

## **Institute for Public Health Genetics**

### **Examples of Dissertation Topics that Incorporate Core Knowledge Areas A and B**

#### **Example 1: Racial Identification in Pharmacogenetic Intervention:**

Heritable differences in drug response can sometimes be mediated by gene variants and/or haplotypes which differ in frequency among individuals from different racial and/or ethnic backgrounds. Pharmacogenetic testing promises to identify relevant variation in advance of therapeutic intervention, stratifying patients with respect to likely efficacy of treatment or risk of adverse reactions. Though such testing could take place in an entirely race-neutral manner, testing could be restricted to cohorts with the highest expected incidence of the relevant variations (e.g. polymorphism CYP2C9\*3, related to warfarin metabolism, is found at higher frequency in populations of European ancestry). In the proposed dissertation, a systematic critical evaluation of the available epidemiological data relevant to, and a formal cost-effectiveness analysis of, an association between specific drug metabolizing enzyme polymorphism allele frequencies and various pharmacological outcomes for which race/ethnicity differences have been implicated, [for example, genotyping for the thiopurine methyltransferase polymorphism in children with leukemia prior to use of 6MP] will be conducted. Here, 'cost' and 'benefit' will be measured via assessment of the clinical, patient, and economic outcomes of using self-identified race/ethnicity to direct pharmacogenetic testing to defined cohorts eligible for testing rather than testing of all patients. An ethical framework for addressing conflicts in the costs and benefits of race-based versus gene-based usage of the drug will be developed. The implications of our findings, and for the development of a more generalized approach to other pharmacogenomic tests, will be addressed. A possible finding of this research may be that genotyping strategies using race are more efficient than those that do not, but lead to serious ethical challenges.

#### **Example 2 - Financial Incentives and Personalized Medicine [idea first presented in seminar in Fall 2005 by Josh Carlson]**

Congress passed the Orphan Drug Act of 1983 to stimulate development of drugs for rare diseases. Recently, it has been suggested that this Act could be applied to encompass therapeutic interventions aimed at genetically identifiable patient subgroups and that this would serve as an appropriate means of encouraging the development of more individually targeted treatment regimes. However, others contend that the extension of the Act in this manner represents a diversion from the original intent of the Act, with potentially worrying implications for the short-to-medium term feasibility of personalized medicine. To evaluate this contention, this dissertation project will examine the historical basis for the creation of the Orphan Drug Act, critically analyzing both the ways in which claims for orphan disease status were advanced and justified, as well as the ensuing economic, clinical, and social consequences of pursuing drug development in such cases. Information will come from both published sources as well as key informant interviews with relevant stakeholders involved with the Act. This analytic frame will then be applied to pharmacogenomics, to ask whether and how specific cohorts (identified by genotyping

or related methodologies) are like or not like the original 'orphan disease' class. Lastly, the implications of the use of the Orphan Drug Act for a current test/drug combination either in development or in clinical use will be addressed. An orphan drug (non-PGx) which has recently been approved, and for which 'off-label' use has or may occur, will be evaluated. In contrast, the potential role of Herceptin as an orphan drug will be examined. The scientific and clinical evidence and rationale for categorization of each of these drugs will be critically evaluated based on a systematic literature review. On the basis of such a comparison, we will be in a better position to make informed predictions concerning the likely effect of such an extension on the current drug development landscape. The dissertation project will thoroughly evaluate the pharmacological research, including both basic and clinical research, that has led to the development of the new drug.

The dissertation project will thoroughly evaluate the pharmacological research, including both basic and clinical research, that has led to the development of the new drug. The area A focus would be evaluating the clinical indication, strength of association identifying responders, and implications for 'off-label' use, etc., in comparison to non-Pgx orphan drug.

### **Example 3: Public Demand and Clinical Reluctance: The Application of Pharmacogenetics in Neuroleptic Therapy**

It has become increasingly clear that mutations in genes that code for drug metabolism and transporter proteins can affect the systemic (blood) exposure of a patient to a standard therapeutic drug dose. Moreover, mutations in the genes coding the pharmacological or toxicological targets of the drug can affect the intrinsic responsiveness of the target protein to a given blood concentration of drug. Depending on the blood level of the target – pharmacological effect relationship, this can lead to individual differences in the likelihood that a patient will respond favorably to the drug therapy and avoid adverse side effects.

There are several therapeutic settings where it has been proposed that prospective pharmacogenetic testing could improve clinical outcomes, either by reducing the risk of toxic events and increasing the chance of optimal beneficial effects or by reducing the time and costs incurred in achieving optimal therapy in every patient. One applicable therapeutic setting involves genetic testing to support the use of certain neuroleptic agents (e.g., anti-depressants and anti-psychotics). There is a growing public perception that genetic testing could help identify patients who might be at greater risk for adverse side effects (including death) from these therapies. Numerous articles on personalized medicine found recently in the lay press will often contain examples of an individual who suffered some debilitation while receiving neuroleptic therapy. Although causality between the drug and the event is rarely if ever established, the public perception is that there was a genetic risk factor related to sensitivity to the drug. Typically the article will include statements that the individual had themselves tested by a commercial lab and the results indicated that they had some deficiency (often very vague about the predicted phenotype; i.e., heterozygote or homozygote PM). Despite the increasing number of anecdotal cases, the psychiatric community has not embraced pharmacogenetic testing

for guiding neuroleptic therapies. It is largely restricted to those tertiary care centers where the basic research was conducted. Much of this reluctance has been attributed to the lack of carefully-designed, prospective, randomized clinical trials to unequivocally demonstrate the value of genetic testing to improve some clinical endpoint; i.e., reduced frequency of adverse side effects.

The current situation with growing public awareness about personalized medicine and the availability of genetic tests through direct-to-consumer advertising offers an optimal time to investigate the interplay between public demand for an intervention and clinical reluctance to change an established paradigm. A potential thesis project could involve working with a public or commercial testing lab tracing the steps involved in providing a new test. Analysis of documents, interview with individuals involved in the start-up of the test. In addition, recruiting consumers who express interest in the test in order to understand: the motivations for seeking a test or avoiding a test; the information conveyed by the testing lab; the information received by the study subject; the accuracy of that information; and how test results subsequently affect health behavior. Choosing a neuroleptic is of particular interest because of the traditional stigma attached with mental health issues, matched by the dramatic increases DTC efforts of these drugs by pharmaceutical industry (especially television and magazines) and the rise in use of these drugs for a whole host of problems.

Potential implications include the question of whether calls for RCT trials of genetic testing for neuroleptic therapy will be facilitated by public pressure, by the clinical community, or through lobbying efforts within the pharmaceutical industry. . . . This type of new technology opens up a number of interesting questions about the state of science of neuroleptic therapy— (A):the basic science needed to assure accuracy of a test; (B): the special vulnerabilities of persons requiring neuroleptic therapy, the ethics of DTC advertising in the area of mental health, and how the potential financial gains to be made in this rapidly growing industry (meds for moods) affect scientific discovery and drug marketing.

#### **Example 4: Decision Making in Newborn Screening: Cystic Fibrosis as a Case Example (John Thompson)**

The overall focus of the dissertation is on decision making in newborn screening (NBS) programs, with cystic fibrosis (CF) as a case example.

CORE KNOWLEDGE AREA B (my "major" track) will have two parts. One is a discussion of how economic analyses are used in Washington State as a part of the decision making process (a requirement that is unique to Washington among state programs). The data that I will gather will come through key informant interviews with public health officials and medical experts from Washington and probably three other states relating to their process for making the decision about CF NBS. My hypothesis is that technological advancements, advocacy pressure and government recommendations each influence the decision to include a new test in the NBS panel.

CORE KNOWLEDGE AREA A (my "minor" track) will be a model I designed comparing different screening algorithms. The first method screens for elevated

immunoreactive trypsinogen (IRT) concentrations in the blood followed by a second IRT screen on a subsequent NBS specimen. An alternative method screens for elevated IRT concentrations in the blood followed by genotyping the original NBS specimen for the most prevalent CF mutations. The model uses reported data about the sensitivity, specificity and positive and negative predictive values from the different methodologies to make predictions for Washington state about screening rates (i.e. false and true positive results, false and true negative results, number of referrals for diagnostic testing, etc.). Pros and cons of direct DNA testing as a second-tier screening method will be discussed.