Shared Health Research Information Network (SHRINE) Prize Opportunity

The Harvard Catalyst Biomedical Informatics Program sponsored this prize opportunity to encourage and support the use of the Shared Health Research Information Network (SHRINE). Applicants were required to perform and then describe a set of innovative SHRINE queries that illuminated interesting population-level phenomena or that set the stage for subsequent large-scale clinical experiments based on SHRINE query results. Winners of these prizes were eligible to later apply for $50,000 one-year research grants to support efforts to secure patient-level data based on SHRINE results.

This funding opportunity, which awarded nineteen $2,500 prizes, was open to any faculty member holding a Harvard Medical School faculty appointment at one of the SHRINE participating hospitals.

Funding decisions for the SHRINE Prizes were announced in June 2012.

For more information about these awards, see the following news article.

Identifying Risk Factors for Peripartum Cardiomyopathy

Principal Investigator: Zolt Arany, MD, PhD, Beth Israel Deaconess Medical Center

Co-Investigator: Sarosh Rana, MD, Beth Israel Deaconess Medical Center

Peripartum cardiomyopathy (PPCM) is characterized by maternal systolic heart failure around the time of delivery. PPCM is an orphan disease: its cause remains elusive. Assessing epidemiological questions with PPCM is not easy, however, because PPCM is a relatively rare disease. No data exist on the prevalence and risk factors for PPCM in the Northeast USA. The objective of this project was therefore to query the SHRINE database for the prevalence of PPCM in our population, and to investigate associated conditions and demographics. 97+/-3 cases of PPCM were identified in SHRINE. Notable identified risk factors for PPCM included: preeclampsia, gestational hypertension, maternal age, and black race. This preliminary study validates the use of SHRINE to study the epidemiology of rare diseases. We hope to obtain IRB approval to extend these findings to chart reviews of the 97 cases, and ultimately to obtain DNA samples for genetic studies.

Utilizing SHRINE and CRIMSON to Study Diagnostic Biomarkers in Respiratory Failure

Principal Investigator: Ednan Bajwa, MD, MPH, Massachusetts General Hospital

Co-Investigators: David Christiani, MD, MPH, Harvard School of Public Health
Kathryn Hibbert, MD, Massachusetts General Hospital
James Januzzi, MD, Massachusetts General Hospital
Robert Owens, MD, Brigham and Women's Hospital
B. Taylor Thompson, MD, Massachusetts General Hospital

The goal of our project is to build a cohort of critically ill patients with congestive heart failure and respiratory failure. We hope to use this cohort to validate one or more diagnostic biomarkers that may help clinicians distinguish between pulmonary edema of different causes. Because of the difficulty in amassing such a cohort, we have sought to take advantage of SHRINE to identify these patients and enable us to enroll them prospectively. We also propose to utilize SHRINE in conjunction with the CRIMSON Biospecimen Core in order to secure plasma samples from these patients. In doing so, we hope to build a unique cohort that can be used to quickly and efficiently answer our research question.

Understanding Genetic Variation in Rare Diseases Using Epidemiological Data from SHRINE

Principal Investigator: Christopher Cassa, PhD, Boston Children's Hospital

The interpretation of clinical testing relies on physician interpretation of how new evidence modifies the prior probability of disease. Unfortunately, for many genetic diseases, there is no curated, publicly available source of disease prevalence data, making it nearly impossible to do this systematically across diseases. This is particularly important in whole genome sequencing (WGS) interpretation, where there are approximately 150,000 variants already associated with disease, but many have little or no structured data describing their penetrance or disease prevalence. Without this data, it is not possible to computationally generate an accurate likelihood of disease in asymptomatic individuals, creating a major bottleneck in clinical interpretation of WGS. We have used SHRINE data, along with other population-based data and gold standard expert estimates to establish estimates for the prevalence of a set of rare genetic diseases. We are interested in using this data to inform the review of genetic variation that is identified in the WGS of asymptomatic individuals.

Bicycle-related Injuries in Boston: Linking Bicycle Environments, Emergency Medical Services, and Emergency Department Clinical Outcomes

Principal Investigator: Christopher Fischer, MD, Beth Israel Deaconess Medical Center

Bicycle ridership is increasing in Boston and around the country. With increasing awareness of the health and social benefits of bicycling comes an increased possibility of bicycle-related injuries. While there has been much focus on improving bicycle infrastructure (e.g. bike lanes, bicycle paths), there is much work that needs to be done to improve our understanding of the causes and effects of bicycle-related injuries.

We propose a new collaboration of emergency clinicians, emergency medical services (EMS) providers, and public health researchers to examine the changes in the number and severity of bicycle injuries treated by emergency medical services (EMS) and in the emergency department (ED) in Boston over the last 10 years. We will specifically examine:
1) Emergency department clinical and demographic data of all patients evaluated for bicycle-related injuries at the Harvard-affiliated hospitals, including injury severity and disposition;
2) EMS data for all bicycle-related injuries, including collision location and helmet use;
3) Data related to bicycling environment at the locations of collisions, including bicycle use and bicycle-related infrastructure improvements.

We will establish a link between bicycle environments, the factors contributing to bicycle collisions, the role of EMS response and transport, and patient-level emergency department and clinical outcomes. This will allow policy makers, clinicians, and public health and injury researchers to improve urban bicycling and improve safety.

Recurrence of Breast Carcinoma *in situ*

Principal Investigator: Aditi Hazra, PhD, Brigham and Women's Hospital

Co-Investigators: Kornelia Polyak, MD, PhD, Dana-Farber Cancer Hospital
Stuart Schnitt, MD, Beth Israel Deaconess Medical Center
Rulla Tamimi, PhD, Brigham and Women's Hospital

Approximately 57,650 women are diagnosed with carcinoma *in situ* (CIS) every year in the US. Since we cannot currently distinguish which women with DCIS will go on to develop invasive breast cancer, most women are treated with similar clinical interventions resulting in unnecessary and potentially harmful side effects from adjuvant radiation, adjuvant hormonal therapy, or mastectomy. To address this public health concern and obtain a robust sample size for biomarker development and validation, we have identified aggregate numbers of patients diagnosed with CIS with (n=2,081) or without invasive recurrence (n=7,446) using the SHRINE database (Aim 1). The next step will be to identify DCIS cases with invasive recurrence and active patients with non-recurrence (controls) at the SHRINE institutions with patient-level clinical data and DCIS tissue specimens. To accelerate the discovery of clinically actionable markers, we will use the clinical DCIS specimens to develop and validate a multi-gene signature that can identify certain DCIS tumors with higher or lower invasive recurrence risk to tailor therapies more appropriately (Aim 2). The completion of these aims may prevent the overtreatment of many women with more indolent DCIS with a low potential for invasive transformation and target more aggressive treatments to the subset of women with DCIS lesions at highest risk of progressing to IBC. Clinically actionable markers (with striking relative risks) for that predict subsequent risk o IBC would provide targets for intervention, chemoprevention, and have a profound impact on clinical decision-making for the 57,650 women diagnosed with DCIS every year.

Using SHRINE to Discover Whether Serious Complications Associated with Multiple Myeloma Decreased After Implementation of Universal Health Care in Massachusetts

Principal Investigator: Robin Joyce, MD, M. Div, Beth Israel Deaconess Medical Center

Co-Investigators: Kelly Bodio, MD, Beth Israel Deaconess Medical Center
Jeremy Warner, MD, Beth Israel Deaconess Medical Center

Multiple myeloma (MM) is an incurable hematologic malignancy which commonly presents with serious complications such as pathologic fracture and kidney damage. If diagnosed early, it is possible that the natural history of complications can be altered. With the advent of universal health care (UHC) in Massachusetts, previously under-insured populations might have been diagnosed earlier in the disease course. We queried SHRINE for patterns of serious complications associated with MM before and after UHC took effect, and found that the overall rate of serious complications decreased from 42% to 37% in an established population of 4,619 MM patients (OR 0.80, $p = 0.0004$). In an exploratory analysis, we found that African Americans, who are disproportionately affected by MM, were also disproportionately affected by serious complications (OR = 1.93, $p < 0.0001$ before UHC and OR = 1.64, $p = 0.006$ after UHC). The complication rate in African Americans appeared to moderate with the advent of UHC (58% to 48%, $p = 0.09$). This study demonstrates that SHRINE can be a powerful tool for cancer-related health services and health disparities research, and suggests that UHC had a beneficial effect on the rate of serious complications associated with MM.

Serotonin Syndrome with Combined use of SSRI/SNRI Antidepressants and Triptans

Principal Investigator: Elizabeth Loder, MD, MPH, Brigham and Women's Hospital

In 2006 the US Food and Drug Administration issued an Advisory about the risk of serotonin syndrome with concomitant use of SSRI/SNRI antidepressants and triptan antimigraine drugs. The Advisory was based on a small number of case reports. Doubts exist about whether these cases actually met criteria for the disorder. An American Headache Society position paper questioned the basis for the Advisory and noted “insufficient information to discern the risk”.

SSRI/SNRI antidepressants and triptans are widely prescribed for depression and migraine, which are highly prevalent, long duration, disabling disorders. These disorders occur together at a frequency greater than chance, so co-prescription is common. One study estimated the FDA Advisory applies to 1.8% of the US population.

There are no population-based studies that link co-prescription with outcomes of serotonin syndrome, so the risk of serotonin syndrome with co-prescription is unknown. The situation for doctors and patients is confusing. Decision support systems issue automatic safety alerts for co-prescription, with substantial disruption of clinical care.

We interrogated SHRINE to find the number of patients with co-prescriptions and outcomes of possible serotonin syndrome, and evaluated changes in co-prescription following the Advisory. From 2001-2010 we found 5282+/- 3 patients with co-prescription with 135 +/-3 cases of possible serotonin syndrome. Future aims are chart review to verify whether cases meet criteria for serotonin syndrome, and their temporal association with co-prescription. We aim to generate precise incidence estimates using the number of unique patients seen at study hospitals and the estimated population market share of each.

Long QT Syndrome and Cardiac Restitution: Predicting Sudden Cardiac Death

Principal Investigator: Keith Marill, MD, Massachusetts General Hospital

Despite major advances in cardiac care over recent decades, sudden cardiac death stubbornly remains a tremendous public health burden with approximately one quarter million cases in the U.S. annually. Torsades de Pointes (TdP) is an important cardiac dysrhythmia and cause of sudden cardiac death in both children and adults. By definition, patients with TdP have a prolonged interval between the Q and T waves on their ECG (QT interval). QT interval prolongation may be caused by congenital genetic channelopathies, or acquired due to metabolic derangement or exposure to a broad array of pharmaceuticals from antibiotics to antineoplastics. The exact mechanism by which QT prolongation leads to TdP and sudden cardiac death is uncertain. As a consequence, clinicians' ability to predict and prevent these events remains elusive. We hypothesize that patients with long QT syndrome have an exaggeration of the normal relationship, termed restitution, between the QT interval of one beat and the relaxation phase or diastolic interval of the preceding beat. This can lead to electrophysiologic instability that causes TdP. Using the SHRINE tool across Harvard hospitals, our team has identified patients with congenital long QT syndrome (LQTS) who also have premature beats that allow measurement of the restitution relationship. By comparing the restitution relationship in these patients to appropriate controls, we will determine if LQTS patients have an exaggerated restitution relationship. If this hypothesis proves true, it may lead to new diagnostic approaches for LQTS patients and for pharmaceutical risk assessment, and new treatments to prevent sudden cardiac death targeted at QT restitution alteration.

Changing Incidence, Demographic and Risk Factor Patterns for Colorectal Cancer Under Age 50

Principal Investigator: Rebecca Miksad, MD, MPH, Beth Israel Deaconess Medical Center

Co-Investigators: Jeffrey Meyerhardt, MD, MPH, Dana-Farber Cancer Hospital
Deborah Nagle, MD, Beth Israel Deaconess Medical Center
David Ryan, MD, Massachusetts General Hospital
Kevin Selby, MD, Beth Israel Deaconess Medical Center

Abstract withheld at the request of the investigator.

Pro-inflammatory vs. Anti-inflammatory Human Physiology: The Cancer/Atherosclerosis Balance

Principal Investigator: Danny Milner, MD, Brigham and Women's Hospital

Co-Investigator: Matthew Li, Massachusetts Institute of Technology

The objective of this study was towards preliminary clarification of the relationship between cancer and atherosclerosis. Atherosclerosis is the major underlying factor for most cardiovascular disease (CVD) and one of leading causes of death worldwide.The seemingly forgotten notion that aspects of cancer may possess the ability to attenuate atherosclerosis provides a new approach towards filling our gap in knowledge between pathology and novel therapy. We believe that cancer provides an anti-inflammatory physiology that is able to attenuate atherosclerosis. In this study, the use of SHRINE has elucidated a distinct disparity in atherosclerotic incidences in patients of cancer vs. normal population control. Our analysis indicates that within each population (control and cancer subgroups), controls had a prevalence of 27.4%, lymphoma/leukemia – 12.57%, lung – 17.63%, colorectal – 18.17%, breast – 9.79%, uterus/cervix – 11.47%, and prostate – 18.40%. From the data, there appear to be nearly half the prevalence of atherosclerotic disease in patients of cancer. This initial result illuminates the notion

that cancer may in fact provide an anti-inflammatory environment that causes atherosclerotic reversal and warrants further in depth studies to evaluate underlying mechanisms.

Autism and Alzheimer's

Principal Investigator: Lindsay Oberman, PhD, Beth Israel Deaconess Medical Center

The clinical, social and financial burden of Alzheimer's Disease and related dementias (AD) is staggering. The CDC estimates that approximately 13% of individuals over the age of 65 are afflicted by AD resulting in a current yearly cost of $183 billion dollars. These striking statistics make understanding of the mechanisms underlying these devastating conditions and the development of novel therapeutic interventions critical.

We argue that the efficiency of neuronal plasticity declines throughout the age-span leading to normal age-related cognitive decline and that excessive and insufficient plasticity may represent the proximal pathogenic cause of Autism Spectrum Disorders (ASD) and AD respectively. We therefore hypothesized that individuals whose cortex begins as hyperplastic (e.g. those with ASD) would be protected from AD, which we suggest is related to a hypoplastic cortex. Based on this hypothesis, we obtained approval to use Shrine to explore the number of patients who hold comorbid diagnoses of ASD AND AD. Consistent with our hypothesis, results indicated that the number was less than 10.

We have now obtained IRB approval to conduct a formal review of the medical records of patients over the age of 55 with ASD at BIDMC and are collaborating with Dr. Kohane to set up a similar study at BWH. If, as we predict, that a minimal number of patients with ASD have a co-morbid diagnosis of AD, we will then submit for funding for a larger-scale study, the results of which have the potential for great the social, clinical and financial impact.

Autism and In-utero Exposure to Antidepressants

Principal Investigator: Roy Perlis, MD, Massachusetts General Hospital

Co-Investigators: Roscoe Brady, MD, PhD, Beth Israel Deaconess Medical Center
Jordan Smoller, MD, PhD, Massachusetts General Hospital

The etiology of Autism Spectrum Disoders (ASDs) remains largely unknown. Autism risk has been associated with both genetic and environmental effects, with recent evidence of a substantial contribution of antidepressant exposure in utero. A challenge in interpreting such results, however, is the risk of confounding; for example, the use of antidepressants is associated with birth complications and maternal depression.

To address these limitations, we propose to compare two cohorts of children delivered in a SHRINE hospital: one diagnosed with ASD and the other with Attention Deficit Hyperactivity Disorder (ADHD). By matching children with maternal data, we will attempt to confirm an association between ASD and antidepressant exposure, with adequate control for confounding effects of major depressive disorder and other medical and psychiatric comorbidity.

The availability of large cohorts from Children's Hospital Boston (N=6081) and Partners (N=3373) indicate the potential of this study to identify the presence or absence of a real association after controlling for confounding such as maternal depression or fetal distress, which may have biased past results.

Fractures in Patients with HIV Infection

Principal Investigator: Daniel Solomon, MD, MPH, Brigham and Women's Hospital

Background: As patients with the human immunodeficiency virus (HIV) are living longer because of effective treatments, rates of comorbid chronic diseases such as osteoporosis are increasing. Recent literature suggests particular antiretroviral medications, such as tenofovir, may be associated with osteoporosis. However, there is conflicting data as to whether tenofovir is associated with increased fracture risk.

Methods: Using the SHRINE patient database, HIV patients seen at either Brigham and Women's hospital (BWH) or Beth Israel-Deaconess medical center (BIDMC) were included in this cohort. The database was queried for numbers of osteoporotic fractures (ie hip, vertebrae, or wrist fractures) among this HIV-positive patient cohort. The database was then queried for tenofovir exposure in both the HIV patients who sustained osteoporotic fracture, as well as for tenofovir exposure in those patients that did not fracture.

Results: 9044 patients with HIV were included in this cohort. Over a third of the patients in this cohort (36.3%) were exposed to tenofovir. The number of osteoporotic fractures in cohort was 218; 98 of these patients were also exposed to tenofovir. Among the 8826 patients who did not fracture, 3175 were exposed to tenofovir. The odds of sustaining an osteoporotic fracture was 1.45 times higher (95%CI 1.11-1.90) in those patients exposed to tenofovir than in those not exposed to tenofovir.

Conclusion: This preliminary data suggests an association between exposure to tenofovir and increased risk of fracture. Studies adjusting for traditional osteoporotic and HIV-specific risk factors are required to investigate this association further.

Identifying Risk Factors in Children and Adults for the Development of Systemic Lupus Erythematosus

Principal Investigator: Mary Beth Son, MD, Boston Children's Hospital

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder that, despite advances in therapy, remains associated with significant morbidity and mortality. The autoimmune processes involved in the pathogenesis of SLE are underway long before the disease becomes manifest. SLE-specific autoantibodies have been detected in the blood of people years before they receive their clinical diagnosis. Both children and adults often present with one or more features of autoimmune disease without meeting full criteria for SLE. Manifestations of a pre-lupus state include autoimmune hematologic disease and polyarthritis. Such patients represent a diagnostic dilemma, as some will progress to develop SLE while others will remain stable or improve. The ability to identify patients at highest risk for future disease would therefore facilitate screening and management while possibly giving clues related to pathogenesis.

We propose to use the SHRINE database to identify a cohort of patients with autoimmune hematologic disorders or polyarthritis who later developed SLE. The ability to study both adult and pediatric groups through this network is a particular advantage as the interval between first presentation and eventual diagnosis may be several years long and bridge pediatric and adult institutions. Using extracted demographic and laboratory data, we hope to identify additional risk factors for the development of SLE. Future directions include sample collection for biomarker analysis to identify novel biochemical markers that help distinguish progressors from non-progressors.

Characterizing the Rise in Precocious Puberty 2001-2009

Principal Investigator: Lisa Topor, MD, Boston Children's Hospital

Early puberty is on the rise, as documented through recent population studies in the United States and Europe. It is also a frequent topic of discussion by the media. In additional to psychological concerns, forms early puberty can be associated with increased risk of adult disease, such as insulin resistance and metabolic syndrome. The etiology of the increased rates of precocious puberty is unclear, though increased weight gain during early childhood and obesity have been identified as risk factors for early puberty in girls.

SHRINE queries revealed a 5-fold increase in annual visits for precocious puberty evaluations in affiliated hospitals between 2001-2009. In the last 3 years included in the search, 14% of children with precocious puberty also had a diagnosis of overweight or obesity and insulin resistance was identified in 27 children seen for precocious puberty between 2001-2009.

Next steps include identifying factors associated with the rise in precocious puberty evaluations, as well as risk factors for comorbidities associated with precocious puberty. We will identify the prevalence of overweight and obesity in children seen for precocious puberty using body mass index. We will characterize the diagnostic evaluation and outcomes for these children. and aim to identify risk factors for comorbidities associated with precocious puberty, such as insulin resistance and anxiety or depression.

Novel Transcription Factor Inhibitors Improve Cancer Risk and Outcomes in Clinical Practice

Principal Investigator: Sarah Walker, PhD, Dana-Farber Cancer Hospital

Co-Investigator: Michael Xiang, Harvard Medical School

Oncogenic transcription factors have been considered difficult targets for cancer drugs, yet they are attractive biological targets due to being at the convergence point of multiple upstream pathways and their role as master regulators of gene expression and cellular phenotype. Here, we describe the drugs disulfiram and atovaquone as novel inhibitors of the oncogenic transcription factors BCL6 and STAT3, respectively. These drugs were discovered by using the Broad Institute’s Connectivity Map to identify compounds that induce gene expression changes that are contrary to the gene expression signatures of BCL6 and STAT3. Follow-up studies established disulfiram and atovaquone as bona fide transcription factor inhibitors with anticancer efficacy in vitro. Since both drugs are FDA-approved (but not as anticancer agents) and already in clinical use, we hypothesized that patients taking these drugs have a lower incidence of cancer and/or improved cancer outcomes. SHRINE queries demonstrated that patients taking disulfiram were significantly less likely to have a diagnosis of BCL6-associated cancers compared to patients not receiving disulfiram (10.8% vs. 15.9%; $p = 0.015$). For atovaquone, we found that leukemia patients who had not undergone bone marrow transplant were significantly more likely to be in remission if they were treated with atovaquone (54.9% vs. 32.0%; $p < 0.001$). In conclusion, using SHRINE, we were able to collect compelling evidence for the *in vivo* anticancer efficacy of these drugs.

Co-Morbidity of Psychiatric Conditions and Sleep Disorders

Principal Investigator: Erin Wamsley, PhD, Beth Israel Deaconess Medical Center

Co-Investigator: Samata Sharma, MD, Brigham and Women's Hospital

Disrupted sleep is a prominent feature of many psychiatric conditions. Historically, sleep problems have been viewed as merely a secondary consequence of psychiatric disturbance. However, recent evidence suggests that sleep disruption may actually play an integral role in the development of certain psychiatric conditions. Understanding large-scale associations between psychiatric diagnoses and abnormal sleep may assist in identifying patient groups for which psychiatric symptoms could be effectively treated by targeting an underlying sleep disturbance. Harvard's SHRINE database provides a unique opportunity to quickly examine the incidence of psychiatric diagnoses in patients with a variety of sleep disorders, using a very large cross-institutional sample. In this project, we used the SHRINE database to describe the prevalence of psychiatric diagnoses within four common sleep disorders. Our results clearly demonstrate that patients with sleep disorders have a much higher rate of psychiatric diagnoses than age-matched controls without history of sleep disruption. Furthermore, we identified two novel patterns of co-morbidity, which have not been explored in the existing literature. First, we observed that patients with sleep apnea were particularly likely to be diagnosed with psychotic disorders. Second, we found that attention deficit disorder was extremely prevalent in narcolepsy patients, relative to other sleep-disorders groups. These observations set the stage for further investigations that may elucidate the role of disrupted sleep in these conditions.

Completeness of Diabetes Diagnoses at Multiple Institutions

Principal Investigator: Adam Wright, PhD, Brigham and Women's Hospital

Abstract withheld at the request of the investigator.

Predicting Clinical Outcome in Comatose Cardiac Arrest Patients

Principal Investigator: Ona Wu, PhD, Massachusetts General Hospital

Co-Investigators: Brian Edlow, MD, Massachusetts General Hospital
David Greer, MD, Massachusetts General Hospital
Eric Rosenthal, MD, Massachusetts General Hospital

Early prediction of functional recovery of comatose patients after cardiac arrest remains challenging. The American Academy of Neurology practice parameters' evidence-based review reported that absent pupillary light response or absent corneal reflexes, or extensor posturing or no motor response to pain 72 hours after resuscitation are associated with poor long-term outcome. Several studies have also shown that large reductions in the apparent diffusion coefficient were predictive of poor outcome. However, these studies often involved patients who were improving, or critically ill patients who died within 72 hours of resuscitation. Imaging and electrophysiology may be of most benefit to patients who are still comatose at 72 hours. The goal of this study is to investigate whether imaging and electrophysiology can be used to predict recovery in these patients. By determining a pattern representing a high likelihood of good outcome, the early withdrawal of care from patients who would otherwise have a chance for recovery could be avoided. We plan to submit a NIH R01 grant application for an observational prospective multicenter study in patients who are comatose at least 3 days after resuscitation. In order to plan for this grant application, we need to perform a feasibility analysis. The Harvard Catalyst Shared Health Research Information Network (SHRINE) will allow us to identify local partner institutions that would be able to participate in this study.