HALT-C Ancillary Study PROPOSAL

Part I

Proposal Name: Statistical methods for prospective evaluation of biomarkers

Proposal PI: Yingye Zheng, PhD, Fred Hutchison

HALT-C PI: Anna S. Lok, MD

Funding Agency and Review Body (e.g., NIDDK; my university/GAC): NIH/CBSS (cancer biomarker study section)

I agree to follow HALT-C Policies and Procedures when conducting this study. I acknowledge that the data obtained from this study will belong to the NIH and will be placed in the HALT-C database for use by other investigators. I understand that I cannot begin experiments using HALT-C specimens/data until I receive approval from the HALT-C Steering Committee and funding from the Scientific Review Body for my proposal. I also understand that the data analysis for this proposal will be performed by NERI (unless otherw approved by the HALT-C study) and that protocols approved by the HALT-C Steering Committee will be placed on the HALT-C Restricted Website.

__ Yingye Zheng _____ Proposal Principal Investigator	_9/20/2007_____ Date
_____ HALT-C Principal Investigator Date	_____ Date

Protocol Part II (4 page limit, single space)

1. AIMS/HYPOTHESES

The broard, long term goal of this research is to develop useful regression methodologies, graphical summaries and software tools for analyzing modern biomarker data and to provide recommendations for efficient design of marker validation studies.

The specific aims of this proposal are:

Aim 1: To develop statistical methods for evaluating the clinical utility of biomarkers evaluated in a prospective cohort study.
The proposed analysis has three major aspects: (1) quantify the time-dependent accuracy of biomarkers; (2) generalize the methods to a combination of several predictive factors in regression framework; and (3) evaluate the accuracy of the biomarker in the presence of other competing outcomes.

Aim 2: **To develop statistical methods for analyzing marker data using cohort sampling and to provide recommendation on optimal sampling strategies in different clinical settings.**
The proposed analysis has two major aspects: (1) develop estimating and inference procedures for calculating the accuracy summaries (time-dependent TPF, FPF, PPV and NPV) using cohort sampling designs such as case-cohort or nested case-control studies; and (2) evaluate the performance of different sampling strategies in biomarker studies to establish optimal study designs in a variety of clinical settings.

Aim 3: **To develop statistical methods for evaluating the predictive accuracy of prognostic markers using longitudinal data.**
The proposed analysis has two major aspects: (1) develop robust and flexible procedures to quantify and update the predictive accuracy of longitudinal markers; and (2) develop and evaluate a decision rule on the basis of risk, incorporating both cross-sectional and longitudinal marker information.

Significance

The public health impact of the proposed work rests on its successful application to actual data collected in clinical studies. In particular, the statistical methods being proposed will be applied to cancer biomarker research to demonstrate their utilities. The transfer of novel statistical methods to analysis of clinical research data is often limited by the availability of user friendly public software. Existing statistical programs and new algorithms developed in this proposal for the analysis of marker data will be made available to the scientific community.

2. BACKGROUND/RATIONALE

Fully characterizing the diagnostic or prognostic potential of both new and current biomarkers will have significant impact in many branches of medicine, including cancer screening and diagnosis, and intervention in chronic disease management. To translate putative markers into standard medical care, rigorous evaluation is required. An increasing number of prospective cohort studies had been used for this purpose recently. Until now there has been little guidance in statistical design and analysis of these studies.

In a prospective study, a marker is often used to make a prediction about the course of a disease. Such an evaluation naturally involves the additional dimension of time. The task can be challenging for

several reasons. First, the disease status of subjects can change over time: subjects initially under observation who are without disease can develop and ultimately succumb to the disease at some future times. Second, the event of interest may be censored due to loss to follow-up, termination of the study or other competing risk events. Third, the effect of biomarker may vary with time: a marker may be more effective at predicting an imminent event than an event that occurs in the distant future. As a consequence, the cross-sectional accuracy summaries commonly used in medical diagnostic research need to be amended to incorporate both the time-varying nature of the biomarker and the varying onset of clinical disease.

A number of cohort studies have been assembled by various research groups. These studies include clinical database and repositories of stored specimens that would allow additional biomarkers to be assayed later. However a full cohort study may not always be feasible, because the assessment of biomarkers can be expensive and labor intensive, or because the biomarker of interest is not sufficiently established for longitudinal evaluation. The development of cost-effective sampling strategies is highly desirable in these settings. Careful statistical analysis is required as cohort sampling can introduce bias if the ascertainment scheme is not properly accounted for. Questions remain as to what will be the optimal sampling strategy to both avoid bias and efficiently use the data collected.

Many clinical measures are obtained serially and used to form subsequent treatment decisions. Updating the risk of disease or death on the basis of current or past covariate measures may provide improved accuracy in guiding patient care. Development and validation of decision rules based on marker history as well as other cross-sectional clinical information will have huge impact on diagnostic and prognostic practice. Statistical tools for evaluating longitudinal markers are not well developed.

3. RELATIONS TO AIMS OF HALT-C STUDY

HALT-C is a prospective study with 1,050 hepatitis C patients followed for more than 4 years. Extensive longitudinal data have been collected to examine the progression of liver disease to cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). Serial blood samples are tested to evaluate the utility of clinical data, routine laboratory test results, histological and endoscopic features, and novel biomarkers in predicting cirrhosis, hepatic decompensation and HCC.

Several aspects of our proposal coincide with the goals of HALT-C. Our proposal may lead to the development of more appropriate or accurate statistical methods to analyze longitudinal data in an attempt to predict disease progression or outcomes. For example, we will evaluate how to quantify the clinical utility of novel cancer biomarkers accommodating the additional dimension of time, how to select a sample from the entire cohort to conduct an efficient study, how to analyze data from the sampled patients to avoid selection bias, can information available from subjects outside the selected sample be used to improve efficiency of the estimates? All of these questions are relevant to HALT-C.

4. STUDY DESIGN, EXPERIMENTAL GROUPS

Nested case-control studies or case-cohort studies of HCC biomarkers and other clinical or laboratory data that are evaluated as predictive factors for outcomes will be considered.

To address various aims of our proposal, we have also obtained data from the following studies:

1. Prostate cancer Pacific Northwest Prostate Cancer Research SPORE study

2. NCI Early Detection Research Network (EDRN) prostate cancer cohort at the San Abtonio Center of Biomakrers of Risk for Prostate Cancer (SABOR)
3. EDRN's Cervical Cancer Clinical Epidemiology and Validation Center (CC-CEVC)
4. EDRN Barrett's esophagus interSPORE study
5. Carvedilol or Metoprolol European Trial (COMET) in heart failure patients.

5. METHODS, DATA USAGE

We wish to use the HALT-C data set relating to HCC risk factors and biomarkers to illustrate our statistical methodology for quantifying the predictive accuracy of new and current biomarkers for HCC. Specifically, several summary measures of biomarker performance including sensitivity, specificity, positive predictive values and negative predictive values, the receiver operating characteristics curves and the positive predictive curves will be considered. These measures of performance will be examined at various time points during the follow-up period in order to understand whether the accuracies of the biomarkers change over time.

The dataset on HCC risk factor analysis will include:

Demographics: race/ethnicity, age, gender
Metabolic factors: BMI, DM
Viral factors: genotype, baseline HCV RNA level
ETOH: lifetime drinking, years of drinking, age when habitual drinking stopped
Smoking: Pack-years
Duration of HCV infection
Baseline labs: CBC, LFT, total AFP, AFP-L3, DCP, CTP, MELD
Liver histology (baseline and M24): inflammation score, fibrosis score, steatosis score, iron grade
Evidence of portal hypertension (W24 or R00): splenomegaly by US, varices on EGD
Other risk factors: hormone use, physical activity
Treatment assignment – ITT and per protocol
Time to HCC diagnosis and tumor stage at diagnosis
Time to other competing risk events such as liver transplant and death

The dataset on HCC biomarkers will include:

Serial values of the following HCC biomarkers:
Total AFP at local lab and at WAKO (q 3 mos)
AFP-L3 at WAKO (q 3 mos)
DCP at WAKO (q 3 mos)
DCP at U Mich lab at baseline and yearly intervals on all patients, and q 3 mos on all HCC cases and matched controls

Data provided in an ASCII format or excel table or SAS data format will suffice.

6. ANTICIPATED RESULTS

We expect to have several estimates for covariate adjusted time-dependent ROC and PPV curves. These estimates will be broadly applicable to a wide range of clinical settings including (i) the effect of marker variation with time; (ii) use of multiple markers for prediction with or without an

independent validation dataset; (iii) outcome of interests being studied in the presence of competing risk events; and (iv) longitudinal measurements of biomarkers over time. We also expect that we will be able to provide comprehensive tools for estimating time-dependent accuracy summaries for use in practice under a wide variety of cohort sampling schemes. The proposed methods will be illustrated using HALT-C data and data from other cancer biomarker studies. The results will be published in statistical journals, journals on cancer biomarkers, and hepatology journals. The software developed will be distributed freely to the scientific community.

Papers arising from HALT-C data will be published jointly with HALT-C investigators, after approval by the HALT-C steering committee.

7. STATISTICAL SUPPORT

The analysis of HALT-C data provided will be performed by the principal investigator of the proposal Dr. Yingye Zheng and a statistical research associate with a master degree in biostatistics.

Statistical support from NERI will not be necessary. However, Dr. Zheng will seek comments and feedback from biostatisticians at NERI prior to publication of data from HALT-C.

8. HALT-C SAMPLES TO BE USED IN THE STUDY

Only datasets as specified in section 5 are requested, no HALT-C samples will be required.

9. FINANCIAL ISSUES

Costs incurred by NERI for creating additional datasets and for consulting service provided by HALT-C investigato, Dr. Anna Lok have been included in our grant application. [Kristin, does NERI need a budget for this?]

Protocol Part III: Sample Requirements

None

Visit	Liver # patients, mm*	Blood # patients, ml	Other (describe) # pts, amount
Screen 1			
Screen 2			
Baseline			
Lead in Week 4			
Week 8			
Week 12			
W16			

Week 20			
Week 24			
Randomized Month 9			
Month 12			
Month 15			
Month 18			
Month 21			
Month 24			
Month 27			
Month 30			
Month 33			
Month 36			
Month 39			
Month 42			
Month 45			
Month 48			
Post-treatment			