TUESDAY MORNING WORKSHOP (8:30 am – 11:30 am)

C. (OBSERVATIONAL) Personalized Medicine for Observational Data (Meeting Room 2)
Organizer/Chairs: Eric Laber, NCSU

1. Learning Adaptive Treatment Strategies for Bipolar Disorder
Speakers: Fan Wu, NCSU

There is substantial uncertainty regarding the efficacy of antidepressants in the acute treatment of bipolar depression. The available evidence from randomized controlled trials is limited and controversial. Furthermore, traditional randomized controlled trials are not designed to tell who (of the target population) will benefit from the intervention and who might do better without. In addition, as bipolar disorders are chronic mood disorders, with a series of interventions being the rule rather than the exception (in case of bipolar depression, to reach remission), they do not closely mimic clinical reality as the effects of previous treatments on the efficacy and tolerability of subsequent treatment are not well captured. Therefore other methodological approaches are urgently needed which allow to practice personalized, evidence-based medicine in patients with bipolar depression.

Dynamic treatment regimes operationalize clinical decision making as a sequence of decision rules, one per stage of clinical intervention, that map up-to-date patient information to a recommended treatment. Dynamic treatment regimes therefore personalize treatment according the evolving health status of each patient. An optimal treatment regime maximizes the expectation of a desired cumulative clinical outcome when applied to a patient population of interest. Thus, estimated optimal dynamic treatment regimes can inform clinical decision making and generate evidence-based hypotheses about time-varying treatment response heterogeneity. Using data from the acute depression randomized care (RAD) pathway of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Sachs et al., 2007, NEJM), we estimate an optimal dynamic treatment regime via Q-learning, an extension of regression to multi-stage decision problems. The estimated optimal dynamic treatment regime performs statistically significantly better than any estimable non-tailored treatment strategy. The estimated optimal dynamic treatment regime presents strong evidence that patients in RAD pathway of STEP-BD with a (hypo)manic episode prior to onset of the current depressive episode should not be given an antidepressant in addition to a mood stabilizer.

2. Data-Mining Methods for Subgroup Identification and Analysis in Clinical Data
Speaker: Ilya Lipkovich, Quintiles

Vast literature has been generated in medical and statistical journals over the last 15 years concerning subgroup analysis methodology and the assessment of validity/credibility of subgroup analysis methods for randomized clinical trials and observational data. We see a shift of emphasis from presenting “good practices” of subgroup analysis to developing more aggressive subgroup identification strategies under the umbrella of “individualized medicine/tailored therapeutics”. This presentation will provide an overview of several recent
subgroup identification methods that originated in data mining and machine learning fields. We discuss some challenges of applying data mining methodology to subgroup identification in the context of clinical data and present a novel recursive partitioning procedure for subgroup identification, SIDEScreen and discuss its key elements. This procedure is an ensemble method based on recursive partitioning. It is different from many other applications of data mining/machine learning to subgroup analysis in that it allows for explicit control of the overall Type I error rates. SIDEScreen procedure will be illustrated using clinical trial example.

Key worlds: data mining, personalized medicine, subgroup analysis, biomarker identification

3. Finding Optimal Treatment Dose Using Outcome Weighted Learning
Speaker: Guanhua Chen, UNC
C. (OBSERVATIONAL) Methodological Developments for Indirect Treatment Comparisons and Network Meta-Analyses (Meeting Room 2)
Organizer/Chair: James Signorovitch, Analysis Group Inc.

1. Bayesian Network Meta-analysis of Randomized Clinical Trials
Speaker: Haito Chu, University of Minnesota

In the absence of sufficient data directly comparing two or more treatments, indirect comparisons using network meta-analyses (NMA) across trials can potentially provide useful information to guide the use of treatments. Under current contrast-based methods for NMA of binary outcomes, which do not model the “baseline” risks and focus on modeling the relative treatment effects, the patient-centered measures including the overall treatment-specific event rates and risk differences are not provided, which may create some unnecessary obstacles for patients to comprehensively understand and trade-off efficacy and safety measures. Most NMAs only report odds ratios which are commonly misinterpreted as risk ratios by many physicians, patients and their caregivers. In addition, we show two serious concerns with the CB method: different odds ratios (ORs) are obtained with different baseline selections using a simple contrast-based approach; and different event rates (back-translated from ORs) are obtained with different reference selections even using the general contrast-based approach. A novel Bayesian hierarchical model, developed from a missing data perspective under missing at random assumption, that borrows information across multiple treatment arms, is used to illustrate how treatment-specific event proportions, risk differences (RD) and relative risks (RR) can be computed in NMAs. Furthermore, we will discuss models handling non-ignorable missingness. Several case studies and simulations will be presented for illustration.

2. Adjusted Indirect Comparisons with Propensity Score Weighting When Individual Patient Data are Unavailable for One Treatment Group: Large Sample Theory and a Simulation Study of Statistical Performance
Speaker: Rajeev Ayyagari, Analysis Group Inc.

Indirect comparisons of treatment outcomes across separate clinical studies are often needed for health technology assessment and comparative effectiveness research. The potential for bias due to cross-study differences is a well-recognized limitation. Matching-adjusted indirect comparisons (MAICs) are an extension of propensity score weighting, and can reduce cross-study differences by adjusting individual patient data from studies of one treatment to match average baseline characteristics published from studies of a comparator treatment. This presentation will describe the causal inference and large-sample theory underlying the MAIC point estimate and its associated variance estimator. The performance of the estimator is investigated through an extensive simulation study. Example applications to real data will also be presented.

Meta-analysis has long been used to summarize direct comparative evidence from multiple head-to-head randomized trials. Over the past decade, extensions of meta-analysis to indirect (i.e. cross-trial) comparative evidence have become important tools for comparative effectiveness research and health technology assessment. Causal inference for direct comparison meta-analyses is relatively uncomplicated, since each head-to-head randomized trial, if well-conducted and reported, estimates a causal effect. Indirect comparisons pose greater challenges for causal inference since they involve cross-trial comparisons of non-randomized treatment groups. Traditional approaches to indirect comparison attempt to adjust for cross-trial differences by measuring treatment effects relative to a common reference arm (e.g., placebo) using an assumed effect measure (e.g., odds ratio or risk difference). However, the often arbitrary choice of an effect measure can significantly impact the results of such a comparison. To address this limitation, we extend Frequentist meta-analytic approaches that adjust for “baseline risk” to the indirect comparison setting, and examine the implications for improving causal inference. The method is illustrated with an example application.
C. (OBSERVATIONAL) Health Outcomes Research with Big Data: Opportunities and Challenges
(Meeting Room 2)
Organizer/Chair: Hong Kan, GlaxoSmithKLine

1. Challenges and Strategies in Conducting Real World Health Economics and Outcomes Research Studies for Orphan Diseases and Orphan Drugs
Speaker: Peter Sun, Kailo Research Group

As more and more patients, physicians, payers and policy makers want to have real-world information on orphan diseases and orphan drugs, the demand for real-world health economics & outcomes research studies for orphan diseases and orphan drugs has increased significantly. However, conducting these studies is difficult because of challenges in data sources, study designs and analytical methods. This presentation will examine these challenges and explore potential strategies that researchers can use to overcome the challenges. Finally, we will use one or two real world examples to show that the challenges are daunting, but the mission can still be accomplishable.

2. Cluster Analysis of Longitudinal Treatment Patterns Using Claims Data
Speaker: Hong Kan, GSK

In disease where patients and physicians make frequent changes of drug treatments for a variety of reasons including lack of responses, safety/tolerability and disease progression, there is a need to understand how drug treatments evolve over time. Longitudinal treatment patterns in diseases with multiple drug choices and complex treatment pathways or no widely-accepted treatment guidelines can quickly become too complex to discern manually. In that situation, cluster analysis as an unsupervised machine learning method may be employed to group longitudinal treatment pathways. The study will demonstrate how effectively k-means cluster analysis may group longitudinal treatment pathways, practical considerations in fine tuning clustering, and potential of applying machine learning methods in health services research.

3. The Emerging Provider Databases and Their Use by Pharmaceutical HEOR Departments
Speaker: Spryos Stavrakas, Market Strategy Group

There has been a dramatic growth in the investment by both payers and providers in creating patient level database research capabilities during the last decade. Most of these investments have yet to produce a dramatic impact, however, in the resources available to Pharmaceutical HEOR departments. It is important to understand the process of how payer and provider created databases have historically been made available to HEOR departments and how the most recent databases differ from the previous ones.

Part of understanding this process is to understand the role of pharmaceutical services firms and how they
1) commercialize databases, 2) the value of current emerging databases to Pharmaceutical
HEOR departments and finally, 3) the strengths and weaknesses of some of these current databases offerings including key considerations when evaluating new patient level database acquisitions.