

# reimagine HEALTH

## Is my fate in my genes?



ARIZONA DEPARTMENT  
OF HEALTH SERVICES

ARIZONA BIOMEDICAL RESEARCH CENTRE



THE UNIVERSITY OF ARIZONA  
COLLEGE OF MEDICINE PHOENIX

Research Office



FLINN  
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# reimagine **HEALTH**: Is my fate in my genes?

## AGENDA

8:00 – 9:00 a.m.

**Breakfast and Registration**

9:00 – 9:10 a.m.

**Welcome and Opening Remarks**

**Paul E. Boehmer, PhD**

Associate Dean for Research (Interim), University of Arizona College of Medicine – Phoenix

**Guy Reed, MD, MS**

Dean, University of Arizona College Medicine – Phoenix

### Keynote Speaker

9:10 – 10:10 a.m.

**Genomic Medicine: Today and Tomorrow**

**Anastasia L. Wise, PhD**

Program Director, Division of Genomic Medicine, National Human Genome Research Institute

10:10 – 10:30 a.m.

**Break**

### Genomics and Genetics

Session Chairs: Michael Fallon, MD / Suwon Kim, PhD

10:30 – 10:55 a.m.

**Aberrant Base Excision Repair and Cancer**

**Joann Sweasy, PhD**

Interim Director, University of Arizona Cancer Center

10:55 – 11:20 a.m.

**Genetics Will Revolutionize the Prevention of Heart Disease**

**Robert Roberts, MD**

Director of Cardiovascular Genomics and Genetics,  
Dignity Health St. Joseph's Hospital and Medical Center

11:20 – 11:45 a.m.

**The Power in Your Genes: Implications of Advances in Genetic Testing for Developmental Brain Disorders**

**Linda Restifo, MD, PhD**

Professor of Neurology, Neuroscience, and Cellular & Molecular Medicine,  
University of Arizona Health Sciences

11:45 – 1:00 p.m.

**Lunch & Networking**

### Gene-Environment Interactions

Session Chairs: Amelia Gallitano, MD, PhD / Shenfeng Qiu, MD, PhD

1:00 – 1:25 p.m.

**Tackling Cancer Health Disparities in Women through Integrated Multi-Omics Approaches**

**Melissa Herbst-Kralovetz, PhD**

Associate Professor, Department of Basic Medical Sciences  
University of Arizona College of Medicine – Phoenix

1:25 – 1:50 p.m.

**Genomic Discovery Leading to New Insights in Cerebral Palsy**

**Michael Kruer, MD**

Director, Cerebral Palsy & Pediatric Movement Disorders Program  
Barrow Neurological Institute, Phoenix Children's Hospital

1:50 – 2:15 p.m.

**Lessons from the Crowd: Genes, Disease, and Lifestyle Factors Associated with the Healthy Aging Brain**

**Matt Huentelman, PhD**

Professor, Neurogenomics Division, Translational Genomics Research Institute (TGen)

2:15 – 2:30 p.m.

**Break**

## Social and Ethical Considerations

Session Chairs: Maria Manriquez, MD / David Beyda, MD

- 2:30 – 2:55 p.m. **Racial Health Inequities: What's Genes Got to do With It?**  
**Joia Crear-Perry, MD**  
President, National Birth Equity Collaborative
- 2:55 – 3:20 p.m. **Genetic Counseling: A Model of Communicating Risks for Complex Issues**  
**Dee Quinn, MS, CGC**  
Director, University of Arizona Genetic Counseling Graduate Program
- 3:20 – 3:45 p.m. **Ethical and Economic Challenges Developing Treatments for Ultra-Rare Diseases: Focus on Mucopolysaccharidoses**  
**Paul Harmatz, MD**  
Professor in Residence, UCSF Benioff Children's Hospital Oakland  
University of California, San Francisco
- 3:45 – 4:00 p.m. **Break**

### Panel: Is my fate in my genes?

- 4:00 – 4:45 p.m. **Moderators:**  
**Melissa Herbst-Kralovetz, PhD**  
Associate Professor, Department of Basic Medical Sciences  
University of Arizona College of Medicine – Phoenix  
**Jonathan Lifshitz, PhD**  
Director, Translational Neurotrauma Research Program  
University of Arizona College of Medicine – Phoenix
- Panelists:**  
**Joia Crear-Perry, MD / Paul Harmatz, MD / Michael Kruer, MD**  
**Dee Quinn, MS, CGC / Robert Roberts, MD**  
**Linda Restifo, MD, PhD / Anastasia L. Wise, PhD**

- 4:45 – 4:50 p.m. **Lightning Round Presentation — Top Overall Abstract**  
Disseminated Coccidioidomycosis (DCM) in Three Generations Associated with a STAT4 mutation; Mice Also Exhibit Increased Susceptibility to Coccidioidal Infection but Can Be Protected by Vaccination  
**John Galgiani, MD**  
Director, Valley Fever Center for Excellence  
Professor, Medicine, University of Arizona College of Medicine—Tucson
- 4:50 – 5:00 p.m. **Closing Remarks**  
**Paul E. Boehmer, PhD**  
Associate Dean for Research (Interim)  
Professor, Department of Basic Medical Sciences,  
University of Arizona College of Medicine – Phoenix
- 5:00 – 6:15 p.m. **Poster Session and Networking**  
Drinks and hors d'oeuvres served in the Grand Canyon Patio



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## **David Beyda, MD**

**Chair and Professor in the Department of Bioethics and Medical Humanism  
University of Arizona College of Medicine – Phoenix**

David H. Beyda, MD, is the Chair and Professor in the Department of Bioethics and Medical Humanism at the University of Arizona College of Medicine – Phoenix. Dr. Beyda is an accomplished Master Educator and critical care physician with more than 40 years of experience practicing pediatric critical care bedside ethics. He teaches the ethics curriculum throughout the four years of medical education. He engages in medical humanism through the lenses of medical ethics at the bedside, stressing “who” the patient (personhood) is while addressing “what” the patient (disease) is.



## **Paul E. Boehmer, PhD**

**Associate Dean for Research (Interim)  
Professor, Department of Basic Medical Sciences  
University of Arizona College of Medicine – Phoenix**

Dr. Paul Boehmer is a founding faculty member at the University of Arizona College of Medicine – Phoenix, joining the college in July of 2006. He served as the Chair of the Department of Basic Medical Sciences from 2009 to 2019 and currently serves as the Interim Associate Dean for Research. Dr. Boehmer received his undergraduate and doctoral degrees in Biochemistry from the University of Newcastle upon Tyne in the UK. Thereafter, Dr. Boehmer pursued post-doctoral training at Stanford University. Prior to his tenure at the University of Arizona, Dr. Boehmer held faculty positions at the University of Medicine and Dentistry of New Jersey-New Jersey Medical School, and the University of Miami-Miller School of Medicine. Dr. Boehmer is interested in elucidating the molecular mechanisms underlying genome integrity. Specifically, his research focuses on mechanisms of DNA replication, recombination and repair in herpes simplex virus, leading to the identification of novel anti-viral drug targets.



## **Joia Crear-Perry, MD, FACOG**

**Founder and President, National Birth Equity Collaborative**

Dr. Joia Crear-Perry is a thought leader around racism as a root cause of health inequities, Speaker, Trainer, Advocate, Policy Expert, and fighter for justice – is the Founder and President of the National Birth Equity Collaborative. Recently, she addressed the United Nations Office of the High Commissioner for Human Rights to urge a human rights framework to improve maternal mortality. Previously, she served as the Executive Director of the Birthing Project, Director of Women’s and Children’s Services at Jefferson Community Healthcare Center and as the Director of Clinical Services for the City of New Orleans Health Department where she was responsible for four facilities that provided health care for the homeless, pediatric, WIC, and gynecologic services within the New Orleans clinical service area. Dr. Crear-Perry has been celebrated for her work to improve the availability and utilization of affordable health care for New Orleans’ citizens post the Hurricane Katrina disaster of 2005. Currently, her focus has expanded nationally and internationally as it relates to Maternal and Child Health. Joia, a proud recipient of the Congressional Black Caucus Healthcare Hero’s award and the Maternal Health Task Force at Harvard University Global Visionary Award for Commitment to Advancing Women’s Health, is most known for her work to remove Race as a risk factor for illness like premature birth and replacing it with Racism. She has been asked to train in Maternal and Child Health and is a sought-after speaker as a result of her articles in a number magazines including Essence, Ms. Magazine, as well as her publications around Structural Racism. After receiving her bachelor’s trainings at Princeton University and Xavier University, Dr. Crear-Perry completed her medical degree at Louisiana State University and her residency in Obstetrics and Gynecology at Tulane University’s School of Medicine. She was also recognized as a Fellow of the American College of Obstetrics and Gynecology. Her love is her family; health equity is her passion; maternal and child health are her callings.



## **Michael B. Fallon, MD**

**Professor of Medicine**

**Chair, Department of Internal Medicine**

**Executive Director, Clinical Research**

**University of Arizona College of Medicine – Phoenix**

Dr. Michael Fallon’s experience in Gastroenterology and Hepatology has been broad, spanning from developing a translational research program in complications of cirrhosis, to implementing clinical care and research programs, to integrating an academic focus into a well-established and productive community based clinical system. These experiences include initiating an externally funded research program as a junior faculty at Yale, building and growing the University of Alabama at Birmingham Liver Center, serving as Chief of Gastroenterology at the Birmingham VA Medical Center, and developing a broad clinical and investigative program as Chief of Gastroenterology at the University of Texas Health Science Center Houston. He is currently the Chair of Internal Medicine at the University of Arizona College of Medicine – Phoenix integrated with Banner University Medical Center.



## **Amelia Gallitano, MD, PhD**

**Associate Professor of Basic Medical Sciences and Psychiatry**

**Associate Professor, Graduate Interdisciplinary Program in Neuroscience**

**Director, Women in Medicine and Science**

**University of Arizona College of Medicine – Phoenix**

Dr. Gallitano received her medical degree, and Ph.D. in Neuroscience, from The University of Pennsylvania School of Medicine. She completed residency training in Psychiatry at Columbia University, New York, and the New York State Psychiatric Institute, followed by a post-doctoral research fellowship at Washington University School of Medicine in St. Louis, where she was a faculty member in the Department of Psychiatry. She is a board-certified psychiatrist. Dr. Gallitano joined the University of Arizona College of Medicine (UACOM) as one of the founding faculty members of the Phoenix campus in 2007. Research in her laboratory investigates how genes activated in the brain in response to stress may mediate the interaction between environment and genetic variations to influence the development of psychiatric illnesses such as schizophrenia and mood disorders. In addition to their molecular investigations, the lab has recently initiated a translational research program to develop a biologically-based diagnostic test for schizophrenia emanating from their basic science findings. Since starting her laboratory, Dr. Gallitano has received numerous grants and awards, including the first National Institute of Health (NIH) R01 grant awarded to an Assistant Professor in the department of Basic Medical Sciences (BMS), and her laboratory has maintained continuous NIH funding since. Dr. Gallitano is a co-founder and Director of the UACOM-Phx Women in Medicine and Science Program.



## **Paul Harmatz, MD**

**Professor in Residence**

**UCSF Benioff Children's Hospital Oakland**

Paul R. Harmatz, MD, is Professor in Residence, Department of Pediatrics, University of California San Francisco and UCSF Benioff Children's Hospital Oakland. He is the Medical Director of the Pediatric Clinical Research Program in Mucopolysaccharidoses (MPS) and Related Disorders. Dr. Harmatz completed his Pediatric internship and residency training at Harbor-UCLA Medical Center. Following a research fellowship in Pediatric Gastroenterology and Nutrition at Massachusetts General Hospital, he remained in Boston until 1992 as faculty in Pediatrics at Harvard Medical School. During the last 20 years, Dr. Harmatz has participated in clinical trials with MPS I, MPS II, IIIa, IIIb, IVa, VI, VII, and has managed clinical care for patients with MPS living in northern California.



## **Melissa Herbst-Kralovetz, PhD**

**Associate Professor, Basic Medical Sciences**

**Director, Women's Health Microbiome Initiative**

**University of Arizona College of Medicine – Phoenix**

Dr. Melissa Herbst-Kralovetz is a first generation student and received her bachelor's degree from Colorado Mesa University in Grand Junction, CO and her doctoral degree from the University of Texas Medical Branch in Galveston, TX in the Experimental Pathology Program. She completed her postdoctoral fellowship at the Biodesign Institute at Arizona State University in the Center for Infectious Diseases and Vaccinology with Dr. Charles Arntzen. Dr. Herbst-Kralovetz joined the University of Arizona, College of Medicine – Phoenix in 2009 as the Hematology/Oncology Block/Course Director in the preclerkship medical curriculum. She is currently an Associate Professor in the Departments of Basic Medical Sciences and Obstetrics and Gynecology and became the Director of the Women's Health Microbiome Initiative at the College of Medicine – Phoenix in 2017. Her research program is focused on understanding the microbiome and host-microbe interactions in the female reproductive tract as it relates to oncologic, reproductive, gynecologic health outcomes and health disparities. Dr. Herbst-Kralovetz utilizes clinical biospecimens, animal models and an innovative 3-D bioreactor system to study human epithelial and immune responses to microbiota at this site and has a long-standing interest in enhancing women's health outcomes through translational research. She has been funded by NIH NIAID and NCI and foundations including the Flinn Foundation, ARDF and most recently the Mary Kay Foundation. Dr. Herbst-Kralovetz enjoys interacting with the media to disseminate research findings and has been interviewed by news outlets including NPR/KJZZ Radio, Forbes Magazine and others. She was most recently recognized as a member of the "40 under 40" Class of 2018 by the Phoenix Business Journal. The award recognizes leaders in their organizations that are making a difference in their companies/organizations, as well as their greater community.



## **Matt Huentelman, PhD**

**Professor, Neurogenomics Division**

**Translational Genomics Research Institute (TGen)**

Dr. Huentelman's research interests center around the investigation of the "-omics" (genomics, transcriptomics, and proteomics) of neurological traits and disease. His laboratory's overarching goal is to leverage findings in these disciplines to better understand, diagnose, and treat human diseases of the nervous system. Dr. Huentelman joined TGen in July of 2004 after completing his doctoral work at the University of Florida's Department of Physiology and Functional Genomics at the McKnight Brain Institute where he investigated the application of gene therapy in the study and prevention of hypertension. His undergraduate degree is in Biochemistry from Ohio University's Department of Chemistry and Biochemistry at Clipping Laboratories. Dr. Huentelman's career includes visiting researcher stints in Moscow, Russia at the MV Lomonosov Moscow State University "Biology Faculty" and in the United Kingdom within the University of Bristol's Department of Physiology. His research focuses on Alzheimer's disease, aging, cognition, and rare disease.



## **Suwon Kim, PhD**

**Associate Professor, Department of Basic Medical Sciences  
University of Arizona College of Medicine—Phoenix  
Associate Professor, Cancer and Cell Biology Division  
Translational Genomics Research Institute**

Suwon Kim, Ph.D. is an Associate Professor in the department of Basic Medical Sciences. Dr. Kim's research focuses on deciphering the molecular mechanisms of cancer in order to develop better therapy and prevention strategies.

Dr. Kim's lab is located in Translational Genomics Research Institute (TGen) where she employs leading-edge technology including whole genome/RNA sequencing and single cell analysis. Dr. Kim is currently the lead principal investigator on several multi-institutional grants addressing precision medicine initiatives, for which she works closely with the clinician at the University of Arizona Cancer Center, Dignity Health, and Baylor Scott & White Research Institute in Texas.

Dr. Kim obtained her undergraduate degree from University of California Berkeley and her PhD from Yale University School of Medicine. She developed her research program as a postdoctoral fellow in the laboratory of Nobel Laureate Dr. J. Michael Bishop at University of California San Francisco.

Dr. Kim joined the UACOM-P founding faculty in 2007 and installed the inaugurating Hematology/Oncology Block in 2008 as a co-block director. She launched the new Personalize Active Learning (PAL) block in 2014. Dr. Kim currently serves as the PAL block director, teaches the subjects of cancer in the preclinical curriculum, and participates in the K-12 education outreach activities each year. She received the Educator of the Year award in 2013.



## **Michael Krueer, MD**

**Director, Cerebral Palsy & Pediatric Movement Disorders Program  
Barrow Neurological Institute at Phoenix Children's Hospital**

Michael Krueer, MD is a pediatric movement disorders neurologist, developmental pediatrician and molecular geneticist. Michael is an Associate Professor of Child Health, Genetics, Neurology and Cellular & Molecular Medicine at the University of Arizona College of Medicine Phoenix. He also serves as director of the Cerebral Palsy & Pediatric Movement Disorders Program at Phoenix Children's Hospital. Dr. Krueer's lab is dedicated to understanding how genetic mutations lead to cerebral palsy and related movement disorders and how genetics can serve as a springboard to improvements in both diagnosis and intervention. Michael is chair of the Cerebral Palsy Genomics Consortium, an international collaboration focused on genomic discovery in cerebral palsy as a major neurodevelopmental disorder.





## **Jonathan Lifshitz, PhD**

**Director, Translational Neurotrauma Research Program  
Associate Professor, Department of Child Health  
University of Arizona College of Medicine – Phoenix  
Barrow Neurological Institute at Phoenix Children’s Hospital  
Phoenix VA Health Care Center**

Jonathan Lifshitz, PhD, directs the Translational Neurotrauma Research Program to develop tools, refine procedures, and grow knowledge in the clinical care of acquired neurological injury. His research efforts investigate traumatic brain injury as a disease process that dismantles, repairs and regenerates circuits in the brain, with a focus on inflammatory mechanisms of injury and experiential learning approaches to rehabilitation. In the community, he develops approaches to account for traumatic brain injury in the domestic violence population in terms of incidence, awareness, education, and availability of care. He continues to lead local, state, and federal funded projects. He and his trainees have won a dozen national or international awards for research on traumatic brain injury and the NCAA/DOD Mind Matters Challenge for Concussion Education. He has more than 80 peer-reviewed publications, in addition to other monographs and book chapters. He chairs the Arizona Governor’s Council on Spinal and Head Injury, co-hosts the COM-P podcast *Relmagine Medicine*, and is the Lead Scientist and Director of Research and Development for The CACTIS Foundation.



## **Maria Manriquez, MD**

**Director, Pipeline Admissions Program & UME Addiction Medicine Education  
Professor, Department of Obstetrics and Gynecology  
University of Arizona College of Medicine – Phoenix**

Maria Manriquez, MD, a University of Arizona College of Medicine – Tucson alumni, directs and supervises activities of pre-matriculation curriculum for pipeline programs. One of the premier programs is the Pathway Scholars Program (PSP), which is a master in medical studies.

Dr. Manriquez is the physician lead for the Pain and Addiction Medicine Curriculum at the UA College of Medicine – Phoenix; she has worked with the Department of Health Services in the development of a curriculum that educates the Undergraduate Medical Education and Graduate Medical Education learners on pain and addiction. Formal education for providers who understand and implement screening, diagnosing and treating of individuals who have substance use disorder (SUD) or who are at high risk for developing SUD is a priority for our State, the Liaison Committee on Medical Education (LCME) and the Accreditation Council for Graduate Medical Education (ACGME).

Her service commitments include multiple leadership positions with the American College of Obstetricians and Gynecologists and as an oral examiner for the American Board of Obstetricians and Gynecologists. Dr. Manriquez continues clinical practice, focusing on substance use disorders in pregnancy and parenting women. Her research and advocacy focus is aimed at investigating innovations in prenatal care models addressing maternal morbidity and mortality, preterm delivery rate and substance use disorders in pregnancy.



## **Shenfeng Qiu, MD, PhD**

**Associate Professor, Basic Medical Sciences  
University of Arizona College of Medicine – Phoenix**

Dr. Shenfeng Qiu earned his Bachelor of Medicine degree from Nanjing Medical University, and his Ph.D. degree from the University of California, Riverside. He completed his postdoctoral training with Dr. Pat Levitt at Vanderbilt. He moved to University of Arizona to start his own lab in 2012, and currently he is a tenured Associate Professor. His lab is interested in how genes and environment affect brain development and contribute to neurodevelopmental disorders, such as autism spectrum disorders and schizophrenia. His work is currently supported by the National Institute of Mental Health.



## **Dee Quinn, MS, CGC**

**Director, University of Arizona Genetic Counseling Graduate Program  
Consultant, MotherToBaby AZ**

Dee Quinn, a board certified genetic counselor, is Director of the newly re-established University of Arizona Genetic Counseling Graduate Program. Our inaugural class of 5 students began this fall. We anticipate that this program and its graduates will provide additional, much-needed genetic counseling services to the state of Arizona. Ms. Quinn has been Director of MotherToBaby AZ since it began in 1999. She is a Clinical Lecturer in the Colleges of Medicine and Pharmacy at the University of Arizona and teaches genetics and teratology to medical students, residents, and other allied health professionals. She received a BSN degree from the University of Bridgeport in 1975 and a Master's degree in Genetic Counseling from Sarah Lawrence College in 1981. At the University of Connecticut from 1981-1989, Ms. Quinn provided prenatal, pediatric, and cancer genetic counseling, as well as developing the Connecticut Pregnancy Riskline. Since coming to the University of Arizona in 1989, she has provided prenatal and teratology counseling. She served as President of the Organization of Teratology Information Specialists (OTIS) from 1999-2001 and Executive Director from 2005-2012.



## **Guy Reed, MD, MS**

**Dean, University of Arizona College of Medicine – Phoenix  
Valley of the Sun Professor**

Dean of the University of Arizona College of Medicine – Phoenix, Guy Reed, MD, MS, is an internationally recognized and renowned cardiologist, physician-scientist and health administrator.

As dean, he spearheads the college's proud tradition of excellence in advancing medical education in the state of Arizona and beyond.

Prior to joining the college, Dr. Reed was the Lemuel Diggs Professor of Medicine and chair of the Department of Medicine at the University of Tennessee Health Science Center, as well as interim executive vice president for Methodist Le Bonheur HealthCare.

Dr. Reed is known for his research on the mechanism of blood clots and vascular disease. Through grant support from the National Institutes of Health, he translated his laboratory research findings into an innovative, clot-dissolving therapy to treat patients with strokes and heart attacks, which is now in clinical trials.

Dr. Reed graduated from Columbia University in New York City, where he received his bachelor's degree in English literature and pre-medical studies. He received a master's degree in mathematical statistics and a medical degree from Stanford University. He completed his internship, residency and chief residency in internal medicine at Yale University. Dr. Reed completed a fellowship in cardiovascular disease at Massachusetts General Hospital and a post-doctoral research fellowship in biochemistry and molecular biology at Harvard Medical School.



## **Linda Restifo, MD, PhD**

**Professor of Neurology, Neuroscience, and Cellular & Molecular Medicine  
University of Arizona Health Sciences**

Dr. Restifo has a lifelong passion to understand the genetics of brain disorders. Currently Professor of Neurology, Neuroscience, and Cellular & Molecular Medicine at the University of Arizona (UA), she earned her MD and PhD (Genetics) degrees from the University of Pennsylvania. After additional training in neurology (Harvard-Longwood) and developmental neurogenetics (Brandeis University), she launched a research program at UA that began with a basic-science emphasis and gradually moved toward translational medicine. Her team demonstrated the extraordinary similarity of genes essential for normal brain development in humans and fruit flies, and the utility of primary cultured mutant neurons as a cellular bioassay for drug discovery. In collaboration with human geneticists, she participated in gene identification for early-onset epilepsy and other severe disorders from whole-exome sequencing data. Other innovative collaborations led to software development for 2D neuron-image analysis and a microfluidic system for dissociation of neural tissues. Her research funding has come from NINDS, NICHD, John Merck Fund, Muscular Dystrophy Association, Autism Speaks, Jerome Lejeune Foundation, and TechLaunch Arizona. As an educator, Dr. Restifo starts with the principle that “the molecule is not the disease,” emphasizing the importance of clinical diagnosis and disease classification prior to study of cellular and molecular mechanisms. She is the Research Director of the University's new graduate program in genetic counseling.



## **Robert Roberts, MD**

**Director of Cardiovascular Genomics and Genetics, Dignity Health St. Joseph's Hospital and Medical Center, Professor of Medicine and Chair ISCTR**

Dr. Roberts has had a notable career as Director of the Coronary Care Unit at Barnes Hospital at Washington University in St. Louis followed by Director of Cardiology for 23 years at Baylor College of Medicine in Houston. He was then recruited to be the President and CEO as well as Chief Scientific Officer of the University of Ottawa Heart Institute for 10 years. He is currently Professor of Medicine at the University of Arizona College of Medicine – Phoenix, holds the Chair in ISCTR and is Director of Genomics and Genetics at Dignity Health, St Joseph Hospital.

Dr. Roberts has had a distinguished and prolific career as a scientist and educator having published over 950 scientific articles and was awarded the Most Highly Cited Researcher in 2002. He developed the MBCK Test which was used as the standard to diagnose heart attacks for three decades. Dr. Roberts is regarded as one of the founders of molecular cardiology. He is world renowned for his scientific contributions particularly in the field of cardiovascular genetics. He discovered several genes responsible for Familial cardiomyopathies. He mapped the first gene for atrial fibrillation, WPW and most recently (2007) discovered the first gene for coronary artery disease (9p21) and subsequently co-authored the discovery of more than 200 genetic risk variants predisposing to CAD.

Dr. Roberts has been Associate Editor of the textbook, Hurst's the Heart, for more than three decades and authored the first textbook, Molecular Cardiology. He is currently Editor-in-Chief of Current Opinion in Cardiology, Associate Editor of JACC-Basic Translational Science and Section Editor of Genomic and Genetics for JACC.



## **Joann Sweasy, PhD**

**Interim Director, University of Arizona Cancer Center  
Associate Director, Basic Sciences  
Maynard Endowed Chair, Cancer Prevention and Control  
Professor, Cellular and Molecular Medicine & Radiation Oncology  
The University of Arizona**

Joann B. Sweasy earned her doctoral degree from Rutgers University, studying the role of the RecA protein in the SOS response to DNA damage, under the direction of Dr. Evelyn M. Witkin. She initiated her research on the fidelity of DNA synthesis at the University of Washington in Dr. Lawrence Loeb's laboratory. After joining Yale University School of Medicine in 1993, she rose through the ranks to become the Ensign Professor of Therapeutic Radiology and Associate Director for Basic Sciences at the Yale Cancer Center. Joann Sweasy is currently a tenured professor in Cellular and Molecular Medicine and is Associate Director, Basic Sciences at the University of Arizona Cancer Center. Joann Sweasy is an internationally recognized expert in the genetics, cell biology, and biochemistry of DNA repair. For the past 25 years her laboratory has been consistently funded by the National Cancer Institute to study the molecular basis of mutagenesis and dysfunctional DNA repair as they relate to human diseases including cancer and autoimmunity. Dr. Sweasy's research team recently discovered that dynamic conformational changes are important for accurate DNA synthesis. The team has also shown that human germline and somatic genetic variants of base excision repair genes are linked to carcinogenesis because they are unable to properly remove damaged DNA bases, leading to genomic instability, mitotic catastrophe, and other cancer-associated phenotypes. The Sweasy laboratory also discovered that aberrant DNA repair leads to the development of lupus. Her current focus in this area is the identification and characterization of germline DNA repair variants that are enriched in individuals with lupus. Dr. Sweasy has significant skills in and commitment to training the next generation of biomedical scientists. Dr. Sweasy is especially proud of being presented with the 2017 Yale Postdoctoral Mentoring Award.



## Anastasia L. Wise, PhD

**Program Director**

**Division of Genomic Medicine**

**National Human Genome Research Institute**

**National Institute of Health**

Dr. Wise is a program director in the Division of Genomic Medicine at the National Human Genome Research Institute (NHGRI). She received her Ph.D. in genetics and genomics from Duke University and joined NHGRI in 2010. At NHGRI she serves as project officer for programs advancing the application of genomics to medical science and clinical care with a focus on perinatal sequencing, undiagnosed and rare disease genomic medicine, and sex chromosome analysis and association methods. Dr. Wise serves as co-coordinator and program director for the NIH Common Fund's Undiagnosed Diseases Network, which aims to form a sustainable national resource to diagnose both rare and previously undiagnosed diseases through team science. She is also a project scientist for the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, which aims to explore the potential implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. Her other research interests include gene-environment interactions in complex disease, pharmaco/toxicogenomics, and ethical, legal, and social issues related to the use of genetic information.

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# Continue the conversation...

## The next episode of the reimagine Medicine Podcast features speakers from the symposium!

### **Episode: reimagine Health: Is my fate in my genes?**

We will discuss research in genomics and genetics, what advancements are under investigation, and what ramifications may be in store for consumers. What factors should be considered in choosing to/not to learn about one's genetic code? The episode will serve as a means to "translate" the research shared at the symposium with real world application.

**Hosts:** Jonathan Lifshitz, PhD / Katie Brite, MD

**Guests:** Anastasia Wise, PhD / Michael Krueger, MD /  
Matt Huentelman, PhD / Dee Quinn, MS, CGC

The episode will be released soon. Please share it with others who were unable to attend the symposium!

[www.phoenixmed.arizona.edu/podcasts](http://www.phoenixmed.arizona.edu/podcasts)

Also available on iTunes, Google Play, Stitcher and Spotify.



Poster Title		Presenting Author
1	Neoantigen fitness model predicts lower immune recognition of cutaneous squamous cell carcinomas than actinic keratoses	Borden, Elizabeth
2	Role of Caveolin-1 in a mouse model of Marfan Syndrome-Associated Aortic Aneurysm	Curry, Tala
3	Single-Cell Transcriptomes Identify Abnormal Endothelial Subpopulation in Pulmonary Arterial Hypertension	Dai, Zhiyu
4	BRCA1: Targeting of triple negative breast cancers with dietary isoflavones	Donovan, Micah
5	S1PR3-related Molecular Biomarker Predicts Survival in Patients with Sepsis	Feng, Anlin
6	Ethnic Disparities in Gastric Cancer Presentation and Screening Practice in US: Analysis of 1997-2010 Surveillance, Epidemiology and End Results-Medicare Data	Florea, Ana
7	Collaborative Arizona and California combined cohort to investigate the role of rare genetic variants in susceptibility to disseminated coccidioidomycosis (Valley Fever)	Berghout, Joanne
8	Valley Fever Phenotypic Presentation: Exploration of a Precision Medicine Approach to Clinical Decision Support	Galgiani, John
9	Disseminated Coccidioidomycosis (DCM) in Three Generations Associated with a STAT4 mutation; Mice Also Exhibit Increased Susceptibility to Coccidioidal Infection	Galgiani, John
10	Identifying Target Populations for Pharmacogenomic Testing Implementation Using a Benefit Tool	Gallo, Tyler
11	Diabetes and environmental risk analysis: convenience stores predict HbA1c control	Giblin, Casey
12	Pharmacogenomics Implementation: Warfarin and Beyond	Heise, Will
13	Genetic Heterogeneity and Variable Expressivity of Ankyloglossia	Jones, Laurie
14	Differential Cytotoxicity of Bacteria and Bacteria-Free Supernatants from Members of Fusobacteria on Human Endometrial Epithelial Cells	Karjala, Sylvia
15	ITGB4 mutation alters mRNA splicing and esophageal cancer cell mobility	Kelly, Gabriel

Poster Title		Presenting Author
16	Excipients in Clinical and Personal Lubricants Inhibit the Growth of Health-Associated Lactobacilli Found in Vaginal Microbiome	Khnanisho, Michael
17	Pilot study on diffuse traumatic brain injury (TBI) induced microbiota dysbiosis: Are there sex-specific effects?	Krishna, Gokul
18	PHD2 Deficiency Induces Nitritative Stress via Suppression of Caveolin-1 in Pulmonary Arterial Hypertension	Liu, Bin
19	Metabolic Hallmarks of Cancer Altered in Hispanic Women Across HPV-Mediated Cervical Carcinogenesis	Maarsingh, Jason
20	The Role of Parenting and Parental Pain in Children's Chronic Pain Experience	Patel, Maya
21	Estrous cycle phase regulates inflammatory response to peripheral immune challenge in mice	Rojas Valencia, Luisa M
22	Mice born to mothers with gestational traumatic brain injury have distorted brain circuitry and differential immune responses.	Saber, Maha
23	Investigating the antimicrobial activity of the bacterial metabolite, glycochenodeoxycholate on vaginal bacteria as a novel therapeutic approach against bacterial vaginosis	Salliss, Mary
24	Mutations in KANK1 cause alterations in cytoskeletal dynamics associated with cerebral palsy	Schafer, Robert
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## 1 - Neoantigen fitness model predicts lower immune recognition of cutaneous squamous cell carcinomas than actinic keratoses

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A low percentage of actinic keratoses progress to develop into cutaneous squamous cell carcinoma. The immune mechanisms that successfully control or eliminate the majority of actinic keratoses and the mechanisms of immune escape by invasive squamous cell carcinoma are not well understood. Here, we took a systematic approach to evaluate the neoantigens present in actinic keratosis and cutaneous squamous cell carcinoma specimens. We compared the number of mutations, the number of neoantigens predicted to bind MHC class I, and the number of neoantigens that are predicted to bind MHC class I and be recognized by a T cell receptor in actinic keratoses and cutaneous squamous cell carcinomas. We also considered the relative binding strengths to both MHC class I and the T cell receptor in a fitness cost model that allows for a comparison of the immune recognition potential of the neoantigens in actinic keratosis and cutaneous squamous cell carcinoma samples. The fitness cost was subsequently adjusted by the expression rates of the neoantigens to examine the role of neoantigen expression in tumor immune evasion. Our analyses indicate that, while the number of mutations and neoantigens are not significantly different between actinic keratoses and cutaneous squamous cell carcinomas, the predicted immune recognition of the neoantigen with the highest expression-adjusted fitness cost is lower for cutaneous squamous cell carcinomas compared with actinic keratoses. These findings suggest a role for the down-regulation of expression of highly immunogenic neoantigens in the immune escape of cutaneous squamous cell carcinomas. Furthermore, these findings highlight the importance of incorporating additional factors, such as the quality and expression of the neoantigens, rather than focusing solely on tumor mutational burden, in assessing immune recognition potential.

## 2 - Role of Caveolin-1 in a mouse model of Marfan Syndrome-Associated Aortic Aneurysm

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Marfan Syndrome (MFS), a connective tissue disorder, resulting from mutations in the Fibrillin-1 gene, is associated with several clinical manifestations with the most life-threatening being aortic aneurysm, dissection, and rupture. The mechanism underlying MFS pathogenesis seems to result from crosstalk between the Angiotensin-II (AngII) pathway and over activation of transforming growth factor-beta (TGF- $\beta$ ) signaling. Studies show that Losartan, an angiotensin II receptor type I (ATRI) blocker, can block progression of aortic aneurysm in mice, partially due to its inhibitory effects on TGF- $\beta$  signaling. It has been established that caveolin-1 (Cav1), a coat protein of caveolae that is highly expressed in endothelial and smooth muscle, regulates AngII and TGF- $\beta$  signaling pathways, through its interactions with their receptors. Interestingly, Cav1 knockout (Cav1KO) animal models illustrated increased elastin synthesis and nitric oxide (NO) production. Our previous study in the MFS mouse model reported reduced NO production in the aortic wall, proposing a potential link between Cav-1 activation and aneurysm progression in MFS mice. Hence, in this study, we aimed to investigate the effects of genetic manipulation of Cav1 expression on the progression of aortic aneurysm in a well-established mouse model of MFS-associated aortic aneurysm, by generating MFS mice lacking Cav1 expression (MFS/Cav1KO).

In vivo imaging of aortic root diameter and pulse wave velocity (PWV) as an index of wall stiffness, were performed in 3, 6, and 9-month-old C57BL/6 (WT), MFS, Cav1KO, and MFS/Cav1KO mice using the Vevo2100 high-resolution ultrasound system. Ex vivo analysis of aortic structure and function was analyzed at 9 months, using small vessel chamber myography. In situ analysis of aortic wall integrity was analyzed at 9 months by Van Geison staining.

Aortic diameter and pulse wave velocity were both increased in MFS and MFS/Cav1KO mice as compared to WT. Interestingly, left ventricular (LV) mass was increased in MFS/Cav1KO and Cav1KO compared to wild type and MFS mice, suggesting that Cav1 plays a protective role in maintaining normal cardiac structure. Using potassium chloride, MFS/Cav1KO mice showed decreased vasoconstriction, suggesting that Cav1 may play a role in normal calcium signaling in aorta. MFS mice showed an increase in elastin fragment count and a decrease in elastin fiber length compared to WT. Interestingly, MFS/Cav1KO fragment count was not different than WT or MFS but average fiber length was normalized.

Our data shows that Cav1 may have protective effects on aortic structure and function during the development of aortic aneurysm in a mouse model of MFS.

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### 3 - Single-Cell Transcriptomes Identify Abnormal Endothelial Subpopulation in Pulmonary Arterial Hypertension

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**Introduction:** Pulmonary arterial hypertension (PAH) is a disaster disease characterized by obliterative vascular remodeling and persistent increase of vascular resistance, leading to right heart failure and premature death. Understanding the cellular and molecular mechanisms will help develop novel therapeutic approaches for PAH patients.

**Hypothesis:** We hypothesize that endothelial plasticity or distinct cell populations are critical for obstructive vascular remodeling in the pathogenesis of PAH.

**Methods:** Here we applied single-cell RNA sequencing (ScRNA-seq) to profile the pulmonary cells in a severe mouse model (Tie2Cre-mediated deletion of *Egln1* [encoding Prolyl-4 Hydroxylase 2 (PHD2)], designated *Egln1Tie2Cre* mice) of PAH.

**Results:** ScRNA-seq revealed 20 discrete cell populations from pooled mouse lung single cells from WT and *Egln1Tie2Cre* mice. We identified five distinct EC subpopulations in both WT and *Egln1Tie2Cre* mice, which expressed classical EC markers *Emcn*, *Pecam1* and *Cdh5*. Unexpectedly, there were markedly difference in second abundant EC Cluster (EC2) between WT and *Egln1Tie2Cre* lung. The number of Cluster (EC2) was markedly increased in CKO lung compared with from WT lung. EC2 cluster (mainly from *Egln1Tie2Cre* lung) was characterized by little expression of *Cldn5*, *Tmem100*, *Tspan7*, *Calcr1* and *Foxf1*. Analysis of genes related to the pathogenesis of PH showed that angiocrine factor genes *Pdgfb*, *Cxcl12*, *Mif* and *Edn1* are significantly increased in all EC subpopulations from *Egln1Tie2Cre* mice compared to WT mice. We also analyzed genes which were found to be mutated in human PAH patients and found that some of these genes (*Sox17*, *Atp13a3* and *Smad4*) were ubiquitously upregulated in all EC subpopulations, some of these genes were selectively downregulated or upregulated in specific EC subpopulation(s) [down: *Bmpr2*, *Acvr11*, *Aqp1*, *Ptgis*, *Cav1*; Up: *Eif2ak4* and *Smad1*] in *Egln1Tie2Cre* mice compared to that from WT mice.

**Conclusions:** ScRNA-seq analysis identifies unique endothelial population only highly enriched in the lung of severe PAH mice.

### 4 - BRCA1: Targeting of triple negative breast cancers with dietary isoflavones

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Breast cancers (BC) that lack BRCA1 tend to be triple negative breast cancers (TNBC), the most aggressive and lethal BC subtype. DNA methylation contributes to *BRCA1* silencing in both sporadic and hereditary (i.e., *BRCA1*-mutated) BC. The aryl hydrocarbon receptor (AHR) is overexpressed in TNBC and its activation results in epigenetic silencing of *BRCA1*. Here, we investigated the effect of the dietary isoflavone genistein (GEN), on *BRCA1* epigenetic regulation and AHR activity in a mouse model and human TNBC cells in culture. We also characterized a mouse model of *BRCA1* mutation carriers. We developed a Cre/Lox model for heterozygous deletion of *Brca1* (*Brca1<sup>+/-</sup>*). Wildtype (*Brca1<sup>+/+</sup>*) mice were administered control or GEN-enriched (4 and 10 ppm) diets from gestation through postnatal 50. TNBC cells with constitutively hypermethylated *BRCA1* (HCC38) and MCF7 cells were used for cell culture studies. Protein levels and mRNA expression were measured by Western blot and real-time PCR, respectively. *BRCA1* promoter occupancy and methylation were analyzed by chromatin immunoprecipitation and methylation-specific PCR, respectively. Cell viability was determined by MTT assay. GEN administered in the diet dose-dependently decreased basal *Brca1* methylation and AHR activity in the mammary gland of adult mice offspring. Normal mammary glands from *Brca1<sup>+/-</sup>* mice had downregulation of *Esr1*, *Pgr*, *ErbB2*, *Ahr*, *Ahr*, *Cyp1a1* and *Cyp1b1* suggesting a trend toward a TNBC phenotype and dysregulation of AHR. HCC38 cells were found to overexpress constitutively active AHR in parallel with *BRCA1* hypermethylation. Treatment of HCC38 cells with GEN upregulated *BRCA1* protein levels which was attributable to decreased DNA methylation and AHR binding at *BRCA1* exon 1a. In MCF7 cells, GEN prevented localization of AHR at the *BRCA1* gene. These effects were consistent with those elicited by control AHR antagonists galangin (GAL), CH-223191 and 6-naphthoflavone. The pre-treatment with GEN sensitized HCC38 cells to the antiproliferative effects of 4-hydroxytamoxifen. We conclude that the dietary compound GEN may be effective for the prevention and reversal of AHR-dependent *BRCA1* hypermethylation, restoring of ER $\alpha$ -mediated response thus imparting sensitivity of TNBC to anti-estrogen therapy.

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## 5 - S1PR3-related Molecular Biomarker Predicts Survival in Patients with Sepsis

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Sepsis is a potentially life-threatening complication of an underlying infection that quickly triggers tissue damage in multiple organ systems. A prognostic biomarker helps to predict the development of a disease which has been already diagnosed. The presence of a sepsis prognostic marker can be beneficial for the selection of patients for special treatment. Sphingosine-1-phosphate (S1P) and its receptor S1P receptor 3 (S1PR3) are firm potential therapeutic targets as biomarkers for sepsis as both are active regulators of sepsis-relevant events including vascular integrity, antigen presentation, and cytokine secretion. Up to now, an effective S1PR3-related sepsis prognostic marker has not been identified. This study aims to obtain a S1PR3-associated biomarker using gene expression profiles of peripheral blood which could predict the clinical outcome of patients with sepsis. With the definition of both S1PR3 co-expression genes and sepsis survival related genes, we identified a 16-gene S1PR3-related molecular signature (SMS) associated with survival of patients with sepsis. Our 16 genes are significantly enriched in multiple key immunity-related pathways that are known to play key roles in sepsis development. Significantly, SMS performs well in a validation cohort containing sepsis patients. We further confirmed SMS, as a newly developed gene signature, performs significantly better than most random gene signatures with the same gene size in whole genome. Our results had confirmed the significant involvement of S1PR3 dependent genes in the development of sepsis and provided a new prognostic biomarker for predicting survival of sepsis patients. Our results emphasized the value of molecular signatures from whole blood cells as biomarkers for predicting sepsis mortality risk and further assisted the improvement of personalized therapies.

Keywords: microarray, S1PR3, sepsis, SMS

## 6 - Ethnic Disparities in Gastric Cancer Presentation and Screening

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**Background:** Chronic infection with *Helicobacter pylori* is the strongest risk factor for distal gastric cancer (GC). While GC incidence has decreased, variation by race and ethnicity is observed. This study describes GC presentation and screening services among Medicare patients by race/ethnicity, place of birth, and history of GC-related conditions.

**Methods:** Using demographic, location and disease staging information, extracted from the Surveillance, Epidemiology and End Results – Medicare gastric cancer database (1997-2010), we compared frequencies of GC-related conditions (e.g. peptic ulcer, gastric ulcer, gastritis) and screening (*H. pylori* testing and endoscopy) from inpatient and outpatient services claims by selected race/ethnicity and place of birth.

**Results:** Data included 47,994 incident GC cases with Medicare claims. The majority (48.0%) of Asian/Pacific Islanders (APIs) were foreign-born, compared to Non-Hispanic Whites (NHWs), Hispanics and Blacks (with 64.4%, 33.9%, and 72.9% US-born, respectively). For NHWs, the most frequently diagnosed GC site was the cardia (35.6%) compared to <15% (P<0.001) for APIs, Hispanics and Blacks. While more than 57% of all cases had a history of GC-related conditions, *H. pylori* testing was reported in only 11.6% of those cases. *H. pylori* testing was highest for APIs (22.8%) and lowest for Blacks (6.5%).

**Conclusions:** Non-cardia GC, associated with *H. pylori* infection, was diagnosed more frequently among APIs, Blacks, and Hispanics than NHWs. Testing for *H. pylori* was low among all GC cases despite evidence of risk factors for which screening is recommended. Studies are needed to increase appropriate testing for *H. pylori* among higher risk populations.

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## 7 - Collaborative Arizona and California combined cohort to investigate the role of rare genetic variants in susceptibility to disseminated coccidioidomycosis (Valley Fever)

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**Introduction:** Disseminated coccidioidomycosis (DCM) is a rare and serious complication of infection with the soil-resident fungal pathogens *Coccidioides* spp. Most symptomatic infections are limited to the lung (pulmonary coccidioidomycosis; PUL), presenting as community acquired pneumonia. However, in ~800 cases per year, infection spreads to other organs causing life-threatening damage. The mechanism of pathogenesis remains unknown, but likely involves deficiencies in the immune response. We hypothesized that genetic risk may be attributable to rare pathogenic variants with allele and gene-level heterogeneity that functionally converge on shared biological processes that are differentially burdened between DCM cases and PUL controls.

**Methods:** We recruited the largest yet cohort of patients for investigation of the genetics underlying dissemination, comprised of 535 Coccidioidomycosis patients (n=147 DCM; n=388 PUL). DNA was extracted from blood, and exomes sequenced. Variants were jointly called and filtered for quality, read depth, and allele frequency. Processed files were annotated using ANNOVAR with additional analyses performed in R.

**Results:** 687,602 SNP and indel variants passed quality control in the complete dataset. Filtering for rare (MAF<0.001) putatively damaging (CADD>20) or loss-of-function mutations retained 41,982 and 2342 variants respectively. Variants in the DCM case cohort included mutations in candidate immune response genes from previously reported DCM cases and previously implicated in susceptibility to fungal infections from immunocompromised patient case studies and in animal models. Work is ongoing to control for demographic confounding, and future work will include gene set burden testing using sequence kernel analysis.

**Conclusion:** This preliminary work describes a new genetically characterized cohort for disseminated coccidioidomycosis and suggests that DCM is associated with discrete mutations in genes associated with immune function.

## 8 - Valley Fever Phenotypic Presentation: Exploration of a Precision Medicine Approach to Clinical Decision Support

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**Background:** Delays in diagnosis of coccidioidomycosis (Valley fever, VF) lead to unnecessary patient suffering, antibiotic use and healthcare costs. Approximately 2/3 of those infected with VF are asymptomatic, and the 1/3 of symptomatic patients display a phenotype that is often mistaken for bacterial community-acquired pneumonia (CAP). In South-Central Arizona, VF causes 25% of CAP and 43% of VF diagnoses are delayed > 1 month. Understanding the clinical presentation patterns indicative of VF CAP would reduce diagnostic delays, avoid hospitalization, and support antibiotic stewardship.

**Objectives:** To identify predictors of VF CAP versus non-VF CAP and explore precision medicine approaches to increase accuracy of VF diagnosis.

**Methods:** From March – September 2019, patients were enrolled in a CDC-funded study if they presented with CAP symptoms and a provider ordered an Enzyme Immunoassay (EIA) test for VF at Banner University Medical Centers in Tucson and Phoenix. At enrollment, patients were interviewed directly or by proxy about the symptoms leading to their healthcare encounter, including fatigue, cough, fever, chest pain, shortness of breath, headache, night sweats, muscle aches, joint pain, and rash. We assessed whether EIA-positivity for VF was associated with any of these symptoms using Chi-Square tests, stratified by outpatient vs. inpatient status.

**Results:** Among outpatients (n=47), 33% of VF EIA-positive patients reported a rash, whereas 2.8% of VF EIA-negative patients reported a rash (p=0.0031). There were no other significant differences in symptoms presentation for outpatients. Among inpatients (n=165), 30% of VF EIA-positive patients reported a rash, whereas 11.7% of EIA-negative patients reported a rash (p=0.027). Only 20% of VF EIA-positive patients reported a fever, whereas 47% of EIA-negative patients reported a fever (p=0.023).

**Conclusions and Future Work:** Preliminary results from a prospective study of patients reporting to Banner Health with CAP indicate that rash is a potentially important predictor of VF in both inpatients and outpatients. Future work could extract EMR notes using natural language processing, and machine learning approaches can be developed to find significant predictors of VF.

## 9 - Disseminated Coccidioidomycosis (DCM) in Three Generations Associated with a STAT4 mutation; Mice Also Exhibit Increased Susceptibility to Coccidioidal Infection but Can Be Protected by Vaccination.

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**Introduction:** Reported coccidioidomycosis has increased with case rates of 198/100,000 in Arizona (2012). In California alone, 2000-2011 hospitalizations were \$2.2B. Dissemination occurs in 8% of reports, resulting in significant morbidity and occasional deaths. DCM was found in a 3-generation family: grandmother (skin), mother (skin), and son (bone). Whole exome sequencing identified the same heterozygous (het) STAT4 missense mutation resulting in p.E626G in all three. This mutation is predicted to alter the phosphotyrosine binding pocket and impair STAT4 function, interfering with i) receptor binding and phosphorylation, ii) nuclear localization, and/or iii) transcription. Expression profiling of antigen stimulated peripheral blood mononuclear cells from one patient showed dampening of known STAT4 targets compared to controls.

**Methods:** Stat4 p.E626G knock-in mouse was created in C57BL/6NJ (WT) using CRISPR-Cas9. With continued breeding, neither homozygous (hom) nor het mice had gross abnormalities. Normal numbers of lymphoid cells and subsets were seen in all tested organs. E626G mice were inoculated intranasally with reduced virulence *C. posadasii* (Cp.) strain 1038. Naïve or  $\Delta cps1$ -vaccinated mice were challenged for resistance using the highly virulent Cp. Strain Silveira.

**Results:** At day 21 post Cp 1038 inoculation, hom, het and WT mice had similar lung fungal burdens ( $\sim 10^{4.7}$  cfu). All p.E626G mice died between days 31 and 39 with lung burden significantly higher ( $\sim 9 \times 10^6$  cfu) than WT mice sacrificed on day 44 ( $7 \times 10^5$  cfu,  $p=0.03$ ). In two separate studies,  $\Delta cps1$  immunized p.E626G and WT mice all had reduced lung fungal burdens 14 days following Cp ( $p<0.001$ ). None of 25 vaccinated p.E626G mice had dissemination to the spleen while all the controls did.

**Conclusion:** Mice carrying one copy of the E626G gene recapitulated patients' increased susceptibility to coccidioidal infection. The decreased fungal burdens seen in  $\Delta cps1$ -vaccinated mice suggest that vaccination may be effective even in some persons genetically susceptible to DCM. Given the increasing frequency and economic burdens of coccidioidomycosis, pursuit of vaccination strategies should continue.

## 10 - Identifying Target Populations for Pharmacogenomic Testing Implementation Using a Benefit Tool

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**Introduction:** Pharmacogenomic (PGx) testing implementation is rapidly expanding, including pre-emptive testing funded by health systems. PGx testing continues to develop an evidence base that it saves money and improves clinical outcomes. Identifying the potential impact of pre-emptive testing in specific populations may aid in the development of a business case. Translation Software Inc. (TSI) has developed a software tool that can evaluate patient medication lists to identify patients most likely to benefit from testing. The benefit scale assigns a potential benefit (scale 1-5, with 1 being limited benefit, and 5 being required) based on the medications a patient is taking. Forty drugs are deemed “critical” by this tool and an additional 45 are considered significant. We utilized this software to evaluate drug lists and identify groups of patients most likely to benefit from implementation of a PGx testing program in the Banner Health population.

**Methods:** De-identified patient medication lists were obtained for various inpatient and outpatient groups including psychiatric, cardiac, diabetic and substance abuse. Each list was designed to have over 1000 subjects. These lists were imported into the TSI PGx benefit tool to determine the percentage of patients that fell into each benefit category. We limited the analysis to 13 specific pharmacogenes for which testing is readily available.

**Results:** Medication lists were obtained for sixteen patient groups with a total of 82,613 patients. The percent of patients in each group with testing recommended, strongly recommended, or required ranged from 12.7% in the psychiatric outpatient age <18 years group to 75.7% in the any adult inpatient age >50 years group. Some of the highest yield drugs identified were citalopram, simvastatin, escitalopram, metoprolol, clopidogrel, tramadol, and ondansetron.

**Discussion:** The PGx benefit tool identified that the any inpatient age >50 years group had the highest percentage of patients that would be likely to benefit from pharmacogenomic testing. The psychiatric inpatient age >17 years and any inpatient age >25 also had testing recommended result >70%. Additional considerations in determining populations to test include potential lifetime value, ease of population identification and reimbursement policies.

## 11 - Diabetes and environmental risk analysis: convenience stores predict HbA1c control

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**Introduction:** Research has shown that as much as 60% of health is related to social determinants of health and environmental factors. Poor health indicators have been linked to consuming food prepared outside the home. The goal of this project is to utilize an EMR and a biomedical informatics approach in coordination with the Phoenix VA to determine if there is an association between nutritional environment and specific health indicators of BMI, HbA1c, and hypertension.

**Methods:** 21,052 food permits were obtained from Maricopa County Environmental Services on 12/14/2018. 11,564 records remained after systematic data cleaning. Permits were classified into categories of: grocery store, convenience store, restaurant, and restaurant subcategory of fast food. Geolocations were obtained from Google's Cloud Computing platform. ArcGIS was used to create point density heat maps on a relative scale and constant scale to visually display 'food deserts' and 'food swamps'. Patient EMR data was sourced from the Phoenix VA healthcare population. 2,350 patient records were selected based on HbA1c levels indicating diabetes mellitus 2 and an absence of other disease based on a Charlson comorbidity index. A Python program was used to assign a count of different types of food permits within various radii of each patient's home. The impact of nutritional environment on health indicators was assessed through statistical analysis software.

**Results:** Significant associations between BMI, HbA1c and distance to convenience stores from individual's homes were found.

**Conclusion:** Associations between social determinant factors and specific health indicators were identified using a novel method. Future research in various fields, like precision medicine, can employ similar epidemiological methods to expand the definition of environment when characterizing gene-environment interactions.

## 12 - Pharmacogenomics Implementation: Warfarin and Beyond

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The use of individual characteristics to personalize medication dosing has been shown to improve efficacy and safety, particularly with warfarin, but implementation is rare due to the lack of expedient tools at the bedside. Clinical decision support (CDS) systems use innovative software incorporated into electronic medical records to guide clinicians in their decision-making process for each patient.

Supported by the Flinn Foundation, we have built the ability to hold discrete, structured pharmacogenomic data in the Cerner medical record, which can be used for pharmacogenomic CDS. Our first project using these data involves warfarin dosing, but others will soon follow to guide treatment for drugs used in oncology, analgesia, mental health, primary care, emergency medicine and cardiovascular disease.

Our group is implementing a CDS system designed to improve safety and decrease the time needed to achieve a stable therapeutic dose of warfarin. This CDS will automatically assist clinicians in the use of an otherwise complicated warfarin dose calculator and will be disseminated across 28 western hospitals, including the three major academic medical centers in Arizona.

This project will enable the delivery of personalized care for warfarin initiation among medically underserved patients at high risk for poor anticoagulation outcomes. It aligns basic science researchers and clinical scientists across Tucson and Phoenix to translate findings to a vast population of patients treated by University of Arizona College of Medicine – Phoenix clinical partners, thus allowing development of new discoveries and rapid application of pharmacogenetics for patients in Arizona.

## 13 - Genetic Heterogeneity and Variable Expressivity of Ankyloglossia

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**Abstract:** Ankyloglossia or “Tongue-Tie” (TT) is a congenital anomaly in which the lingual frenulum is unusually short and restricts the mobility of the tongue. It can be associated with Upper Lip Tie (ULT) and have an adverse effect on oromuscular function, breast feeding, dentition and speech. A common treatment for TT is surgical frenectomy. Its prevalence in the newborns is ~ 5% and there have been reports of familial TT with X-chromosome linked inheritance. We follow over 7000 patients with TT in our clinics and investigated its hereditary nature in a pilot study.

**Methods:** We identified patients with TT / ULT by clinical exam and obtained photographs as well as detailed family histories during clinic visits. Families completed a scoreable questionnaire of symptoms. The pedigrees were recorded using Progeny Clinical software. The following diagnostic criteria were used: 1) Affecteds: documented TT on physical exam by one of the authors, a history of TT surgery 2) Non-Affecteds: no exam finding of TT, no symptoms of feeding, speech or dentition difficulty; 3) Unknowns: History of symptoms of feeding, speech or dentition difficulty with no exam findings available or exam findings not diagnostic of TT.

**Results:** We identified 9 pedigrees with multigenerational transmission suggesting Autosomal Dominant (AD) inheritance. There was variable expression of different symptoms of TT/ LT. Male to male transmission was seen in 8 / 9 families suggesting non-X linked inheritance. Out of the 18 affecteds, 8 were male and 10 were female.

**Conclusion:** We identified familial TT with AD inheritance and variable expressivity. Prior reports have suggested an X linked inheritance and an association with TBX22 gene. The variable expressivity seen in our pilot study suggests that there is likely significant contribution of gene-gene or gene-environment interactions. Studies are currently underway to identify additional families with inherited TT/ ULT and to develop DNA banking for such patients. Identifying the underlying genes and gene environment interactions can help to gain more insight into the pathogenesis of this condition.

## 14 - Differential Cytotoxicity of Bacteria and Bacteria-Free Supernatants from Members of Fusobacteria on Human Endometrial Epithelial Cells

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Fusobacteria are gram-negative, anaerobic microorganisms that are primarily found in the gut and oral cavity. Several members of fusobacteria have been associated with human disease. *Fusobacterium nucleatum* has been linked to colon cancer. *F. nucleatum* has also been isolated from the amniotic fluid and associated with pre-term birth. Another *Fusobacterium* species, *F. gonidiaformans*, can be found in the female reproductive tract (FRT), however its relationship to the host is unknown. Furthermore, *Sneathia* species, members of the order Fusobacteriales, are frequently found in women with bacterial vaginosis and have been associated with cervical cancer. The pathophysiological mechanisms of fusobacteria in the FRT have not yet been evaluated. We hypothesized that the fusobacteria secrete proteins or metabolites with cytotoxic properties to human endometrial epithelial cells (HEC-1A). Bacterial cultures were grown in liquid media for 48 hours under anaerobic conditions. Live bacteria were separated from supernatants through centrifugation and filtration. Five bacterial strains were tested: *F. nucleatum*, *F. gonidiaformans*, *S. sanguinegens*, and two *S. amnii* strains. Cytotoxicity was measured through crystal violet staining and microscopic imaging. Cellular density was quantified using Fiji. The analysis revealed that live *S. amnii* induced the highest cytotoxicity, *F. nucleatum* was less toxic, and other strains were nontoxic. Bacteria-free supernatants from *F. nucleatum* cultures induced cell stress, which was evidenced through cell shrinkage as well as cell membrane stretching. Bacteria-free supernatants from other bacterial species did not show evidence of cellular stress, indicating that they do not secrete cytotoxic compounds. Scanning electron microscopy (SEM) analysis of *S. amnii* and *S. sanguinegens* in a 3-D FRT model, showed differences in colonization patterns: *S. amnii* formed clusters of short rods whereas *S. sanguinegens* formed long filamentous structures attached to the epithelial cells. SEM imaging of *F. nucleatum* will be a future endeavor. In summary, we found that strains of fusobacteria, particularly *F. nucleatum* and *S. amnii* are cytotoxic to human endometrial epithelial cells. Future studies will validate and extend these findings to further evaluate host response mechanisms.

## 15 - ITGB4 mutation alters mRNA splicing and esophageal cancer cell mobility

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Integrin  $\beta 4$  (ITGB4, gene code *ITGB4*) is an important transmembrane receptor protein involved in cellular signaling, cell-matrix communication, and endothelial cell barrier function, with implications in various cancers and other diseases. Four long variants (A, B, C, and D) of ITGB4 are created by complete removal of intron 21-22, but inclusion of 37 bps of the intron would produce the short E splice variant (ITGB4E), which lacks most of the intracellular domain. Although many cancers are known to increase *ITGB4* gene expression, alterations in *ITGB4* variant expression are largely unknown in cancer.

We analyzed publicly available cancer expression data from the Cancer Genome Atlas (TCGA), which showed that ITGB4C (the most abundant long ITGB4 variant) and ITGB4E mRNA expression changes in a number of cancers. The ratio between the two remained the same in all cancers except esophageal cancer, where ITGB4E is preferentially upregulated. Eleven mutations registered in the Catalogue of Somatic Mutations in Cancer (COSMIC) found in cancer tissues are located near the splice site with only one mutation found in esophageal cancer (COSM4436788). We next established a *ITGB4* minigene containing exon 21, intron 21-22, and exon 22 to validate the effects of this mutation on ITGB4 splicing. We verified that this mutation influences splicing in the esophageal cancer cell line OE21 in favor of ITGB4E, consistent with the findings in human cancer tissues. To understand the functional effects of ITGB4E, we measured migration rates of cells with altered long ITGB4 (ITGB4A-D) or short (ITGB4E) levels by both siRNA and adenovirus infection of the esophageal cancer cell line OE21. A higher expression ratio of short ITGB4E compared to long ITGB4 slowed cell migration in a scratch assay.

Our results indicate that ITGB4 expression levels change in many cancers, and splicing is altered in esophageal cancer, with one particular esophageal cancer related mutation influencing ITGB4 splicing in favor of ITGB4E. ITGB4E retards cell mobility compared to other long ITGB4 variants. These data suggest ITGB4 splicing is impacted by cancer related mutations to exert influences over tumor behavior.

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## 16 - Excipients in Clinical and Personal Lubricants Inhibit the Growth of Health- Associated Lactobacilli Found in Vaginal Microbiome

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Lubricants are commonly used in the clinical setting during gynecological exams while also used personally to help with vaginal dryness and dyspareunia. Many clinical and personal lubricants contain compounds such as methylparaben (MP), propylparaben (PP), and chlorhexidine gluconate (CG), which exhibit bacteriostatic properties. Our objective was to evaluate the impact of these excipients on *Lactobacillus* species that are commonly found in the vaginal microbiome and associated with vaginal health. The parabens and CG were tested for growth on the four predominant vaginal *Lactobacillus* species: *L. crispatus* (ATCC and BEI strains), *L. iners*, *L. jensenii*, and *L. gasseri*. Ethanol (a solvent for parabens) and bleach were used as negative and positive controls, respectively. The impact of these excipients on *Lactobacillus* growth was tested using disk diffusion (zone of inhibition) assays and minimal inhibitory concentration (MIC) assays. Statistical significance was determined using ANOVA. The disk diffusion assay showed that growth of *L. crispatus* strains, *L. gasseri*, and *L. jensenii* (under 5% CO<sub>2</sub>) had significant zones of inhibition from all chemicals tested when compared to ethanol. For *L. iners* and *L. crispatus*, which were grown anaerobically, only CG and bleach caused significant bacterial growth inhibition when compared to ethanol. MP and PP showed similar levels of bacterial growth inhibition across all lactobacilli. CG was shown to inhibit lactobacilli at a significantly higher magnitude than parabens. MIC assay revealed that MP and PP inhibited bacterial growth at 0.8% for all lactobacilli except *L. iners*. MP and PP inhibited *L. iners* at 0.2% and 0.1%, respectively. CG was shown to inhibit *L. crispatus* and *L. iners* at 0.005%, *L. jensenii* and *L. gasseri* at 0.000125% and *L. crispatus* at 0.001%. Ethanol was not inhibitory for any lactobacilli. These analyses demonstrated that CG is more inhibitory than parabens, as CG inhibited lactobacilli growth at much lower concentration levels than parabens. These findings demonstrate that these excipients inhibit the growth of the health-associated vaginal *Lactobacillus* species. Future clinical studies are needed to determine the impact of lubricants, containing bacteriostatic excipients, on vaginal microbiome composition and stability.

## 17 - Pilot study on diffuse traumatic brain injury (TBI)-induced microbiota dysbiosis: Are there sex-specific effects?

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The pathophysiological consequences of traumatic brain injury (TBI) extends beyond the central nervous system affecting enteric function. Recent reports indicate that TBI alters gut microbiota acutely (as early as 1 day) suggesting these microbial communities may fluctuate over time post-injury contributing to pathological and behavioral deficits. Further, women are more likely to have continuing post-concussive symptoms and longer recovery than men. We hypothesize that assessment of sex-specific TBI-induced microbial dysbiosis over time post-injury can capture important aspects of disease pathology crucial for understanding post-concussive symptoms driven by the gut-brain axis. Young adult male and female Sprague Dawley rats were subjected to either midline fluid percussion-induced diffuse TBI or sham surgery (n=1/group/sex). Fecal pellets were collected prior to brain injury (as baseline measure) and one day post-injury (dpi). The microbial DNA was extracted, the variable region (V3) of the 16s rRNA was amplified and sequenced using MiSeq platform. Fecal microbiota species diversity was assessed based on operational taxonomic units (OTU) richness showed distinctive gut microbial composition determined by both sex and injury. Preliminary analysis of baseline and 1dpi samples indicated higher abundance of TBI-responsive *Proteobacteria* in female rats when compared to males, agreeing with previous reports (Nicholson et al., 2019). We observed that males and females were less enriched for *Lactobacillus* after TBI (Treangen et al., 2018). Interestingly, the distribution of microbial genus between males and females were substantially different, which may relate to their differential response to TBI. These pilot data serve as proof of concept that diffuse TBI may cause sex-dependent microbiota disruption at 1dpi. Importantly, our initial observations are similar to previously reported microbiota changes in other focal TBI models. Longitudinal studies are ongoing to assess the microbial crosstalk between mucosal sites as it relates to TBI-induced chronic behavioral morbidity, especially in females. Experimental outcomes are important to advance our understanding on the role of microbiota and why female sex suffer more from chronic TBI morbidity. Funding source: Valley Research Partnership (VRP) P1-4010

## 18 - PHD2 Deficiency Induces Nitritative Stress via Suppression of Caveolin-1 in Pulmonary Arterial Hypertension

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Nitritative stress is characteristic feature of the pathology of human pulmonary arterial hypertension (PAH). However, the role of nitritative stress in the pathogenesis of obliterative vascular remodeling and severe PAH remains unclear. Our recent studies identified a novel mouse model (*Egln1<sup>Tie2Cre</sup>*) with obliterative vascular remodeling and right heart failure, which provides us an excellent model to study nitritative stress in PAH. We found that nitritative stress was elevated whereas endothelial Caveolin-1 (Cav1) expression was suppressed in the lungs of *Egln1<sup>Tie2Cre</sup>* mice. ROS scavenger manganese (III) tetrakis (1-methyl-4-pyridyl) porphyrin pentachloride (MnTmPyP) treatment suppressed severe PAH in *Egln1<sup>Tie2Cre</sup>* mice. Genetical restoration of endothelial Cav1 expression in *Egln1<sup>Tie2Cre</sup>* mice normalized nitritative stress and inhibited right ventricular (RV) systolic pressure and RV hypertrophy, as well as improved right heart function. These data suggest that suppression of endothelial Cav1 expression secondary to PHD2 deficiency augments nitritative stress, which contributes to severe vascular remodeling and PAH. Thus, ROS scavenger might have great therapeutic potential for the inhibition of obliterative vascular remodeling and severe PAH.



## 19 - Metabolic Hallmarks of Cancer Altered in Hispanic Women Across HPV-Mediated Cervical Carcinogenesis

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Cervical cancer (CC) is a leading cause of death in women and is mediated by high-risk human papillomavirus (hrHPV) subtypes. U.S. Hispanic women are at greater risk of CC incidence and mortality, indicating a health disparity in this population. Dysbiotic vaginal microbiota (VMB) communities, defined by depletion of *Lactobacillus*-dominance (LD) increases HPV infection risk. *We hypothesize that alterations in the metabolic microenvironment increases the risk of viral persistence and HPV-mediated carcinogenesis.* Our group and others have shown that Hispanic women are more prone to vaginal dysbiosis, hrHPV infection and CC. As such, there is an urgent unmet need to understand the mechanisms that contribute to this health disparity in Hispanic women.

Untargeted liquid chromatography-mass spectrometry-based metabolomics was utilized to identify 483 metabolites in cervicovaginal lavages of five groups of women: healthy HPV(+) (n=18) and HPV(-) (n=11) controls, low-grade dysplasia (LGD, n=12), high-grade dysplasia (HGD, n=27), or invasive cervical carcinoma (ICC, n=10). Hispanic (n=36) and non-Hispanic (n=42) ethnic groups were evenly represented among our patient cohort (Fisher's exact test,  $p=0.15$ ). Ten metabolic pathways known to be associated with hallmarks of cancer between Hispanic and non-Hispanic women were analyzed. Glutamine, a good discriminator between HPV(-) and HGD regardless of ethnicity (AUC = 0.801, ROC analysis), was elevated in Hispanic ICC relative to healthy Hispanic HPV(+) women ( $p=0.037$ , 1-way ANOVA), however, no difference was found in similar comparisons of non-Hispanic patients, indicating an area of future investigation. The glutamine metabolic pathway was also significantly enriched ( $p=0.014$ ) in Hispanic vs. non-Hispanic women among all groups. Hispanic women with LGD had significantly greater levels of pro-inflammatory sphingomyelin lipids relative to non-Hispanic women with LGD ( $p<0.0001$ , 2-way ANOVA), but not HGD or ICC. LD depletion was associated with greater sphingomyelins, glutamine, and Hispanic ethnicity. Further exploration of alterations in the microbiome-mediated metabolic microenvironment will provide insights into the mechanisms of how dysbiotic VMB promotes HPV persistence and carcinogenesis and may help resolve this health disparity.

## 20 - The Role of Parenting and Parental Pain in Children's Chronic Pain Experience

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**Objectives:** Children's chronic pain has many contributing factors, including family environment, genetics, and parenting. Still, pediatric pain remains understudied, and little research has been conducted on predictors of child pain onset. This study examined the heritability of child pain and the relationship between parental pain, parenting style, and child pain.

**Methods:** This twin study included 141 primary caregivers, 99 secondary caregivers, and their 8-year-old twins (n= 428). Primary and secondary caregivers completed questionnaires regarding their own pain, their children's pain, and their parenting styles. Twin intraclass correlations were used to estimate the amount of variance in child pain that can be attributed to genetics, shared environmental influences, and non-shared environmental influences. Study variables were tested using multi-level regression analyses to account for covariates and twin interdependence. SPSS software was used for all analyses, and  $p < 0.05$  was considered statistically significant.

**Results:** We found that 23% of variance in childhood pain frequency can be attributed to non-shared environment, 17.6% can be attributed to shared environment, and 59.4% can be attributed to genetics. Both primary and secondary caregiver pain were significant predictors of child pain ( $p = 0.05$  and  $p = 0.007$ , respectively). However, neither primary nor secondary caregiver pain predicted parenting style, suggesting that parenting does not mediate the relationship between parental pain and child pain.

**Conclusions:** Child pain is heritable, and both maternal and paternal pain are significant predictors of child pain. Parenting styles are not influenced by parental pain and therefore do not mediate the relationship between parental and child pain. Future research should aim to identify other predictors of child pain to better inform prevention strategies and effective management of this condition.

**Funding:** The National Institute of Child Health and Human Development funded the Arizona Twin Project, from which this data was obtained.

## 21 - Estrous cycle phase regulates inflammatory response to peripheral immune challenge in mice

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Progesterone and estradiol hormonal levels define the estrous cycle phase. The hormones regulate female reproductive cycle and have cellular properties, such as anti-inflammatory effects. As laboratory, translational, and clinical research incorporates more female and minority subjects, the foundational knowledge of inflammation is challenged. We hypothesize that the hormonal effect of each estrous cycle phase could influence the outcome of an inflammatory challenge. The aim of the study was to determine the inflammatory response to lipopolysaccharide (LPS) as a function of the estrous cycle phase. Female C57bl/6 mice (n=23) were tracked for estrous cycle phase by daily vaginal smears taken at the same time of day for 8 days prior to LPS administration (1.2 mg/kg, i.p). Blood collected at baseline, before LPS injection (submandibular), and at 24 hours post-injection (terminal blood) was analyzed by flow cytometry to quantify myeloid cell populations and by ELISA to quantify peripheral cytokine levels (IL-6, TNF- $\alpha$ , IL-1 $\beta$ ). Vaginal smears (8 day cycling and 24 hours post-LPS) were stained with Hematoxylin to define the stages of estrous cycle based on observed cell types (neutrophils, cornified cells, epithelial cells).

Most of the animals (n= 14, 58%) were in the estrous phase 24 hours post-LPS injection. At 24 hours post-LPS, IL-6 levels in estrous phase mice were 141.67 pg/ml compared to 343.56 pg/ml in diestrus phase mice (242.5 % increase). There was no statistical difference between estrous cycle phases for IL-1 $\beta$  and TNF- $\alpha$  levels after LPS injection. Thus, a differential inflammatory response emerges between female mice depending on the estrous cycle phase. Pro-inflammatory peripheral cytokine levels are an initial indicator of cycle-dependent inflammatory responses, with quantification of immune cell populations pending.

## 22 - Mice born to mothers with gestational traumatic brain injury have distorted brain circuitry and differential immune responses.

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Behavioral disorders are complex and result from a combination of genetic and environmental risk factors. Environmental risk factors such as stress, peripheral inflammation, and infection, during development, may be augmented by gestational TBI in mothers and may be linked to epigenetic modifications. We hypothesized gestational TBI in mothers would lead to increased anxiety-like behavior, susceptibility to infection, dysbiosis in gut microbiome, and distorted brain circuitry in offspring. Pregnant dams received either diffuse TBI or sham injury 12 days post-coitum. After giving birth, a subset of mixed-sex pups from TBI and sham mothers were assessed for cortical circuitry using laser scanning photostimulation (LSPS) at PND25-32. All other pups were assessed for cognitive, anxiety-like, and depressive-like behaviors and gut microbiome from PND30-80. After PND80, pups received LPS (1 mg/kg, i.p.) and blood was drawn 6hrs post-LPS. After 24hrs, pups were euthanized and blood and tissue were harvested. TBI and sham offsprings were comparable sizes. Using LSPS functional circuit mapping, we found significantly altered intralaminar connectivity onto pre-frontal layer 5 pyramidal neurons in male TBI offspring compared to males sham offspring ( $F(15, 208) = 10.82, p < 0.0001$ ). After LPS injections, pups from TBI mothers had significantly smaller neutrophil populations in blood 6hrs post-LPS than pups from sham mothers ( $t(23) = 3.253, p = 0.0035$ ), without significant differences 24hrs post-LPS. No overt behavioral differences were observed between litters, behavior and microbiome analyses are ongoing. These results show the first developmental consequences of TBI during pregnancy on offspring's cortical circuitry and inflammatory system. These findings necessitates intervention through public health and rapid TBI therapy to mitigate two lives affected by post-injury symptoms. Future studies will determine whether gestational brain injury causes epigenetic modifications in the fetus that can be carried on through multiple generations. Funding: PCH Mission Support and BNI@PCH

## 23 - Investigating the antimicrobial activity of the bacterial metabolite, glycochenodeoxycholate on vaginal bacteria as a novel therapeutic approach against bacterial vaginosis

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Previously *Lactobacillus* species in the gut have been found to produce secondary bile acids, such as glycochenodeoxycholate (GCDC). Primary bile acids, which are produced by the liver, are modified by commensal gut bacteria, to form secondary bile acids, that function as antimicrobials against gut pathogens and pathobionts. A *Lactobacillus*-dominated vaginal microbiome is defined as being optimal for vaginal health. In a previous clinical study, we demonstrated that healthy women with a *Lactobacillus*-dominated microbiome had high levels of GCDC in cervicovaginal secretions, and through bioinformatics analysis we predicted that vaginal *Lactobacillus* species are capable of producing GCDC. This study aimed to investigate the effects of GCDC on the growth of the vaginal microbiota, including lactobacilli and bacterial vaginosis-associated bacteria (BVAB). In addition, the level to which GCDC impacted cellular integrity was measured *in vitro* on human genital epithelial cells. We hypothesized that GCDC would exhibit antimicrobial properties against BVAB, but not vaginal *Lactobacillus* species. An initial disk diffusion assay with both lactobacilli and BVAB strains demonstrated growth inhibition for all bacterial strains tested, and the magnitude of inhibition was species-specific. Then, we confirmed and extended these findings by performing minimal inhibitory concentration assays (MIC), to quantify the minimum concentration required to inhibit bacterial growth. These data revealed that *A. vaginae* was more sensitive to GCDC compared to other vaginal bacteria and was inhibited at 0.039%, whilst *P. bivia*, *G. vaginalis* and all *Lactobacillus* species tested, were inhibited at 1.25%. Initial crystal violet stains indicated that GCDC was cytotoxic at 2.5%, to all cell lines tested. However, crystal violet, coupled with trypan blue exclusion, revealed that GCDC concentrations of 0.06%, 0.04% and 0.02%, were less cytotoxic to all cell lines. Future studies utilizing our 3-D human bioreactor models, will elucidate the level of GCDC-mediated inflammation within the cells, and its impact in the context of vaginal bacteria colonization. Additional studies are required to further evaluate GCDC as a candidate BV therapeutic, specifically targeting *A. vaginae*.

## 24 - Mutations in KANK1 cause alterations in cytoskeletal dynamics associated with cerebral palsy

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KANK1 is an actin adaptor protein involved in several different pathways including cytoskeletal regulation and cell migration. It has been demonstrated that KANK1 regulates actin dynamics and cell migration through modulation of RhoA via interactions with Akt and 14-3-3. More recently, KANK1 has also been shown to play a role in focal adhesion complex formation. Mutations in or deletions of the *KANK1* gene have been linked to several human diseases including spastic quadriplegic cerebral palsy, the underlying cellular mechanisms have yet to be elucidated. We have identified several cryptogenic CP patients, as part of our ongoing genomics work, harboring novel predicted deleterious *KANK1* variants (p.F512S, p.K1088N, and p.R1348Q). To assess any potential molecular contributions of these variants to the CP phenotype, we interrogated changes in overall F-actin and cellular morphologies. In addition to the microscopy experiments we also assessed cell migration capabilities using the Incucyte S3 live cell imaging platform. Our data indicates that two of these variants exhibit altered functionality compared to wild type and these mutant alleles may contribute to defects in neuronal morphology and/or neuronal migration that ultimately lead to cerebral palsy.

## 25 - Epigenetics of Triple-Negative Breast Cancer in Hispanic and non-Hispanic White Women

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Breast cancer is the most commonly diagnosed cancer in Hispanics, yet the incidence is lower than in non-hispanic white (NHW) women. Despite the relatively lower incidence of breast cancer in Hispanics, their risk of mortality is higher than in NHW women. Compared to NHW women, Hispanics are also more likely to be diagnosed at an earlier age (25% compared to 12% breast cancer diagnoses under age 50) and with hormone receptor-negative breast cancer subtypes, including triple-negative breast cancer (TNBC), which lacks the estrogen (ER) and progesterone (PR) receptors and human epidermal growth factor receptor-2 (HER2). Hormone receptor-negative breast tumors have limited treatment options. Compared to NHW women, Hispanic women are more likely to receive neoadjuvant chemotherapy. Lastly, Hispanics have a higher prevalence of obesity (~45%) compared to NHW women (~33%), which is an established risk factor for TNBC. Previously (BMC Cancer 15:1026), we reported that breast tumors classified as TNBC have higher levels of the aromatic hydrocarbon receptor (AhR). Agents that induce the AhR are categorized as "obesogens". AhR is constitutively upregulated in TNBC with hypermethylated *BRCA1*.

This project addresses epigenetic factors that contribute to breast cancer disparity between Hispanic and non-Hispanic White (NHW) women. The term *epigenetics* refers to changes in gene expression in the absence of DNA sequence modifications and includes DNA CpG methylation, posttranslational histone modifications, and changes in the expression of non-coding RNAs.

We found that compared to TNBC from NHW women, TNBC from Hispanic women have higher *AhR* expression and hypermethylated *BRCA1*. Our data also suggest that *AhR* expression is ~4.0-fold higher in TNBC from Hispanic compared to NHW women, whereas no differences between the two ethnic groups are detected in control HER2-overexpressing tumors. As well, *BRCA1* CpG methylation in TNBC from Hispanic women is double compared to that of NHW women. Finally, we found that in breast cancer MCF-7 cells in culture prostaglandin E2 (PGE2) lowers *BRCA1* expression, which is rescued by cotreatment with AhR antagonists.

Overall, these data suggest a possible link between overexpression of the AhR and markers of obesity on epigenetic determination of TNBC phenotype.

## 26 - Distinct genetic etiologies and pathways indicated in analysis of environmental and cryptogenic cerebral palsy genes

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**Introduction:** Cerebral palsy is a developmental movement disorder with both genetic and environmental contributions. Gene set over-representation analysis (ORA) has become an essential approach in case cohort studies for grouping genes into functionally and biologically relevant gene sets. We present a gene set over-representation analysis for exome sequencing results of a cerebral palsy cohort identifying gene mutations from cases only. The goal of the study was to do functional and pathway analysis of mutated genes in cohort.

**Methods:** Whole exome sequencing was done for 250 cerebral palsy patients identified as cryptogenic/idiopathic (CRP, n=157) or environmental (ENV, n=84) cases (Unknown, n=9). Data was analyzed using GATK best practices and a pipeline developed in-house. Cryptogenic was defined as cases with no known cause for the disability. Environmental were cases with any perinatal causes including prematurity (estimated gestational age <32 weeks), stroke, intra-ventricular hemorrhage, birth asphyxia/hypoxic-ischemic injury in utero infections. 163 genes were identified in ENV cases and 406 genes in CRP cases. Gene set over-representation analysis (ORA) was conducted using DAVID and PANTHERdb.

Hypergeometric analysis was done for gene sets overlapping with disease-associated genes extracted from DisGeNET database.

**Results:** ENV genes were enriched for extracellular matrix organization/interaction, specifically non-integrin membrane-ECM interactions (p=0.004, DAVID-REACTOME R-HSA-3000171). CRP genes were enriched for Rho-GTPases signaling genes (p=8.9e<sup>-4</sup>, PANTHER-REACTOME R-HAS-194315). Hypergeometric analysis using genes in the DisGeNET database showed that CRP genes had significant overlap with autism spectrum disorder (ASD, p=0.0018), intellectual disability (ID, p=7.91e<sup>-14</sup>) and epilepsy (p=0.003). ENV genes had significant overlap with ID (3.24e<sup>-4</sup>) and epilepsy (0.0215) but not ASD.

**Discussion:** Different mechanisms may lead to CP in environmental and cryptogenic patients. Different genetic predisposing factors may also be present in the two groups.

Predictive modeling methods applied to CP studies may benefit by separating the two groups in order to get more robust results.

## 27 - Chronic life stress predicts depressive outcomes in the first year of invasive breast cancer: Moderation by the serotonin-transporter polymorphism

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**Background:** Depression in cancer patients predicts decreased survival, as well as adverse quality of life outcomes, and early identification of risk for depression is needed. Depression is higher in the contexts of both childhood adversity and chronic life stress but their collective influence on depressive outcomes in the first year after breast cancer diagnosis is unknown. Genetic polymorphisms related to socioemotional functioning may moderate the associations among childhood adversity, chronic life stress, and depressive outcomes, specifying which women are most at risk.

**Methods:** 460 women diagnosed with invasive breast cancer completed 7 assessments of depressive symptoms and CIDI-determined major depressive episodes across 1 year. Interactions among childhood adversity, chronic life stress, and the serotonin-transporter (HTTLPR) polymorphism were examined with depressive outcomes using multilevel modeling, multinomial logistic regression, and logistic regression.

**Results:** Higher chronic life stress predicted greater depressive symptoms at study entry, greater relative risk for belonging to a High/Recovery vs. Low depressive trajectory class, and greater odds of having a major depressive episode during the year. The influence of chronic life stress on depressive symptoms over time was moderated by HTTLPR genotypes, with no decline in symptoms for women with high chronic stress and the ss genotype vs. significant improvement in depressive symptoms in the face of chronic life stress for women with the ll/ls genotype. Childhood adversity did not predict any depressive outcomes, and there was no significant interaction of childhood adversity with chronic life stress or with HTTLPR genotypes.

**Conclusion:** During the initial period following cancer diagnosis, chronic life stress predicts heightened depressive symptoms. Women with greater chronic life stress are also at risk for high unremitting depressive symptom trajectories and MDEs during the first year after diagnosis. Variation in HTTLPR polymorphisms was relevant for identifying the degree of change in women's depressive symptoms longitudinally. These findings suggest that women with high chronic life stress and the HTTLPR ss genotype may benefit from early intervention to prevent and treat depression after breast cancer diagnosis.

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## 28 - Development and characterization of a mouse model overexpressing a farnesoid-x-receptor transgene with reduced intestinal inflammation.

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**Objective:** The farnesoid-X-receptor (FXR) regulates bile acid (BA) homeostasis, protecting against colonic inflammation and cancer. Conversely, increased intestinal levels of BA and expression of cyclooxygenase-2 (COX-2) increase the risk of inflammation and cancer of the colon. Earlier studies from our laboratory show that a diet rich in *n*-6 linoleic acid (*n*-6HFD) epigenetically activates *Fxr*, inducing the expression of downstream factors that regulate BA homeostasis. However, the chronic exposure to *n*-6HFD induces COX-2 expression through CpG demethylation of the *PTSG-2* gene and activates the  $\beta$ -catenin pathway. The objective of this study is to determine in a mouse and cell culture models the influence of an *n*-6HFD on endpoints of intestinal inflammation and the modifying effects of overexpression of *FXR*.

**Methods:** A mouse line overexpressing FXR in the intestine was developed by injecting an *FXR* transgene (*Fxr*<sup>TG</sup>) construct driven by the *villin* promoter into FVB zygotes, and then crossed with C57BL6 mice. The small intestine and colon tissue were collected from male founders. Changes in gene expression and DNA methylation were measured by real-time PCR (RT-PCR). Cell culture experiments were performed in colonic human fetal cell (FHC) cells treated with linoleic acid (LA).

**Results:** Expression analyses by RT-PCR reveal increased expression of *Fxr*<sup>TG</sup> in distal small intestine and proximal and distal colon. These changes are paralleled by accumulation of ileal bile acid-binding protein (IBABP) and small heterodimer partner (SHP), two downstream targets of FXR, and a reduction in expression of COX-2. Western blot of colon FHC shows LA induces expression of COX-2.

**Conclusions:** We conclude that increased expression of FXR triggers the expression of genes involved in BA homeostasis and downregulates genes involved in inflammation. The *Fxr*<sup>TG</sup> mouse model is being used to investigate the modifying effects of diets varying in fatty acid level and profile on endpoints of inflammation and cancer.

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## 29 - Endothelial Prolyl-4 hydroxylase 2 Deletion Induces Cardiac Hypertrophy and Heart Failure via Hypoxia Inducible Factor-2 $\alpha$ Activation

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**Background:** Cardiac hypertrophy is a common adaptive response to injury and stress, and can eventually lead to heart failure. The role of endothelial Prolyl-4 hydroxylase 2 (PHD2)/hypoxia inducible factors (HIFs) signaling in the pathogenesis of heart failure is unclear. We hypothesize that endothelial PHD2/HIF signaling dysfunction contributes to cardiac hypertrophy and heart failure.

**Methods:** Mice with Tie2-Cre-mediated deletion of *Egln1* (encoding PHD2) (*Egln1*<sup>Tie2-Cre</sup>), as well as double knockout mice with both *Egln1* and *Hif1a* or *Egln1* and *Hif2a* were generated. *Egln1*<sup>fl/fl</sup> bone marrow cells were transplanted to lethally irradiated *Egln1*<sup>Tie2-Cre</sup> mice to determine the contribution of bone marrow cells in cardiac hypertrophy. Mice carrying *Egln1*<sup>fl/fl</sup> were bred into EndoSCL-Cre-ER(T) mice containing tamoxifen-inducible *Cre* to generate mice with *Egln1* deletion only in endothelial cells in adult mice (*Egln1*<sup>SCL-Cre</sup>) after tamoxifen injection. Echocardiography were measured to study cardiac size and function. Histological examination was also performed.

**Results:** *Egln1*<sup>Tie2-Cre</sup> mice exhibited left ventricular hypertrophy evident by increased thickness of anterior and posterior wall and left ventricular mass, as well as cardiac fibrosis. *Egln1* deletion in bone marrow cells did not contribute to cardiac hypertrophy. Tamoxifen induced endothelial *Egln1* deletion in adult *Egln1*<sup>SCL-Cre</sup> mice also induced left ventricular hypertrophy and heart failure. Genetic ablation of *Hif2a* but not *Hif1a* in *Egln1*<sup>Tie2</sup> mice normalized cardiac size and function. Additionally, we observed a marked decrease of PHD2 expression in heart tissues from patients with dilated cardiomyopathy.

**Conclusion:** This studies define for the first time an unexpected role of endothelial PHD2 deficiency in inducing cardiac hypertrophy and heart failure in a HIF-2 $\alpha$  dependent manner. Thus, targeting PHD2/HIF-2 $\alpha$  signaling represents a novel therapeutic approach for the treatment of heart failure.

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