Charles A. King Trust
Postdoctoral Fellowship Program
Clinical and Health Services Research

2023 Grant Recipients

Ezgi Caliskan Guzelce, M.D.
Postdoctoral Fellow
Brigham and Women's Hospital
Mentor: Gail K. Adler, M.D., Ph.D.
"The role of Glucagon-like Peptide 1 (GLP-1) Receptor Agonist Treatment of Overweight/Obese Individuals for Improving Adverse Cardiometabolic Phenotype Associated with CAV-1 Deficiency"

Obesity is a chronic, multifactorial, and relapsing disease with an increasing prevalence that leads to insulin resistance, diabetes mellitus, hypertension, dyslipidemia, and cardiovascular diseases. Weight loss is known to improve metabolic and cardiovascular risk profiles. Although calorie restriction and increased physical activity represent the cornerstone of weight management treatment, clinical guidelines suggest adjunctive pharmacotherapy, particularly for adults with a BMI of 30 kg/m2 or greater or 27 kg/m2 or greater with coexisting conditions. Glucagon-like peptide 1 receptor agonists (GLP1 RAs) are highly effective in inducing weight loss in overweight and obese adults and have also been shown to improve cardiovascular outcomes. Elevated blood pressure (BP) is a well-known cardiovascular risk factor. Although GLP1 RAs improve insulin resistance, dyslipidemia, and type 2 diabetes, the beneficial effects of GLP1 RAs on BP are variable. This proposal's fundamental goal is to understand the mechanisms underlying this variable BP response to GLP1 RAs and investigate whether there is a variable response to weight loss.
Caveolin 1 is a protein on cell membrane that interacts with the GLP1 receptor and regulates its action. Our research laboratory previously demonstrated that a common polymorphism of the caveolin 1 (CAV1) gene (minor allele [C] at rs926198), which is associated with caveolin 1 deficiency, is strongly associated with higher BP and other components of the metabolic syndrome. This proposal will test the hypothesis that CAV-1 genotype will affect the CV and metabolic responses to treatment of overweight/obese individuals with a GLP-1 RA. Overall, demonstrating that a common variant in the CAV1 gene identifies the blood pressure and weight loss responses to GLP-1 RAs would be a very significant clinical outcome as GLP1 RAs use is rapidly increasing and would help lead to personalized therapy for obesity treatment.

Charles A. King Trust Postdoctoral Fellowship Program

2023 Grant Cycle

Allison Wu, M.D.

Boston Children's Hospital
Mentor: Elsie Taveras, MD, MPH
"Intervening in Food Insecurity to Reduce and Mitigate (InFoRM) Childhood Obesity"

Childhood obesity prevalence is rising in the U.S. and is known to track into adulthood, increasing the risks of chronic diseases such as type 2 diabetes. Households of children with obesity also face unmet social needs, such as food insecurity. Because food insecurity and childhood obesity coexist in Black, Hispanic, and lower-income households, there is an urgent need to examine and intervene in the social determinants associated with rising childhood obesity prevalence.

Dr. Wu seeks to expand on her research in the determinants, risks, and disparities in childhood obesity to develop and test interventions to support food and nutrition security in children and families. Specifically, her proposal aims to pilot the feasibility of a novel meal kit delivery intervention in families and children with food insecurity and obesity (Aim 1) and evaluate the implementation of the pilot intervention (Aim 2). These are the critical next steps toward achieving her long-term goal to systematically develop the evidence base to support interventions and policies ensuring nutrition security for children and families to prevent and treat obesity and other nutritional disorders over the life course.

This career development award will provide Dr. Wu with the necessary mentored training and research opportunities to 1) design and conduct nutrition and lifestyle intervention trials, and 2) obtain a foundation in implementation science and training in qualitative methods to translate interventions into routine practice. She is supported by outstanding mentorship provided by experts in health services research, food insecurity, implementation science, clinical trials in pediatric obesity, and qualitative research in child health. Her training and research activities will be conducted in the unparalleled academic environments at Boston Children's Hospital and Harvard Medical School, which are firmly committed to Dr. Wu's successful transition to independence as a clinician-researcher.

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2022 Grant Cycle

2022 Grant Recipients

Khashayar Afshari, M.D., M.P.H.

University of Massachusetts Chan Medical School
Mentor: Mehdi Rashighi, MD
"Roles of cutaneous T peripheral helper cells as a marker for photosensitivity and disease activity in dermatomyositis"

Dermatomyositis (DM) is a rare autoimmune disease that causes significant morbidity through photosensitivity, chronic disfiguring rash, pruritus, and debilitating muscle weakness. DM has a bimodal age distribution; it disproportionately affects women and individuals with skin of color. Importantly, the course of skin and muscle disease in DM is often discordant and approximately 20% of patients with DM lack muscle involvement. The mainstay of the treatment in DM is systemic immunosuppressive therapies. However, the treatments are not targeted and many patients continue to suffer from recalcitrant skin symptoms. The disease pathogenesis of DM is not completely understood. Previous studies indicated a high upregulation of type I interferons (IFN-Is) in the skin, muscle, and blood of patients with DM which is highly correlated with the disease activity. One of the characteristic clinical features of cutaneous DM is the photodistribution of the rash which is suggested to have strong relationship between ultraviolet B (UVB) light exposure. Using the minimally invasive suction blistering biopsies and archival tissues, we plan to study DM skin involvement by comparing lesional, non-lesional DM, and healthy skin. We will analyze samples using single-cell and spatial RNA sequencing, as well as epigenetics studies. Using our preliminary data, we have identified a distinct population of T cells expressing high levels of CXCL13 unique to DM lesional skin. Their immunophenotype (CD4+/PD-1hi/CXCR5-) is characteristic of T peripheral helper (Tph) cells, a T cell subset recently identified from studies on synovial fluid and tissue of patients with rheumatoid arthritis. The major goals of this proposal are to define the underlying mechanisms of photosensitivity and disease pathogenesis in patients with cutaneous DM, as well as to dissect how skin epithelial and immune cells in DM respond to UVB exposure and explore novel specific disease markers with potency to be used as therapeutic targets.

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2022 Grant Cycle

Arturo Arrona Palacios, Ph.D.
Postdoctoral Fellow
Brigham and Women's Hospital
Mentor: Dr. Charles Czeisler, Ph.D
"Development of a Proteomic Biomarker for Human Circadian Timing"

The goal of the project is to optimize human health by developing robust diagnostic biomarkers for circadian timing to identify, from a single biospecimen, the biological time within an individual. Our understanding of the importance of circadian timing to human health is increasing; disruption of circadian timing is associated with metabolic disorders, cardiovascular disease, immune dysregulation, and cancers. Building on this emerging knowledge, we should be able to regularize circadian timing to prevent disease, and to administer many short half-life drugs at their ideal circadian time to increase efficacy and/or reduce side effects. However, current methods for assessing circadian timing require sampling over many hours (or even up to a day) while the patient is in controlled conditions. Our preliminary data show the strong feasibility of developing a proteomic biomarker to predict internal biological timing from a single biospecimen in healthy adults. However, further evaluation of this method is needed in different patient populations, such as sighted adults with circadian rhythm sleep-wake disorders and adults who are blind (due to their high rate of circadian disruption).

Therefore, in Aim 1 we will test the hypothesis that the plasma protein-based circadian time predictor PlasmaTime, developed in healthy adults, accurately predicts internal biological time in sighted adults with circadian rhythm sleep-wake disorders. In Aim 2 we will test the hypothesis that the plasma protein-based circadian time predictor PlasmaTime accurately predicts internal biological time in adults who are blind. In all cases, circadian timing estimates from the protein biomarker panel will be compared with the timing of secretion of melatonin, a hormone controlled by the circadian system. The proposed project has the potential to: 1) pave the way for improved diagnosis and treatment for patients with suspected circadian rhythm disorders and other sleep pathologies; 2) advance personalized medicine through individualized treatment timing (chronomedicine).

Charles A. King Trust Postdoctoral Fellowship Program

2021 Grant Cycle

2021 Grant Recipients

Christopher Manz, M.D.
Instructor in Medicine
Dana-Farber Cancer Institute
Mentor: Deborah Schrag, MD MPH
"A research program to promote cancer care equity for incarcerated and recently incarcerated individuals in Massachusetts and the United States"

Despite decades of progress in the prevention and treatment of cancer in the US, disparities in cancer incidence and survival are significant. Factors such as racial/ethnic minority status, low educational attainment, and poverty have been consistently associated with cancer disparities, and nearly all of these disadvantaging factors converge upon one particularly vulnerable population: incarcerated and recently incarcerated individuals. Incarcerated patients appear to have a higher risk of developing cancer and worse survival than the general population, but existing evidence is weak. Incarcerated patients have a constitutional right to healthcare but historically have received substandard healthcare and remain among the most vulnerable patients with cancer. An essential first step toward reducing the burden of cancer for incarcerated populations is to better understand cancer incidence, mortality and barriers to treatment for this vulnerable patient population.

My long-term goal is to develop interventions that reduce disparities in cancer incidence and mortality for currently and recently incarcerated individuals. As an initial step towards this goal, this proposal will 1) leverage a novel linkage of state incarceration and cancer registry data to determine cancer incidence and mortality for currently and recently incarcerated patients in Massachusetts and North Carolina, and 2) identify barriers to timely diagnosis, treatment and follow-up delivery of cancer care to incarcerated patients. These two complementary approaches will allow me to identify strategic interventions that I can apply in subsequent research to help achieve the long-term goal of reducing disparities. Specifically, I will:

Aim 1: Characterize the disparities in stage-specific cancer incidence and mortality for currently and formerly incarcerated as compared to non-incarcerated individuals.

Aim 2: Identify barriers to the diagnosis, treatment and follow-up for incarcerated patients with cancer through key informant telephone interviews with a broad representation of prison staff and clinicians involved in providing cancer care to incarcerated patients.

Charles A. King Trust Postdoctoral Fellowship Program

2021 Grant Cycle

Amir Mohareb, M.D.
Instructor
Massachusetts General Hospital
Mentor: Kenneth Freedberg, MD, MSc.
"Reducing the burden of liver cancer in sub-Saharan Africa by treating chronic hepatitis B infection"

Liver cancer is the second most common cause of cancer death in the world, and its burden continues to rise. More than 80% of liver cancers occur in resource-limited countries where patients are diagnosed late in the course of their disease and few treatment options are available. For example, in sub-Saharan Africa, the median age of diagnosis of hepatocellular carcinoma (HCC) is 45 years-old, and 90% of people die within one year of diagnosis.

My hypothesis is that the burden of liver cancer in sub-Saharan Africa can be addressed through the expanded treatment of chronic hepatitis B virus (HBV) infection. The high cost of HBV care, including laboratory monitoring, liver biopsies, and antiviral treatment, all present barriers to the scale-up of HBV treatment. I believe that a more efficient management strategy that expands HBV treatment eligibility will prevent the early mortality from HCC.

In my post-doctoral fellowship, I developed and validated a population-level simulation model of chronic HBV infection. This model projects the incidence of HCC for different levels of HBV activity. My objective is to demonstrate the clinical impact and cost-effectiveness of early HBV treatment as a means of preventing HCC incidence and mortality. I will focus my research in Côte d'Ivoire, a country in West Africa at the forefront of the fight against both HBV and HCC. The results of this study will be broadly applicable across sub-Saharan Africa.

My proposed aims are:
(1) To expand the HBV simulation model to incorporate the safety and efficacy of HBV antiviral treatment.
(2) To project the clinical impact of expanded HBV treatment as a means of preventing HCC incidence and mortality in Côte d'Ivoire.

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2021 Grant Cycle

Zheng Sun, Ph.D.
Postdoctoral Fellow
Brigham and Women's Hospital
Mentor: Yang-Yu Liu, Ph.D.
"Discovering Microbial Features for Breast Cancer Diagnosis"

Breast cancer (BC) is the second most common cancer and the fifth leading cause of death worldwide. Women at the highest risk, accounting for 5–10% of cases, are those who inherit gene mutations associated with specific high-penetrance genes. In addition to genetics, environmental factors also contribute to the development of BC. Indeed, recent studies have demonstrated that BC shows substantial microbial contributions. Our central hypothesis is that the presence of microorganisms in the blood is related to the risk of BC and can be used as a biomarker for diagnosis and early detection of BC. We will leverage the existing blood samples from our in-house cohort study --- the Nurses' Health Study II (NHS2) to systematically test this hypothesis. Our overall objective is to discover microbial features for BC diagnosis and early detection by pursuing the following two specific aims:

Aim1: Develop a sequencing pipeline to profile blood microbiome with strain-level resolution. We will integrate strain-specific marker databases and a G-score based thresholding algorithm to provide more accurate taxonomic profiling results for low microbial load samples (e.g., blood samples). After systematic validation, this pipeline will be applied to the blood samples in NHS2 to generate high-precision, strain-level taxonomic profiles for downstream analysis.

Aim2: Develop a deep-learning framework to predict BC based on blood microbiome profiling. We will develop a classification framework on graph convolutional networks. We will systematically validate this framework using the WGS sequencing data from The Cancer Genome Atlas (TCGA) blood samples. Then we will apply it to the strain-level taxonomic profiles of NHS2 blood samples to (i) distinguish BC from health and other cancers; (ii) classify the development and subtypes of BC; (iii) predict the likelihood of BC.

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2020 Grant Recipients

Rachel Epstein, M.D., M.Sc.
Assistant Professor
Boston Medical Center
Mentor: Benjamin Linas, MD, MPH
"Leveraging Perinatal Touchpoints to Improve the Hepatitis C Virus and Opioid Use Disorder Care Cascades"

Amidst the current opioid overdose crisis, 1.4 million women of reproductive age report non-medical opioid use. Both opioid use disorder (OUD) and hepatitis C virus (HCV) prevalence among pregnant women have quadrupled since 2000. Many women (30-56%) begin medications to treat OUD during pregnancy, but retention post-partum declines significantly and is associated with high opioid overdose and mortality rates. Furthermore, nationally, only 50% of adults with HCV are aware of their infection, and fewer than 40% of those diagnosed have been treated. Research is needed to identify venues to increase efforts to improve OUD and HCV treatment and prevention.

Perinatal care provides longitudinal access to women over a nearly one-year period, and pregnancy may be a motivating time for women to address heath care needs. Yet, little data exist to measure the role of the perinatal care venue to improve OUD and HCV care engagement. This study aims to: (1) Characterize OUD and HCV care cascade follow-up: testing, diagnosis, linkage to care, treatment initiation and retention, to compare outcomes in women of reproductive age with and without a past 2-year perinatal care touchpoint, and (2) Build a microsimulation model using Aim 1 data and literature estimates to analyze the clinical and health economic effects of leveraging the perinatal care venue to reduce opioid overdoses and infant and population-level HCV transmission. Together, these projects will identify the impact of the perinatal (prenatal and post-partum) care venue on improving follow-up along each cascade, and delineate how resource allocation at different steps along the cascades could help achieve national opioid overdose and HCV elimination goals. This will also provide a model platform to incorporate additional disease processes, such as HIV, to help determine the most clinically- and cost-effective care interventions for families at the center of the opioid overdose, HCV and HIV epidemics.

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2020 Grant Cycle

Yan Yan, Ph.D.
Postdoctoral Fellow
Harvard T.H. Chan School of Public Health
Mentor: Curtis Huttenhower, PhD
"Strain-level Epidemiology and Diet-linked Gut Metatranscriptome Risk Factors in Colorectal Cancer"

Colorectal cancer (CRC) is one of the leading causes of cancer-related death globally. While its genetics have been studied extensively, the contributions of environmental factors, such as the intestinal microbiota, are less clearly understood. Neither the causal mechanisms nor corresponding microbial strains have been pinpointed for CRC. We focus on identifying strain-specific microbial variants and genetic products that could contribute to CRC, and characterizing their regulatory behavior and interaction with dietary and lifestyle factors.

Aim 1: Test the hypothesis that CRC risk and tumorigenesis is driven by specific strains, subspecies, and their associated functional genetic content within species associated with the disease.
1.1 Test for significant phylogenetic enrichment with respect to CRC for subspecies within CRC-associated clades.
1.2 Identify individual microbial features that define CRC-associated strains and their resulting functional potential.
Aim 2: Test the hypothesis that CRC-associated genes within risk-associated or protective gut microbes are differentially regulated with respect to dietary and lifestyle factors.
2.1 Determine the baseline transcriptional regulatory behavior of CRC-associated species' pangenomes in the human gut.
2.2 Find significant associations between gut microbial transcriptional regulatory responses and known CRC-risk or protective dietary and lifestyle factors.

The proposal includes data summarizing novel strain- and gene- based meta-analyses of the largest CRC population to date, results from my recent study of the role of microbiome in Lynch syndrome, and our analysis platforms for meta'omic human microbiome epidemiology. My long-term career goal is to pursue translational epidemiological research in the CRC microbiome, which is supported by my background in human microbiome and microbiology. The fellowship will support my work with Dr. Huttenhower and help to continue my early-stage career in CRC prevention and mitigation with access to the resources of his laboratory, the Harvard Chan School, Harvard University, and the rich Boston life sciences community.

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2019 Grant Cycle

2019 Grant Recipients

Avika Dixit, MBBS
Instructor
Boston Children's Hospital
Mentor: Maha Farhat, MD
"Insights into multidrug resistant tuberculosis using large scale genomic data"

Introduction: The purpose of this proposal is to leverage large scale public data to generate country specific drug resistance estimates for tuberculosis (TB) and to characterize the factors driving the spread of drug resistance (DR). These data will be useful in the roll-out of the newer treatment regimens and in designing public health interventions targeted to geographic regions.

Methods: I will utilize more than 20,000 publicly available Mycobacterium tuberculosis genomes and use machine learning methods to determine genotype-phenotype associations between mutations and DR. I will employ machine learning methods previously validated and improve the predictive ability of the algorithm with the larger dataset available to me. I will determine DR for second line anti-tubercular drugs and aggregate these data at the country level, thus creating country-specific antibiograms. I will use WHO reported multidrug resistant TB estimates to correct for oversampling of DR. I will create a mechanism to have these data be periodically updated and available publicly. Additionally, I will employ methods utilized in my previous work including phylogenetic analyses and molecular dating methods to characterize the acquisition, evolution and transmission of DR across the world. I will perform additional analyses to interpret the spread of DR in the context of programmatic factors, and identify bacterial factors associated with it. I will perform a sub-analysis focused on compensatory mutations affecting the spread of fluoroquinolone resistant in TB.

Expected Impact: Estimates are currently available for DR prevalence to first- and second-line anti-TB drugs. My proposed work will not only provide current estimates but will also create a mechanism to continually improve the prediction accuracy and update estimates as newer genomic data becomes available. The study of DR spread at a global scale will provide historical context to this ever-expanding public health problem and help identify potential targets for intervention.

Charles A. King Trust Postdoctoral Fellowship Program

2019 Grant Cycle

Jason Maley, M.D.
Research Fellow
Beth Israel Deaconess Medical Center / Harvard Medical School
Mentor: Jennifer P. Stevens
"Development of a Novel Model to Understand Health-Care Waste and Value in the Intensive Care Unit"

The intensive care unit (ICU) is a costly and complex setting of care, yet the value, or benefit relative to cost, of many practices in the ICU is unknown. Healthcare spending that does not benefit patients is considered waste, and is common throughout medicine, including within the ICU. Given the continued rise of healthcare costs in the setting of limited critical care resources, research examining value and waste in the ICU is urgently needed.

One opportunity to reduce healthcare waste may come from understanding the excessive use of ICU resources. After an ICU patient's critical illness has stabilized and no longer requires ICU-level care, he or she often remains in the ICU for monitoring. However, there is no consensus around how long these patients need to be safely monitored. This time period, after stability and before transfer to a less acute level of care, comes at a cost to both patient and healthcare system. Fundamentally, excessive monitoring in the ICU represents a misalignment of clinical need and hospital resources, and is controlled by physician discretion. Stabilized patients remaining in ICU beds are unable to progress in their care. More acutely, critically ill patients elsewhere in the hospital and waiting to transfer into those occupied beds may have meaningful and harmful delays in care. Understanding and mitigating this waste would reduce healthcare costs and increase ICU bed availability for critically ill patients.

To develop a novel approach to improve value in the ICU, I aim to: 1) investigate drivers of variation in the discretionary use of ICU resources and 2) examine if this variation in discretionary resource use affects patient outcomes and health-system performance. This will serve as the foundation for my NIH mentored K-level grant application, which will focus on understanding the value of care delivered to critically-ill patients.

Charles A. King Trust Postdoctoral Fellowship Program

2018 Grant Cycle

2018 Grant Recipients

Joshua Barocas, M.D.
Assistant Professor of Medicine
Boston University School of Medicine/Boston Medical Center
Mentor: Benjamin P. Linas, MD, MPH
"Hospital-based Innovations to Decrease Overdose and Serious Bacterial Infections Among People who Inject Drugs"

In the US in the last decade, injection opioid use has more than doubled and heroin-related overdose deaths have quadrupled. Along with overdose, HIV, and hepatitis C virus (HCV), people who inject drugs (PWID)—specifically opioids--are also at risk of significant morbidity and mortality associated with serious bacterial infections such as infective endocarditis. Hospitalizations for these infections have increased up to twelve-fold in the last decade. Longitudinal investigation of interventions to decrease these infections is necessary to improve outcomes in this population, but is challenging due to stigma associated with drug use as well as the transient and heterogeneous nature of PWID. Simulation modeling can augment clinical trials and cohort studies by projecting the clinical and economic outcomes over longer time horizons and can be adapted to model different populations. Given the rapid expansion of the US opioid epidemic, novel studies of the impact of interventions are urgently needed. Touch points with the healthcare system, such as during hospitalization, are opportunities for intervention. I propose the following specific aims: 1) To develop and empirically validate a simulation model of injection opioid use that accounts for changes in individual injecting behavior over time and project the medical consequences of injection opioid use, including overdose and bacterial infections, and 2) To determine the clinical impact, costs, and cost-effectiveness of inpatient initiation of medications for opioid use disorder for hospitalized persons who inject opioids. When I have completed the model development process, I will have generated an outstanding platform for research identifying strategies to improve outcomes for PWID.

Minttu Roenn, Ph.D.
Research Associate
Harvard T.H. Chan School of Public Health
Mentor: Joshua Salomon, Ph.D
"Adverse Reproductive Health Outcomes in the United States Associated with Chlamydia and Gonorrhea"

Sexually transmitted infections (STI) are a significant cause of adverse reproductive health outcomes. Chlamydia and gonorrhea are common bacterial STI associated with pelvic inflammatory disease, ectopic pregnancy and tubal factor infertility. The ability of current testing and treatment practices for chlamydia and gonorrhea to prevent adverse reproductive health outcomes in women is not well understood. There is evidence of protective effect of chlamydia screening against pelvic inflammatory diseases. Currently, annual screening for chlamydia and gonorrhea for women below age 25 is recommended in the United States. We aim to estimate the impact of chlamydia and gonorrhea screening in the United States on associated adverse reproductive health outcomes for 2000-2015, and

estimate the predicted future impact under different policy scenarios allowing for changes in testing and treatment patterns. We will use calibrated transmission models to estimate the frequency, duration and health and economic consequences of sequelae. One of the advantages of transmission models is their ability to account for indirect effects of interventions. We have developed transmission models of chlamydia and gonorrhea, and they have been calibrated to time series data for the United States using case report data and prevalence estimates. By adding adverse sequelae to the models as explicit health states, we can extend the analyses to cover broader adverse health outcomes caused by the infections. Sequelae probability and associated quality of life measures and costs will be estimated through literature reviews. The key products of this work will include estimates of the number of sequelae averted by existing prevention efforts, and gains in quality of life, as well as cost-effectiveness of screening interventions, and the analyses will provide estimates of outcomes if services are improved or reduced in the future.

Chad Straight, M.S., Ph.D.
Postdoctoral Research Associate
University of Massachusetts Amherst
Mentor: Mark Miller, Ph.D., M.S.
"Sex-Specific Mechanisms of Obesity-Induced Muscle Weakness in Older Adults"

A hallmark of human aging is a shift in body composition towards reduced skeletal muscle mass and greater adiposity. This shift in body composition is accompanied by a steep decline in physical function, which is exacerbated by the presence of obesity. Notably, older women are at greater risk for obesity-related disability than men. Skeletal muscle power (force x velocity) is a critical determinant of physical function in older adults, and overweight and obese older adults have lower specific power (power per unit muscle size) than their normal weight counterparts. As a result, obese older adults are more likely to have difficulty with activities of daily living, such as rising from a chair or climbing stairs. Currently, there is limited research regarding the fundamental molecular and cellular mechanisms underlying obesity-induced muscle weakness, and this knowledge gap represents a critical barrier to our understanding of how obesity results in poor physical performance and disability in older adults. Preliminary data from our laboratory indicate that cellular muscle function is related to adiposity in a sex-specific manner among healthy older adults, such that women are more affected than men. Thus, the objective of our application is to identify the effects of adiposity at the molecular and cellular levels that cause reductions in whole muscle power among obese older adults. In this context, the aims of this study are two-fold: 1) elucidate the sex-specific effects of adiposity on skeletal muscle function at the molecular, cellular and whole muscle levels in older adults and 2) identify the sex-specific effects of adiposity on skeletal muscle composition and size at the molecular and cellular levels. Characterizing the fundamental mechanisms that lead to reduced skeletal muscle power should aid in the development of targeted, and, potentially sex-specific, exercise and pharmaceutical countermeasures to forestall physical disability in obese older adults.

Charles A. King Trust Postdoctoral Fellowship Program

2017 Grant Cycle

2017 Grant Recipients

Lisa Bebell, M.D.
Instructor, Harvard Medical School and Assistant in Medicine, Massachusetts General Hospital
Massachusetts General Hospital
Mentor: Ingrid Bassett, M.D. M.P.H.
"HIV Infection, Antiretroviral Therapy and Placental Inflammation in Uganda: Potential Mechanisms for Poor Outcomes in HIV-Exposed Infants"

Introduction: Recent success in preventing mother-to-child HIV transmission with antiretroviral therapy has decreased the incidence of congenital HIV. However, >1 million infants are HIV-exposed but uninfected (HEU) annually, and have poorer early-life outcomes than HIV-unexposed infants. We hypothesize that placental inflammation is a potential mechanism for poor early-life outcomes in HIV-exposed infants; and that HIV infection of the placenta and high placental tenofovir disoproxil fumarate (TDF) levels are drivers of placental inflammation.

Methods: We propose to 1) compare the prevalence of histologic chronic placental inflammation (CPI) between HIV-infected and HIV-uninfected women, 2) determine mechanisms by which HIV leads to CPI, and the effect of CPI on birth and neonatal outcomes. To accomplish these aims, we will enroll a prospective cohort of 160 HIV-infected and 160 HIV-uninfected women in Mbarara, Uganda where HIV prevalence is 12%. We will perform placental histopathology to determine presence of CPI and neonatal heelstick DNA PCR to determine neonatal HIV status. We will evaluate the presence of HIV in the placenta using immunohistochemistry (IHC) stains and determine the association between placental HIV and CPI. Lastly, we will measure TDF diphosphate (TDF-DP) levels in umbilical cord erythrocytes and determine the association between TDF-DP levels and CPI among HIV-infected women. We will use multivariable logistic regression to determine independent predictors of CPI, and fit additional models restricted to HIV-infected women.

Expected Results: We hypothesize HIV-infected women have a higher prevalence of histologic CPI than HIV-uninfected women. In addition, we hypothesize that placental HIV infection and high TDF-DP levels are associated with histologic CPI and may contribute to poor early-life outcomes among HIV-exposed infants. We will publish three manuscripts from this work, and our findings will form the foundation of an NIH K23 career development proposal comparing early-life outcomes between children born to HIV-infected mothers with and without CPI.

Jonathan Iaccarino, M.D.
Postdoctoral Fellow
Boston Medical Center
Mentor: Renda Wiener MD MPH
"Comorbidities in Lung Cancer Screening: Improving Decision-Making and Patient Selection"

The purpose of this proposal is to evaluate how comorbidities influence patient and clinician decision-making for lung cancer screening in order to improve patient selection and screening outcomes. The National Lung Screening Trial demonstrated a 20% decrease in lung cancer mortality with yearly low-dose computed tomography (LDCT) screening of high-risk smokers. Screening-eligible patients with

serious comorbidities are less likely to experience this mortality of benefit of screening, while simultaneously having greater risk of experiencing potential harms. As a result, multiple organizations recommend LDCT screening, but advise against screening patients with serious comorbidities that limit life expectancy. At some unknown threshold, the severity of a patient's comorbidities will cause risks of screening and subsequent diagnostic and therapeutic interventions to outweigh potential mortality benefits. In order to optimize LDCT screening outcomes, it is imperative to help clinicians discriminate patients who can benefit from screening from those who are more likely to experience harm. As a first step, we must understand the profile of comorbid disease among the real-world population being screened, how comorbidities influence LDCT screening referral, and how comorbidities factor into patient and decision decision-making for LDCT screening. This study will utilize a mixed methods approach, combining quantitative and qualitative analyses to evaluate patients who have undergone LDCT screening at Boston Medical Center. Data from these approaches will be used to accomplish the following aims: 1) Characterize comorbidities that are associated with referral for LDCT screening; 2) Assess how clinicians and patients incorporate comorbidities into decisions about whether to pursue LDCT screening. Results from this study will help to improve patient and clinician decision-making for LDCT screening and will inform a future multicenter study evaluating the comorbidity threshold at which the harms of screening outweigh the benefits.

Ryan Jacoby, Ph.D.
Clinical Fellow
Massachusetts General Hospital
Mentor: Sabine Wilhelm, Ph.D.
“The Role of Cognitive Control in the Transdiagnostic Conceptualization of "Intrusive Thoughts"”

Transdiagnostic conceptualizations have identified phenomenological similarities across three types of repetitive, negative thinking (i.e., "intrusive thoughts"): obsessions in obsessive compulsive disorder (OCD), worries in generalized anxiety disorder (GAD), and ruminations in depression. However, the majority of research examining commonalities of these mental intrusions has relied solely on self-report questionnaires; which while appropriate for comparing thought content, are less adept at measuring thought processes. Impairments in inhibiting and disengaging from maladaptive intrusions (i.e., cognitive control) is one hypothesized behaviorally-quantifiable process across intrusive thoughts; yet, this theory has not been empirically tested. Accordingly, the proposed study utilizes in vivo behavioral paradigms of executive functioning and attention as well as psychophysiological measures to examine: (a) whether cognitive control (i.e., response inhibition, set shifting) is a transdiagnostic mechanism of action underlying these three patterns of thinking, and (b) the extent to which such impairments are associated with in vivo experiences of intrusive thoughts utilizing standardized procedures of script-driven imagery to induce obsessions, worries, and depressive ruminations in the laboratory. This paradigm will allow for examination of potentially important conceptual differences among intrusions using self-report (e.g., ego-dystonic nature), behavioral (e.g., eye tracking), emotional (e.g., facial expressions), and psychophysiological (e.g., skin conductance) measures. Given the recent RDoC initiative at the National Institute of Mental Health, which emphasizes the identification of transdiagnostic neurally-linked mechanisms, this project is well-aligned with national funding priorities. This multi-method study will provide pilot data for an NIMH Career Development award proposal, in which I will conduct a comprehensive examination of the neural mechanisms of cognitive control across intrusive thoughts. My ultimate aim is to use this knowledge to reduce the substantial public health impact and burden of these disorders (OCD, GAD, depression) by tailoring transdiagnostic interventions to address maladaptive, intrusive thinking patterns.

Charles A. King Trust Postdoctoral Fellowship Program

2016 Grant Cycle

2016 Grant Recipients

Franziska Plessow, Dr. rer. nat.
Massachusetts General Hospital
Mentor: Elizabeth Lawson, M.D., M.M.Sc.
"Cognitive Control as a Biomarker and Target for Novel Interventions in Low-Weight Eating Disorders"

Low-weight eating disorders (EDs) are characterized by extremes in food consumption and eating-related behavior, resulting in marked low weight. Their consequences are severe and often persist, and the illness onset is early with peak in the second decade of life, during a critical period of brain development. The pathophysiology of low-weight EDs, specifically the mechanisms determining restrictive eating versus restriction with binge/purging and differences in illness course, are mostly unknown. I hypothesize that alterations in cognitive control, the mechanisms that enable individuals to act on goals despite competing response tendencies, to flexibly adapt to environmental changes, and to prioritize long-term goals over short-term gains, represent a biomarker for adolescent low-weight EDs with distinct characteristics for different phenotypes and illness trajectories. In low-weight EDs, cognitive control processes and their neural pathways are markedly altered with findings indicating phenotype-specific profiles. Pilot data point toward an association between control alterations and symptom severity in adult ED patients. However, the prevalence of alterations in cognitive control in early disease stages and during adolescence as prime onset period and its relation to future clinical outcome is yet to be established. Using an innovative multi-component multi-level approach to cognitive control and leveraging an ongoing NIMH R01, I will characterize cognitive control competencies together with resting-state functional connectivity of the cognitive control network in 10-21 year-old females with restrictive eating and/or binge/purge behavior and healthy controls. I hypothesize that: (1) Altered cognitive control underlies patterns of restriction, binge eating, and purging, and differentiates low-weight ED patients from healthy, normal-weight controls. (2) Cognitive control abilities at baseline determine 4.5- and 9-month clinical outcome. This work aims to provide a systematic test of the predictive value of cognitive control profiles for phenotype and trajectory of low-weight EDs, identifying novel therapeutic targets to improve clinical care for this high-risk population.

Donald Robinaugh, Ph.D.
Massachusetts General Hospital
Mentor: Naomi Simon, M.D., M.Sc.
"Examining Symptom Decoupling and Propagating Causal Influence as Intra-individual Mechanisms of Change in Psychotherapy"

There is extensive evidence that many forms of psychotherapy are effective in treating a wide range of mental disorders. Yet, despite substantial advances in our understanding of what is effective, we know very little about how psychotherapies have their effect. In the proposed project, I will take a novel intra-individual network analysis approach to studying mechanisms of change complicated grief therapy (CGT), an empirically supported treatment for complicated grief (CG). According to the network approach, CG is a causal system of mutually reinforcing symptoms that arise together following the death of a loved one and settle into a pathological equilibrium. From this perspective, the symptoms are not passive diagnostic indicators of an underlying condition. Rather, they are active psychological

variables that play a causal role in the maintenance of the disorder. Consequently, the symptoms themselves and the relations among them become potential targets for intervention and, thus, potential mechanisms by which treatments may have their effect. In the proposed study, I will conduct an open-trial of CGT and will use intensive time-series data and recently- developed intra-individual network analyses to examine two plausible mechanisms of change by which CGT may have its effects: (a) a decoupling of the associations among CG symptoms and (b) propagating causal influence among CG symptoms in which reductions in symptoms central the CG network initiate a cascade of change that leads to reductions in overall CG severity. The findings from this study will identify mechanisms of change in CGT and, thereby, will allow for the development of new tools that better target those mechanisms as well as efforts to tailor interventions to target the processes most relevant to individual patients. In doing so, this study will pioneer a new method of examining and promoting change in psychotherapy for mental disorders.

Charles A. King Trust Postdoctoral Fellowship Program

2015 Grant Cycle

2015 Grant Recipients

Jennifer Stevens, M.D.
Beth Israel Deaconess Medical Center
Mentor: Bruce Landon, M.D., MBA
"Inpatient Specialist Consultation: Understanding Drivers of Variation and Hidden Resource Use"

Inpatient consultation is the process of involving specialists in the care of a hospitalized patient, something which happens every two seconds in the United States. Despite its prevalence, very little research has explored this common physician practice. Our long-term research objective is to describe the multiple drivers of variation in the use of inpatient consultation, to understand the patient- and system-level value of this widely used exposure, and to develop interventions to measure and improve the quality of inpatient consultation. Our prior work was the first step in this process and was the first large-scale description of consultation nationally among all Medicare patients. This research proposal represents the next step in this line of investigation. The overall goal of this proposal is to identify drivers to inpatient consultation with a focus on type of physician (e.g., hospitalist, primary care physician) and to quantify the downstream consequences of inpatient consultation. To pursue this goal, we propose two specific aims: (SA1) to identify sources of variation in inpatient consultation by quantifying the effect of hospitalists on the likelihood of inpatient consultation; and (SA2) to examine the impact of consultation on health care resource use following discharge. We will study these questions retrospectively among Medicare beneficiaries with medicine admissions to generalist physicians extracted from Medicare claims over a two-year period. We will employ the necessary hierarchical modeling techniques to address the complex relationships between patients, physicians, hospitals and region of the country and use propensity score analyses to accommodate inherent confounding by indication. Completion of this proposal will result in the first quantification of downstream consequences of specialty use in the hospital and identification of possible areas of under- and overuse of this hospital resource.

Sarinnapha Vasunilashorn, Ph.D.
Beth Israel Deaconess Medical Center
Mentor: Edward R. Marcantonio, M.D., S.M.
"The Psychoneuroimmunology of Postoperative Delirium and its Associated Long-Term Cognitive and Functional Outcomes in Older Adults"

Delirium (an acute change in cognition) is common, morbid, and costly among hospitalized elders, yet our knowledge of its pathophysiology and its associated long-term cognitive and functional outcomes remain limited. Recently, an exciting neuroinflammatory model has emerged that addresses these gaps. In this model, individuals predisposed to a heightened inflammatory response when exposed to an acute stressor, such as surgery or infection, are at increased risk for delirium. These systemic inflammatory mediators may cross the blood brain barrier, result in neuroinflammation, which manifests as delirium, and may in-turn may lead to direct neuronal injury, with resulting long-term cognitive and functional consequences. Two biological mechanisms related to brain distress and neuropsychiatric disorders include the catechol-O-methyltransferase (COMT) gene and S100ß protein (S100ß). COMT, an enzyme that degrades catecholamines (stress hormones), is a key regulator of the

stress response and has been associated with cognitive function. Elevated levels of S100ß, a glial-specific marker of neuronal injury, have been related to traumatic brain injury and stroke. Since COMT and S100ß have been linked to several brain disorders, the same mechanisms may be important in delirium. This project will extend and elucidate current work surrounding these biological mechanisms of brain distress and neuropsychiatric disorders, including: the COMT gene and post-translational modification, and S100ß. I will use the Successful AGing after Elective Surgery Study of 566 non-demented adults age =70 who underwent major noncardiac surgery. My Specific Aims: 1) examine the relationship between COMT genotype and methylation, with postoperative inflammation and incidence of delirium, and 2) investigate the role of neuronal injury as a mediator of postoperative delirium and long-term outcomes. This work will advance the field by enhancing our understanding of the mechanisms of delirium by: elucidating whether genetic regulation of the stress response influences postoperative inflammation and delirium, and determining whether adverse long-term outcomes after delirium are attributed to direct neuronal injury. These findings may be used to identify patients at greatest risk for developing delirium, to assist with delirium monitoring and prognosis, and to develop interventional strategies to reduce the impact of this important geriatric syndrome that threatens independence in older adults.

Charles A. King Trust Postdoctoral Fellowship Program

2014 Grant Cycle

2014 Grant Recipients

Noah Berman, Ph.D.
Massachusetts General Hospital
Mentor: Sabine Wilhelm, Ph.D.
"Differential Effects of Positive and Negative Mood on OCD Treatment Response"

Obsessive Compulsive Disorder (OCD) is a significantly impairing psychiatric illness that affects 2-3% of the population and is recognized as one of the ten leading causes of disability worldwide. Given the high prevalence, degree of impairment, and substantial financial burden, OCD is recognized as a major public health concern. Research aimed at better treating this debilitating disorder has increased over the past few decades, and exposure with response prevention (EXRP) has emerged as the most effective psychological treatment. However, a sizeable number of patients drop out of, or do not respond to, this intervention. Researchers have posited that the daunting nature of exposure-based therapy is a significant contributor to attrition and that patients' mood state can influence drop out, as well as the perceived acceptability and effectiveness of this intervention. No empirical work, however, has identified how mood affects EXRP. The present study therefore seeks to examine the mechanisms by which mood influences exposure-based treatment. Specifically, I aim to investigate how positive and negative mood states affect the interpretation of OCD-related stimuli and the subjective and physiologic habituation process following exposure.

To examine this research question, I will utilize a well-characterized sample of individuals with OCD. Following diagnostic interviews, participants will be randomly assigned to a sad, neutral (i.e., control), or positive mood induction. To maintain the effects of the mood induction, participants will then be administered an attention-training paradigm. To then assess how participants interpret idiosyncratic OCD-related stimuli, I will utilize self-report scales, pulse oximetry and facial electromyography (fEMG). Lastly, subjective and objective measures of habituation processes will be assessed in the context of a behavioral avoidance test (BAT). This multi-method study will provide pilot data for an NIMH Career Development award proposal, in which I will conduct a more comprehensive examination of how mood affects successful exposure-based therapy by investigating the interaction of psychosocial, neurobiological, and physiological factors. In identifying how mood states impact EXRP, I aim to reduce the substantial public health impact and financial burden of OCD by tailoring interventions to improve the acceptability of exposure-based therapy and account for the affect of comorbid mood disorders.

Kathryn Papp, Ph.D.
Brigham and Women's Hospital
Mentor: Reisa A. Sperling, M.D.
"Using Semantic Memory to Differentiate Normal Aging from Preclinical Alzheimer's Disease"

Background: Alzheimer's disease (AD) and its precursor MCI (Mild Cognitive Impairment) are characterized by frank declines in episodic memory and semantic memory (i.e., memory for meaning, factual knowledge). Recently published guidelines suggest that subtle alterations in cognition may emerge prior to the stage of MCI, in clinically normal (CN) older adults. While episodic memory as it relates to AD-specific biomarkers has been extensively explored in CN older adults, semantic memory

has been comparatively understudied. Famous face naming is an ecologically valid and useful semantic memory task that is sensitive to MCI/AD. But no studies, to our knowledge, have explored semantic memory using famous faces in CN adults in relation to AD-specific biomarkers.

Objective: The goal of this project is to determine if decrements in semantic memory are a marker specific to preclinical AD in CN older adults. Doing so may 1) provide a relevant outcome measure to be used in future clinical trials of disease-modifying drugs and 2) provide clinical guidelines for whether declines in semantic memory (the most common cognitive complaint of older patients) is a harbinger of AD.

Methods: We will administer a novel cognitive test of semantic memory entitled the Famous Face Association Test (FFAT) to 100 CN and early MCI older subjects participating in Harvard Aging Brain study. We will assess the relationship between the FFAT and traditional cognitive markers of episodic and semantic memory, amyloid burden, APOE epsilon4 gene status, and structural MRI volumetrics.

Aims and Hypotheses: Our first aim is to identify the psychometric properties of the FFAT and to investigate its relationship to other cognitive markers. We expect the FFAT to be reliable, exhibit good convergent and discriminant validity, and to be associated with episodic memory failure and memory complaints. Our second aim is to determine whether semantic memory decrements are associated with markers of preclinical AD. We expect poorer FFAT performance to be associated with biomarker evidence of increased risk for AD, including greater amyloid burden seen on brain imaging, greater genetic burden (greater number of APOE epsilon4 alleles), and decreased volume in brain areas important for memory (i.e., hippocampus).

Charles A. King Trust Postdoctoral Fellowship Program

2013 Grant Cycle

2013 Grant Recipients

Jason Andrews, M.D.
Massachusetts General Hospital
Mentor: Edward T. Ryan, M.D., DTM&H
"Evaluating Novel Diagnostic Strategies for Enteric Fever in Rural Nepal"

Every year, 21.6 million people worldwide develop typhoid, with the majority of cases and deaths occurring in South Asia. Serologic diagnostics have limited sensitivity and specificity, while the best available diagnostic--blood culture--is not available in rural, resource-limited settings due to lack of reliable electricity, laboratory infrastructure, and trained laboratory personnel. Working with colleagues at M.I.T., I designed a simple procedure to make culture-based diagnosis feasible without requiring these resources. I led the laboratory development of this procedure and a clinical validation study in urban Nepal that demonstrated excellent concordance with conventional blood cultures. In this research proposal, I detail a series of aims focused on improving diagnosis and treatment of typhoid in resource-limited settings through combining robust clinical prediction rules with this electricity-free culture-based diagnostic. I will do so by 1) applying advanced Bayesian statistical approaches to data generated from a careful study of typhoid among patients presenting with undifferentiated fever; 2) using the electricity-free culture procedure to obtain data on incidence of typhoid and drug-resistance among febrile patients presenting to rural Nepalese clinical settings; and 3) developing and populating a decision analytic, cost-effectiveness model for diagnosis and treatment of typhoid, using data generated from these clinical studies. Study sites for this research will include Patan Hospital, where we validated the innovative diagnostic, and Bayalpata Hospital, a rural Nepalese hospital where I have worked for the past five years. This research will be mentored by Dr. Edward T. Ryan, an expert in diagnosis of enteric diseases with a focus on South Asia, and Dr. Rochelle P. Walensky, a leader in model-based analysis of cost-effectiveness for infectious diseases diagnostics. This work builds upon my training in epidemiology and modeling and will serve as a foundation for a K01 career development award focused on modeling, operations research and implementation science for enteric diseases diagnostics.

Kimberly Bertrand, Sc.D.
Brigham and Women's Hospital
Mentor: Rulla Tamimi, Sc.D.
"Adolescent Diet, Mammographic Density, and Breast Cancer Risk in Premenopausal Women"

Mammographic density is one of the strongest risk factors for breast cancer and is considered an intermediate marker of risk. We will conduct an epidemiologic investigation to study associations between adolescent diet, mammographic density, and breast cancer risk in premenopausal women. The specific aims of this project are:

1. To test the hypotheses that intakes of total energy, total fat, animal fat, and dairy fat as well as red meat and alcohol during adolescence are positively associated with mammographic density while intakes of carbohydrate, fiber, and vitamin D during adolescence are inversely associated with mammographic density in premenopausal women.

2. To evaluate whether associations observed between adolescent dietary risk factors and premenopausal mammographic density are modified by early life anthropometric characteristics.

3. To test the hypothesis that adjustment for premenopausal breast density accounts, at least in part, for associations between specific adolescent dietary factors and risk of breast cancer.

To address these aims, we will use the unique resources available in the Nurses' Health Study (NHS) II, a long-term follow-up study of premenopausal women. We collected screening mammograms from NHSII participants included in a nested case-control study of breast cancer. Percent breast density was assessed from mammograms using a computer-assisted method. High school dietary data were assessed by a food frequency questionnaire. Data will be available for approximately 967 cases and 1410 controls. We will use multiple linear regression, adjusting for potential confounders, to examine specific adolescent dietary risk factors in relation to average percent breast density among controls. We will also evaluate associations within subgroups defined by early life anthropometric characteristics (e.g., childhood/adolescent somatotype). Finally, we will quantitatively determine whether adolescent diet and premenopausal mammographic density are independently associated with breast cancer risk.

The proposed research will address critical gaps in current knowledge about the nutritional etiology of breast cancer. More importantly, dietary factors during adolescence are potentially modifiable determinants of risk. Identifying such novel risk factors will have a direct impact on prevention messages and future reductions in breast cancer incidence and mortality.

Andrea Enzinger, M.D.
Dana-Farber Cancer Institute
Mentor: Holly Prigerson, Ph.D.
"Characteristics of Effective End-of-Life Communication: Discussing Prognosis and Curability with Advanced Cancer Patients"

For patients with advanced incurable cancer, an accurate understanding of prognosis is fundamental to the ability to accept terminal illness and make appropriate plans at the end-of-life (EOL). Although most patients want accurate prognostic information, a large proportion of advanced cancer patents substantially overestimate their prognosis and inaccurately believe that palliative chemotherapy may cure their disease.

Gaps in communication likely contribute to patients' poor understanding of prognosis, curability and treatment intent, compromising informed decision-making, and contributing to overutilization of aggressive medical care near EOL. Research indicates substantial variability in how oncologists discuss prognosis and EOL medical care. These difficult topics are often discussed selectively, or with vague or euphemistic terminology to soften their emotional impact. Unfortunately, patients could easily misinterpret subtle or ambiguous prognostic messages. Research is needed to understand what communication approaches are most effective at improving patients' understanding of prognosis, curability, and the goals of palliative therapy.

We propose to analyze data from Coping with Cancer 2 (CwC2), an ongoing NCI-funded, multi-site, prospective cohort study, targeting enrollment of 400 patients with advanced metastatic cancer. As part of CwC2, clinic visits after a restaging scan are audiotaped, enabling study of conversations relating to

disease progression, prognosis, and EOL planning. Pre- and post-visit surveys assess patients' understanding of curability, prognosis and treatment intent. We will analyze the content of audio-recorded visits (1) to determine the frequency and approach (e.g. direct versus vague) in which prognosis and curability are discussed, and (2) to determine communication elements that favorably impact patients' understanding of prognosis and curability. Secondly, we propose a cross-sectional study of 75 advanced cancer patients, employing semi-structured interviews to explore their perspectives regarding how effectively prognosis, curability, and treatment intent were communicated during their initial oncology consultations. We will probe for specific phraseologies or communication approaches they perceived as particularly informative, or difficult to understand.

Our findings will inform future research in prognostic communication, including the development of a communication training intervention. Moreover, our findings have potential to enhance physicians' communication about prognosis and palliative treatment, improving the informed consent process, and supporting informed decision-making about palliative therapies at EOL.

Charles A. King Trust Postdoctoral Fellowship Program

2012 Grant Cycle

2012 Grant Recipients

Dae Hyun Kim, M.D., M.P.H.
Beth Israel Deaconess Medical Center
"Comparative Effectiveness of Self-Reported Information, Physical Performance Tests, and Noninvasive Measurements of Vascular Disease Burden in Predicting Persistent Disability in Aging Population"

Over 20% of older Americans report difficulty with at least 1 activity of daily living (ADL) and, in 2004, $135 billion was spent to treat older adults with ADL impairments. Loss of independence (or dependence) in ADLs is an important patient-centered outcome, because it is 'the final common pathway' in aging and the disabling process that results from multiple disease conditions and is a strong predictor of institutionalizations, hospitalizations, and mortality. Therefore, early identification of individuals at risk for ADL dependence is a crucial first step to prevent disability and reduce healthcare costs.

Extensive research has identified a wide range of risk factors and elucidated causal pathways to ADL dependence, but the translation of scientific knowledge into clinical risk prediction has been slow. Our systematic review of the literature found that previous studies of risk factors for disability are limited by: different definitions of ADL disability; failure to consider the severity and duration of disability; lack of information on the optimal combination of previously identified risk factors for prediction; and the absence of comparison among different risk assessment methods, such as self-reported information, physical performance tests, or non-invasive measurements of subclinical disease burden, especially vascular disease.

Leading up to this proposed research, we have recently developed a simple model that uses self-reported information and brief cognitive assessment to predict the 5-year risk of persistent (more than 1 year) dependence with 3 or more ADLs in a large cohort of community-dwelling older adults. Building upon this research, we now propose to: 1) validate our prediction model in an independent dataset, the Cardiovascular Health Study; 2) examine whether our model also predicts other health outcomes, i.e., mortality and hospitalizations; and 3) compare our model with alternative prediction models that use physical performance tests (gait speed, repeated chair stands, and balance) or non-invasive measurements of vascular disease burden (electrocardiography, carotid ultrasound, and ankle-arm index).

In the end, we hope to disseminate a simple assessment tool for persistent ADL dependence and provide comparative evidence on different risk assessment tools. This research will help clinicians objectively assess patients' prognosis and make individualized long-term care plans.

Luke Stoeckel, Ph.D.
Massachusetts General Hospital
"Self-Regulation of Brain Activation in Addiction"

Smoking-related illness causes over 440,000 deaths in the US and over 5 million deaths worldwide annually, and this figure is increasing. Although effective existing therapies double to triple cessation rates, relapse rates remain high. Up to 90% of people who quit smoking relapse within the first year,

even with the best treatment available. Thus, we face a critical need to develop a better understanding of the neurobiological underpinnings of addictive processes, and of relapse in particular, in order to develop targeted relapse prevention therapies that help people to maintain abstinence. Most relapse occurs following smoking cue exposure. Tools now exist to evaluate individual patterns of abnormal cortical and subcortical brain reactivity to smoking cues in relapse prone smokers and to train people to modulate this abnormal smoking-related cue-associated brain reactivity with the aim of ameliorating disease-associated craving and compulsive urges. This revised project will test such a tool, real-time functional magnetic resonance imaging (fMRI) neurofeedback used with emotion regulation strategies, as a novel approach to understanding and potentially modulating the neurobiology of addiction. This study is made possible by an ongoing collaboration between our research team at the Massachusetts General Hospital (MGH) Center for Addiction Medicine, who have a track record of study of novel treatments for nicotine dependence, and Drs. John Gabrieli, Susan Whitfield-Gabrieli, and Ann Graybiel, a highly innovative and productive team of cognitive neuroscientists at the Massachusetts Institute of Technology (MIT), who have pioneered this novel imaging technique. The proposed work has the potential to produce improved understanding of brain mechanisms underlying relapse and potentially, a novel therapy that could reduce the enormous morbidity and mortality caused by chronic, relapsing addiction to smoked tobacco, and also offers the potential for improved understanding and treatment of related disorders such as gambling and certain phenotypes of obesity that involve compulsive urges and failure of inhibitory control.

Charles A. King Trust Postdoctoral Fellowship Program

2011 Grant Cycle

2011 Grant Recipients

David Chan, M.D., M.Sc.
Brigham and Women's Hospital
"Social Networks and Peer Effects among Emergency Department Physicians"

The notion that physicians can be socially incentivized by the presence of their peers is intuitive. However, to my knowledge, the nature of these "peer effects" among physicians has not previously been studied. My long-term objective is to study the effect of social networks on the behavior of individual physicians and on the overall productivity of health care organizations.

Specifically, I will evaluate the effects of emergency department physicians on each other as they work together. My specific aims are threefold. First, I will measure peer effects on individual productivity -- along dimensions of speed of care, quality of care, and teaching. I predict tradeoffs between more observable dimensions (e.g., speed of care) and less observable ones (e.g., quality of care), and I expect that peer effects will be stronger among more socially connected peers. Second, I will study peer effects on the choice of patients by physicians. Individual physicians may want to choose easy patients (i.e., "cherry pick"), but social networks may mitigate this by social pressure and appropriate coordination of work. Third, I will study the effect on overall emergency department productivity under a new system that disallows physicians from choosing their own patients.

Two complementary features of my research design will allow us to accomplish my aims. First, I have detailed, longitudinal data on individual physicians and the patients that they see, involving sufficient variation in the teams of physicians working with each other. Second, my emergency department is undertaking a natural experiment in March of 2011 in which the rules of patient assignment will disallow physicians from choosing their own patients.

My research will shed light on how health care organizations should design their social networks implicit in team structures and the rules that govern behavior within teams. Specific implications include how organizations should match peers with each other, how transparent they should make productivity measures among peers at the expense of less transparent measures, and how much they should constrain implicitly social behaviors such as the choice of patients among physicians.

Peter Smulowitz, M.D., M.P.H.
Beth Israel Deaconess Medical Center
"Massachusetts Health Reform and Emergency Department Utilization by Underserved Populations"

With the passage of the Patient Protection and Affordable Care Act (ACA) of 2010, the landscape of the US health system will change markedly. Similar to the ACA, the Massachusetts health reform legislation enacted in 2006 was designed to reduce the number of Massachusetts residents without health insurance.

One of the principal expected benefits of the Massachusetts legislation was that it would result in decreased utilization of Emergency Departments (EDs). However, ED use may be impacted by many

factors aside from insurance status. The ED is used disproportionately by underserved populations without access to adequate primary care, many of whom are members of racial and ethnic minorities who lack insurance or are insured by the Medicaid program.

The proposed study will take advantage of comprehensive statewide data on ED utilization available in Massachusetts to study the impact of MA health reform on use of the ED. Thus, the results of this study will be an important guide to policy makers about the potential impact of health reform on ED utilization as the ACA is implemented across the nation.

Using data from the Massachusetts Division of Health Care Finance and Policy Acute Hospital Case Mix Databases from the years 2005 through 2010, we will examine the following specific aims:

Aim 1: To determine the impact of Massachusetts health care reform on ED utilization for low severity and ambulatory care sensitive visits using geographic variation (at the zip code level) in the percentage insured as our method of identification of changes resulting from health reform.

Aim 2: To estimate the effect of health reform on ED utilization by underserved populations -- defined by race and zip-code derived measures of socioeconomic status and social disorganization.

In order to accomplish these aims, we will utilize a validated algorithm to measure ED visit severity and a difference-in-differences analytic framework that will allow us to make causal inferences.

Charles A. King Trust Postdoctoral Fellowship Program

2010 Grant Cycle

2010 Grant Recipients

Yee-Ming Chan, M.D., Ph.D.
Massachusetts General Hospital
"Using Kisspeptin to Interrogate the Human GnRH Neuron in vivo"

Natalie Shaw, M.D.
Massachusetts General Hospital
"Effect of Sleep Apnea on Nocturnal GnRH/LH Secretion in Children in Early Puberty"

Charles A. King Trust Postdoctoral Fellowship Program

2009 Grant Cycle

2009 Grant Recipients

Stacey Kenfield, Sc.D., M.Sc.
Harvard School of Public Health
"Diet, Lifestyle, Biomarkers, and Prostate Cancer Survivorship"

Angela Leung, M.D.
Boston University Medical Center
"Breast Milk Iodine and Perchlorate Concentrations: Effect on Infant Thyroid Function"

Charles A. King Trust Postdoctoral Fellowship Program

2008 Grant Cycle

2008 Grant Recipients

Kimmie Ng, M.D., M.P.H.
Dana-Farber Cancer Institute
"Influence of the vitamin D pathway on survival in patients with colorectal cancer"

Joshua Roffman, M.D.
Massachusetts General Hospital
"Altered one-carbon metabolism in schizophrenia: molecular and neuroimaging correlates of folate response"

Charles A. King Trust Postdoctoral Fellowship Program

2007 Grant Cycle

2007 Grant Recipients

Mary Keebler, M.D.
Massachusetts General Hospital
"Identification of Common DNA Sequence Variants Related to Blood Lipid Traits"

Jaime Murphy, M.D.
Boston University Medical Center
"Circulating Mesenchymal Precursors with Fibrogenic Potential in Asthma"

Charles A. King Trust Postdoctoral Fellowship Program

2006 Grant Cycle

2006 Grant Recipients

Serena Mascieri, M.D.
Dana-Farber Cancer Institute
Prevalence of Germline E-Cadherin Mutations in Women with Lobular Breast Cancer

Maitreyi Mazumdar, M.D., M.P.H.
Children's Hospital Boston
"Health Insurance and Utilization of Services by Children with Epilepsy"

Charles A. King Trust Postdoctoral Fellowship Program

2004 Grant Cycle

2005 Grant Recipients

Robert Ajemian, Ph.D.
Massachusetts Institute of Technology
"Dynamic Motor Learning in Alzheimer's Disease"

Jinbo Fan, Ph.D.
Massachusetts Institute of Technology
"Linkage Disequilibrium Mapping on Candidate Genes Across Chromosome 6q16-22 Bipolar Disorder Locus"