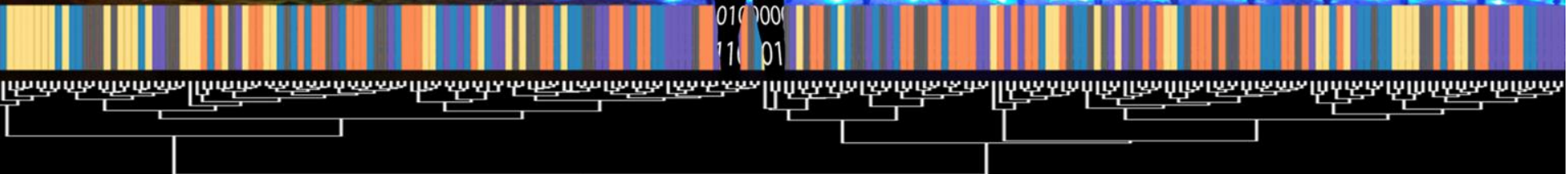


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A Computational Medicine Center (virtual) Symposium

# The Big in Big Data: Breakthrough Discoveries, Disease Disparities, and Precision Medicine

SEPTEMBER 8 – 9, 2020



**Co-sponsors:**

Sidney Kimmel Cancer Center & The University of Kansas Cancer Center

## Program - Day 01 – September 08, 2020

08:00-08:10 – Opening – Remarks by **President Stephen Klasko** and **Provost Mark Tykocinski**

08:10-08:20 – Opening – Remarks by **Karen Knudsen** (SKCC) and **Roy Jensen** (KUCC)

08:20-08:30 – Opening – Remarks by **Danny Welch** and **Isidore Rigoutsos**

### Session #1 / Day 01

08:30-09:00 – **Tiffany Wallace:** [Advancing Cancer Disparities Research: Opportunities for Big Data, Translational Research, and Precision Medicine](#)

09:00-09:30 – **Nikki Nollen:** [Understanding Race Differences and Improving Tobacco Treatment Outcomes in African American Smokers](#)

09:30-10:00 – **Grace Lu-Yao:** [From Byte to Bedside](#)

10:00-10:30 – Break – Break – Break

10:30-11:00 – Round Table: [Meryl Weinreb](#) and Session speakers

### Session #2 / Day 01

11:00-11:30 – **Charnita Zeigler-Johnson:** [Using Cancer Registry Data to Inform Community-Based Interventions](#)

11:30-12:00 – **Hope Krebill:** [Engaging Community Cancer Centers To Accelerate Research and Improve Health Equity](#)

12:00-12:45 – Break – Break – Break

12:45-13:15 – **Ronald Myers:** [Developing a Lung Cancer Learning Community and a Strategy for Screening Outreach in Vulnerable Populations](#)

13:15-13:45 – **Gary Doolittle:** [Providing Oncology Care via Telemedicine](#)

13:45-14:15 – Round Table: [Broderick Crawford](#) and Session speakers

14:15-14:45 – Break – Break – Break

### Session #3 / Day 01

14:45-15:15 – **Hee-Soon Juon:** [Racial Disparities in Occupational Risks and Lung Cancer Incidence: Analysis of the National Lung Screening Trial](#)

15:15-15:45 – **Nicole Simone:** [Harnessing Metabolic Function to Impact both Tumor Progression and Radiation Response](#)

15:45-16:15 – **Steven Patierno:** [RNA Splicing and Ancestry-related Molecular Targets in Precision Oncology and Cancer Disparities](#)

16:15-16:45 – Round Table: [Cheryl Jernigan](#) and Session speakers

## Program - Day 02 – September 09, 2020

08:00-08:10 – Opening – Remarks by **Provost Mark Tykocinski**

### Session #4 / Day 02

08:10-08:40 – **Isidore Rigoutsos**: [Short Regulatory RNAs and their Impact Depend on Personal Attributes: Implications for Identifying Novel Biomarkers and Novel Therapeutic Targets, and for Precision Medicine](#)

08:40-09:10 – **Eric Londin**: [Towards a More Complete Characterization of the Human MicroRNAome](#)

09:10-09:40 – **Yohei Kirino**: [Expression and Function of Cyclic Phosphate-containing RNAs: a Hidden Layer of the Transcriptome](#)

09:40-10:10 – Round Table: [Meryl Weinreb](#) and Session speakers

10:10-10:30 – Break – Break – Break

### Session #5 / Day 02

10:30-11:00 – **Louise Laurent**: [Using Big Data on Small RNAs to Understand Human Development](#)

11:00-11:30 – **James Eberwine**: [Single Cell Multiomics Informs Emergent Cell Biologies](#)

11:30-12:00 – **Panagiotis (Panos) Roussos**: [Big Data and Genetic Liability to Neuropsychiatric Disease](#)

12:00–12:30 – **Frank Slack**: [Toward Personalized microRNA Therapeutics](#)

12:30-13:00 – Round Table: [Jerome Jourquin](#) and Session speakers

13:00-13:45 – Break – Break – Break

### Session #6 / Day 02

13:45-14:15 – **Brid Ryan**: [Population Diversity in Lung Tumor Biology in the United States](#)

14:15-14:45 – **George Calin**: [About Chomsky, Motifs, Non-Coding DNA and RNA and Cancer Therapy](#)

14:45-15:15 – **Danny Welch**: [Mitochondrial Polymorphisms Affect Metastatic Efficiency. Do they also Explain Population based Disparities in Tumor Aggressiveness?](#)

15:15-15:45 – Round Table: [Barbara Segarra-Vazquez](#) and Session speakers

15:45-16:00 – Closing Remarks: **Danny Welch** and **Isidore Rigoutsos**

## Session #1 / Day 01



### **Tiffany Wallace**

National Cancer Institute, National Institutes of Health

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### **Advancing Cancer Disparities Research: Opportunities for Big Data, Translational Research, and Precision Medicine**

NCI's Center to Reduce Cancer Health Disparities (NCI CRCHD) promotes workforce diversity and research to advance understanding of cancer health disparities. This presentation will provide a brief review of the field of disparities research, including discussion of recent advancements and current challenges. It will also discuss how big data might be harnessed to translate advancements in understanding cancer disparities into improved population health. Lastly, NCI's priorities for promoting the intersection of cancer disparities research and big data will be discussed while highlighting current NCI initiatives/FOAs in this space.



### **Nikki Nollen**

University of Kansas Medical Center

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### **Understanding Race Differences and Improving Tobacco Treatment Outcomes in African American Smokers**

Tobacco-related health disparities are strikingly acute among African American smokers who experience significantly greater smoking attributable morbidity and mortality compared to Whites despite lower daily cigarette consumption. Biopsychosocial factors impact tobacco use, characteristics of nicotine dependence, pharmacotherapy response, and smoking cessation outcomes. This presentation will summarize findings from clinical trials to improve tobacco dependence treatment outcomes among African American smokers, with a specific focus on mechanisms to explain lower quit rates in African Americans relative to Whites.



### **Grace Lu-Yao**

Thomas Jefferson University

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### **From Byte to Bedside**

Patients with multiple comorbidities may not benefit from medications recommended in the treatment guidelines because these patients are often under-represented in the clinical trials. BIG DATA can help fill the knowledge gaps and provide useful insights to guide treatment decisions.



### **Meryl Weinreb**

Komen Philadelphia

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Meryl Weinreb is a retired pharmaceutical marketing executive with extensive experience in oncology – both from an industry and personal perspective. As a 3-time breast cancer survivor, she was uniquely equipped to successfully lead consumer marketing strategy and execution for AstraZeneca's US oncology portfolio. She was responsible for a number of awarding-winning patient education and support programs for breast, prostate, and lung cancer therapies. Ms. Weinreb served for 7 years on the executive board of the Philadelphia affiliate of the Susan G. Komen Foundation, a nonprofit organization that educates the community about breast cancer and funds research, screening,



and support programs. She currently is the affiliate's Education and Public Policy Chair. In 2013, she was invited to join Komen's Advocates in Science Program and recently became a member of the group's national steering committee. As a Komen Scholar, she chairs the Advocate in Science Committee on Peer Review and is Vice Chair of the group's Education and Training subcommittee.

She has extensive experience as a patient advocate reviewer for the Department of Defense's Breast Cancer Research Program and the Cancer Prevention Research Institute of Texas, as well as for Komen award programs. She assists researchers - locally, across the country and sometimes abroad - with their grant applications, and currently is collaborating as a patient advocate on several breast cancer research projects where she helps to assure a patient focus in their scientific work.

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## Session #2 / Day 01



**Charnita Zeigler-Johnson**

Thomas Jefferson University

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### Using Cancer Registry Data to Inform Community-Based Interventions

Although cancer survival has improved over the years due to early detection and improved treatment options, socioeconomic and racial disparities persist in cancer screening, advanced disease, and cancer mortality. Cancer registry data can be used to identify high-risk groups and high-risk geographic areas for targeted interventions. We have used state Cancer Registry data to examine local trends by race/ethnicity and to identify neighborhoods with a high burden of prostate cancer, specifically. We utilized a mixed-methods approach involving quantitative analyses of state cancer registry data and focus groups to help us to develop and test a prostate cancer educational intervention designed to increase knowledge and intent to discuss screening with a physician. Similar strategies can help us to understand cancer in the community and to develop appropriate targeted interventions.



**Hope Krebill**

University of Kansas Medical Center

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### Engaging Community Cancer Centers To Accelerate Research and Improve Health Equity

There are many potential barriers that impact enrollment on clinical trials. An important barrier is the geographical isolation of rural communities from larger academic research centers located in larger metro areas. Focused on overcoming this barrier, the Masonic Cancer Alliance (MCA) was created in 2008 as the outreach network of The University of Kansas Cancer Center. The MCA members are a network of cancer centers and hospitals from across Kansas and western Missouri. The goal of the network is to enhance the health of the region through community engagement, outreach, continuing education, and to extend the reach of clinical research into under-represented communities. MCA engages health care providers through 1) extending clinical trials and research, 2) telemedicine second opinions and genetic counseling for oncology patients, 3) discipline specific education and networking tele-conference and televideo meetings, and 4) program technical assistance in survivorship care. This presentation will focus on organizing and operating The University of Kansas Cancer Center's outreach network to improve research participation and survivorship care.



## Ronald Myers

Thomas Jefferson University

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### Developing a Lung Cancer Learning Community and a Strategy for Screening Outreach in Vulnerable Populations

**Background:** The Centers for Medicare & Medicaid Services approved coverage for annual lung cancer screening in 2015. Screening rates are low and must be increased to reduce lung cancer mortality, especially in vulnerable populations experiencing disparities. A large urban health system embraced this challenge in 2018 by launching the Lung Cancer Learning Community (LC2) Initiative. The LC2 Initiative aims to: 1) Engage health system patients, primary care providers, and other stakeholders in designing a novel screening outreach program for patients from vulnerable populations, 2) Implement the screening outreach program to enhance existing health system screening activities, and 3) Evaluate outreach program implementation processes and outcomes.

**Methods:** In 2018, Jefferson began to form a health system learning community by engaging patients, primary care providers, and community stakeholders committed to the shared purpose of achieving LC2 aims. Initially, learning community members joined specific committees and agreed to attend scheduled meetings to develop and implement a lung cancer screening outreach program. Meeting occurrence and attendance were tracked, outreach program developmental activities were documented, and program components were operationalized. Results from learning community development and program operationalization are presented here.

**Results:** Initially, Jefferson convened a Strategic Management Team (SMT) and a Coordinating Team (CT), which represent patient care, population health, and cancer research constituencies in the health system. The SMT and CT groups worked together to catalyze learning community formation by identifying and engaging over 90 patients, providers, and other stakeholders who were committed to achieving LC2 aims in the learning community. Each of these individuals agreed to serve on one or more of the following LC2 committees: a Steering Committee (SC) that includes persons representing health system administration, state/local public and private health plans, and community organizations; a Patient and Stakeholder Advisory Committee (PASAC) which represents primary care patients and providers; and a Research and Evaluation Committee (REC) that brings health system population science researchers and data management/analysis personnel together. Each committee contributed to the development of a unique aspect of an outreach program, which was designed to enhance the health system's existing lung cancer screening program. This collaborative effort served to generate an outreach program that seeks to identify primary care patients who are eligible for lung cancer screening, supports the delivery of literacy appropriate and culturally sensitive screening education to patients, engages patients in shared decision making about screening, and navigates interested patients through the screening process. Findings from the project, which involves approximately 2,500 primary care patients, will guide plans to scale outreach efforts to support lung cancer screening across the health system.

**Conclusions:** The learning community has developed a combined intervention strategy that targets primary care patients eligible for lung cancer. Findings from the planned intervention project will help to shape health system efforts to increase lung cancer screening rates.



## Gary Doolittle

University of Kansas Medical Center

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### Providing Oncology Care via Telemedicine

Telemedicine, the use of telecommunications technology to provide services to populations with limited access to care, can be beneficial for urban patients for chronic disease management and for medically underserved communities in rural locations where provider shortages exist. Oncologists from The University of Kansas Cancer Center started a 'tele-oncology' practice in 1994, initially to provide ongoing cancer care and second opinions for rural cancer patients throughout the state of Kansas. Over time, and at the request of communities in the state, additional telemedicine services were offered to support the care of the cancer patient including: psycho-oncology evaluations, symptom management and palliative care consultations, genetics consultations, survivorship services, cancer care support groups, hospice care, multidisciplinary case conferences, provider continuing education events, and most recently, access to cancer clinical trials. This discussion will review two services, tele-oncology and telehospice, with an emphasis on organizational aspects that must be addressed when launching and running a telemedicine practice.



## Broderick Crawford

NBC Community Development Corporation

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Broderick Crawford is President of the NBC Community Development Corporation which was created as an outreach arm of the New Bethel Church of Wyandotte County, Kansas City, Kansas. Today, the NBC Community Development Corporation works on a wide range of projects with many collaborators to continue to provide services to Wyandotte County residents. The NBC Community Development Corporation's mission is "to empower our youth for a greater future, cherish our seniors to honor the past, increase quality of life in health, education, business, and hope, honoring our God so residents are celebrating life, the community is strengthened, and we foster reconciliation." Broderick is a member of the KU Cancer Center's PIVOT (Patient and Investigator Voices Organizing Together) which seeks to build productive and long-lasting relationships between cancer researchers and research advocates. He is a member of the NCATS Recruitment Innovation Center National Advisory Board and the KU Medical Center Frontiers (CTSA) Patient partners group and the KU Medical Center Diversity, Equity and Inclusion Cabinet. He also serves as Board Chair of the KU Cancer Center Advisory Committee.

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## Session #3 / Day 01



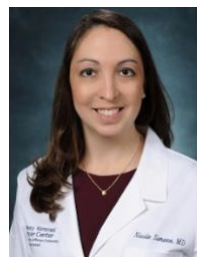
## Hee-Soon Juon

Thomas Jefferson University

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### Racial Disparities in Occupational Risks and Lung Cancer Incidence: Analysis of the National Lung Screening Trial

We will examine racial disparities in occupational risk and lung cancer diagnosis between whites and blacks using the National Lung Screening Trial (NLST) data. Occupational exposure is defined as a work history of at least 1 year in an industry listed as involving exposure to various chemicals, fumes, or dusts. These occupational exposures are categorized into 3 groups: 1) any exposure; 2) asbestos exposure; and 3) silica exposure (sum of coal, hard rock mining, sandblasting, foundry or steel mining). Descriptive analyses using Chi-square and multivariate logistic regression models will be presented.



## Nicole Simone

Thomas Jefferson University

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### Harnessing Metabolic Function to Impact both Tumor Progression and Radiation Response

As the landscape of medicine changes to a precision approach to treating patients based on novel therapeutic interventions, the metabolic landscape of our country's population has also been changing at a rapid pace. As rates of metabolic disorders such as obesity and diabetes continues to increase in this country, so will the incidence of cancer. It is well established that patients who present with metabolic disorders such as obesity or diabetes often have increased recurrence rates, poor survival and increase toxicity despite standard treatments of chemotherapy and radiation. Unfortunately, this has created a new type of health disparity. To date, there has been no emphasis on creating novel therapeutics to address the metabolic profile created by an interplay of the patient, or the host, and the tumor. To begin to evaluate if metabolic processes can be altered to enhance radiation and chemotherapy, we began to employ caloric restriction as a concurrent treatment with cytotoxic therapy. Preclinical models demonstrated that caloric restriction could increase local control and overall survival and decrease distant metastases. We have now completed a

clinical trial to determine that caloric restriction could be used as a therapeutic option in patients undergoing radiation or chemotherapy and noted this treatment to be tolerated well by patients while decreasing typical toxicities of treatment. The preclinical and clinical effects of modulating the metabolic landscape of the patient and the tumor will be discussed as well as future directions.



## **Steven Patierno**

Duke University School of Medicine

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### **RNA Splicing and Ancestry-related Molecular Targets in Precision Oncology and Cancer Disparities**

Individuals of under-represented minority ancestry are at disproportional risk for higher incidence and mortality rates for particular cancers. The unequal burden of cancer in certain racial and ethnic groups, known as “cancer disparities”, can be attributed to a multilevel interplay among neighborhood and population-wide social, psychosocial, lifestyle, environmental, health system, and biological determinants of health. ARS is a key step in gene expression enabling individual genes to encode multiple proteins, and is emerging as a major driver of abnormal phenotypic heterogeneity including gaining aggressive characteristics and tolerance to anticancer therapy. RNA splicing–related genetic and genomic variation in tumors includes oncogenes dysregulated by ARS, spliceosome-dependent transformation, RNA splicing–related immunogenic epitopes and race–related cancer aggressiveness and drug response. Our laboratory has conducted a number of studies in multiple cancers stratified by race (both self-identified and by ancestral genotyping) using either deep RNAseq or array-based technologies on retro- and prospectively banked tissue samples, as well as computational analysis of publicly available databases such as TCGA. We have shown that the burden of race-related differential ARS (D-ARS) is much higher than differential gene expression, and that many of the D-ARS are functionally involved in oncogenic signaling pathways and statistically associate with survival. We have built an application, “CanSplice”, to mine genomic datasets for D-ARS by patient race and ethnicity. We have also begun to identify and test, preclinically and clinically, approaches to modulate and exploit ARS for therapeutic application, including splice-switching oligonucleotides, small molecules targeting RNA splicing or RNA splice variants, and combination regimens with immunotherapies. Our findings identify race-related ARS targets that may aid in the development of new biomarkers and precision therapeutic agents that have the potential to mitigate cancer disparities.



## **Cheryl Jernigan**

Patient Advocate, The University of Kansas Medical Center

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Cheryl L. Jernigan, CPA, F.A.C.H.E., is a co-survivor with her husband, who had HPV tonsil cancer (6 years) and died of metastatic prostate cancer January 2018. She is also a 24-year breast cancer "thrivor" and cancer research advocate.

Cheryl was previously CEO of the Kansas City Area Hospital Association with over 18 years of experience in health policy, advocacy and community/national leadership on behalf of hospitals. Currently, she is the Lead Advocate for: Patient & Investigator Voices Organizing Together (PIVOT), an unique University of Kansas Cancer Center initiative; the Frontiers Clinical Science Translation Award; the Kansas Institute for Precision Medicine; and the Greater Plains Collaborative (a Clinical Data Research Network in the Patient-Centered Outcomes

Research Initiative (PCORI) PCORnet grant.

Nationally, Cheryl was a founding member and currently serves on the steering committee of Susan G. Komen’s Advocates in Science program. She has served as a Komen Scholar from 2010 to 2018; and April 2019 started a new term. She has been actively involved in Komen’s BD4BC (Big Data for Breast Cancer) initiative, including the development of their advocate training program (BD4P). She also served as a member of Komen’s Scientific Advisory Board from 2012-2018.

An active research advocate, Ms. Jernigan is a member of the National Cancer Institute’s (NCI) Central Institutional Review Board for Adult Late Phase Clinical Trials; Rutgers Cancer Institute of New Jersey External Advisory Board; the Clinical Trials Transformation Initiative's Steering Committee; and the Multi-Regional Clinical Trials Center’s Working Groups on Returning Clinical Trial Results to Participants and Returning Individual Results. She serves as an Advocate Member on the Cancer Prevention & Epidemiology Committee and as a member on the Patient Advocate Committee of SWOG for Cancer Research, which is part of the National Cancer Institute’s National Clinical Trials Network. Cheryl is a past member of NCI’s Director’s Consumer Liaison Group (DCLG);



and has served as an advocate reviewer for Komen's Research Program, the V Foundation, the U.S. Congressionally-Directed Breast Cancer Research Program, and the LiveStrong Foundation.

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## Session #4 / Day 02



### Isidore Rigoutsos

Thomas Jefferson University

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#### Short Regulatory RNAs and their Impact Depend on Personal Attributes: Implications for Identifying Novel Biomarkers and Novel Therapeutic Targets, and for Precision Medicine

We have been studying three types of short regulatory RNAs. They include: the isoforms of microRNAs that are known as "isomiRs"; the short RNA fragments that are derived from nuclear and mitochondrial transfer RNAs and are known as "tRFs"; and, the short RNA fragments that are derived from nuclear and mitochondrial ribosomal RNAs and are known as "rRFs." By analyzing datasets from thousands of healthy individuals and patients, we were able to show that isomiRs, tRFs and rRFs are produced in a regimented manner and are not degradation products. We also showed that the identities and abundances of all three RNA types depend on personal attributes such as sex, population-of-origin, and race/ethnicity, as well as on tissue, tissue state, and disease. Moreover, parallel work by others and us showed that isomiRs, tRFs and rRFs regulate messenger RNA and protein abundance. Taken together, the findings strongly suggest that, in health and in disease, the abundance of proteins in a given tissue depends on a person's sex, population-of-origin and race/ethnicity. In fact, the available data indicates that all three categories of molecules are implicated in mechanistic events that contribute to disparities by race/ethnicity or by sex. So far, we have provided evidence to this effect for a number of diseases with documented disparities including triple negative breast cancer, prostate cancer, lung cancer, bladder cancer, and kidney cancer.

In this presentation, I will provide an overview of our work with these molecules. I will also discuss how isomiRs, tRFs and rRFs can serve as powerful biomarkers for diagnosis and prognosis, and as novel candidate therapeutic targets. Lastly, I will describe the implications of these findings for the study of the molecular underpinnings of health disparities and for Precision Medicine.



### Eric Londin

Thomas Jefferson University

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#### Towards a More Complete Characterization of the Human MicroRNAome

microRNAs (miRNAs) are short non-coding RNAs that have emerged as key regulators of biological processes in animals. Guided by Argonaute (AGO) proteins, these molecules interact with target proteins to post-transcriptionally regulate their expression through either translation inhibition or mRNA degradation. The complex networks formed between miRNAs and their target genes function in every cellular process and are essential for animal development, cellular differentiation and homeostasis. Based on these functional activities, it is not surprising that deregulation of miRNA function is associated to numerous diseases. As small RNA-seq has become a robust method to characterize microRNAs, they have captured miRNA isoforms (isomiRs). IsomiRs, are sequences with 5' and/or 3' nucleotide additions or subtractions that collectively make up the totality of a miRNA locus. Recent work has shown that isomiRs have distinct expression profiles that are dependent upon the tissue type and disease type, and have distinct sets of mRNA targets. The presence of many thousands of additional molecules will greatly increase the regulatory power the miRNAs and whose functional roles are currently uncharacterized. Understanding these critical regulatory molecules will provide new insights into the biological mechanisms of disease.



**Yohei Kirino**

Thomas Jefferson University

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### Expression and Function of Cyclic Phosphate-containing RNAs: a Hidden Layer of the Transcriptome

Cellular RNA molecules contain phosphate or hydroxyl ends. A 2',3'-cyclic phosphate (cP) is one of the 3'-terminal forms of RNAs mainly generated from RNA cleavage by ribonucleases. Although transcriptome profiling using RNA-seq has become a ubiquitous tool in biomedical research, cP-containing RNAs (cP-RNAs) form a hidden layer of transcriptome, because standard RNA-seq is unable to capture them. Despite cP-RNAs' invisibility in RNA-seq data, increasing evidence indicates that they are not accumulated simply as non-functional degradation products; rather, they have physiological roles in various biological processes, designating them as noteworthy functional molecules. We will present a comprehensive, genome-wide identification of short cP-RNA expression repertoire in cell lines and tissues, which has been achieved by our developed cP-RNA-seq. Our experimental data on the expressional regulation and functional roles of cP-RNAs in cancers, asthma, and infectious diseases will be further presented and discussed.



**Meryl Weinreb**

Komen Philadelphia

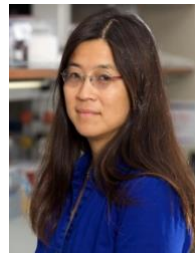
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Meryl Weinreb is a retired pharmaceutical marketing executive with extensive experience in oncology – both from an industry and personal perspective. As a 3-time breast cancer survivor, she was uniquely equipped to successfully lead consumer marketing strategy and execution for AstraZeneca's US oncology portfolio. She was responsible for a number of awarding-winning patient education and support programs for breast, prostate, and lung cancer therapies. Ms. Weinreb served for 7 years on the executive board of the Philadelphia affiliate of the Susan G. Komen Foundation, a nonprofit organization that educates the community about breast cancer and funds research, screening, and support programs. She currently is the affiliate's Education and Public Policy Chair. In 2013, she was invited to join Komen's Advocates in Science Program and recently became a member of the group's national steering committee. As a Komen Scholar, she chairs the Advocate in Science Committee on Peer Review and is Vice Chair of the group's Education and Training subcommittee.

She has extensive experience as a patient advocate reviewer for the Department of Defense's Breast Cancer Research Program and the Cancer Prevention Research Institute of Texas, as well as for Komen award programs. She assists researchers - locally, across the country and sometimes abroad - with their grant applications, and currently is collaborating as a patient advocate on several breast cancer research projects where she helps to assure a patient focus in their scientific work.

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## Session #5 / Day 02



**Louise Laurent**

University of California San Diego

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### Using Big Data on Small RNAs to Understand Human Development

Our research group is interested in developing a molecular regulatory understanding of normal human development, and in discovering the molecular mechanisms underlying pregnancy complications. Here, we will present our recent work in these areas, in which we have analyzed comprehensive small RNA profiling data from different biological compartments to discover the interactions between different tissues, cells, and extracellular carriers in normal and complicated pregnancy.



## James Eberwine

University of Pennsylvania

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### Single Cell Multiomics Informs Emergent Cell Biologies

Recent advances in single cell biology have focused attention on whole cell molecular variation, such as transcriptome differences between seemingly identical cells. The functional significance of observed molecular variation at the level of single cells is unclear, however it is curious that physiological differences between cells seem agnostic to many of these molecular differences. In this context cells are not just simple building blocks of higher-level complex structures. Cells possess complex structures, which perform independent and interdependent processes that integrate to elaborate the resultant complex functions of the cell. In this presentation data from my lab, detailing how the internal genomics of a cell contribute to the characteristics of said cell and help to define its “phenotype” will be described. In particular novel assays have been developed to perform robust single cell chromatin analysis, to assess RNA granule dynamics, to quantify single mitochondrial heteroplasmy and to investigate the multigenic nature of single cell functional genomics. These studies have been undertaken to discern how these, and other subcellular structures, work together to elicit a – “more than the sum of its parts” – biology, which in the context of cellular variability, requires selective cellular and subcellular analysis of these structures. It is anticipated that the biological insights from these and other studies will contribute to the development of a dynamical “Theory of Cell Type”, similar to the historical development of the concept of Biological Species.



## Panagiotis (Panos) Roussos

Icahn School of Medicine at Mount Sinai

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### Big Data and Genetic Liability to Neuropsychiatric Disease

Common neuropsychiatric illnesses, such as schizophrenia, bipolar disorder and Alzheimer’s disease, carry considerable morbidity, mortality, and personal and societal cost. While recent large-scale genetic association studies have identified numerous risk loci, the mechanisms through which they contribute to disease remain largely unknown. By applying single cell molecular approaches to the affected tissue (in this case, the human brain), we can uncover novel cellular subpopulations that are associated with disease. In parallel, cell type-specific molecular studies allow us to characterize the effect of genetic variation on the 3-dimensional configuration of the genome and on the complex mechanisms that regulate gene expression in those cells relevant to disease. All these brain-specific multi-scale data are leveraged to interpret the genetic architecture of neuropsychiatric illnesses in large-scale biobank datasets.



## Frank Slack

Harvard Medical School

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### Toward Personalized microRNA Therapeutics

We study the roles and uses of microRNAs and their targets in development, disease, and aging. We were part of the team that discovered the first human microRNA, let-7 and subsequently showed that it is a tumor suppressor that controls key cancer genes, such as RAS, MYC, and LIN28. We are developing let-7 and a second microRNA, miR-34, as novel cancer therapeutics with miR-34 already in Phase I clinical trials. We also proved that microRNAs act as oncogenes and developed strategies to target these oncomiRs for cancer therapy. One of these oncomiRs, miR-155 is currently in Phase I clinical trials for lymphoma. Our research also extends to discovery of additional novel small RNAs in development, cancer, aging, and diabetes as well as identifying novel single nucleotide polymorphisms (SNPs) in the non-coding portions of the genome with an eye to identifying the next generation of targets in cancer.



## Jerome Jourquin

Senior Manager, Data Science, Komen Foundation

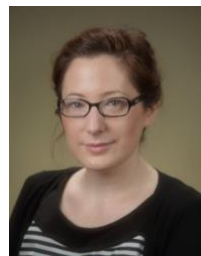
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Dr. Jerome Jourquin joined Susan G. Komen® in January of 2011 as a member of the team managing the money provided to breast cancer researchers around the world. In 2015, he started managing the Komen Scholars, a group of breast cancer research and advocacy leaders guiding Komen as advisors. Since 2019, he became Senior Manager, Data Science, a position in which he oversees Komen's Big Data for Breast Cancer (BD4BC) Initiative that aims at using big data to fuel scientific discoveries and accelerate the delivery of equitable, patient-focused care. Committed to the Nashville community where he is based, Dr. Jourquin sits on Komen Central Tennessee's More Than Pink Walk® Planning Committee and is the treasurer of the Alliance Française of Nashville.

Prior to joining Komen, Dr. Jourquin completed in 2010 a Masters in Bioinformatics at Vanderbilt University, where he developed GLAD4U (<http://bioinfo.vanderbilt.edu/glad4u/>), a National Library of Medicine-awarded web-service designed to build prioritized gene lists based on user queries. With a particular interest in data mining and data sharing, Dr. Jourquin was also part of a multidisciplinary team of experimentalists, mathematicians, engineers, and bioinformaticists studying breast cancer invasion at Vanderbilt. Dr. Jourquin, a French native, earned a Ph.D. in Neurosciences from the University of Aix-Marseilles (2003) and a Master in Cell Biology and Animal Physiology from the University of Paris 7 – Denis Diderot (1997). In addition to authoring a book chapter on laminins and cancer, his research studies have been published in various scientific journals.

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## Session #6 / Day 02



## Brid Ryan

Center for Cancer Research, National Cancer Institute

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### Population Diversity in Lung Tumor Biology in the United States

Worldwide, lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related death. According to the most recent GLOBOCAN report, it accounts for 12% of all cancers in men and women, and 1 in 5 of all cancer-related deaths. Despite decades of evidence-based policy and cancer control strategies, the global burden of lung cancer remains significant, and in some countries, is rising.

There are clear geographic differences in both lung cancer incidence and mortality. Lung cancer rates vary more than 20-fold across geographic regions, something that largely reflects the historical temporality of the tobacco epidemic and differences in patterns of tobacco exposure, including intensity and duration of smoking, type of cigarettes used, and smoking topography. Germline genetic differences in genes involved in nicotine metabolism, including CYP2A6, also contribute to these trends.

Since public health records began tracking differences in lung cancer incidence and mortality by racial and ethnic groups within the U.S., disparities between European Americans (EAs) and African Americans (AAs) have also been identified. Specifically, lung cancer incidence is higher in AAs, especially among men. AAs also have the highest mortality rate and the lowest 5-year survival rate compared with other racial and ethnic groups. The factors contributing to this health disparity are multifactorial. For example, access to high quality health care is an important factor in lung cancer outcomes. In terms of incidence, it is likely that tobacco plays a role in the observed differences given that it is the leading etiological exposure associated with lung cancer development. However, AAs have a lower tobacco consumption overall compared with EAs and data show that the difference in lung cancer incidence persists at equal categories of cigarettes smoked per day. This suggests a divergence in the etiology of lung cancer in the U.S. between racial and ethnic groups. As the



etiology of lung cancer is closely linked with both its histological presentation and molecular features, it is possible that such differences in disease etiology could be reflected at the genomic level.

This molecular classification of tumors is important for understanding both a patient's prognosis and likelihood of response to targeted therapies and, as such, is tightly linked to both survival and mortality patterns. Our current understanding of lung cancer biology is primarily derived from populations of European descent. Given the persistent disparities that exist in lung cancer incidence and survival between AAs and EAs, it is important to characterize tumor biology across racial and ethnic groups. Over the past number of years, our group has been focused on characterizing the genomic landscape of lung cancer from AAs. We find that while most tumor biology is shared between EAs and AAs, significant differences are found, including somatic mutations, somatic copy number changes, and indeed at the transcriptomic level. These data emphasize the complexity of tumor biology specifically in lung cancers from AAs and highlight new potential targets for lung cancer treatment.



## **George Calin**

MD Anderson Cancer Center

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### **About Chomsky, Motifs, Non-Coding DNA and RNA and Cancer Therapy**

The newly discovered differential expression in numerous tissues, key cellular processes and multiple diseases for several families of long and short non-codingRNAs (ncRNAs, RNAs that do not codify for proteins but for RNAs with regulatory functions), including the already famous class of microRNAs (miRNAs) strongly suggest that the scientific and medical communities have significantly underestimated the spectrum of ncRNAs whose altered expression has significant consequences in diseases. MicroRNA and other short or long non-codingRNAs alterations are involved in the initiation, progression and metastases of human cancer. The main molecular alterations are represented by variations in gene expression, usually mild and with consequences for a vast number of target protein coding genes. The causes of the widespread differential expression of non-codingRNAs in malignant compared with normal cells can be explained by the location of these genes in cancer-associated genomic regions, by epigenetic mechanisms and by alterations in the processing machinery. MicroRNA and other short or long non-codingRNAs expression profiling of human tumors has identified signatures associated with diagnosis, staging, progression, prognosis and response to treatment. In addition, profiling has been exploited to identify non-codingRNAs that may represent downstream targets of activated oncogenic pathways or that are targeting protein coding genes involved in cancer. Recent studies proved that miRNAs and non-coding ultraconserved genes are main candidates for the elusive class of cancer predisposing genes and that other types of non-codingRNAs participate in the genetic puzzle giving rise to the malignant phenotype. Last, but not least, the shown expression correlations of these new ncRNAs with cancer metastatic potential and overall survival rates suggest that at least some member of these novel classes of molecules could potentially find use as biomarkers or novel therapeutics in cancers and other diseases.



## **Danny Welch**

University of Kansas Medical Center

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### **Mitochondrial Polymorphisms Affect Metastatic Efficiency. Do they also Explain Population-based Disparities in Tumor Aggressiveness?**

We have developed colonies of mice which share the same nuclear genome but differ only by mitochondrial genomes, called mitochondrial-nuclear exchange (MNX) mice. Using female MNX mice bred with transgenic mice which develop metastatic mammary tumors, we have demonstrated that tumorigenicity and metastatic efficiency are affected based upon natural single nucleotide polymorphisms (SNP) in mtDNA. Similar results were found for spontaneous autochthonous tumor formation. Directly injecting syngeneic mammary carcinoma or melanoma tumor cells into MNX mice, thereby assessing the impact of stromal mtDNA polymorphisms on tumor cell behavior, resulted in strain-specific mtDNA increases or decreases in experimental metastasis. Stromal changes include changes in immune cell profiles and functions as well as microbiota composition. Thus, alterations of tumor cell behavior are the result of both intrinsic and extrinsic impacts of mtDNA. Since mtDNA SNP are genetic determinants of race (or strain

in mice), the results may provide a partial explanation for disparities in tumor behavior based upon race. The presentation will also explore possible molecular mechanisms responsible for mitochondrial regulation of cancer behavior.



## **Bárbara Segarra-Vázquez**

University of Puerto Rico

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Bárbara Segarra-Vázquez, D.H.Sc., has been a faculty member at the University of Puerto Rico for more than 30 years, is the Dean of the School of Health Professions, and the Principal Investigator of the Hispanic Clinical and Translational Research Education and Career Development (HCTRECD) program (R25MD007607) funded by NIH. Dr. Segarra-Vázquez is a two-time breast cancer survivor and became an advocate after her first diagnosis. She became a volunteer for Komen Puerto Rico and was Board President for four years. Under her leadership the PR Affiliate received the Komen Promise Award. She has also traveled to Komen Global Initiative to meet with different groups that provided services to breast cancer patients and participated in a public activity of breast.

Dr. Segarra-Vázquez is very active as a research advocate and one of her main focus is to increase diversity in clinical trials. She has served several times as a consumer reviewer for the Breast Cancer Research Program of the Department of Defense Congressionally Directed Medical Research Programs. She is the Vice-Chair of the Susan G. Komen Advocates in Science Steering Committee, and is a member of SWOG Patient Advocates Committee and the Cancer Care Delivery Committee. She was a member of the Puerto Rico Cancer Control Coalition for ten years. She is the co-founder and co-investigator of HIDEAS (Hispanics Increasing Diversity to Enhance Advocacy in Science).