymorphism, Kazakh population

Association of 5 Single Nucleotide Polymorphisms in Type 2 Diabetes Mellitus Risk in the Kazakh Population

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Background: This study aimed to evaluate the association between 5 single nucleotide polymorphisms and type 2 diabetes mellitus (T2DM) risk in a Kazakh cohort.

Methods: A total of 1,336 subjects including 408 type 2 diabetic patients and 928 control subjects were recruited from an outpatient clinic. Written informed consent was obtained from the participants. DNA samples were genotyped by the TaqManOpenArray Real-Time PCR Platform. Statistical analysis was performed using R software (version 3.1.2.(

Results: Significant associations were found between the single nucleotide polymorphisms rs9939609 (FTO), rs13266634 (SLC30A8), rs4402960 (IGF2BP2), rs7961581 (TSPAN8/LGR5), rs1799883 (FABP2) and type 2 diabetes mellitus (rs9939609: OR=1.52, CI [1.03–2.26], P=0.0368; rs13266634: OR= 0.68, CI [0.49–0.93], P=0.0192; rs4402960: OR=1.89, CI [1.32–2.74], P=0.000657; rs7961581: OR=1.54, CI [1.05–2.27], P=0.0261; rs1799883: OR=1.51, CI [1.06–2.13], P=0.0241.(

Conclusion: We replicated the associations between polymorphisms within the SLC30A8, IGF2BP2, TSPAN8/LGR5, FABP2, and FTO genes and the susceptibility to T2DM in a Kazakh cohort.