Summary of ICTR UW-Marshfield Pilot Grant Awards, Round 6, 2022

Decomposing direct and social genetic effects on health outcomes in a rural Wisconsin population, Scott Hebbring (Research Scientist, MCRI) and Qiongshi Lu (Asst Professor, Biostatistics & Medical Informatics)

Recent evidence suggests that a substantial fraction of genetic associations for complex diseases may be mediated by the family environment. In particular, family members' genotypes could affect the family environment through their complex behaviors, which could subsequently affect the phenotypes of individuals included in genome-wide association studies (GWAS). As a result, a person's genotypes, which also reside in his or her biological parents, siblings, and children, could associate with the person's phenotype both directly (through biological processes) and indirectly (through the environment created by relatives). However, these important social genetic determinants of health are nearly always unmeasured in typical genetic studies due to constraints in data and analytical approaches. Our central hypothesis is that genetic associations identified in obesity and asthma GWAS are mixtures of direct and social genetic components; identifying and understanding indirect genetic effects will shed important light on the complex interplay between genetics and environments and their joint roles in disease etiology.

Optimizing wastewater-based surveillance resources for community-level virus decision-making, Maria Sundaram (Assoc Research Scientist, MCRI) and Thomas Friedrich (Professor, Pathobiological Sciences)

During the COVID-19 pandemic, wastewater-based epidemiology (WBE) and surveillance has been instrumental for COVID-19 disease epidemiology, community preparedness, and policymaking. The use of WBE in SARS-CoV-2 epidemiology has also recently prompted WBE surveillance for other viral pathogens, including influenza. However, outcomes from WBE can vary substantially based on numerous factors, such as ambient temperature, influent volume, and sampling location. This variability causes challenges in using SARS-CoV-2 WBE to predict the number and timing of incident cases in communities. In most environments where WBE is used to inform public health policy, predicting the number and timing of incident cases is limited because there is no simultaneous, systematic confirmation of COVID-19 illnesses in the community to which WBE can be linked. Including updated parameters and updated model assumptions for wastewater-based surveillance measures for SARS-CoV-2 and influenza will improve predictions of the number and timing of clinical illnesses found in the community. We have a unique opportunity to connect wastewater-based metrics of SARS-CoV-2 and influenza in Marshfield, WI and Oregon, WI to documented, laboratory-confirmed COVID-19 and influenza illnesses measured in large-scale observational studies. The direct linkage between WBE and laboratory-confirmed illnesses will aid in the prediction of the number and timing of respiratory illnesses expected to occur in the community.

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Summary of ICTR UW-Marshfield Pilot Grant Awards, Round 5, 2021

Germline Risk and Exposures in Clonal Hematopoiesis in Cancer Patients
Tonia Carter, PhD, Marshfield Clinic Research Institute; **Jane Churpek, MD, MS** UW School of Medicine & Public Health
Collaborators: Jens Eickhoff, UW SMPH
Co-Funding: Marshfield Clinic Research Institute
Clonal hematopoiesis (CH) prevalence is particularly high in cancer patients following cancer therapy exposures and has been associated with adverse outcomes including therapy-related myeloid neoplasm development and shorter survival. Why CH develops in some cancer patients but not in others remains poorly understood. No study has been performed to understand whether the timeline of CH initiation starts well before a cancer diagnosis or only after cytotoxic exposures—not having such key data limits the ability to design methods of prevention. We will use the Marshfield Clinic Personalized Medicine Research Project's population-based biobank with health survey data and peripheral blood DNA samples from 2002 along with longitudinal electronic health record
follow-up, a unique and powerful resource, to answer these questions. If CH is significantly enriched pre-cancer, this study would be paradigm changing—shifting attention from focus on cancer treatment effects alone toward mechanisms underlying inherited genetic and/or exposure risk factors and their interactions.

Identifying Microbiome and Virome Markers of Multiple Sclerosis
Sanjay Shukla, PhD, Marshfield Clinic Research Institute; **Karthik Anantharaman, PhD,** UW College of Agriculture and Life Sciences
Collaborators: Robert Valenzuela, Marshfield
Co-Funding: Marshfield Clinic Research Institute
Gut microbiome analysis of multiple sclerosis (MS) patients may guide research and development efforts for novel therapeutic agents. Despite evidence of microbial dysbiosis in patients with MS, no study has simultaneously investigated the role of host's risk alleles in association with gut dysbiosis, under treatment naïve status and with treatment regimens. By assessing the virome and bacteriome of relapsing-remitting MS (RRMS) cases with and without the disease modifying agents (treatment vs treatment naïve), we expect to gain novel insight into the etiopathogenesis of MS that is possible only because we have access to matched fecal and blood biobanked samples (see materials and methods). We anticipate that MS patients with RRMS subphenotype will have a distinct gut bacteriome and virome that are altered in response to disease modifying treatments that play a role in mitigating or enhancing MS symptoms.

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