Sixteenth Annual Child Health Research Symposium
Sponsored by The Jack and Lucy Clark Department of Pediatrics and
The Mindich Child Health and Development Institute

Program and Abstracts

Image Courtesy of Manish Arora, MPH, PhD (Department of Preventive Medicine): “Stylized image of tooth biomarker showing elemental growth rings used to reconstruct chemical exposure profile during pre-natal and post-natal developmental windows.”

April 2-3, 2014
Hatch Auditorium & Annenberg West Lobby
A Program of

The Jack and Lucy Clark Department of Pediatrics and
The Mindich Child Health and Development Institute

Child Health Research Symposium
Steering Committee:

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Robert Wright, MD, MPH
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Administrator: Carla Monaco

Breakfast is courtesy of the
Dr. Howard Rappaport Memorial Lectureship Fund

Grand Rounds Special Guest Speaker:

Richard J. Smith, M.D.
Icahn School of Medicine at Mount Sinai
Sixteenth Annual Child Health Research Symposium
Schedule of Events

April 2, 2014 – Annenberg West Lobby
5:00-6:30 p.m. Poster Review #1

April 3, 2014 – Hatch Auditorium
7:45-8:00 a.m. Coffee and Tea
8:00-8:10 a.m. Welcome and Introduction
Lisa M. Satlin, MD, Chair, The Jack and Lucy Clark Department of Pediatrics
Bruce D. Gelb, MD, Director, The Mindich Child Health and Development Institute
8:10-9:05 a.m. Grand Rounds: The Dr. Howard Rappaport Memorial Lecture
“C3 Glomerulopathies – State of the Art 2014”
Richard J. Smith, MD
Director, Iowa Institute of Human Genetics
Professor of Otolaryngology, Pediatrics, Internal Medicine, Molecular Physiology and Biophysics
University of Iowa Carver College of Medicine
9:05-9:30 a.m. Breakfast
9:30-11:30 a.m. Plenary Presentations – Hatch Auditorium
Moderators: Aaron Lipskar, MD and Supinda Bunyavanich, MD
9:30-9:45 a.m. Uncovering Developmental Windows of Susceptibility to Chemical Mixtures Using Micro-Spatial Analysis of Teeth
Manish Arora, Christine Austin, Birgit Claus Henn, Brent Coull, Robert O. Wright
9:45-10:00 a.m. Relationship Between Body Mass Index (BMI), Age of Sexual Debut and Risky Sexual Behavior
Lonna Gordon, Christopher Ochner, Angela Diaz
10:00-10:15 a.m. Profile of Food Allergen-Specific T Cells in Allergic and Clinically Tolerant Individuals
David Chiang, Alexander Grishin, Madhan Masilamani, Miriam Merad, Karolina Palucka, Hideki Ueno, Wesley Burks, Stacie Jones, Andrew Liu, Scott Sicherer, Robert Wood, Wendy Davidson, Hugh Sampson, Cecilia Berin
10:15-10:30 a.m. Effects of Prenatal Stress and Maternal Dietary Intakes on Infant Behavior: Does Race Matter?
Kelly J. Brunst, Michelle Bosquet Enlow, Srimathi Kannan, Kecia N. Carroll, Brent A. Coull, Rosalind J. Wright
10:30-10:45 a.m. Multifaceted Roles of miR-1s in Repressing the Fetal Gene Program in the Heart
Siwu Peng, Yusheng Wei, Meng Wu, Ravi Sachidanandam, Zhidong Tu, Shihong Zhang, Christine Falce, Eric A. Sobie, Djamel Lebeche, Yong Zhao
10:45-11:00 a.m. Urinary Complement Gene Expression in Acute Kidney Graft Rejection Patients
Hyoungtae E. Kwon, Karen Keslar, Paolo Cravedi, Peter S. Heeger, Jessica Reid-Adam
11:00-11:15 a.m. p53-mediated Apoptosis is Responsible for Disease in a Zebrafish Model of Mpi-Deficient Congenital Disorder of Glycosylation
Angela Liu, Jaime Chu
11:15-11:30 a.m. Children’s Consumption of Juice and Sugar-Sweetened Beverages-Does Parental Knowledge of AAP Guidelines on Juice Intake and Parental Consumption Make a Difference?
Christine SanGiovanni, Mallory Mandel, Robert Fallar, Leora Mogilner
11:45 a.m.-12:45 p.m. Poster Session #2 and Lunch (Poster Session #1: April 2, 2014 5:00-6:30 p.m.)
Annenberg West Lobby
12:45-1:00 p.m. Poster Presentation Awards Ceremony
Presented by M. Cecilia Berin, PhD
Icahn School of Medicine at Mount Sinai
Sixteenth Annual Child Health Research Symposium
Thursday, April 3, 2014

WELCOME

We welcome you to the 16th Annual Child Health Research Day at Mount Sinai! This event aims to highlight the outstanding research activities of students, housestaff, clinical and research post-doctoral fellows, research staff, social workers, nurses and junior faculty in the Department of Pediatrics at Mount Sinai and our affiliates, as well as The Mindich Child Health and Development Institute (MCHDI). The basic, translational and clinical research, broadly related to the health and welfare of infants, children and adolescents, presented in today’s plenary and poster sessions, exemplifies the commitment to scientific discovery and scholarship central to our academic mission. The event provides a unique opportunity for young investigators in the Department of Pediatrics and MCHDI to share the results of their research with colleagues, and thereby discover new applications for their work or identify potential future areas for collaboration. We thank you for attending and congratulate all the participants on their accomplishments!

Lisa M. Satlin, MD
Chair, The Jack and Lucy Clark Department of Pediatrics

Bruce D. Gelb, MD
Director, The Mindich Child Health and Development Institute
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Introduction: The concept of critical developmental windows includes toxic insults that occur at specific life stages producing maladaptive neurophenotypes. Researchers have been limited in their ability to determine critical developmental windows specific to many chemicals because of the absence of a direct fetal biomarker.

Hypothesis: We propose a methodology to reconstruct exposure to individual chemicals and chemical mixtures in the second and third trimesters, in early childhood, and also cumulative life-long exposure.

Methods: The Early Life Exposures in Mexico and NeuroToxicology (ELEMENT) study, based in Mexico City, is a prospective birth cohort. Detailed neurodevelopmental measures have been undertaken in children at various ages and numerous maternal and childhood biomarkers, including naturally shed deciduous teeth were collected from the children at ages 7 years and older. Using laser ablation inductively coupled plasma mass spectrometry, we measured Mn, Pb and other metals in discrete layers of tooth dentine and reconstructed a fine scale longitudinal exposure history over the prenatal and early childhood periods.

Results: Tooth Mn measurements at multiple prenatal time points were positively associated with IQ (beta range: >0 to 0.1; p<0.05). The Mn-IQ association changed markedly when considering co-exposure to Pb: at high Pb levels (tooth Pb>median), the positive association with IQ during the prenatal period was attenuated; postnatally, Mn was inversely associated with IQ in children who have higher Pb levels (beta range = 0 to -1; p<0.05).

Conclusion: Using this novel biomarker we have identified specific exposure windows that are important for individual and joint effects of Mn and Pb on neurodevelopment.
Relationship Between Body Mass Index (BMI), Age of Sexual Debut and Risky Sexual Behavior

Author Name(s): Lonna Gordon, Christopher Ochner, Angela Diaz

Department: Pediatrics

Division: Adolescent Medicine

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Introduction: Adolescent obesity has tripled over the last thirty years particularly in adolescents who are minorities or from low socioeconomic backgrounds. The psychological consequences of obesity in adulthood has led to an interest in the impact of obesity during adolescence on peer relationship formation and functioning; particularly as it relates to sexual debut due to its important reproductive health consequences. This study seeks to investigate the relationship between weight status and age of sexual debut and progression of sexual behavior practices in predominantly minority and low socioeconomic status adolescent women.

Hypothesis: We hypothesize that increase in BMI will be inversely correlated to age of sexual debut. We also anticipate that increasing BMI will be positively correlated with increased markers of risky sexual behavior.

Methods: Linear regression was utilized to measure the degree of association between BMI and age of sexual debut for various types of sexual (oral, vaginal and anal) intercourse in 860 adolescent women.

Results: BMI was inversely correlated with age of first giving oral intercourse (p=0.001) and age of first anal intercourse (p=0.04). It was positively correlated with number of lifetime and recent partners for vaginal (p=0.039, p=0.016) and anal intercourse (p=0.003, p=0.006).

Conclusions: In a population of predominantly minority and low socioeconomic status adolescent women increases in BMI are associated with younger age of sexual debut and riskier sexual practices. These findings contrast previously reported findings in majority populations and emphasize the need for further studies on differing psychological impacts of obesity in various groups.
Profile of Food Allergen-Specific T Cells in Allergic and Clinically Tolerant Individuals

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Introduction and Hypothesis: The interplay between antigen-specific T-effector and T-regulatory cells in food allergy and tolerance is poorly understood in humans. We hypothesized that regulatory T cells are lacking in food allergic states.

Methods: Using blood from children allergic to peanut and/or egg versus clinically tolerant controls (including healthy, outgrown food allergy, or allergic to other foods), we designed 13-color flow cytometry panels to profile peanut or egg-specific T cell responses 6-18h after stimulation. Antigen-specific cells were identified as live/CD3+/CD4+/CD40L+, and profiled for regulatory markers (CD25/CD127/Foxp3), cytokines (IL-4/IL-13/IL-10/IFN-γ), and homing markers (CCR6/CCR4/CXCR5/CCR9).

Results: Allergic subjects had detectable peanut-responsive CD40L+ T cells above background (median 206 per million CD4 vs. 37 at 6h and 408 vs 56 at 18h, n=20 and 13, p<0.0001 and p=0.0002). In healthy controls, there were few detectable peanut-responsive cells above background at 6hrs (84 vs. 66, n=3). Similar responses were observed in egg-stimulated samples from children allergic (n=13) or clinically tolerant (n=6) to egg. Egg and peanut-specific T cells in allergic subjects co-expressed IL-4 and IL-13, but little or no IFN-γ or IL-10. In controls, cytokines were minimal (IFNg, IL-10) or absent (IL-4, IL-13. Antigen-specific “Tregs”, defined as CD40L+/CD25+/CD127+/FoxP3+, were significantly increased beginning 18h after allergen stimulation, were present in both allergic and tolerant individuals, and highly expressed CCR4 and CCR6.

Conclusions: Antigen-specific “Tregs” with tissue homing phenotypes are detectable in both allergic and tolerant subjects, while antigen-specific Th2-effector cells are unique to allergic individuals. These results suggest that food allergy is not due to a quantitative deficiency in allergen-specific Tregs; regulatory function remains to be addressed.
Introduction: Prenatal stress has been linked to poor infant neurobehavior. Prenatal antioxidant/anti-inflammatory nutrient intakes, including vitamin E and polyunsaturated fatty acids (PUFAs), may ameliorate stress effects. Blacks may be particularly vulnerable to environmental stimuli and oxidative stress.

Hypothesis: Higher prenatal dietary intake of vitamin E and an increased PUFA n3:n6 ratio will attenuate the effects of maternal stress on infant behavior, particularly among Blacks.

Methods: Subjects were 215 mother-infant dyads from urban Boston, MA. Prenatal stress was indexed by a negative life events (NLEs) using the Crisis in Family Systems-Revised survey. Total daily intakes of PUFAs (n3, n6) and vitamin E (alpha-tocopherol) were estimated from an FFQ; n3:n6 ratios were calculated. Mothers completed the Infant Behavior Questionnaire-Revised when children were 6 months old. Factor analysis confirmed three behavior dimensions: Orienting/Regulation, Extraversion, and Negative Affectivity. Associations among prenatal stress, nutrient intakes, and race on infant behavior, controlling for covariates, were examined.

Results: Mothers were primarily minorities [18% Blacks (AA); 49% Hispanics]. In the Black subgroup, prenatal stress effects on infant Orienting/Regulation scores were attenuated by higher maternal n3:n6 ratios (p=0.002); the association between increased prenatal stress and Extraversion was modified by Vitamin E intake (p=0.008). The three-way interaction for NLEs*n3:n6*race was significant for Orienting/Regulation (p=0.001). These effects were not observed in Caucasians or Hispanics.

Conclusions: Optimal antioxidant and anti-inflammatory nutrient intakes may protect the fetus from stress effects on infant behavior, particularly among Blacks. These findings may have implications for later neurodevelopment impacted by early orienting/regulation abilities (e.g., executive attention, internalizing/externalizing behaviors).
Multifaceted Roles of miR-1s in Repressing the Fetal Gene Program in the Heart

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Introduction: miRNAs are an important class of regulators that have roles in cellular homeostasis and disease. Muscle-specific miRNAs, miR-1-1 and miR-1-2, have been found to play important roles in regulating cell proliferation, cardiac conduction, and skeletal muscle proliferation and differentiation. Redundancy between miR-1-1 and miR-1-2 has previously impeded a full understanding of their roles in vivo.

Hypothesis: We hypothesized that miR-1s critically regulate cardiac function in vivo.

Methods and Results: We generated mice lacking miR-1-1 and miR-1-2. miR-1 double knockout (miR-1 dKO) mice were viable and not significantly different from their littermate controls at postnatal day 2.5. Thereafter, all miR-1 dKO mice developed dilated cardiomyopathy and died before P17. Massively parallel sequencing showed that a large portion of up-regulated genes after deletion of miR-1s is associated with the cardiac fetal gene program including cell proliferation, glycolysis, glycogenesis, and fetal sarcomere-associated genes. Consistent with gene profiling, glycogen content and glycolytic rates were significantly increased in miR-1 dKO mice. Estrogen-related Receptor α and β (Errα and Errβ) were identified as direct targets of miR-1 that can regulate glycolysis, glycogenesis, and the expression of sarcomeric proteins. Cardiac specific overexpression of Errβ led to glycogen storage, cardiac dilation, and sudden cardiac death around 3-4 weeks of age.

Conclusions: miR-1 and its primary targets Errα and Errβ act together to regulate the transition from prenatal to neonatal stages by repressing the cardiac fetal gene program. Loss of this regulation leads to a neonatal dilated cardiomyopathy. Our data revealed a potentially novel mechanism for pediatric dilated cardiomyopathy.
Urinary Complement Gene Expression in Acute Kidney Graft Rejection Patients

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Introduction: Kidney transplantation is the optimal treatment for end stage renal disease. Advances in immunosuppression have led to decreased rates of transplant rejection; however acute rejection remains a significant cause of morbidity among kidney transplant recipients and can drastically shorten the life of a donor kidney. The exact mechanism of acute rejection of graft is still not fully understood, leaving much-desired therapeutic and diagnostic options still undiscovered. Mouse models suggest that complement produced by immune cells can enhance T cell immunity and accelerate allograft rejection.

Hypothesis: Complement components modulate human T cell associated graft rejection.

Methods: We serially collected urine from renal transplant patients with acute rejection (n=15) and without acute rejection (n=14) and quantified the urinary cell mRNA of 12 selected complement genes using quantitative real-time PCR.

Results: Rejection patients’ urinary cell mRNA obtained at or around the time of biopsy-proven acute rejection (BPAR) show statistically higher expression of 9 complement component genes than the collection time-point matched mRNA samples from stable patients (P<0.01). Also, we observed a strong trend that serial expression levels of C3, C3aR, CFB, and ITGB2 were consistently higher than those of matched controls leading up to timepoints of biopsy-proven acute rejection.

Conclusions: These data suggest the involvement of complement proteins in the pathogenesis of acute rejection and suggest that targeting complement components for rejection therapy merits further investigation. Also, these preliminary findings support further study of quantifying complement urine mRNA as a method for monitoring and diagnosing acute rejection.
p53-mediated Apoptosis is Responsible for Disease in a Zebrafish Model of Mpi-Deficient Congenital Disorder of Glycosylation

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Introduction: Children with congenital disorders of glycosylation (CDG) have multi-systemic developmental defects with high morbidity and mortality; however, its pathophysiology is not well understood. Mannose phosphate isomerase (MPI) interconverts mannose-6-phosphate and fructose-6-phosphate in N-glycosylation, and children with MPI-CDG present with severe gastrointestinal symptoms and coagulopathy. MPI-CDG is a unique CDG as patients can be treated with oral mannose supplements to ameliorate nearly all symptoms. We established a zebrafish model of MPI-CDG, with cornerstones comparable to MPI-CDG patients, including mannose rescue, to further investigate the pathophysiology of CDG.

Hypothesis: p53 is responsible for the Mpi-deficient phenotype in our zebrafish model of MPI-CDG.

Methods: To evaluate cell death in Mpi-deficient zebrafish embryos, we used acridine orange and cleaved caspase 3 assays. We then sought to establish the relationship between p53 activation and Mpi deficiency using qPCR and western blotting through a time course from 6 hours post-fertilization (hpf) to 4 days post-fertilization (dpf).

Results: mpi morphants at 24 hpf are characterized by apoptosis, p53 transcriptional upregulation, and increased p53 protein levels as compared to control. Pro-apoptotic genes are activated in the hours preceding cell death. Elimination of p53 in our Mpi-deficient embryos eliminated cell death and restored normal phenotype at 4 dpf, despite persistent knockdown of Mpi activity. Mannose supplementation also alleviates cell death in mpi morphants.

Conclusion: p53-mediated apoptosis is responsible for the phenotype of Mpi-deficient zebrafish embryos, revealing a new metabolic intersection of p53 and N-glycosylation. Further studies will focus on the interplay of mannose metabolism and p53.
Introduction: In the past decade, children's consumption of sugar-sweetened beverages (SSBs) and 100% fruit juice has increased significantly along with the rise of obesity. Programs to decrease children's intake of these beverages at schools have had limited success, leading many to believe parental influence has a much more substantial impact on children's habits of drinking these beverages. The objectives of this study were to evaluate parental knowledge of AAP guidelines for juice consumption and quantify children and parents' consumption of juice and SSBs.

Hypothesis: We hypothesized that parents who had knowledge of AAP recommendations regarding juice intake were more likely to report lower children's consumption of juice and SSBs. In addition, parents who report a higher consumption of juice and SSBs are more likely to have children who have a higher consumption of juice and SSBs.

Methods: Parents of children between 2-12 years old, who are seen regularly in an urban pediatric residency group practice in East Harlem, completed a survey asking about their child's habits of drinking juice and SSBs as well as their own juice and SSB consumption. Parental knowledge about AAP guidelines regarding juice consumption was also assessed.

Results: Fifty-two parents completed the survey. 50% were Hispanic, 38% African-American, 8% mixed ethnicity, and 4% Asian. Forty-six percent of parents reported that their child drank more than 2 servings of juice and SSB per day ("high juice/SSB consumer"). Only 12.5% of parents with a child who was a high juice/SSB consumer scored well on a test of knowledge about AAP juice recommendations (>65% correct) while 42.9% of parents with a child who was a low juice/SSB consumer scored well on the knowledge test (p=0.03). In addition, 64.3% of parents with a child who was a high juice/SSB consumer also reported themselves to be high juice/SSB consumers, compared to 25% of parents with a child who was a high juice/SSB consumer and actually reported themselves as a low juice/SSB consumer (p=0.006).

Conclusions: There is a significant association between parental practice and knowledge of AAP recommended limits on juice consumption and children's consumption of juice and SSBs. Interventions providing parents with AAP recommendations on juice limits for children as well as encouraging parents to decrease their own consumption of juice and SSBs may be most helpful in decreasing children's consumption of juice and SSBs. Ultimately, this may have an impact on decreasing children's risk of overweight and obesity. Further research including larger studies evaluating these parental factors is needed.
Infants with Idiopathic T Cell Lymphopenia Identified on New York State Newborn Screen: A Follow Up Report from Mount Sinai

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Introduction: Quantification of T-cell receptor excision circles (TRECS) through newborn screening has introduced early diagnosis of idiopathic T cell lymphopenia (ITCL), which is not yet well described.

Hypothesis: As the TREC assay is relatively new, we hypothesized that reporting clinical characteristics, laboratory monitoring, and outcomes of ITCL would be important.

Methods: From September 29, 2010 through July 26, 2013, infants with low TREC values were referred to Mount Sinai Immunology for diagnostic evaluation. This report is a retrospective chart review looking at the follow up for patients diagnosed with ITCL.

Results: Fourteen patients had absolute T cells <2000/cubic mm, and 6 were followed in clinic for ITCL. Initial TREC levels averaged 76 copies/µl, and initial absolute T cell counts averaged 934/cubic mm. The number of flow cytometries performed ranged from 2 to 4, and follow up flow was generally done around 4 months, 9 months, and 1 year of age. Vaccination was deferred until T cell counts had an upward trend towards normal, and prophylactic antibiotics were only used in 2 patients. Patients who were not followed longitudinally did not necessarily have a higher absolute T cell count on their final flow, but were clinically asymptomatic over a period of months with levels close to the normal range. All the patients generally did well without significant infections or complications.

Conclusions: ITCL may be identified more readily as the TREC assay is included in more state-mandated newborn screens. While patients seem to do well clinically, more information is needed on monitoring and outcomes.
Educational Attainment and Measures of Obesity: A Sex-specific Genotypic Based Approach to Investigating Causality and Pathways

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Introduction: Several reports demonstrate lower educational attainment in obese compared to normal-weight individuals in high-income countries, particularly in women. The co-occurrence of lower levels of education and obesity may have many possible explanations, including confounding by other factors, education protecting against current and future obesity, or obesity impairing cognitive ability.

Hypothesis: We hypothesized that genotypes associated with measures of educational attainment and obesity could be used as unconfounded proxies in a sex-specific bi-directional Mendelian Randomization approach and elucidate causal relationships between these two sets of traits.

Methods: Summary statistics were obtained for previously conducted genome-wide association studies (GWAS) for the number of years’ schooling and for College completion on over 100,000 individuals. They were also obtained for GWAS conducted on body mass index (BMI; n>300,000), body fat percentage (n>70,000) and waist-hip ratio adjusted for BMI (n>190,000). Genotypes significantly associated with each measure were used to construct genetic scores to index the measures in men and women. The genetic scores for educational attainment were used to estimate their effects on measures of obesity. The genetic scores for measures of obesity were used to explore reverse causality.

Results: Genotypes associated with higher educational attainment were associated with lower measures of obesity in both sexes (p-values<0.001). Genotypes associated with increased measures of obesity were associated with lower educational attainment in both men and women (p-values<0.001).

Conclusions: The use of genotypic proxies obtained from GWAS summary statistics provided evidence for causal associations between educational attainment and BMI in both directions in both sexes.
Studies on Cohort of Infants With Di-George Syndrome Detected By New York State Newborn Screening For Severe Combined Immunodeficiency (SCID)

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Introduction: Di-George syndrome is a heterogeneous constellation of signs and symptoms including severe lymphopenia in some patients.

Hypothesis: Infants with Di-George Syndrome with T-cell lymphopenia are detected by NYS newborn screening for SCID allowing for early intervention.

Methods: We collected clinical and laboratory data on infants with Di-George Syndrome referred to Mount Sinai, one of 8 referral centers in New York State. Patients with levels of T-cell receptor excision circles (TRECs) of below 125 were referred. Data collected included TREC values, CD3, CD4, CD8, NK and B cell absolute numbers as well as genotype and phenotype.

Results: In the first 33 months of newborn screening we saw 6 patients at Mount Sinai finally diagnosed with Di-George syndrome. 5 of these patients were female. 4 patients had undetectable TREC levels at birth (ranging from average 0 to 188 (?) and 0 to 889 on 2-4 follow up visits). All but one of those patients also had congenital heart defects of different degrees.

T-cell lymphopenia ranged from 0 to 2189/cu mm absolute CD3. At least half of the patients were known to have a 22q11 deletion. One patient with 22q11 deletion had hypocalcemia and lymphopenia but no cardiac involvement. Another patient had complete Di-George Syndrome without chromosomal deletion due to maternal diabetes and subsequently successfully underwent thymic transplantation. A third patient with maternal history with Di-George syndrome and 22q11 deletion was found to have Di-George syndrome with the same chromosomal abnormality.

Conclusions: Newborn screening for SCID can identify patients with Di-George syndrome with varying degrees of lymphopenia.
Rett-Like Phenotype: Boosting Gene Discovery with Next Generation Sequencing Approaches

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Introduction: Rett syndrome (RTT) is a rare neurodevelopmental disorder (NDD) but a common cause of severe intellectual disability in girls. Though RTT remains a clinical diagnosis, mutations in MECP2, CDKL5 and FOXL1 are identified in the majority of classic RTT and up to half of variant RTT patients.

Hypothesis: Since a significant proportion of RTT patients do not present mutations in any of these three genes, we hypothesized that other genes are likely to cause the disease.

Methods: We collected a cohort of 31 children diagnosed with RTT (and MECP2/CDKL5 negative). Of these, 22 were screened with 720K arrays and whole-exome sequencing. SNVs and indels were filtered as follows: exclusion of synonymous and common variants; preference for de novo, homozygous/compound heterozygous, maternally inherited X-linked variants. Impact of variants was predicted using in silico tools and gene prioritization took into consideration biological function, genetic/protein interactions, brain expression and KO mice phenotype.

Results: Mutations in genes previously implicated in NDD but not specifically in RTT were identified: STXBP1, SHROOM4 and SLC35A2. Mutations in novel NDD candidate genes were also detected: ZBTB18, GABBR2 and SMARCA1. Network analysis reveals that these genes interact by means of genetic and protein interactions with each other and with the already known RTT genes. Genotype-phenotype correlation allows for the delineation of a core phenotype as well as distinctive clinical features that could help guide/interpret genetic testing in future patients.

Conclusions: We expanded the phenotypic spectrum of previously known NDD genes to encompass RTT and identified new candidates for RTT.
Brain Activity During Attention Task in Children with Obstructive Sleep Apnea (OSA): Effect of Adenotonsillectomy (AT)

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Introduction: OSA affects 3% of children, is implicated in neurocognitive dysfunction, and is treated by AT. In the only RCT examining efficacy of AT in OSA, neurocognitive measures were unaffected post-AT. More sensitive tests are needed.

Hypotheses: Children with OSA have event-related electrophysiological changes (ERP) which predict cognitive deficits compared to controls before AT and these will normalize post-operatively.

Methods: 20 children participated in the Oddball ERP task and neurocognitive battery including NEPSY at initial session and follow up after 6-month interval in which the OSA group underwent AT. ERP data formed spatial models localizing brain activity. ERP differences between OSA children and controls related to neurocognitive outcomes through MR.

Results: OSA children had negative frontal activation 468 ms post-stimulus (p<0.01) and positive activation at parietal (p<0.01) and occipital (p=0.01) sites in response to the target during initial test. Source localization showed OSA children activated brain associated with auditory processing at early latencies when control children activated areas linked to working memory and consolidation. At 468 ms controls had sources in the precuneus and left superior temporal gyrus, suggesting working memory. At follow-up, control children activated the amygdala for frequent stimuli and superior temporal gyrus for target. Control children scored higher than OSA children on the NEPSY Memory and Learning Domain (p<0.02). Central activation at 468 ms positively predicted NEPSY scores, accounting for 20.8% of variance (p<0.03).

Conclusions: The central executive is adversely impacted by OSA, which underlies behavioral problems reported in OSA and appears to be reversible after AT.
Identifying Regions of Homozygosity using Whole Exome Sequencing

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Introduction: Consanguineous matings lead to homozygosity by descent, increasing autosomal recessive trait frequency. Congenital heart disease (CHD) is more common with consanguinity. Regions of homozygosity (ROH) are robustly detected with SNP microarray genotyping, but might be identified using whole exome sequencing (WES).

Hypothesis: ROHs can be accurately identified using WES.

Methods: SNP genotype (Illumina 1M or 2.5M) and WES data were obtained for four CHD probands and their consanguineous parents. Agile’s Variant Mapper, autoSNPa, and IBDFinder were used to identify ROHs. Exon regions covered by each method were identified and intersected to obtain overlapping ROHs per individual. After optimization, WES data from 30 CHD probands from consanguineous matings were analyzed for ROHs.

Results: The specificity of WES to detect ROHs in the exome was 99.9% (range 99.8-100%), while the sensitivity was 80.7% (range 65.4-92.4%) compared with array data. An average of 11.3 ROHs, spanning 148.2 Mb of the genome (1.2 Mb exome coverage), and 15.0 ROHs, spanning 160.8 Mb of the genome (2.2 Mb exome coverage) were identified in the WES and array data, respectively. Mean genome and exome coverage were 5.2% and 6.8% in the WES group compared to 5.6% and 7.9% in the array group.

In the larger CHD group, an average of 14.2 ROHs, spanning 131.3 Mb (4.6%) of the genome, were found per individual. Mean exome coverage was 1.8 Mb (6.40%). Mean region size was 9.5 Mb.

Conclusions: WES is a reasonable alternative to array data for determining ROHs. Further research delineating overlapping ROHs within CHD groups and their significance should follow.
**Pediatric Cardiac Re-Transplantation: Waitlist Mortality Stratified by Age and Era**

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**Introduction:** Waitlist mortality among children listed for primary heart transplant (HTx) has been well characterized, while limited data exist for cardiac re-transplantation (CRTx) after pediatric primary HTx.

**Hypothesis:** We sought to characterize the population listed for CRTx and to determine the factors that affect waitlist mortality.

**Methods:** All individuals listed for CRTx >1 year after pediatric primary HTx between 10/01/87-10/14/12 were identified in the OPTN Database. Baseline characteristics and waitlist mortality were compared between different age groups (<11 years; 11-18 years; ≥18 years) and over three successive eras (1987-1999; 1999-2006; 2006-2012).

**Results:** Six-hundred-thirty-two subjects were listed for CRTx >1 year after pediatric primary HTx and formed the cohort. Median age was 4.0 years (0-17) at primary HTx and 14.0 years (1-40) at relisting. Median time from primary HTx to relisting was 7.3 years (1.0-23.5). Median waiting time was 75.3 days (0-2818). Overall mortality was 25.0% (158/632). The most frequent relisting diagnoses related to graft vasculopathy (62.5%). The leading causes of death were chronic rejection and vasculopathy (51%). Waitlist mortality significantly decreased after 2006 (31% vs. 17%) (p-value <0.0001), despite a relatively constant CRTx rate (67% vs. 65%). By univariate analysis, era, age, listing status, and life support (MCSD, ECMO, vent, inotropes) were significant predictors of mortality. Multivariate analyses showed that later era (2006-2012), ages 11-18 years, and listing status 2 predicted decreased mortality.

**Conclusion:** Waitlist mortality for CRTx in children and young adults has decreased by almost 50% over time. Individuals relisted as adults have significantly increased waitlist mortality.
**Complement 2 Deficiency**

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**Introduction:** Complement deficiencies are a rare group of disorders in which markedly low complement levels can result in immunodeficiency. The phenotype of complement deficiency is broad, ranging from asymptomatic to recurrent serious illnesses. Here we present a case series of Complement C2 deficiency (C2D) and comparison of their clinical courses.

**Hypothesis:** Patients with C2D have a variable clinical course.

**Methods:** Cases were obtained from medical records of patients seen at the Allergy and Immunology Clinic at Mount Sinai Hospital from 2008 – 2013.

**Results:** Patient 1 is a 5 year old boy with a history of multiple infections at an early age including cellulitis, pneumonia and pneumococcal meningitis. The patient was diagnosed with C2D as his complement levels were notable for undetectable levels of C2 and low CH50. He was placed on daily prophylactic antibiotics and his immunizations for meningococcal and pneumococcal vaccinations were updated. Patient 2 is a 58 year old healthy female who was diagnosed with C2D as her complement levels were notable for undetectable levels of C2 and low CH50. Her immunoglobulin levels were notable for a marginally low IgG 650 mg/dl (700-1600 mg/dl) with normal IgA and IgM levels. She did not have protective titers for *Hib, pneumococcus* or meningococcus after vaccination.

**Conclusion:** Patients with complement deficiencies have broad clinical presentations. They may be asymptomatic, have poor response to vaccine titers or have serious recurrent infections that require prophylactic antibiotics.
The BK Channel Localizes to Lipid Rafts in the Apical Membrane of the Cortical Collecting Duct (CCD)

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Introduction: The BK channel, present in principal (PC) and intercalated (IC) cells but more abundant in IC in the CCD, mediates flow-induced K secretion (FIKS) but local mechanotransduction mechanisms is inactive at slow tubular (urinary) flow rates. In non-renal cells (i) BK channels localize to sphingolipid-cholesterol-rich lipid rafts (LRs) and (ii) channel activity is regulated by the composition and/or integrity of LRs.

Hypothesis: BK channels in CCD localize to LRs which provide a structural foundation for signaling complexes that regulate channel activity.

Methods: CCDs from NZW rabbits were microperfused in vitro for immunolabeling of endogenous BKα and the LR marker caveolin 1 (Cav-1). IC-like MDCK C11 cells, transfected with c-myc-tagged BKα, were immunolabeled for c-myc and Cav-1. Transfected cells were exposed to low (0.1) or high (0.4 dyn/cm²) fluid shear stress (FSS) for 30 min at 37°C. LRs were isolated from these cells by sucrose density fractionation and analyzed by Western blotting for c-myc and Cav-1; CoIP was performed for c-myc-BK/Cav-1.

Results: Endogenous and recombinant BKα colocalize with Cav-1 in the apical membrane of native CCD and C11 cells, respectively. In C11 cells exposed to low FSS, immunodetectable recombinant BKα and Cav-1 were identified in the same sucrose fraction, corresponding to LRs; CoIP studies demonstrated that Cav-1 and BKα are physically associated. High fluid shear led to loss of BKα from LR fractions.

Conclusions: High FSS disrupts the association of BKα with LRs in the apical membrane of the CCD, presumably activating BK channel by a mechanotransduction pathway currently under investigation.
The Mechanosensitive BKα/β1 Channel Localizes to Cilia of Principal Cells (PCs) in Rabbit Cortical Collecting Duct (CCD)

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Introduction: The density of conducting BK channels, which mediate Ca²⁺-dependent flow-induced K secretion (FIKS) in vivo, in the apical membrane of acid-base transporting intercalated cells (ICs) exceeds that in PCs, cells traditionally considered to mediate Na absorption and K secretion, in the CCD. Apical expression of immunodetectable BKβ (subunit containing channel pore) is robust in ICs but absent in PCs in cryosections of kidney. PCs possess a single apical cilium which projects into the lumen where it serves as a mechanosensor, responding to direct manipulation with increases in cell Ca²⁺.

Hypothesis: BKα is localized to cilia of PCs and mediates FIKS.

Methods: Single CCDs from NZW rabbits were microperfused in vitro, fixed and labeled with antibodies directed against BKα, β1 or β4 subunits, and visualized by confocal microscopy. Cilia in confluent monolayers of PC-like mpkCCD cells expressing a recombinant cilia-specific fluorescent label were subject to patch clamp analysis to examine K-selective channel activity.

Results: BKα and β1 subunits colocalize in cilia and along the apical membrane of cilia-expressing PCs in the microperfused CCD; β4 subunits are distributed diffusely throughout the cytoplasm of both PCs and ICs but do not colocalize with BKα. Single channel recordings in cilia patches reveal K selective channels with kinetics typical for the BK channel (conductance > 200 pS).

Conclusions: BKα/β1 is present on cilia of PCs, where the subunits appear to constitute a functionally active channel. Microperfusion studies are in progress to determine whether deciliation of the CCD eliminates FIKS.
Over-The-Counter Dietary Supplements Genistein and Ipriflavone Suppress Peanut Allergy Symptoms

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Introduction: Genistein and Ipriflavone are popular dietary supplements used for the treatment of post-menopausal disorders. Both genistein and ipriflavone belong to a group of anti-inflammatory compounds called isoflavonoids. Ipriflavone is an anabolic synthetic daidzein-derivative. We tested the effect of these molecules on peanut allergic mouse models and in ex vivo basophil degranulation in food allergic subjects.

Methods: 6-8 week old female C3H/HeJ mice were fed a soy-free diet (n=28), diet containing 1500 ppm each of genistein (n=14), ipriflavone (n=17) or genistein+ipriflavone (n=11). Mice were sensitized, boosted and challenged orally with peanut extract. The allergic symptoms (anaphylaxis scores and body temperature) were recorded after 60 min of challenge at week 10. Whole blood from 6 peanut- and 6 milk allergic subjects was pre-incubated with 100uM genistein, ipriflavone or genistein+ipriflavone for 30 min. Basophil degranulation assays were performed in the presence of allergenic extracts +/- isoflavones.

Results: Dietary genistein+ipriflavone significantly suppressed peanut-induced anaphylaxis in mice compared to soy-free diet (mean scores: 0.18 Vs 1.13, p<0.001; mean temperature change: 0.6 vs -1.6, p<0.001). Switching from soy-free diet to genistein+ipriflavone diet in “peanut-allergic” mice reduced the allergic symptoms. Ipriflavone+genistein dose-dependently suppressed anti-IgE mediated basophil degranulation and suppressed allergen-induced degranulation in food allergic subjects (mean fold change compared to control stimulation: 11 vs 18 for peanut, p<0.01 and 6 vs 11 for milk, p<0.001).

Conclusion: Unlike soy-derived isoflavone mixtures, synthetic genistein and ipriflavone are well documented to be safe for humans and allergen-free. We are currently investigating whether dietary Ipriflavone and genistein supplementation can be used therapeutically for food allergy.
Identifying Prenatal Windows of Susceptibility to Particulate Air Pollution on Asthma Onset in Early-school Aged Urban Children

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Introduction: Fetal lung development begins in utero. We examined windows of susceptibility to prenatal air pollution on childhood asthma onset and effect modifications by maternal pre-pregnancy obesity and gender in N=560 full-term children in a Boston pregnancy cohort.

Hypothesis: Prenatal windows of susceptibility to particulate matter with a diameter ≤2.5μm (PM_{2.5}) on asthma onset may differ by maternal obesity and gender.

Methods: Prenatal individual daily exposure to PM_{2.5} was estimated using a satellite-based spatio-temporal resolved model, based on address during pregnancy. Children's physician-diagnosed asthma was ascertained by maternal reports up to age 7 years. We examined associations between weekly averaged prenatal PM_{2.5} and asthma using distributed lag models and logistic regressions. Analyses were adjusted for child’s gender, season of birth, postnatal PM_{2.5}, and maternal education, race/ethnicity, atopy, smoking and stress.

Results: Mothers were primarily ethnic minorities (55% Hispanics, 27% African Americans) with ≤12 years of education (66%); 18.3% had asthma. Distributed lag models demonstrated significant associations between PM_{2.5} levels at 13-27 weeks gestation and asthma for children born to non-obese mothers. In multivariable-adjusted logistic regression models, the association between averaged PM_{2.5} over this identified vulnerable period and asthma was again only significant in children born to non-obese mothers (OR=1.35, 95% CI: 1.04-1.74; p for interaction=0.02). The three-way interaction among prenatal PM_{2.5}, male gender, and obesity was also significant (p<0.01).

Conclusions: Children exposed to increased levels of prenatal air pollution in the second trimester may be at greater risk of developing asthma, particularly for boys born to non-obese mothers.
Challenges of Breastfeeding the Early Term Infant:
A Comparative Study of Early and Late Term Infants

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Background: Infants born at 37–38 weeks are now referred to as Early Term (E.T.), as they are less developed and at higher risk for complications than infants born later. There is a dearth of studies on the breastfeeding challenges of these infants.

Goals: The purpose of the study is to describe the breastfeeding patterns of E.T. infants compared to L.T. infants during postpartum hospitalization and at one month.

Methods: We prospectively studied 171 mothers of E.T. and L.T. infants who intended to breastfeed. Infants were A.G.A., not admitted to the N.I.C.U. and had no contraindications to breastfeeding. Mothers were interviewed during the first 72 hours and one month of age. A power analysis was performed and the study had I.R.B. approval. Data was analyzed with χ², t-tests, Mann-Whitney and Fisher’s Exact Test.

Results: While all mothers intended to breastfeed, only 93% of E.T. infants were breastfed in the hospital compared to 100% of L.T. infants (p=.049). E.T. infants had less exclusive breastfeeding in the hospital (37% vs. 55%, p=.019) and at one month (66% vs. 81%, p=.045), and lower breastfeeding intensity in the hospital (74% vs. 83%, p=.031) and at one month (87% vs.95%, p=.04). E.T. infants were less likely to be breastfed in the first hour of life (55% vs. 81%, p=0.004) and more likely to be sleepy during breastfeeding (11% vs. 3%, p=0.040).

Conclusions: E.T. infants have decreased breastfeeding at initiation and one month. We speculate that increased lactation support for these infants would increase breastfeeding success.
Epicutaneous Tolerance Induction for the Treatment of Colitis

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Introduction: Crohn’s disease patients have an inherent defect in inducing T regulatory cells (Treg) via the gut. When Tregs are generated externally in response to food antigen and infused into patients, they suppress inflammation in Crohn’s disease via bystander suppression.

Hypothesis: We hypothesized that Tregs could be induced by applying antigen to the skin, and after migration to the gut could block inflammation via bystander suppression.

Methods: Mice were exposed epicutaneously daily for 5 days to ovalbumin (OVA) 1mg. To determine if exposure blocked T-effector responses, mice were then immunized with OVA, and cytokine production by draining lymph nodes (LN) was assessed by ELISA. Treg development in the mesenteric LN, spleen and intestines were determined. To determine if epicutaneous tolerance induction could abrogate colitis, mice were epicutaneously exposed to OVA, mice were gavage fed OVA to induce Treg homing to the gut, and colitis was induced with dextran sodium sulfate (DSS). Weight loss and inflammatory cytokine production by MLN and colon were assessed.

Results: Epicutaneous exposure to OVA induced tolerance as demonstrated by suppression of OVA-specific IFN-γ. OVA exposure induced proliferation of OVA-specific Tregs in the spleen, MLN, small intestine and colon. In the DSS colitis model, prior epicutaneous OVA exposure followed by oral feeding of OVA decreased inflammatory cytokine production (IFN-γ and TNF-α) from the MLN and colon (p<0.01).

Conclusions: Epicutaneous exposure induces Tregs, which can migrate to the gut and suppress inflammation. Thus, epicutaneous tolerance induction has potential as a treatment for Crohn’s disease and warrants further study.
Associated Extracardiac Malformations in the Congenital Heart Disease Population: Current Estimates and Temporal Variation In Prevalence

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Introduction: Previous studies established association between congenital heart disease (CHD) and certain extracardiac congenital malformations (ECM).

Hypothesis: Prenatal diagnosis and termination of pregnancy for fetal anomalies (TOPFA) has created a selection bias in the prevalence of ECM rendering previous estimates obsolete.

Methods: We reviewed the Nationwide Inpatient Sample (NIS) database from 1998-2008 and compared birth prevalence of ECM among all live births with CHD diagnosis (case) and all live births without CHD diagnosis (control) based on ICD9 codes. Longitudinal analysis was performed to determine temporal variation of ECM prevalence in the CHD population.

Results: Our cohort consisted of 97,154 and 12,078,482 subjects in the case and control group respectively. In the CHD population, prevalence of non-syndromic congenital malformation (NSCM), genetic syndrome (GS), and overall extracardiac congenital malformation (ECM) were 11.4%, 2.2%, and 13.6% respectively. In the control group, prevalence of NSCM, GS, and ECM were 6.7%, 0.3%, and 7.0% respectively. Compared to control, NSCM (OR: 1.8 CI: 1.7-1.8), GS (OR: 2.5 CI: 2.4-2.6) and overall ECM (OR: 2.0 CI: 2.0-2.1) were strongly associated with CHD. Longitudinal analysis showed that although prevalence of overall ECM remained unchanged, prevalence of GS (p=0.01) and multiple CM (p=0.01) decreased significantly over the study period.

Conclusion: Our study showed strong association between CHD and ECM. This is the largest and most comprehensive population-based estimate of ECM prevalence in the CHD population. We speculate that temporal decrease in prevalence of associated genetic syndromes and multiple CM may be due to effect of TOPFA.
Changing Prevalence of Severe Congenital Heart Disease: A Population-Based Study

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Introduction: Severe congenital heart disease (CHD) account for most of the morbidity and mortality attributed to CHD. Published data suggest increased rate of termination of pregnancy for prenatally diagnosed severe CHD and other severe fetal anomalies.

Hypothesis: Birth prevalence of severe CHD changed over time.

Methods: We reviewed the Nationwide Inpatient Sample (NIS) database and identified all cases of severe CHD diagnoses among all live birth entries from 1999 to 2008. We then performed time trend analysis to determine temporal variation in birth prevalence of severe CHD diagnoses, as well as analysis of the effect of sociodemographic variables.

Results: Our cohort showed overall severe CHD prevalence of 147.4 per 100,000 live births. There was a temporal decrease in prevalence from 168.9 per 100,000 in 1999 to 129.3 per 100,000 in 2008 (p=0.03). Among the 12 severe CHD diagnoses analyzed in our cohort, prevalence of tetralogy of Fallot (p=0.001); truncus arteriosus (p=0.02); hypoplastic left heart syndrome (p=0.001), and pulmonary atresia (0.01) decreased significant during the study period. Observed prevalence trends varied significantly by race (Caucasians), socioeconomic class (upper income quartiles) and geographic location (Northeast and West regions).

Conclusions: Our study showed temporal decrease of severe CHD prevalence, which varied by race, socioeconomic status and geographic locations. We speculated that the observed trend might be due to increased termination of fetuses with prenatally diagnosed CHD. Impact of sociodemographic variables on the observed prevalence trend might be due to differences in access to fetal heart program and/or willingness to terminate affected fetuses.
Introduction/Hypothesis: Congenital malformation (CM) is a leading cause of infant mortality. We hypothesized that current estimates of prevalence of CM are obsolete due to increased termination of fetuses with severe CM and widespread use of prenatal vitamins. This is a descriptive study to determine the current prevalence of congenital malformations, and the impact of gender and prematurity on birth prevalence of congenital malformations.

Methods: This is a population-based cross-sectional study to analyze effect of gender and prematurity on CM prevalence. All data was derived from 2008 birth entries in the Nationwide Inpatient Sample (NIS) database.

Results: We identified 29,312 patients with CMs among 1,013,261 live births yielding CM prevalence of 28.9 per 1,000 live births. 1172 (4%) had associated genetic syndromes. Among newborns with non-syndromic CM, 91% were isolated CM while 9% were multiple CM. Cardiovascular system was the most commonly involved organ-system. Risk of CM was significantly higher in preterm newborns for isolated CM (OR 1.5; CI 1.4-1.5), multiple CM (OR 2.1; CI 2.0-2.3), and overall CM (OR 1.4; CI 1.3-1.5). Males had higher risk of isolated CM (OR 1.3; CI 1.2-1.5) but there was no gender difference in risk of overall CM.

Conclusion: We reported up-to-date national estimates of CM prevalence, which is important for monitoring trends, determining service planning and assessing disease burden. We also showed strong association between CM and prematurity. Further study of this association is needed to provide insight into the etiology of these relatively common public health problems.
Racial Differences in the Birth Prevalence of Congenital Malformations in the United States

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**Introduction/Hypothesis:** Racial variability in certain prenatal risk factor such as prenatal vitamin supplementation and termination of pregnancy for fetal anomaly has altered the racial prevalence of congenital malformation (CM). Analysis of a single large representative population is required to analyze current racial differences in prevalence of CM in the United States.

**Method:** This is a population-based cross-sectional study to analyze racial differences in prevalence of CM diagnoses. We reviewed all live births in the 2008 Nationwide Inpatient Sample (NIS) database and determined birth prevalence of 55 selected CM diagnoses in Caucasians. We then calculated the relative risk of these CM diagnoses in African-American, Hispanics and Asians relative to Caucasians.

**Result:** Overall CM prevalence was 29.2 per 1,000 in a cohort of 1,048,252 live births of which 51% were Caucasians. Compared to Caucasian, risk of overall CM was lower in African-Americans (RR= 0.9, C.I 0.8-0.9) and Hispanics (RR= 0.9, C.I 0.8-0.9). Risk of overall CM was similar in Caucasians and Asians. Relative to the Caucasians, African-Americans had lower risk of cardiac, genitourinary, and craniofacial malformations but higher risk of musculoskeletal malformations. Hispanics had lower risk of genitourinary and gastrointestinal malformation. Asians had higher risk of craniofacial and musculoskeletal malformation.

**Conclusions:** This is a comprehensive description of racial difference in risk CM in the United States. Observed racial differences in risk of CM may be related to genetic susceptibilities, to cultural or social differences that could modify exposures, or to the many potential combinations between susceptibilities and exposures.
Autism Mental Status Exam: A Novel Data Collection, Documentation, and Diagnostic Tool for Developmental-Behavioral Pediatrics

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**Introduction:** Early diagnosis of Autism Spectrum Disorder (ASD) is limited by poor access to specialists and lengthy evaluations. The Autism Mental Status Exam (AMSE) structures brief assessment of eight reported and observed indicators of (ASD), yielding a score from 0 (no evidence) to 16 (maximum evidence). Demonstrating initial diagnostic validity, the AMSE may facilitate diagnostic efficiency in Developmental-Behavioral Pediatrics (DBP). The AMSE’s capacity to measure ASD signs and symptoms in DBP is investigated to establish proof-of-concept.

**Hypothesis:** Within a DBP clinic, patients diagnosed with ASD will have higher AMSE scores than patients who do not meet ASD criteria.

**Methods:** Forty patients (29 males) evaluated in a DBP clinic, age 17 months - 15 years ($M = 4.77, SD = 3.15$), received standard evaluations by a developmental pediatrician with the addition of the AMSE. AMSEs were scored by an independent rater and linked to final diagnosis. One participant was included in the study but excluded from analysis due to incomplete evaluation.

**Results:** 15% of participants met DSM-5 ASD criteria. Total AMSE scores for the ASD group ranged from 6 - 9 ($M = 7.33, SD = 2.30$), while total AMSE scores for the non-ASD group ranged from 0 - 8 ($M = 3.39, SD = 1.21$). Mean total AMSE scores differed significantly between diagnostic groups ($p < .001$).

**Conclusions:** Within a DBP clinic, AMSE scores differentiated between participants meeting criteria for ASD and those who did not. The AMSE shows promise as a brief ASD assessment tool within DBP. Further validation is indicated.
Risk Factors for Type 2 Diabetes Among a Population of Children with Type 2 Diabetes

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Introduction: There have been several reports of a rising incidence of Type 2 diabetes among youth in recent decades.

Hypothesis: Examination of the characteristics upon presentation of a population of children with type 2 diabetes could inform clinicians about possible risk factors for type 2 diabetes.

Methods: This representative observational study examined the characteristics of a population of children with type 2 diabetes diagnosed at an age of less than 22 years old. The incidence of these risk factors is reported using descriptive statistics and logistic regression. Measures included age at diagnosis, ethnicity, diabetes related antibodies, Body Mass Index Z-score, HbA1c, family history of diabetes, and presence of acanthosis nigricans and other obesity-related comorbidities (hypertension, polycystic ovarian syndrome, and dyslipidemia).

Results: The average age at diagnosis was 15, with a minimum age of 8. Out of 61 patients, 34 were female (56%) and 27 were male (44%). The mean BMI Z-score at presentation was 2.03, with a range of 0.15 to 3.31. The mean HbA1c was 9.6%, with a range of 5.2% to 15.0%. One patient had positive GAD antibodies. 15 patients (25%) had family histories significant for type 2 diabetes.

Conclusions: There are a number of risk factors common in a population of children with type 2 diabetes. Health outcomes can be improved by screening for type 2 diabetes among at risk populations in order to make a diagnosis at younger age.
Novel Urinary Exosome Isolation as a Platform to Study Diabetic Nephropathy (DN)

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**Background**: DN remains a major cause of end-stage renal disease (ESRD) worldwide. Discovery of early and reliable biomarkers of disease progression promises to help physicians develop personalized care plans for patients based on their risk of ESRD. Exosomes are plasma membrane bound vesicles secreted by all cells which contain protein, mRNA and miRNA, representative of the cells of their origin. The goal of these studies is to test the hypothesis that urinary exosomal miRNAs, which originate from cells lining the genitourinary tract, are an ideal source of biomarkers for DN.

**Methods**: Urinary exosomes were isolated from patients without diabetes (DM; controls), early DN, and moderate DN. RNA was extracted and microRNAs assayed by qRT-PCR array (Exiqon).

**Results**: 742 miRNAs were assayed in 4 control (no DM, normal kidney function, no proteinuria), 3 early DN (normal kidney function, with microalbuminuria), and 4 later stage DN (serum creatinine>1.3) subjects. Because this novel technique is unvalidated, we tested whether the miRNAs known to play a role in research models of DN (miRNA-192, 21, 29a, 216a, 217, 377, 200b, 93, and 29C) were expressed in urinary exosomes of DN patients compared to controls, recapitulating the prior studies. Finally, of the 742 miRNAs evaluated 89 (12%) were dysregulated in exosomes derived from DN patients compared to controls. Of these 89 dysregulated miRs, miR-200b, miR-99b, and Let-7b were upregulated in DN patients and have been implicated in TGF-β-dependent fibrosis, TGF-β-dependent epithelial mesenchymal transition, and podocyte-specific laminin downregulation, respectively.

**Conclusions**: Six of nine miRNA dysregulated in models of DN were also dysregulated in urinary exosomes of DN patients, suggesting that miRNAs associated with DN are expressed in exosomes. Evidence from our array also suggests potentially novel miRNAs are associated with DN.

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A Text Message Support System for Effective Continuation of Contraception in Female Adolescents: 'BC 2U'

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Introduction: Many women, especially adolescent women beginning a new contraceptive method, struggle with adherence to contraception. Cell-phone texting may serve as a tool to augment contraception information, dispel myths and encourage contraceptive use.

Hypothesis: We hypothesize that receiving informative text messages will improve contraceptive continuation in adolescent females.

Methods: This study analyzes data from 220 urban, minority adolescent females (ages 15-19 years) presenting for contraceptive initiation in a comprehensive, free-of-cost, adolescent health center in NYC. Following standard contraceptive counseling, participants choose a new contraceptive method (three-month supply of the pill, patch, or ring; a DepoProvera injection; or placement/referral for an IUD). After random assignment, the intervention group receives adolescent-friendly text messages (three messages a week, then tapered over four months) tailored specifically to address her new form of contraception. The control group receives standard in-person, non-text message counseling. Data collected at four months post intervention (n=176) examined contraceptive continuation rates between study groups.

Results: Study groups (intervention vs control) were found to be similar in regards to demographics, sexual/reproductive history, partner, mood, and pregnancy intention characteristics. Across study groups, a substantial number of adolescent females failed to continue their new contraceptive method at four months follow-up: 52.9% of participants in the intervention group (n=89) discontinued their contraceptive method compared to 49.4% of the control group (n=87). However, preliminary subgroup analysis shows that those in the intervention who initiated IUD had improved continuation compared to those in the control.

Conclusion: Text messages may have greatest utility when used to promote the use of long acting contraception. The quality of the content, design, dose and timing of text messages to target the adolescent population about contraception continuation needs to be explored.
A Novel Protocol for Characterizing Long-Noncoding RNAs in Autism Spectrum Disorders

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Introduction: Most genetic studies of autism spectrum disorders (ASD) still focus on protein-coding genes, while the contribution of the remaining genomic landscape has been largely unexplored. Long non-coding RNAs (lncRNAs) have so far been implicated in gene transcriptional regulation, and have been suggested to play a role in ASD and other neurodevelopmental disorders. Making use of a curated list of lncRNA genes released by GENCODE, we are developing a novel protocol to sequence full-length lncRNAs as a first step towards incorporating lncRNA expression profiles into the analysis of gene regulatory networks underlying these disorders.

Hypothesis: As proof-of-principle, we have designed a lncRNA-Seq custom-capture protocol for the purpose of uncovering gene structure details, sequencing of full-length isoforms, and identification of splice variants and novel isoforms of lncRNAs in the vicinity of ~1000 protein-coding genes implicated in, or candidates of, ASD, intellectual disability or epilepsy.

Methods: We are designing custom-capture probes targeting lncRNA exons that do not overlap exons of protein-coding genes, and generating full-length cDNA libraries using total RNA extracted from a neuroblastoma cell line. The cDNA libraries are hybridized to our custom capture probes to select for our lncRNAs of interest and subsequently sequenced on the PacBio RS platform.

Results: The full-length sequencing results from this lncRNA-Seq capture protocol will serve as a proof-of-principle for the identification and characterization of lncRNAs genome-wide or around any gene of interest.

Conclusions: Once our protocol has been tested successfully on cell lines, we will use it to profile lncRNA expression in brain tissue from ASD cases and controls.
The Effects of an Educational Intervention on Physician Knowledge and Screening for Postpartum Depression

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Introduction: Postpartum depression (PPD) is a common medical problem, affecting 10-20% of mothers. A significant portion of affected women never receive the proper diagnosis or treatment. Screening for PPD is not currently a uniform practice among pediatricians.

Hypothesis: An education intervention on PPD will increase pediatricians' comfort, practices, and knowledge about screening for PPD in an urban residency group practice.

Methods: Pediatric residents and faculty completed a survey about their comfort, practices, and knowledge of PPD. As part of a conference series, a new lecture was given on PPD. Two months later, residents and faculty again completed the survey.

Results: Forty physicians completed the PRE survey and 29 completed the POST survey. Nine (22%) of the PRE group reported screening for PPD depression always or most of the time, compared to the 12 (68%) of those who had attended the conference (p=0.0009). When tested on general knowledge, the mean score in the PRE group was 55% compared to a score of 70% in the POST group of those who attended the conference (p=0.04). Looking at the POST group of respondents alone, those who had attended the conference had a mean score on the knowledge portion of 71% compared to a mean score of 49% in those who had not attended (p=0.01).

Conclusions: An educational lecture on PPD increased physician self-reported screening for PPD and general knowledge about PPD. Future research will investigate whether documentation of screening and referrals for treatment were affected by this educational intervention.
Thyroid Ultrasound is More Sensitive Than $^{131}$I Imaging in Detecting Recurrence of Papillary Thyroid Cancer in Youth

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Methods: Chart review

Introduction: ATA guidelines recommend routine Tg screening and periodic $^{131}$I scan and/or US depending on recurrence risk. Improvements in ultrasound (US) techniques and technology have increased the sensitivity of this imaging modality. We describe 2 youths diagnosed with papillary thyroid carcinoma (PTC) who had noted recurrences on US after normal $^{131}$I scans.

Patient 1: 16 yo female presented with a neck mass for 6-9 months. FNA consistent with PTC. She underwent total thyroidectomy (TT) and lymph node (LN) dissection; staging was pT1N1bMX. 2 months postoperatively, whole body $^{131}$I scan showed residual thyroid bed tissue without distant metastases. $^{131}$I ablative therapy followed. $^{131}$I scan 9 months later revealed no uptake in the neck. Thyroglobulin (Tg) increased from 0.3 ng/mL to 2.3 ng/mL after rhTSH stimulation (negative Tg antibodies). TSH remained suppressed after ablation (0.01-0.26 µIU/mL). 2 years post-ablation, US revealed a 1.7 x 0.6 x 1.5 cm heterogeneous, hypoechoic vascular structure without normal LN architecture below surgical bed. Follow-up US 3 and 6 months later remained unchanged. $^{131}$I scans performed 2 and 3 years after ablation showed no uptake in the area of concern. PET imaging revealed a 1.3 x 0.6 cm mildly hypermetabolic focus consistent with the area of concern on US. FNA consistent with PTC. Patient had surgical resection and pathology confirmed PTC within a cervical LN.

Patient 2: 13 yo female presented with goiter for 2 years. She was euthyroid with negative thyroid antibodies. US revealed a multinodular goiter with dominant hypervascular lobulated nodule occupying the isthmus of the gland. $^{131}$I scan had normal 24 hr uptake of 28.5% (10-30%) with a cold nodule. She had TT with central LN dissection. Pathology confirmed PTC, stage pT3N1MX, with involvement through the capsule and 10 perithyroid LN. She had $^{131}$I ablation 1 month after TT. TSH remained suppressed after ablation (0.01-0.9 uIU/mL). Tg increased from <1-1.7 ng/mL to 10-14 ng/mL after rhTSH stimulation (negative Tg antibodies). Subsequent $^{131}$I scans and PET imaging were normal. 2 yr following ablation, US revealed a 1.6 x 0.5 x 1.0 cm hypoechoic structure with hypervascularity and non-shadowing echogenic foci suspicious for calcifications. Pathology of the concerning LN was consistent with recurrent PTC.

Discussion: In the patients presented, US detected recurrence of PTC in the setting of multiple negative $^{131}$I scans, as well as negative PET imaging (case 2). The patients demonstrate the benefit of US over $^{131}$I scan in 2 non-iodine-avid recurrences. This suggests that in patients with initial metastases localized to the neck, US may be the ideal imaging modality for follow up and should be used in the setting of elevated Tg and negative $^{131}$I scan.
The Skin as a Primary Site of Sensitization to Peanut Allergens

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Introduction: Exposure to food allergens through skin has been proposed to be a risk factor for food allergy. In mice, allergic sensitization can occur via the skin in an adjuvant-dependent fashion. Atopic dermatitis, which is a common risk factor for food allergy, is associated with presence of Staphylococcal enterotoxin B (SEB). We hypothesized that adjuvanticity required for sensitization could come from the allergen itself, or through toxins like SEB.

Hypothesis: Peanut and SEB trigger innate immune responses in the skin leading to sensitization.

Methods: Mice were epicutaneously exposed to peanut or SEB prior to assessing innate and adaptive immune responses.

Results: Epicutaneous exposure to peanut alone results in allergic sensitization and anaphylaxis after peanut challenge, while exposure to a weak allergen like β-lactalbumin (ALA) from milk does not. Exposure to ALA with either SEB or peanut induces sensitization to ALA, showing that both peanut and SEB have adjuvant activity. Peanut induces expression of innate cytokines IL-1, IL-6 and IL-33 in skin, and Th2 responses in draining lymph nodes, while SEB induces both Th2 and T follicular helper (Tfh) responses. IL-33 is required for peanut-induced Th2 responses while blocking IL-1 and IL-6 impairs SEB-induced responses.

Conclusions: Peanut has adjuvant activity on skin, which may explain why cutaneous exposure predisposes to food allergy and why peanut is such a potent food allergen. SEB, a superantigen associated with atopic dermatitis, primes Th2 and Tfh responses to bystander antigens. These findings highlight mechanisms by which normal or inflamed skin can be a physiologic route of sensitization to foods.
C-Peptide is Detected in 40% of Youth with Longstanding Type 1 Diabetes: A Pilot Study

Author Name(s): Evan Graber, Molly Regelmann, Elizabeth Wallach, Lindsey Waldman, Marina Goldis, Michelle Klein, Dennis Chia, Robert Rapaport

Department: Pediatrics
Division: Endocrinology
Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: Longstanding type 1 diabetes mellitus (LSDM) has been associated with relatively complete insulin deficiency after an initial remission phase. Residual β-cell activity has been reported in a few adult patients with T1DM for as long as 50 years. Recent studies predominantly in adults with LSDM found detectable C-peptide (CP) by ultrasensitive assays (UA). Few such data exist in youth with LSDM.

Hypotheses: To ascertain if CP is detectable in youth with LSDM using UA.

Methods: Random serum samples and simultaneous glucose (finger stick) were collected in patients with T1DM for >1 year and age <21 yr. Patients with all other types of diabetes were excluded. CP was analyzed by ultrasensitive ELISA assay (Mercodia Inc, sensitivity 0.5 pmol/L). Analyses included age at diagnosis, duration of T1DM, HgA1c at diagnosis (DxA1c), latest HgA1c, and total daily insulin dose per kg (TDD). Statistical analyses included t-tests and ANOVA.

Results: Out of 50 patients, 40% had detectable CP (Table). There was no association between detection of CP and DxA1c, current A1c, or TDD.

Conclusions: Using an UA, CP was detectable in 40% of youth who had T1DM for 1-15yr, suggesting demonstrable residual β-cell function. While the clinical significance of these results is unknown, if confirmed, these data could prompt novel treatment regimens and investigational interventions in youth with even LSDM.

<table>
<thead>
<tr>
<th></th>
<th>Total N=50</th>
<th>Group 1 (detectable CP) N=20</th>
<th>Group 2 (undetectable CP) N=30</th>
<th>p (Group 1 vs Group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Age</td>
<td>13.9 ± 4.6 yr</td>
<td>14.3 ± 4.4 yr</td>
<td>13.7 ± 4.7 yr</td>
<td>0.64</td>
</tr>
<tr>
<td>Sex</td>
<td>29M</td>
<td>16M</td>
<td>13M</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>203 ± 116 mg/dL</td>
<td>204 ± 93 mg/dL</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>6.7 ± 3.9 yr</td>
<td>9 ± 4 yr</td>
<td>5.2 ± 3.1 yr</td>
<td>0.001*</td>
</tr>
<tr>
<td>0-6yr (n=21)</td>
<td></td>
<td></td>
<td>4/21 (19%)</td>
<td></td>
</tr>
<tr>
<td>6-12yr (n=23)</td>
<td></td>
<td></td>
<td>11/23 (48%)</td>
<td></td>
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<tr>
<td>13-15yr (n=6)</td>
<td></td>
<td>5/6 (83%)</td>
<td>17/21 (81%)</td>
<td></td>
</tr>
<tr>
<td>ANOVA NS</td>
<td></td>
<td></td>
<td>12/23 (52%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1/6 (17%)</td>
<td></td>
</tr>
<tr>
<td>Duration of T1DM</td>
<td>7.2 ± 4.2 yr</td>
<td>5.3 ± 3.3 yr</td>
<td>8.4 ± 4.4 yr</td>
<td>0.006*</td>
</tr>
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<td>0-5yr (n=25)</td>
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<td>13/25 (52%)</td>
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<td>6-10 yr (n=15)</td>
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<td>5/15 (33%)</td>
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<tr>
<td>11-15yr (n=9)</td>
<td></td>
<td>2/9 (22%)</td>
<td>12/25 (48%)</td>
<td></td>
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<tr>
<td>&gt;15yr (n=1)</td>
<td></td>
<td>0/1 (0%)</td>
<td>9/15 (60%)</td>
<td></td>
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<td>7/9 (78%)</td>
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<td></td>
<td></td>
<td>1/1 (100%)</td>
<td></td>
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<td>ANOVA NS</td>
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</tbody>
</table>
Late-Onset Severe Congenital Hypothyroidism Due to Dyshormonogenesis

Author Name(s): Evan Graber, Marina Goldis, Lindsey Waldman, Dennis Chia, Molly Regelmann, Michelle Klein, Elizabeth Wallach, Robert Rapaport

Department: Pediatrics
Division: Endocrinology
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Introduction: Congenital hypothyroidism (CH) usually presents with mild, nonspecific symptoms or with no symptoms at all. Symptoms, if present, usually manifest soon after birth. Late onset of CH is known to occur in premature infants.

Methods: Case series

Results: Twin A was born at 32 weeks gestation, appropriate for gestational age (AGA). Newborn screen was negative for hypothyroidism 3 times. Following discharge from NICU at DOL 20, her parents noted she was a less vigorous feeder, slept more, cried infrequently, and appeared “chubbier and shorter” than her identical twin. She did not have a hoarse cry. She became harder to feed and developed jaundice. On DOL 72, the patient was seen by the pediatrician who found her to be lethargic and hypothermic to 93.9°F. She was admitted to the hospital and evaluated for sepsis, resulting in negative work-up. On DOL 75, the patient became bradycardic and a TSH was sent, which was 755 µIU/mL. Free T4 was 0.09 ng/dL (normal 0.7-1.3 ng/dL). Levothyroxine (LT4) was started at 15 µg/kg. Thyroid US was normal. 123I scan revealed decreased uptake at 24h compared with 4h, consistent with dyshormonogenesis.

Urinary iodine after imaging was elevated. Breast milk iodine was elevated while the mother was taking prenatal vitamins and normal when she was asked to stop. Genetic testing for DUOX2, DUOXA2, IYD, SLC5A5, TG and TPO mutations were negative. The patient is now 12 months old and is growing and developing normally. She remains on LT4 at a dose of 3.5 µg/kg.

Twin B was also AGA and had 3 negative newborn screens. She had no symptoms of CH until DOL 127 where decreased feeding was noted. TFT’s revealed mildly elevated TSH (8.26 µIU/mL) and free T4 0.77 ng/dL. Thyroid US showed a gland slightly small for age. 123I scan showed markedly reduced uptake. She was started on LT4 at 8µg/kg. She is also growing and developing normally.

Discussion: Severe symptomatic CH is rare due to early detection by newborn screening. Mutations in the same gene for dyshormonogenesis are known to cause phenotypes with varying severity. Iodine overexposure is also known to cause hypothyroidism, although it is unclear why the presentation of CH in these infants was so different given that they were feeding the same breast milk. CH should be considered in ill infants without a clear etiology for their illness even in the setting of normal newborn screening.
Screening for Celiac Disease in Youth with Type 1 Diabetes: Are Current Recommendations Adequate?

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Division: Endocrinology

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: The prevalence of celiac disease (CD) is higher in youth with type 1 diabetes (T1DM) than in the general population. CD in children with T1DM is suspected more often on screening tests than on clinical symptoms. ADA guidelines state that children with T1DM should be screened for CD “soon after...diagnosis” whereas ISPAD guidelines recommend CD screening “at diagnosis and then annually for 5 years.”

Hypothesis: To determine how long after T1DM diagnosis CD may first be identified.

Methods: Retrospective chart review of 340 patients with T1DM who were screened at diagnosis and/or yearly for CD antibodies (Ab). CD was suspected based on positive anti-tissue transglutaminase, anti-endomysial, or anti-gliadin Ab. Most patients had CD Ab measured at Prometheus Laboratories.

Results: Prevalence of CD Ab in our population was 9.7% (33/340) (73% female). 66.7% of those with positive CD Ab were detected between T1DM diagnosis and 5yr after T1DM diagnosis. Another 33.3% were detected >5yr after T1DM diagnosis. 27/33 with CD Ab were diagnosed with T1DM at our center, 9 were tested for CD Ab at diagnosis. 3/9 had positive CD Ab at the time of T1DM diagnosis. 11/27 had multiple negative CD screens prior to making a diagnosis (mean = 2 screens, 4.7 ± 4.2 yr). 20/33 patients underwent biopsy and 12/20 had biopsy-confirmed CD (mean time from T1DM diagnosis 3.2 ± 2.6yr, 9 female). 3/12 had positive biopsies within 1yr of T1DM diagnosis and 3/12 >5yr after T1DM diagnosis. No patients with biopsy confirmed CD had high clinical suspicion prior to diagnosis.

Conclusion: In the population, 41% of patients needed multiple screens to find positive CD Ab. 33% tested positive for the first time >5 years from T1DM diagnosis and ¼ with biopsy-proven CD were diagnosed >5yr after T1DM diagnosis. Most patients did not have symptoms of CD. These data are more in line with the ISPAD rather than ADA guidelines. Therefore, revision of screening guidelines may be needed to include screening beyond 5 years.
Modeling Hypertrophic Cardiomyopathy using Patient-Specific Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes

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Department: Pediatrics

Institute Affiliation: The Mindich Child Health and Development Institute

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: The “RASopathies” are a family of developmental disorders due to mutations in the RAS/MAPK pathway. One such disorder, cardio-facio-cutaneous syndrome (CFCS), is caused primarily by BRAF mutations. 40% of CFCS patients develop hypertrophic cardiomyopathy (HCM), for which no cure exists, and the underlying molecular mechanisms are unknown.

Hypothesis: We hypothesized that differentiated patient-specific human induced pluripotent stem cells (hiPSCs) would demonstrate cell autonomous and non-autonomous defects driving the HCM phenotype and underlying signaling pathway dysregulation.

Methods: hiPSCs were generated from healthy controls and CFCS patients with the BRAF T599R and Q257R mutations. iPSC-derived cardiomyocytes and fibroblasts were purified by sorting using CD90 and SIRPa expression, achieving >95% purity.

Results: Compared to controls, CFCS cardiomyocytes displayed cellular enlargement (p=0.0002), increased expression of hypertrophy-associated genes such as ANP and BNP (p<0.0001), and altered expression of the Ca^{2+} handling genes SERCA2a and PLN (p<0.0001; p=0.0077). Accordingly, CFCS cardiomyocytes displayed increased stored Ca^{2+} content (p=0.0002), and irregular Ca^{2+} transients (28% vs 6%; p<0.0001). Conditioned media from CFCS fibroblasts induced hypertrophy in WT cardiomyocytes (p=0.0002), and this effect was blocked by pre-incubation with a TGFβ neutralizing antibody (p=0.02). Both CFCS cardiomyocytes and fibroblasts displayed increased pERK activation compared to WT, and exposure to BRAF or MEK inhibitors rescued the hypertrophy in CFCS cardiomyocytes (p=0.01).

Conclusions: Our studies show that cardiomyocyte autonomous and non-autonomous defects underlie RASopathy-associated HCM. Treatment with pathway inhibitors rescued the disease phenotype, validating iPSC-derived CFCS cardiomyocytes as a useful model for the identifying novel therapies for CFCS-associated HCM.
The Use of the ISAC Microarray Platform in Food Allergic Patients

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Department: Pediatrics

Division: Allergy and Immunology

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: In the diagnosis of food allergy, skin prick testing and food sIgE levels have numerous drawbacks, including that positive results to tolerated foods are not uncommon. Allergen component-resolved diagnostics have garnered a lot of attention in recent years, offering the possibility of a more accurate assessment while requiring less serum. There is one commercially available protein microarray assay for allergy, the ImmunoCAP® ISAC sIgE (Thermo Fisher).

Hypothesis: The ISAC microarray is a helpful tool for predicting oral food challenge (OFC) outcomes in the diagnosis of food allergy.

Methods: We recruited children in our university-based, outpatient practice referred for OFC; subjects were challenged to egg (35), baked egg (34), peanut (43), walnut (27), cashew (18), soy (25), sesame (31), and wheat (32). Challenge outcomes were compared with IgE levels to allergens available on ISAC.

Results: 10 patients reacted to egg, 15 to baked egg, 16 to peanut, 12 to walnut, 5 to cashew, 12 to soy, 14 to sesame and 19 to wheat. Egg and baked egg reactive patients had significantly higher median Gal d 1 levels and Gal d 2 levels compared to non-reactive patients (P=.020 and .008 respectively). Peanut reactive patients had significantly higher Ara h 2 and Ara h 6 levels compared to non-reactive patients (P=.030 and <.001 respectively). The median Jug r 1 level was significantly higher in the walnut reactive patients (P=.004). The median Ses i 1 level was significantly higher in the sesame reactive patients (P=.002). No significant differences were seen for any of the cashew, wheat, or soy components between the reactive and non-reactive patients.

Conclusion: Current ISAC component testing may be a helpful tool in predicting OFC outcomes for some foods, including egg, peanut, walnut, and sesame, but cashew, soy, and wheat need additional components.
Genotype/ Hormonal Phenotype Mismatch in the Diagnosis of 17 β Hydroxysteroid 3 Dehydrogenase Deficiency

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Department: Pediatrics

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Institution Affiliations: Icahn School of Medicine at Mount Sinai

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Introduction: Steroid 17β-hydroxysteroid Dehydrogenase 3 (17β-HSD3) deficiency is a rare autosomal recessive disorder that usually presents at birth with ambiguous genitalia in a patient with a 46, XY karyotype. Since the 17β-HSD3 enzyme converts delta-4 androstenedione (Δ4) to testosterone (T), an increased Δ4 to T ratio, when the patient undergoes a human chorionic gonadotropin stimulation (hCG) test, is expected in 17β-HSD3 deficiency.

Hypothesis: Hormonal diagnostic standards of 17β-HSD3 deficiency may need revision and that molecular genetic analysis is superior to hormonal tests for this diagnosis.

Methods: Two patients were studied with 17β-HSD3 deficiency in whom the diagnosis was confirmed genetically but had a normal Δ4 to T ratio they demonstrated a decreased ratio of Δ4 to T.

Results: The first patient is a 12 year old 46 XY Brazilian who was born with ambiguous genitalia and was assigned to the female sex. Differential diagnosis included partial androgen insensitivity syndrome but was ruled out by normal androgen receptor sequencing. Pelvic ultrasonography confirmed normal appearing bilateral testicles bilaterally. HCG stimulation test at 5 months of age revealed a normal basal LH and FSH along with a normal increase in testosterone and dihydrotestosterone levels without any accumulation of precursor steroids, hCG stimulated Δ4 to T ratio was 0.4. At 8 months of age, she underwent a feminizing genitoplasty and bilateral orchiectomy. Later on she was screened for mutations in the HSD17β3 gene. The patient was found to be a compound heterozygote for c.608 C>T (p.Ala203Val) and c.625 T>C (p.Ser209Prol).

The second patient is a 10 year old 46 XY Yemenite also born with ambiguous genitalia and assigned to the female sex. Pelvic ultrasonography revealed the absence of a uterus and the presence of bilateral inguinal structures that were interpreted by the radiologist as possible testes which interpretation was further confirmed by MRI. The patients hCG stimulated Δ4 to T ratio was 0.4 and biochemical criteria for the diagnosis of 5 alpha reductase 2 deficiency were met. However, 5 alpha reductase 2 deficiency was ruled out after sequencing of the SRD5A2 gene. Single nucleotide polymorphism microarray analysis revealed regions of homozygous region comprising the HSD17β3 gene. Further genetic analysis confirmed homozygous mutation of c.608 C>T (p.Ala203Val) in the HSD17β3 gene. Both mutations are predicted to be deleterious by in silico analysis and were not found in the 1000 genomes project.

Conclusions: The diagnosis of 17β-HSD3 deficiency was not made in both patients relying on elevated levels of Δ4 and Δ4 to T ratios. Our data indicate that genetic analysis is superior to hormonal tests for the diagnosis of 17β-HSD3 deficiency. We suggest that the hormonal diagnostic standards of 17β-HSD3 deficiency may need revision and that molecular genetic analysis is superior to hormonal tests for this diagnosis.
Two Cases of Neonatal Systemic Juvenile Xanthogranulomatosis with Liver Involvement Treated with LCH-based Therapies and Review of the Literature

Author Name(s): Diana Kirschner, Yara Thomas, Birte Wistinghausen, Henrietta Rosenberg, Pamela Merola

Department: Pediatrics

Division: Hematology and Oncology

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: Juvenile Xanthogranuloma (JXG) is the most common form of non-Langerhans cell histiocytosis (LCH). JXG disease typically presents as benign skin lesions that spontaneously resolve within years. Extracutanous (systemic) forms, while rare, are well described in the literature and have been associated with considerable morbidity and mortality particularly when presenting with liver disease and in the neonatal period. Currently, there is no standard treatment regimen for systemic JXG. We report two cases of neonatal systemic JXG with liver involvement that were treated with LCH-based therapies. Both patients responded well to chemotherapy, most dramatically upon addition of antimetabolite agents.

Hypothesis: The prompt initiation of treatment with LCH-based therapies and the use of antimetabolite medications contributed to favorable outcomes in these two patients.

Methods: We report two cases of neonatal systemic JXG with liver involvement that were treated with LCH-based therapies.

Results: Both patients responded well to chemotherapy, most dramatically upon addition of antimetabolite agents.

Conclusions: Systemic JXG is associated with considerable morbidity and mortality particularly when presenting with liver disease and in the neonatal period. Currently, there is no standard treatment regimen for systemic JXG. This report demonstrates that symptomatic neonates can be successfully treated with LCH based regimens that include both corticosteroids, vinca alkaloids, and the addition of antimetabolite agents. It is important to pursue the reporting of patients with systemic JXG and their treatments in effort to determine the most efficacious therapy for these sick children.
Preseason Pediatrics: A Preclinical Curriculum for Medical Students

Author Name(s): Benjamin M. Laitman¹, Suzanne Friedman², Scott Moerdler², Alefiyah Malbari², Blair Hammond², Kathleen Gibbs²

Department: ¹Medical School, ²Department of Pediatrics

Division: General Pediatrics

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Background: Medical students at the ISMMS are exposed to limited pediatric training in their first two years of school. We sought to create a preclinical experience focused on pediatric-specific clinical skills and knowledge and to enhance mentorship opportunities.

Methods: A needs assessment survey was sent to 4th year students who completed their pediatric clerkship. The survey assessed pediatrics experiences, opinions on opportunities for preclinical exposures, and future career plans.

Results: Response rate was 23% (n=30). Ten students had pediatric ASM sites, three had pediatric LCE patients, five participated in pediatrics-related organizations, and four conducted pediatric shadowing during preclinical years. While 60% (n=18) did not plan on a pediatric career, 77% (n=23) believed they would have felt better prepared for their clerkship with more preclinical pediatrics training, and 87% (n=26) thought that students would benefit from additional/optional pediatrics training.

Conclusions: These data served to guide curricular development for “Preseason Pediatrics.” To date, 60 students are participating. The curriculum consists of a monthly didactic session, focused on specific knowledge and skills, taught by residents/faculty, followed by opportunities in which students apply skills learned in a clinical setting supervised by pediatric resident mentors to which they are assigned. Students will explore topics including newborn physical exams, developmental milestones, murmurs, and common pediatric infectious diseases. We plan to survey the participants to assess clinical knowledge and attitudes towards pediatric patients. We anticipate that increased clinical exposure will result in improved pediatric knowledge/skills, and that mentorship opportunities will enhance medical students perception of a potential career in Pediatrics.
Clinical Relevance of Sensitization to Individual Cow’s Milk Proteins

Author Name(s): Tricia D. Lee, Gustavo Gimenez, Galina Grishina, Hugh Sampson, Supinda Bunyavanich

Department: Pediatrics

Division: Allergy and Immunology

Introduction: Cow’s milk allergy is the most common food allergy in children. Most patients with cow’s milk allergy are sensitized to the major milk proteins, casein and whey (alpha-lactalbumin, beta-lactoglobulin). Co-sensitization is also common. In formula-fed infants, extensively hydrolyzed or amino acid-based infant formulas are typically recommended.

Hypothesis: We hypothesized that patients with individual cow’s milk allergy specifically to whey can tolerate partially hydrolyzed whey formula.

Methods: We did skin prick testing and serum IgE to individual cow’s milk proteins on a case patient. We did a western blot of the patient’s serum to the partially hydrolyzed whey formula and cow’s milk.

Results: The case patient was sensitized to only casein and tolerated partially hydrolyzed whey formula. The patient’s serum had no binding to the partially hydrolyzed whey formula but did to cow’s milk.

Conclusions: When milk allergy is specific to selected cow’s milk proteins, formula selection may not have to be as restrictive.
7, 4’-dihydroxyflavone Isolated from Glycyrrhiza uralensis a Constituent of ASHMI™ Prevents Dexamethasone Enhancement of Eotaxin-1 Secretion by Human Lung Fibroblasts

Author Name(s): Changda Liu, Nan Yang, Ryan Robalino, Dana Greene, Janaki Patcl, Jiachen Zi, Shuwei Zhang, Joseph Goldfarb, Hugh Sampson, Jixun Zhan, Xiu-Min Li

Department: Pediatrics
Division: Allergy and Immunology
Institute Affiliation: The Mindich Child Health and Development Institute
Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: Eotaxin-1 is chemotactic for eosinophils, basophils and Th2 cells, and plays a role in allergic inflammation. Dexamethasone (Dex), a potent glucocorticoid anti-inflammatory drug, has dual effects on lung fibroblast eotaxin-1 production. Although initially reducing eotaxin, by 72 hr, Dex increases secretion, which is associated with STAT-6 up-regulation. Clinical studies showed that in severe asthma cases, eotaxin production persists during systemic corticosteroid use. This indicates that corticosteroids may not be an ideal therapy for eotaxin-1 mediated inflammatory diseases.

Hypothesis: Glycyrrhiza uralensis (GU) flavonoids may suppress eotaxin production and prevent dexamethasone long term exposure-induced exacerbation of eotaxin production by human lung fibroblast via modulation of STAT6 and HDAC-2.

Methods: We isolated and identified 7, 4’-DHF from GU using chromatographic fractionation and isolation methods and compared its inhibition of human lung fibroblast (HFL-1 cells) eotaxin-1 production to that of Dex. We also determined combination effects of 7, 4’-DHF with Dex on eotaxin-1 production and the molecular mechanisms underlying these effects.

Results: Dex increased constitutive and IL-4/TNF-α stimulated eotaxin-1 production after 72 hr culture. In contrast, 7, 4’-DHF inhibited constitutive as well as IL-4/TNF-α stimulated eotaxin-1 production at this time point in a non-toxic manner. Interestingly, the presence of 7, 4’-DHF (10μM) prevented Dex (10μM) enhancement of both constitutive and stimulated eotaxin-1 production. This result was associated with down-regulation of Dex induced STAT6 and up-regulation of Dex decreased HDAC-2 expression.

Conclusion: 7, 4’-DHF may prove to be useful in treating eosinophilic inflammatory diseases either alone or complementary to corticosteroid therapy.
**Cholesterol Is a Biomechanical Regulator of Flow-Mediated Prostaglandin E2 (PGE2) Secretion in the Renal Collecting Duct (CD)**

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**Background:** Essential hypertension (HTN) affects millions of adults worldwide, the etiology of which remains obscure. Deficiency in renal prostaglandin E2 (PGE2) synthesis, which augments renal sodium (Na) avidity, is suspected to contribute to essential HTN. Moreover, dyslipidemia and, in particular, hypercholesterolemia is also associated with the development of HTN. Evidence from endothelial cells suggests that cholesterol-rich lipid rafts (LRs) act as flow sensors. Tubular flow rate in collecting ducts (CDs) mediates PGE2 release, and led us to hypothesize that cholesterol, and its incorporation into LRs, regulates mechanotransduced signaling pathways; specifically, suppressing flow-induced PGE2 release that, in turn, enhances Na absorption in the distal nephron.

**Methods:** PGE2 secretion is measured in flow-exposed CD cells and microdissected CDs before and after manipulating plasma membrane cholesterol.

**Results:** Cholesterol extraction of inner medullary CD3 (IMCD3) cells stimulates basal-(cholesterol replete vs. deplete cells; 3.8±0.9 vs. 31.5±1.5 pg/mL PGE2 per ug protein; p<0.05) and flow-(cholesterol replete vs. deplete cells; 24.7±2.3 vs. 83.4±16.8 pg/mL PGE2 per ug protein; p<0.05) mediated PGE2 release while cholesterol integration suppresses flow-(6.9±0.7 pg/mL PGE2 per ug protein; p<0.05) mediated PGE2 synthesis. Cholesterol extraction raised intracellular Ca2+ ([Ca2+]i) and chelation of [Ca2+]i suppressed cholesterol-dependent PGE2 release, implying that cholesterol extraction raises [Ca2+]i to release PGE2. To validate our in vitro experiments in vivo, mice were fed a control or high cholesterol diet, injected with isotonic saline to generate high urine flows, and CDs microdissected in media. The PGE2 secreted into the media by CDs from control mice was 221±50 vs. 113±34 pg/mL/mm tubule (n=3, p<0.05) from cholesterol fed mice.

**Conclusions:** Plasma membrane cholesterol regulates flow-stimulated PGE2 release in CDs, in vitro and in vivo, which presumably affects Na transport. We speculate that hypercholesterolemia leads to Na retention and HTN, by suppressing CD PGE2 release.

**Funding:** Veterans Affairs Support
Association Analyses of 100720 Individuals Reveal 8 New Loci Associated with Body Fat Mass

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(on behalf of the Giant body fat percentage meta-analysis consortium)

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Introduction: Inter-individual genetic differences account for 40-70% of the variation in obesity risk. Large-scale GWAS meta-analyses for readily-available adiposity measures (BMI, WHRadjBMI, and obesity risk) have identified at least 75 loci that contribute to obesity-related traits in adults and children.

Hypothesis: While these commonly studied adiposity traits are easily measured in large populations, they represent heterogeneous phenotypes. We conducted a genome-wide association meta-analysis of body fat percentage (BF%), which more accurately assesses adiposity.

Methods: In our primary meta-analysis, we combined the results of genetic associations with BF% for up to 100,720 individuals from 47 GWAS and 15 MetaboChip studies, which were predominantly of European ancestry. For loci that reached genome-wide significance, we examined their association with a number of cardiometabolic traits available from other GWAS consortia.

Results: SNPs in 12 loci reached genome-wide significance, two of which had been identified in previous GWAS for BF%, and six have previously been reported for BMI. Four of the 12 loci (near GRB14-COBLL1, IGF2BP1, PLA2L6, and CRTCI) were novel. Cross-trait analyses showed that association signatures were not always consistent with phenotypic correlations. E.g. the BF% increasing allele of the COBLL1-GBR14 locus was associated with reduced WHRadjBMI, an improved lipid profile and increased insulin sensitivity.

Conclusion: Our meta-analysis for BF% identifies novel loci that were not previously identified, revealing pathways that suggest a role of peripheral mechanisms involved in adipocyte and lipid metabolism and insulin sensitivity, complementing the central nervous pathways that are highlighted in GWAS for BMI and obesity risk.
Impairment of T-independent Antibacterial IgM Responses due to IRAK-4- and MyD88-deficiencies

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Division: Allergy and Immunology

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Introduction: Bacterial infections remain major causes of pediatric morbidity and mortality, as young children have immature antibacterial antibodies and limited vaccines available. CD27^IgM^IgD^ B cells reside in the splenic marginal zone and mount robust T-independent antibody responses against bacteria even in infancy, yet factors regulating this B cell subset are poorly understood.

Hypothesis: Human genetic deficiency of IRAK-4- or MyD88, molecules that mediate signaling through toll-like receptors (TLR), heighten susceptibility to invasive bacterial infection by impairing T-independent antibody responses.

Methods: Children with a history of invasive bacterial infection, including those with IRAK-4- or MyD88-deficiency, were recruited and compared with age-matched controls. ELISA and carbohydrate array were used to analyze antibodies from sera and PBMC culture after TLR stimulation. Comparison was made with splenectomized subjects after T-independent vaccination.

Results: Patients with IRAK-4- and MyD88-deficiencies have impaired production of IgM, but not IgG, recognizing carbohydrates (p < 0.01), including those expressed by S. pneumoniae or S. aureus (p < 0.01). IgM is produced robustly by CD27^IgM^IgD^ B cells after TLR stimulation, with IRAK-4- and MyD88-deficiency inhibiting antibody production and replication of this B cell subset. T-independent IgM after immunization was abated by splenectomy, correlating with reduced CD27^IgM^IgD^ B cells.

Conclusions: IRAK-4- and MyD88-deficiencies impair T-independent antibacterial IgM responses, parallel to those post-splenectomy. IRAK-4 and MyD88 appear vital for T-independent IgM responses and CD27^IgM^IgD^ B cell replication in response to bacteria. Accordingly, IRAK-4 and MyD88-mediated signaling offers a potential therapeutic target for T-independent IgM responses that may be useful in augmenting antibacterial immunity.
Improved Height Outcome and Decreased Prevalence Rate of TARTs in Males with Non-Classical Congenital Adrenal Hyperplasia Under Treatment

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Introduction: The long-term outcome of final height in 25 males with Non-classical Congenital Adrenal Hyperplasia owing to 21-Hydroxylase Deficiency (NC-21OHD) and treated with glucocorticoids was evaluated. Usually, advanced bone age owing to elevated adrenal androgen secretion results in poor height prediction, with un-treated patients frequently failing to reach their respective target heights.

Hypothesis: In this retrospective study, we predict from clinical experience that glucocorticoid treatment will improve height and decrease rates of testicular adrenal rest tumors (TARTs).

Methods & Results: Group 1 consisted of 16 patients who had reached their final height after adolescence either by having a growth rate of less than 1 cm per year or with a bone age of greater than 17 years. Final heights of 14 out of 16 patients either met or exceeded their respective target heights with a 2% margin of human error. Group 2 consisted of 9 males who were still growing at the time of data collection for whom the predicted final height was calculated before and after treatment. Almost all had improved final height predictions with glucocorticoid treatment. Testicular sonograms in 6 of the 25 patients were evaluated for the presence of TARTs with only one abnormal finding of TART.

Conclusions: Our data from Group 1 and Group 2 demonstrated slowing of bone age advancement in conjunction with improved height prediction, suggesting a therapeutic effect of cortisol in lowering androgen levels and thereby estrogen levels which have been documented to increase epiphyseal fusion. The cortisol therapy also decreases chronic ACTH stimulation of testicular adrenal rests. This prevents hypertrophy and destruction of the testicular parenchyma leading to improved fertility and normal testosterone levels in males.
Epinephrine Use in Positive Oral Food Challenges Performed as Screening for Food Allergy Therapeutic Trials

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Introduction: Studies indicate that 9-12% of positive oral food challenges (OFCs) for confirming food allergies require treatment with epinephrine. Epinephrine use for positive OFCs performed as screening for enrollment in therapeutic trials for food allergy has not been reported.

Hypothesis: Epinephrine is used more often to treat positive OFCs done as screening for enrollment in food allergy therapeutic trials.

Methods: Outcomes of positive screening OFCs from two treatment, Food Allergy Herbal Formula-2 (FAHF-2) and Milk Oral Immunotherapy (MOIT) performed at Mount Sinai were reviewed. In the FAHF-2 study, 45 subjects had positive OFCs (mean age 16.6 years, 60% male). Median food specific IgE levels were (kU/L): peanut 33.25, walnut 40.7, cashew 4.05, sesame 49.35, salmon 2.82, cod 1.94. Median skin prick test (SPT) wheal was 9.0 mm. In the MOIT study, 29 subjects had positive OFCs (mean age 9.6 years, 74% male). Median milk specific IgE was 29.1 kU/L and median SPT was 8.5 mm.

Results: OFC outcomes were similar in these two studies. Symptoms included: oral 89%, skin 46%, gastrointestinal 54%, respiratory (upper and lower) 57%, and cardiovascular 3%. Epinephrine was administered in 39%. Other treatments included antihistamine 100%, steroids 16.2% and intravenous fluids 9%.

Conclusions: Subjects undergoing screening OFCs for enrollment in therapeutic trials are highly sensitive and react at low levels or allergen exposure. Reactions are more severe and require more aggressive treatment than OFCs performed to assess natural tolerance to food allergens.
Ovarian Carcinoma in a 14-Year-Old Female Patient with Congenital Adrenal Hyperplasia

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Introduction: A 14-year-old female with classical congenital adrenal hyperplasia owing to 21-hydroxylase deficiency underwent bilateral adrenalectomy at 6 years old due to poor hormonal control. At 12 years of age, 17-hydroxyprogesterone was 748 ng/dL, total testosterone was 612 ng/dL, and androstenedione was 150 ng/dL with ACTH of 1334 pg/mL. Owing to persistently elevated androgens, she was given high doses of dexamethasone to achieve adrenal suppression.

Hypothesis: Because the patient was adrenalectomized, extra-adrenal androgen production was suspected.

Methods: Imaging studies including pelvic ultrasound and pelvic MRI were obtained to evaluate for adrenal rest tumors of the ovaries. Abdominal MRI was obtained to evaluate for residual adrenal tissue.

Results: Ultrasound revealed a large cystic structure within the right adnexa as well as thickening of its wall. MRI demonstrated a cystic lesion arising from her right ovary suspicious for ovarian neoplasm. The patient underwent right salpingo-oophorectomy, and histopathological examination revealed ovarian serous adenocarcinoma, low-grade, and well-differentiated. Tumor marker CA-125 was elevated and additional ovarian cancer staging workup confirmed stage IIIC due to one lymph node positive for carcinoma. The patient then developed a large left ovarian cyst, which led to a complete total abdominal hysterectomy and removal of the left ovary and fallopian tube. Pathology confirmed ovarian serous adenocarcinoma with microscopic focus of carcinoma in the left ovary. The patient had no further evidence of disease after this surgery and CA-125 levels fell.

Conclusions: To our knowledge, this is the first reported case of an ovarian serous adenocarcinoma in a patient with CAH. This evaluation led to the discovery of an ovarian serous adenocarcinoma. The relationship between CAH and ovarian carcinomas has yet to be established.
Effect of Endocrine Disruptors on Gut Microbiome in a Rodent Model

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Introduction: This proof-of-principle study was aimed to exam whether the composition of gut microbiome are affected by exposures to the endocrine disruptors. Using Sprague-Dawley rat model, three commonly-used endocrine disruptors (EDs), i.e. phthalate, paraben and triclosan and their mixture, were administrated to the animals from birth through adulthood.

Hypothesis: We hypothesized that rats exposed to these endocrine disruptors would have an altered composition of their gut microbiome.

Methods: The fecal samples were collected at postnatal day (PND) 61 and PND 181. The rat gut microbiome was profiled by 16S rRNA sequencing on hyper-variable 16S v3-v4 region followed by the taxonomic assignment and the diversity analysis.

Results: Our result showed a diverse gut microbiota in every experimental condition. Compared to fecal samples collected at PND 61, significant enrichment of Bacteroidetes and reduction of Firmicutes (p-value <0.001) were observed in samples at PND 181, suggesting an age-related microbiota changing dynamics. Importantly, the overall bacterial composition significantly differed with respect to types of ED exposures. More specifically, gut microbiota at PND 61 showed that, at taxa level, the Clostridiales was enriched in phthalate- or triclosan- group; the Betaproteobacteria was enriched in phthalate, paraben and mixture group; and Bacilli was reduced in triclosan group. Surprisingly, no taxon differences were observed by ED exposures at PND 181, suggesting that the gut microbiome might be more susceptible to ED exposure at early developmental stage.

Conclusions: Our study provides initial evidences that low dosage ED exposure may affect early microbiota composition in gut; whether these changes leads to down-stream health effects, even later in life, needs to be further investigated.
Altered T Cell Receptor Development and Differentiation in X-linked Agammaglobulinemia

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Introduction: X-linked agammaglobulinemia (XLA) caused by mutations in the Btk gene primarily affects B-cell development and immunoglobulin production. We have recently demonstrated defects in T-cell receptor repertoire in common variable immunodeficiency, which is also characterized by hypogammaglobulinemia and susceptibility to similar infections.

Hypothesis: We hypothesized that absence of B cells and/or immunoglobulin affects the development of the TCR repertoire in children with XLA.

Methods: Here we obtained PBMC DNA from 15 patients with XLA and anonymized banked PBMC DNA from age-appropriate pediatric controls. TCR β CDR3 was sequenced using the Illumina HiSeq platform, and data was analyzed using the ImmunoSEQ analyzer. We compared the two groups for TCR structure as characterized by numbers of deletions and insertions and V genes used and clonal data, evidenced by clonality and sharing of clones between individuals.

Results: An average of 2,982,843 sequences and 2,349,978 sequences each for XLA patients and controls respectively. XLA patients have fewer insertions and deletions compared to healthy controls suggesting that the TCRs are more germline compared to controls. XLA patients utilized different V genes compared to controls. XLA patients significantly favored V families 2, 14, 18 and 29 whereas they had fewer sequences using V families 6, 20 and 30. We observed that though sequences were not any more clonal compared to controls there was increased sharing of clones between individuals.

Conclusions: The development of T cells and the T cell repertoire is altered in patients with XLA.
Nasogastric Tube Feeding at Home: Analyzing Outcomes in a Pediatric Population

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Introduction: Home enteral nutrition is regarded as a safe and effective method to provide nutrition to children with chronic diseases. Pediatric data with regards to follow up after discharge is limited.

Hypothesis: The majority of patients do not continue nasogastric (NG) feeds long term after hospital discharge; therefore the impact on growth is minimal.

Methods: A retrospective chart review was conducted of pediatric patients discharged from Mount Sinai on NG feeds between January 2010 and June 2013.

Results: A total of 87 patients were included. Average age was 1.2 years. The most common diagnoses were congenital heart disease (47%), metabolic disease (17%), neurologic impairment (10%), liver disease (9%), prematurity (8%), and inflammatory bowel disease (6%). At time of most recent follow up visit, 44(50.6%) were on full oral feeds, 8(9.2%) were on NG feeds, 9(10.3%) had a gastrostomy tube placed, 9(10.3%) were deceased, and 17(19.5%) were lost to follow up or transferred care. Average time to discontinuation of NG feeds was 4.8 months. 37/41 patients (90.2%) with CHD underwent corrective heart surgery, of which 20/37(54%) were able to come off NG feeds after surgery (median 31 days). Change in weight Z-score was significant for neurologic impairment (-1.35 to -0.04, p-value 0.03). Height Z-score change was significant for prematurity (-3.84 to -3.34, p-value 0.02). There was no significant change in height or weight Z-scores for the other diagnoses.

Conclusions: NG feeds help to maintain weight and linear growth in a subset of children with chronic illnesses, but for the majority short-term therapy does not impact growth.
**Bullying and Food Allergy – Longitudinal Follow-Up**

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Fordham University, Department of Psychology, Bronx, NY

**Introduction:** Bullying is frequently reported by children with food allergy (FA), but no longitudinal studies have been reported regarding persistence.

**Hypothesis:** To explore bullying and QoL at yearly follow-up.

**Methods:** Identical questionnaires were mailed ~1 year (T2) following baseline (T1) assessments of 251 children with FA attending the Jaffe Food Allergy Institute clinical practice. Questionnaires included bullying and allergy characteristics, quality-of-life (QoL), demographics, and anxiety, as previously reported for this cohort (Pediatrics. 2013;131(1):e10-7).

**Results:** 124 (49%) patient-parent packets were returned. Reported bullying due to food allergy decreased insignificantly: 31.5% in T1, 28.2% in T2. There were 8 new cases of bullying in T2 (6.5% of the T2 sample). QoL scores did not differ between patients who were bullied in both T1 and T2 (persistent bullying) compared with those who were bullied only in T2 (t=-1.37, p=.18). Regarding T2 completers who reported being bullied in T1, logistic regression showed that both a younger age (p < .01), and a parental report that the parent “did something about the bullying”, predicted resolution of bullying at T2 (p =.03). Childrens’ report of telling the parent about being bullied, or parents’ report that they knew about the bullying, did not significantly predict resolution (p=.20).

**Conclusions:** New and persistent bullying had a similar impact on QoL, reinforcing previous conclusions that any bullying (long or short term) is associated with lower QOL. The results also suggest that resolution of bullying required an active parental intervention; parents’ merely knowing that bullying occurred was not enough.
Can Training Improve Allergists’ Ability to Accurately Identify Anxiety in Children with Food Allergy?

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**Introduction:** Anxiety is common in children with food allergy and is associated with decreased quality of life; we therefore evaluated a brief workshop to improve allergists’ detection of anxiety.

**Hypothesis:** To explore the utility and acceptability of clinician training for detection of anxiety.

**Methods:** 39 food-allergic children and their allergists separately completed the Screen for Child Anxiety Related Disorders (SCARED), a validated questionnaire. The 5 participating allergists attempted to estimate their patient’s responses. We analyzed the differences between patients’ and allergists’ reports. A child psychiatrist and a psychologist delivered a 60-minute workshop, in which four items with the highest rate of discrepant answers were discussed, and specific verbal screening questions were suggested. Following the workshop, the same allergists completed the SCARED for a different cohort of 39 children.

**Results:** Following the workshop, clinicians’ “do not know” responses to questionnaire items decreased from 70% to 5%. However, the correlation between clinician and child responses remained insignificant (r = .31, p = .32, before workshop; r=.30, p =.068, after). 20% (8 patients) of the first cohort exceeded the SCARED threshold score for clinically meaningful anxiety, 10% (4 patients) met that threshold in the second cohort. Clinicians identified 1/8 of the cases in the first; and 1/4 of the cases in the second. Additionally, clinicians expressed poor acceptability of the screening.

**Conclusions:** This brief educational workshop was neither useful nor acceptable in improving allergists’ ability to screen for anxiety, and different modalities, such as self-administered screens, are likely needed.
The Association Between Children’s Cognitive Function and Blood Metal Levels: A Pilot Study in Italy

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**Division:** Environmental Health

**Institute Affiliation:** The Mindich Child Health and Development Institute

**Institution Affiliation:** Icahn School of Medicine at Mount Sinai

**Introduction:** Childhood lead exposure is known to manifest neurological deficits, however, the combined effects of other metals such as manganese and chromium are understudied.

**Hypothesis:** We hypothesized that children with increased blood manganese and/or chromium levels would exhibit deficits in executive function cognitive tests, and that blood lead levels would mediate this association.

**Methods:** We assessed cognitive function using standardized CANTAB testing software (Cambridge Cognition) in 30 children ages 11-18 that reside in three Italian villages with known exposure to metals including manganese. Children’s blood metal levels were measured via inductively coupled plasma-mass spectrometry. Linear regression was performed to test for the association between cognitive function and multiple blood metals. The models were adjusted for children’s age, gender, body mass index, socioeconomic status and location of study site.

**Results:** We found significant associations between children’s blood lead levels and median decision latency times as well as percent correct responses (p<0.05) for specific executive function and memory domain tests. There was also a significant negative association between increasing blood manganese levels and emotion recognition decision latency times (p<0.05).

**Conclusions:** Our pilot study detected significant deficits associated with individual childhood exposure to lead, manganese, and chromium. This suggests that multiple childhood metal exposures are associated with poorer cognitive outcomes. It remains unclear whether manganese or chromium modifies the association between children’s blood lead and poorer cognitive outcomes.
Disagreement Between Skin Prick Test and Specific IgE in Young Children

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**Division:** Allergy and Immunology

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**Introduction:** Skin prick testing (SPT) and measurement of serum specific IgE (sIgE) level are important tools for the clinician to diagnose allergic sensitization. However, little is known about the agreement between the two methods in young children.

**Hypothesis:** We hypothesized, that there is a substantial disagreement between SPT and sIgE results in young children.

**Methods:** SPT and sIgE levels were assessed simultaneously for 14 common inhalant and food allergens at ages ½, 1½, 4 and 6 years in 389 children from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort born to mothers with asthma. Agreement between the two methods for diagnosing inhalant and food allergic sensitization at the four age-points was analyzed using kappa statistics.

**Results:** The prevalence of inhalant allergen sensitization increased during childhood when diagnosed from sIgE levels (p<0.0001) and SPT results (p<0.0001). In contrast, the prevalence of food sensitization increased during childhood when diagnosed from sIgE levels (p<0.0001), but decreased when diagnosed from SPT results (p=0.05). Overall, the agreement between SPT and sIgE results for inhalant allergens was poor to moderate (all κ-coefficients≤0.60) and decreased from moderate to slight for food allergens by increasing age (κ-coefficients: 0.46 to 0.31 to 0.16 to 0.14).

**Conclusion:** There is a substantial disagreement between SPT and sIgE for diagnosing allergic sensitization in young children, and this disagreement is increasing with age for food sensitization. Choice of assessment method therefore has a major impact on test results with wide implications for both clinical practice and research.
Lifetime Exposure to Potentially Traumatic Events and Hair Cortisol in a Multi-Ethnic Sample of Pregnant Women

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**Department(s):** ¹Pediatrics, ²Preventive Medicine

**Institution Affiliation:** Icahn School of Medicine at Mount Sinai ³
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**Institution Affiliation (outside of ISMSS):** Program for Behavioral Science, Department of Psychiatry, Boston Children’s Hospital ⁵
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Department of Psychology, Southern Methodist University ⁷

**Introduction:** Exposure to traumatic events may alter key physiological systems, including the hypothalamic-pituitary-adrenal (HPA) axis. How lifetime exposure to traumatic events influences HPA axis functioning during pregnancy, particularly among women of different racial/ethnic backgrounds, remains unknown, despite important implications for offspring. Hair cortisol (HC) is emerging as an integrated measure of HPA axis reactivity in relation to chronic stress, although few studies have examined this biomarker in pregnant women.

**Hypothesis:** Women exposed to greater lifetime trauma will have higher HC levels in pregnancy. This relationship will be stronger among minority women.

**Methods:** Pregnant women (N=180; 36% Caucasian, 19% Black, 46% Hispanic) reported demographics and completed the Life Stressor Checklist–Revised, a measure of lifetime exposure to potentially traumatic events and current symptoms of traumatic stress. Hair samples were collected at the end of pregnancy and cut into 3cm segments to allow for HC measurement during each trimester.

**Results:** Compared to Caucasian women, Black and Hispanic women had higher HC levels throughout pregnancy (ps < .05). Greater lifetime exposure to traumatic events was positively associated with HC levels during all trimesters (ps < .01). Following stratification by race/ethnicity, greater exposure to traumatic life events was positively associated with higher HC levels among Black women only (all trimesters, ps <.05).

**Conclusions:** This is the first study to consider these relationships in a racially mixed, pregnant sample. Greater lifetime exposure to traumatic events was associated with higher HC levels, especially among Black women, raising important questions about implications for offspring of these women.
Objective: We describe emergency department (ED) use for asthma by children age 2-5 years in terms of explicit appropriateness criteria.

Study Design: We reviewed EPIC records for a random sample of 91 of 807 children identified with “asthma” and an ED visit identified from the data warehouse. 40 of 91 children had at least one ED visit with asthma first or second diagnosis. Including no more than 3 ED visits per child, we describe 77 asthma ED visits that were abstracted onto a standardized form, using an IRB approved protocol.

Principal Findings: 34 (44%) had documented: labored breathing/retractions; 27 (35%) decreased breath sounds; 8 (10%) were admitted; and 1 (1%) had O2 saturation below 90%. Overall, 41 (53%) of ED visits documented at least one reason that made the ED an appropriate level of care according to criteria developed by a national expert panel using a RAND Delphi process. Of note, 26 children (72%) of the 36 visits who lacked documentation to identify a reason the visit was appropriate were labeled urgent during nurse triage.

Conclusion: 53% of these visits for asthma have documentation in EPIC that satisfy clinical criteria to establish the ED as an appropriate level of care. For the 47 percent whose visits were of questionable appropriateness, we don’t know if they fell short because of limited documentation of clinical findings, insufficient clinical severity, or other justifications for the visit not captured in the chart review. 14% neither met criteria nor were considered urgent at triage.
Quality of Care for Young Children Presenting to the Emergency Department with Asthma

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Department(s): \textsuperscript{1}Health Evidence and Policy; \textsuperscript{2}Emergency Medicine

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Objective: As part of a national pediatric quality measure development initiative, we use explicit criteria to describe aspects of the quality of care for pediatric asthma managed in the emergency department (ED).

Study Design: We reviewed a random sample of 91 of 807 children in the MSMC data warehouse to identify 40 children who had ED visits with asthma as first or second diagnosis. We included up to 3 visits per child, yielding 77 asthma ED visits, which were abstracted onto a standardized form, using an IRB approved protocol. Criteria come from a national expert panel that used the RAND/UCLA modified Delphi process.

Principal Findings: For three indicators on timeliness of care: 74 of 77 children (96.1\%) were triaged within 30 minutes of arrival (75\% within 11 minutes). All visits had O2 saturation documented within 45 minutes of arrival, 95\% in less than 30 (50\% by 7 minutes). 59 visits (76.6\%) were evaluated by a physician within 60 minutes of arrival (50\% within 31 minutes).

Three indicators regard the connection between ED and primary care: 57 of 77 visits (74.0\%) identified the primary care clinician (PCC); 14 (18.2\%) documented follow-up appointment made by ED staff, and 9 (11.7\%) documented real-time contact with the PCC.

Conclusion: Although timely care was typical, there were some undesirable delays: nearly one quarter waited more than an hour to be assessed by a physician. There is evidence of limited efforts to coordinate care with the PCC.
Association Between Traffic-Related Black Carbon Exposure and Postpartum Depressive Symptomatology: ACCESS Cohort

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Division: Preventive Medicine

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Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: Evidence links air pollution and adverse neuropsychological effects in adults albeit this has not been studied in pregnant women. Identifying preventable causes of maternal prenatal/postpartum depression is of interest because of known implications for child development, particularly in higher risk, urban ethnic minority communities.

Hypothesis: Higher prenatal traffic-related Black Carbon (BC) exposure is associated with increased postpartum depressive symptomatology.

Methods: Analyses included N=777 women in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) cohort. Women completed the Edinburgh Postpartum Depression Scale (EPDS) during pregnancy and in the first 4.5 months postpartum (range 0-30), analyses considered a dichotomous cut-off (≥12) for “probable depression.” Prenatal BC averaged over pregnancy was estimated using a validated spatio-temporal land-use regression model; levels were dichotomized at the median. Logistic regression was used to examine associations between BC and depression adjusting for maternal race/ethnicity, education and season of birth.

Results: Women were primarily ethnic minority (52% Hispanic, 33% Black) with lower education (67% ≤ 12 years) and 26.6 ± 5.9 years old; 21% and 16% of women had probable depression (EPDS ≥ 12) pre- and postnatally, respectively. Higher BC was not associated with prenatal depression [Odds Ratio, OR=0.76 (95% confidence interval, CI: 0.3-1.3)]; there was a suggested increased risk of postpartum depression among women exposed to BC above the median [OR=1.75 (95% CI: 0.4-7.2)].

Conclusions: These preliminary analyses suggest that exposure to higher traffic-related pollution prenatally may be associated with increased depression in the postpartum period.
Environmental Chemical Exposure in the Neonatal Intensive Care Unit

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Division(s): Newborn Medicine, Environmental Health

Institute Affiliation: The Mindich Child Health and Development Institute

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Introduction: Neonates admitted to the intensive care unit are exposed to the chemical-laden hospital environment during a developmentally sensitive time period. Community-based studies have shown associations between in utero exposure to common organic chemicals with abnormal childhood neurobehavior. Three small cohorts have shown high biomarkers of these same chemicals in spot urine specimens of preterm infants hospitalized in the neonatal intensive care unit (NICU).

Hypothesis: Chemical exposure in the NICU persists, can be associated with exposure to specific medical equipment, and correlates with neurodevelopmental outcomes.

Methods: We conducted a prospective observational study of 81 preterm infants admitted to the NICU. We collected serial urine specimens and medical equipment exposure history. We measured early neurodevelopmental outcome, growth, and thyroid function.

Results: In this preliminary analysis, we present serial biomarker measurements reflecting a panel of 25 endocrine disrupting organic chemicals for 20 study subjects. Biomarker levels are lower than those previously reported for NICU inpatients, both overall and when analyzed by intensity of medical intervention. There has been a progressive decline in biomarker levels in each of the 3 sequential NICU inpatients, both overall and when analyzed by intensity of medical intervention. There has been a progressive decline in biomarker levels in each of the 3 sequential NICU-based studies reported in the literature. NICU exposure levels remain comparable to or higher than those that raise concern in population-based studies.

Conclusions: NICU-based exposure to endocrine disrupting chemicals associated with adverse neurodevelopmental outcome is lower in our cohort than in two previous studies. Because of the developmental time point at which exposure occurs, current NICU-based exposure to environmental chemicals remains a concern for negative impact on childhood cognitive, motor, and behavioral outcome.

See Tables Below:

Table 1. Comparison of urinary biomarkers of selected phthalates from NICU inpatients with previously published values (median (IQR) in ng/mL)

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<tr>
<td>Low</td>
<td>25 (11, 56)</td>
<td>4 (0.6, 18)</td>
<td>0.35 (0.35, 4.1)</td>
<td>21 (1.4, 19)</td>
<td>23.5 (18.5, 49.7)</td>
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<tr>
<td>Medium</td>
<td>40 (11, 80)</td>
<td>28 (3.61)</td>
<td>0.35 (0.35, 3.2)</td>
<td>22 (7.70)</td>
<td>15.3 (7.7, 41.7)</td>
</tr>
<tr>
<td>High</td>
<td>89 (32, 188)</td>
<td>86 (21, 171)</td>
<td>3.6 (1.6, 9.1)</td>
<td>20 (12, 45)</td>
<td>3.7 (3.5, 9.0)</td>
</tr>
</tbody>
</table>

Table 2. Comparison of urinary biomarkers of selected phens from NICU inpatients with previously published values (median (IQR) in ng/mL)

<table>
<thead>
<tr>
<th>Equipment Exposure</th>
<th>Biphenol A (BPA)</th>
<th>Benzophenone-3 (BP-3)</th>
<th>Methyl-Paraben (mP)</th>
<th>Propyl-Paraben (prP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>23 (13, 47)</td>
<td>29.6 (11, 5, 35.6)</td>
<td>177 (69, 1560)</td>
<td>4.2 (2.7, 15.1)</td>
</tr>
<tr>
<td>Medium</td>
<td>38 (18, 45)</td>
<td>46.7 (4, 8, 88.7)</td>
<td>114 (43, 325)</td>
<td>24.5 (9.5, 71.4)</td>
</tr>
<tr>
<td>High</td>
<td>17 (15, 32)</td>
<td>24 (10, 4, 54.6)</td>
<td>340 (158, 1450)</td>
<td>12.6 (9, 0, 26.7)</td>
</tr>
</tbody>
</table>

Table continued...
De novo Generation of Gastrointestinal Regulatory T Cells in Response to OIT and EPIT

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Institution Affiliation(s): Icahn School of Medicine at Mount Sinai¹
DBV Technologies, Bagneux, France²

Introduction: Epicutaneous immunotherapy (EPIT) and oral immunotherapy (OIT) are being investigated as approaches to induce desensitization or tolerance to food allergens.

Hypothesis: We hypothesized that these two approaches may differ in their capacity to induce gastrointestinal regulatory T cells (Tregs) in sensitized mice.

Methods: To examine de novo induction of Tregs, we transferred CFSE-labeled (naïve OVA-specific) DO11.10 cells into naïve or orally- or skin-sensitized mice. Mice were then exposed to ovalbumin (OVA) by the oral or epicutaneous route (using OVA-Viaskin®), and lymph nodes and spleens harvested at 7 days for phenotyping by flow cytometry.

Results: Oral exposure of naïve mice to OVA (OVA-OIT) led to the generation of a population of CFSE-low DO11.10 cells in the mesenteric lymph node (MLN) that were LAP+/Foxp3- (consistent with Th3 cells) as well as Foxp3+ cells (consistent with iTregs). De novo Th3 and iTreg induction in DO11 cells after OVA-OIT was significantly impaired in both orally- and skin-sensitized mice. Mice sensitized to peanut did not have impaired Th3 or iTreg induction in MLN after OVA-OIT, indicating that there is not a general defect in tolerance pathways in sensitized mice. Exposure of mice to OVA-EPIT led to the generation of Th3 cells but not iTregs in the MLN, and in contrast to OVA-OIT, this was not impaired by prior sensitization.

Conclusions: De novo generation of gut regulatory T cells is suppressed in sensitized mice during OIT but remains intact during EPIT. The functional role of Th3 cells and iTregs in tolerance induction in food-induced anaphylaxis is currently being investigated.
TEEN HEED: A Community-Based Adolescent Diabetes Prevention Study

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Introduction: Rates of diabetes in youth are projected to quadruple by the year 2050 without preventive measures. Our study objectives were to: 1) Use a community-based participatory research approach to modify an evidence-based adult diabetes prevention program for pre-diabetic adolescents. 2) Screen overweight/obese adolescents for pre-diabetes. 3) Pilot the intervention with 20 pre-diabetic adolescents.

Hypothesis: Participation in TEEN HEED will lead to maintenance/decrease in body mass index (BMI) and decrease in diabetes risk.

Methods: We screened overweight/obese adolescents for pre-diabetes using oral glucose tolerance testing and completed related lifestyle and biologic measurements. Pre-diabetic adolescents were invited to complete 8 weekly peer-led diabetes prevention workshops and post intervention (3 month) follow-up evaluations.

Results: Overall, 47% of 186 adolescents pre-screened were overweight/obese based on measured BMI, 64% (n=56) of whom returned for diabetes testing. Fully 19 (34%) tested positive for pre-diabetes and 1 (1.8%) tested positive for diabetes. Most (14/19) pre-diabetic adolescents enrolled in the workshop; 9 completed >50% of the sessions, and 16 returned for follow up. Five of 9 adolescents completing the workshop no longer had pre-diabetes at follow up.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change in BMI p=0.3</th>
<th>Decreased BMI N (%)</th>
<th>Mean change in fasting glucose p=0.2</th>
<th>Decreased fasting glucose N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed &gt;50% of workshop (n=9)</td>
<td>-0.3 kg/m2</td>
<td>5 (56%)</td>
<td>-6 mg/dl</td>
<td>7 (78%)</td>
</tr>
<tr>
<td>Completed &lt;25% of workshop (n=7)</td>
<td>+0.3 kg/m2</td>
<td>2 (29%)</td>
<td>+1 mg/dl</td>
<td>4 (57%)</td>
</tr>
</tbody>
</table>

Conclusion: Despite small numbers, a pilot lifestyle workshop showed promising preliminary results on BMI and glucose outcomes among those who completed the intervention.
Prevalence and Outcomes of Coronary Artery Ectasia Associated with Isolated Congenital Coronary Artery Fistula

Author Name(s): Cheryl A. Vinograd¹, Stefan Ostermayer¹, Irene D. Lytrivi¹, H. Helen Ko¹, Ira Parness¹, Miwa Geiger¹, Laurie E. Panesar², Barry Love¹, Shubhika Srivastava¹

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Division: Cardiology

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Introduction: Isolated congenital coronary artery fistula (CAF) is rare and varies with respect to hemodynamic significance. The prevalence of coronary artery ectasia in association with isolated congenital CAF, regardless of size, and post-closure of large fistulae has not been systematically evaluated. We aim to characterize the demographic and echocardiographic differences among patients with large and small fistulae, and to describe outcomes with respect to coronary ectasia among those who underwent closure.

Hypothesis: We hypothesized that there is much that distinguishes small from large fistulae, in addition to hemodynamic significance, and that coronary ectasia persists even after closure of large fistulae.


Results: Small fistulae were noted to arise mostly from the left anterior descending artery, drain into the pulmonary artery, and have a low incidence of ectasia (n=3/92), with a mean coronary artery diameter z-score among these 3 patients of 3.45 +/- 1.15. Large CAF had a female predominance, with most originating from the right coronary artery and emptying into the right atrium; among the 12 patients who underwent surgical or transcatheter closure of large CAF, all feeding coronary arteries remained ectatic post-closure, with a mean coronary artery diameter z-score of 9.54 +/- 5.66 after a total mean follow-up time of 3.95 +/- 4.07 years.

Conclusion: The occurrence of coronary ectasia justifies long-term follow-up despite fistula size and successful closure of large CAF.
Evolving Growth Hormone Deficiency

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Introduction: The Growth Hormone (GH) Research Society guidelines recommend further investigation of the GH-IGF-1 axis in children with sustained poor height velocity (HV) even in the absence of severe short stature. GH stimulation test (GHST) results are not always reproducible. However, together with physical, laboratory and axiological findings, GHST are an integral part of making the diagnosis of growth hormone deficiency (GHD). Exclusion of GHD is necessary for the diagnosis of growth failure of unknown etiology (GFUE), also known as idiopathic short stature (ISS).

Hypothesis: Some patients initially considered to have GFUE may have evolving GHD.

Objective: To reevaluate patients with persistent GFUE who had a previous normal GHST (GH ≥ 10ng/mL).

Methods: Retrospective chart review of children with normal GH peak on initial testing who underwent repeat GHST for continued suboptimal HV. Second GHST was performed with arginine and L-dopa.

Results: 17 patients, 6 male, mean age 9.48 ± 2.27 years were identified as having a second GHST for GFUE. Mean peak GH on initial testing was 14.65 ± 5.86 ng/mL and 10.21 ± 4.68 ng/mL on repeat GHST. Eleven of 17, mean age 9.32 ± 2.78 years (64% male) had a peak GH response (< 10 ng/mL) on repeat GHST. The mean duration between tests was 2.02 ± 1.03 years (0.3-4.5 years). In the GHD group, the mean peak GH on the first test was 15.8 ± 6.98 ng/mL and 7.4 ± 2.34 ng/mL on repeat GHST. The mean height for patients found to be GHD at initial GHST was -1.93 ± 0.82 SDS and at repeat was -2.12 ± 0.74 SDS. Mean height of non-GHD patients at initial GHST was -1.91 ± 0.31 SDS and at repeat GHST was -1.95 ± 0.26 SDS. All of the GHD patients were started on GH treatment (mean GH start dose 0.26mg/kg/week). At 3-6 months of hGH HV increased from 4.03 ± 1.92 cm/yr to 11.19 ± 3.66 cm/yr (p < 0.01).

Conclusions: The diagnosis of GFUE/ISS poses a clinical dilemma in the face of persistent suboptimal HV. While GHST may not always be consistent, the patients found to have GHD on second GHST had HV response to treatment consistent with GHD. Patients with initial diagnosis of ISS/GFUE should continue to have HV monitored and in the absence of any other clinical cause for poor growth, repeat evaluation of the GH-IGF-1 axis should be considered.
An Isocaloric, High Fructose Dietary Trial to Link Alterations in Colonic Microbiota, Intestinal Permeability and Inflammation Markers in Humans: Study Design and Research Strategy

Author Name(s): Ryan W. Walker, Inga Peter, Jeremiah Faith, Jianzhong Hu, Jeanine Albu, Ruth J. Loos

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Institute Affiliation(s): The Charles Bronfman Institute for Personalized Medicine
The Mindich Child Health and Development Institute

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: In addition to associations with adverse metabolic outcomes, excess dietary fructose intake has also been linked to increased intestinal permeability, plasma endotoxin levels and inflammatory cytokines. Malabsorption of fructose in the small intestine is common which may provide a source of fructose for bacteria in the colon and alter the diversity and abundance of gut microbiota.

Aims: We aim to determine the effects of excess fructose consumption on intestinal permeability, markers of inflammation and the gut microbiome in humans.

Methods: We will enroll 20 healthy, non-obese participants and randomize them to a 28-day, isocaloric weight-maintaining high fructose diet (30% total energy from fructose) or a control diet and 1) obtain \( \text{H}_2 \) breath test values and pre and post resting metabolic, 2) collect stool and blood samples and anthropometrics before the intervention and across the 28-day intervention, 3) sequence 16S rRNA in stool for between-group bacterial population comparison and determine intestinal permeability pre and post via a lactulose/mannitol test.

Results (expected): We expect that an isocaloric, 28-day high fructose diet will increase intestinal permeability and plasma markers of inflammation. Furthermore, colonic microbiota abundance and diversity will be altered by the high fructose diet and species that favor fructose as a substrate will proliferate. These effects will be independent of weight gain.

Conclusions: Alterations of the gut microbiome by excess dietary fructose may help explain why high fructose consumption is so tightly linked to deleterious metabolic outcomes. This trial may provide insight into a new, gut bacteria-related mechanism by which excess fructose impacts health negatively.
The Role of Maternal Diet, Microbiome and Infant Feeding in Initializing the Fetal Gut Microbiome and Establishing the Infant Gut Microbiome: Study Design and Research Strategy

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Introduction: Maternal health, nutrition and feeding practice have a potential influence on child gut microbiota in utero and postnatally. This may be due to the vertical transmission of bacteria from mother to infant in utero, during delivery and/or via breastfeeding. These gut bacterial alterations early in life might influence child health and associated disease risk in the long term.

Aims: We aim to determine the origins of the neonatal microbiome by assessing the role of nutrition on maternal microbiome/intestinal permeability during pregnancy and on the early microbiome of offspring. Additionally, we will assess the role of postpartum maternal nutrition and feeding practice on the early development of gut microbes in children.

Methods: We will enroll 40 pregnant women and collect dietary data, stool and blood during pregnancy. Maternal, paternal and infant stool will be collected over 90 days after birth. We will sequence 16S rRNA in stool, maternal tissues and breastmilk for bacterial population comparisons.

Results (expected): We speculate that bacteria detected in maternal tissues will appear in early infant meconium and that unhealthy maternal diets will be associated with increased maternal intestinal permeability. Furthermore, we expect that mothers with higher gut permeability will have infants with more similar gut bacteria and that breastfed children will have bacterial profiles more similar to their mothers than formula fed children.

Conclusions: This study may generate valuable insights into the early establishment of gut microbes in newborns. The role of maternal nutrition and feeding method on infant microbiota may inform novel strategies for promoting child health in early development.
Integrated Pipeline for Detection and Prioritization of SNVs, Indels and CNVs in Neurodevelopmental Disorders

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Introduction: Copy number variants (CNVs) intersecting genes and loss-of-function single nucleotide variants (SNVs) are known to contribute to the risk for neurodevelopmental disorders, including autism spectrum disorders (ASD). Recent advances in variant detection tools and mutation evaluation algorithms, have made it easier to detect (e.g. GATK, Pindel) and prioritize (e.g. POLYPHEN-2, LRT, MutationTaster) genomic variations. Nevertheless, there still exists a lack of a coherent approach in variant discovery and prioritization, despite the availability of several software options.

Methods: To streamline this process, we are developing an integrated pipeline that combines state-of-art variant calling tools, such as GATK and Stampy/Pindel, with a familial analysis module and downstream annotation and prioritizing procedures for both coding and non-coding variants. Our pipeline also includes a set of in-house databases and brain gene expression data to optimize variant prioritization for neurodevelopmental disorders.

Results and Prospects: We are applying our integrated framework, to both small family trios and large pedigrees with multiple members affected with ASD, to identify key deleterious variants. In our pipeline, Pindel accurately detects small indels (1-20 bp) and deletions up to 10 kb, while the GATK haplotype caller is generally balanced and consistent for calling SNVs, as well as indels. With the combined power of these two tools, our newly developed modules for aiding prioritization, and our family-based approach, we are able to narrow down our search space to a dozen of candidate variants per ASD family, facilitating follow-up studies.
Pharmacokinetics of Berberine, a Bioactive Compound in Butanol Purified Food Allergy Herbal Formula-2

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Departments: ¹Pediatrics, ²Hematology

Division: Allergy and Immunology

Institute Affiliation: The Mindich Child Health and Development Institute

Institution Affiliation: Icahn School of Medicine at Mount Sinai

Introduction: Food Allergy Herbal Formula 2 (FAHF-2) prevents peanut-induced anaphylaxis in a murine peanut allergy model. Butanol extracted FAHF-2 named B-FAHF-2 is equally effective at only 20% of the FAHF-2 dose. We found previously that berberine isolated from these formulas inhibit IgE production and basophil activation. The aim of this study was to determine the pharmacokinetics of berberine.

Methods: Berberine standard and B-FAHF-2 were dissolved in acetonitrile and several concentrations were analyzed by liquid-chromatography-mass-spectrometry (LC-MS). Calibration curves were generated by plotting the chromatographic peak area as a function of berberine concentration. C3H/HeJ mice were randomly separated into three groups and 12 mg of B-FAHF-2, 2 mg of berberine, and water were orally administered. Blood samples were collected at several time points after feeding. In addition, berberine was detected in sera from subjects in a controlled phase I FAHF-2 Study. All serum samples were protein-precipitated with acetonitrile and berberine was detected by LC-MS.

Results: The percentage of berberine present in B-FAHF-2 was calculated to be 9.1 ±1.8%. Serum concentration-time curves of berberine were plotted. T_{max} was determined to be 60 minutes and the C_{max} was 172.5 ± 27.6 ng/mL. Berberine alone was absorbed at a lower rate than was berberine in B-FAHF-2. Berberine was also detected in sera from patients receiving FAHF-2, but not placebo, in a phase I study.

Conclusions: Berberine is a bioactive compound in B-FAHF-2 and other components composed in B-FAHF-2 may enhance berberine bio-availability.