

**Integrating Biomarkers in Population-based Research**  
**Summer Course offered at**  
**The University of North Carolina at Chapel Hill**  
**June 2-6, 2008**  
**Room 1305 McGavran-Greenberg Hall**

**FACULTY**

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**COURSE GOAL**

The course will introduce students interested in population research to the collection and analysis of biospecimens and their incorporation into epidemiologic, biomedical, and social science frameworks. Topics include concepts of study design and interdisciplinary research, sample collection, processing, and storage, working with laboratories, quality assurance and quality control, specimen management, ethical issues, assessing costs, and assembling an interdisciplinary team. The course will provide a general introduction and discussion of topics with examples drawn from case studies.

**READINGS**

Links to all readings are provided through a secure website available to students in the course. Mary Jane Hill, course assistant ([hill@unc.edu](mailto:hill@unc.edu)) will assist with access.

Students are encouraged to read a limited number of articles (provided through the website) prior to coming to the course.

General readings will be provided via the website. These materials provide a broad overview of biomarkers and population research.

References, including websites will also be provided via the website. There is no requirement that these all be read (some are quite lengthy). They are provided as references for future research work done by students for their own research incorporating biomarkers.

**LAPTOPS**

There will be class exercises that will benefit from each student having a laptop. Laptops can be configured on the first day to have wireless access, although this will not be required.

**COURSE OVERVIEW**

Page 3 provides an overview of the class. Information about individual sessions are provided below.

## **BROAD COURSE OBJECTIVES**

### **Hypothesis Objective**

Student should be able to:

- (1) enumerate the advantages and disadvantages of choosing various biomarkers for specific hypotheses
- (2) list specific challenges in collecting biomarkers
- (3) illustrate investigator decisions that go into the decision about study design when biomarkers are involved

### **Ethical Objective**

Student should be able to:

- (1) recognize ethical concerns that arise from the collection of biomarkers that are different from other forms of data.
- (2) write sections of a consent form involving collection of biomarkers

### **Barriers Objective**

Student should be able to:

- (1) evaluate the costs and benefits for decisions about inclusion of common biomarkers

### **Study Design Objectives: Population-based designs and clinic-based study designs**

Student should be able to:

- (1) describe the unique components of a population-based design and a clinic-based design
- (2) describe the strengths and weaknesses of each design
- (3) differentiate the sampling strategies and their role in feasibility, cost, quality of measures, inference, and generalizability from these designs

### **Integrating Objective**

Student should be able to:

- (1) give examples of biomarkers appropriate for a specific study
- (2) articulate the benefits and challenges associated with these choices

### **Specimen Management Objectives**

Student should be able to:

- (1) identify key elements required for developing detailed protocols for specimen collection and management
- (2) operationalize field activities for a specific biomarker.

### **Selecting a Lab Objectives**

Student should be able to:

- (1) enumerate important elements of choosing a lab and the collaboration requirements.

### **Quality Assurance/Quality Control Objective**

Student should be able to:

- (1) review and assess a QA/QC plan provided by a lab

### **Advanced Lab Techniques & Emerging Approaches Objective**

Student should be able to:

- (1) enumerate new biomarker techniques that are available or underway
- (2) identify the strengths and weaknesses of using these techniques in a population-based study vs. a controlled environment

**Biomarker summer course schedule, June 2-6, 2008, 1304 & 1305 McGavran-Greenberg Hall**

	<b>Monday, 6/2/08</b>	<b>Tuesday, 6/3/08</b>	<b>Wednesday, 6/4/08</b>	<b>Thursday, 6/5/08</b>	<b>Friday, 6/6/08</b>
<b>9:00-10:15 Concepts</b>	Introduction --course logistics & reference materials --big-picture models --general concepts --biomarker examples --intro to course sessions (Olshan)  <i>[wireless setup]</i>	Population-based vs. clinic-based designs (Barbara Entwisle)	Selection of biomarkers to address hypotheses -- broad scope -- examples of biomarkers -- intro to DNA (Olshan)	Biomarker collection in international settings (Steve Meshnick)	Advanced lab techniques & emerging approaches (David DeMarini)
<b>10:30-12:00 Specifics &amp; exercises</b>	Overview of studies with biomarkers: --Add Health --National Children's Study (Dole)  <i>{wireless setup}</i>	Specimen management & selecting a lab (Dole & Olshan)	QA/QC working with a lab (Jeannette Bensen)	Human subjects --exercise of opt-in or opt-out of genetic components --local institution IRB forms or UNC's biospecimen consent form (Dole, Olshan)	Politics of using biomarkers -- advisory boards to review use of banked specimens How to build a collaborative team (Kathie Harris, John Thorp, Olshan, Dole)  <i>[course evaluation]</i>
<b>1:30-5:00 Applied</b>	Add Health & NCS biomarker review and collection specifics with collection kit --exercise reviewing draft and final saliva collection protocols --kit to collect saliva that night and next morning (Dole, Carmen Cuthbertson)	SPLIT CLASS BETWEEN THE FOLLOWING 2 SESSIONS: DNA collection --intro to collecting & processing DNA --Biospecimen Processing facility lab visit (Tricia Basta, Olshan) ----- Review saliva collection experience Tracking systems --bar codes --organizing specimens from tubes to freezers Visit CPC freezer room (blood spot processing) (1:30-2:00 Carolyn Halpern; Jodie Lee, Janne Groner, Dole)		Estimating costs of collecting biomarkers -- exercise of selecting biomarkers to collect and developing a draft budget and justification (students work on their own laptop) (Dole)	

## **JUNE 2**

### **Concepts Session [9:00-10:15]**

#### **Introduction to the Course**

Presenters: Dr. Andy Olshan, Dr. Nancy Dole, Ms. Mary Jane Hill

**SESSION** content includes

- course logistics and references
- review how the course website working group is organized
- general concepts and integration across disciplines
- biomarker examples
- introduction to course sessions

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### **Specifics & Exercises Session [10:30-12:00]**

#### **Overview of Case Studies Collecting Biomarkers**

Presenters: Dr. Nancy Dole

Introduction to two case studies of population-based research that includes collection of biomarkers – the National Longitudinal Study of Adolescent Health (Add Health) and the National Children’s Study (NCS).

Add Health website: <http://www.cpc.unc.edu/addhealth>

National Children’s Study (NCS) national website: <http://www.nationalchildrensstudy.gov/>

North Carolina Study Center for the NCS website: <http://www.cpc.unc.edu/ncs>

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### **Applied Session [1:30-5:00]**

#### **Add Health and National Children’s Study – Specifics about Collecting Biomarkers**

Presenters: Dr. Nancy Dole, Ms. Carmen Cuthbertson

**SESSION** content includes

- review of the specific biomarkers and what they will measure in each study
  - plans for archiving specimens for future use
  - example of the field supplies used for Add Health
  - exercise reviewing a draft and final saliva collection kit used in a pregnancy cohort study
  - exercise collecting saliva
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## **JUNE 3**

### **Concepts Session [9:00-10:15]**

#### **Broad Concepts in Study Design: Population-based designs and clinic-based study designs**

Presenters: Dr. Barbara Entwisle

Featured case study: National Children's Study

**SESSION** content includes

- distinction between source of the population and the population at risk
  - how numerators and denominators of the candidate and actual study population are determined
  - how specific aims involving biomarkers are formulated to match the study's hypotheses
  - descriptions from interdisciplinary research that has integrated biomarkers
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### **Specifics & Exercises Session [10:30-12:00]**

#### **Specimen Management & Selecting a Lab**

Presenters: Dr. Nancy Dole, Dr. Andy Olshan

**SESSION** content includes

- collection protocols and supplies
  - processing the specimens
  - explain storage and shipping requirements and options (aliquots, thaw/refreeze cycles, returned samples)
  - automated tracking systems
  - freezer maintenance, alarms, call lists
  - integration of staff; importance of multiple staff involved
  
  - research labs vs. commercial labs
  - challenges of speaking a different language
  - getting written protocols from the lab
  - identifying lab collaborators
  - environmental health & shipping safety
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### **Applied Session [1:30-5:00]**

*CLASS WILL BE SPLIT INTO TWO GROUPS – SESSIONS WILL BE REPEATED ON JUNE 4*

#### **Group 1: DNA collection**

Presenters: Dr. Tricia Basta, Dr. Andy Olshan

**SESSION** content includes

- Biospecimen Processing (BSP) facility lab visit
- intro to collecting & processing DNA
- collect a mouth rinse for DNA assessment
- see a lab in action running the specimens
- lab person walks through steps from collection to assay and storage

**Group 2: Tracking Systems, Blood Spot Processing, & Freezer Room Organization**

Presenters: Dr. Nancy Dole, Dr. Carolyn Halpern, Ms. Jodi Lee, Ms. Janne Groner

**SESSION** content includes

- review saliva collection experience, pilot experiences from the Add Health Study
- discuss tracking systems
  - bar codes
  - organizing specimens from tubes to freezers
- visit CPC freezer room
- observe processing of Add Health blood spots coming in from the field

## **JUNE 4**

### **Concepts Session [9:00-10:15]**

#### **Selection of Biomarkers to Address Study Hypotheses**

Presenter: Dr. Andy Olshan

**SESSION** content includes

- broad scope
  - examples of biomarkers
  - what specimens to collect to address specific hypotheses
  - what should be measured, why, and when?
  - can it be collected in the population of interest?
  - is a goal of the study to bank specimens? if so, why?
  - integration of scientific goals and lab capabilities early in the research project process
  - examples of studies that have incorporated biomarkers and why
  - introduction to DNA
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### **Specifics & Exercises Session [10:30-12:00]**

#### **Quality Assurance/Quality Control (QA/QC)**

Presenter: Dr. Jeannette Bensen

**SESSION** content includes

- making sure QA/QC measures are in place in the lab processing specimens and/or doing assays
- how to identify and deal with lab errors
- repeat assessments across batches and/or across labs
- what data does the lab report to the study?
- what's important in different disciplines (laboratory, epidemiology, social science)

#### **REFERENCE**

EPA website on QA/QC: <http://www.epa.gov/quality/qatools.html>

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### **Applied Session [1:30-5:00]**

REPEAT OF JUNE 3 APPLIED SESSION

#### **Group 1: Tracking Systems, Blood Spot Processing, & Freezer Room Organization**

Presenters: Dr. Nancy Dole, Dr. Carolyn Halpern, Ms. Jodi Lee, Ms. Janne Groner

#### **Group 2: DNA collection**

Presenters: Dr. Tricia Basta, Dr. Andy Olshan

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## **JUNE 5**

### **Concepts Session [9:00-10:15]**

#### **Biomarker Collection in International Settings**

Presenters: Dr. Steve Meshnick

**SESSION** content includes

- political & legal issues
  - limited in-country resources – staffing, supplies
  - ethical issues
  - special requirements for collection and shipping
  - special barriers
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### **Specifics & Exercises Session [10:30-12:00]**

#### **Human Subjects Issues**

Presenters: Dr. Nancy Dole, Dr. Andy Olshan

**SESSION** content includes

- description of what is being collected for consent
- what results should be reported to study participants or the community
- provision of treatment or counseling
- long-term storage and use as consent protocols change
- establishing policies to make biomarkers available to other researchers (storage, consent, sharing)
- specific discussion of confidentiality
- changing respondent behavior or health status (especially if results are reported and design is longitudinal — not unique to biomarkers)

Exercises include:

- opt-in or opt-out of genetic components
- completing their own IRB requirements or UNC's biospecimen consent form

Exercise requires laptop needed.

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### **Applied Session [1:30-5:00]**

#### **Estimating Costs of Collecting Biomarkers**

Presenter: Dr. Nancy Dole

**SESSION** content includes

- cost to collect, process, store, assay
- logistics (cold chain, adequately trained staff for all components in desired setting)

Exercise of students selecting biomarkers they want to collect and developing a draft budget and justification (students need their own laptop for this exercise)

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## **JUNE 6**

### **Concepts Session [9:00-10:15]**

#### **Advanced Lab Techniques & Emerging Approaches**

Presenter: David DeMarini

**SESSION** content includes

- what is coming and caveats
  - assessment, e.g., proteomics, metabolomics
  - emerging genomic studies
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### **Specifics & Exercises Session [10:30-11:30]**

#### **Politics and Logistics of Incorporating Biomarkers into Population Research – panel discussion**

Presenters: Dr. Kathie Harris, Dr. John Thorp, Dr. Andy Olshan, Dr. Nancy Dole)

**SESSION** content includes

- advisory boards to review use of banked specimens
  - how to build a collaborative team
  - banking “local” samples in a multi-site study
  - respondent burden and effect on response rate
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### **Course Evaluation [11:30-12:00]**

Presenter: Dr. Nancy Dole

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**Course ends at Noon**

## GENERAL READINGS & REFERENCES

The following are readings and references that may be of use in your future work with biomarkers:

- Banalata S, Mahadevan B, DeMarini DM. 2007. [Transcriptional responses to complex mixtures—A review](#). Mutation Research 636(1-3): 144-77.
- Bergen AW, Haque KA, Qi Y, Beerman MB, Garcia-Closas M, Rothman N, Chanock SJ. 2005. [Comparison of yield and genotyping performance of multiple displacement amplification and OmniPlex™ whole genome amplified DNA generated from multiple DNA sources](#). Human Mutation 26: 262–70.
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- Claudino WM, Quattrone A, Biganzoli L, Pestrin M, Bertini I, Di Leo A. 2007. [Metabolomics: Available results, current research projects in breast cancer, and future applications](#). Journal of Clinical Oncology 25(19): 2840-6.
- Eiseman E, Bloom G, Brower J, Clancy N, Olmsted SS. 2003. [Case studies of existing human tissue repositories: “Best Practices” for a biospecimen resource for the genomic and proteomic era](#). Santa Monica: RAND Corporation. 243 p.
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- Goodman GE, Thornquist MD, Edelstein C, Omenn GS. 2006. [Biorepositories: let's not lose what we have so carefully gathered!](#) Cancer Epidemiology, Biomarkers & Prevention. 15(4): 599-601.
- Harville EW, Savitz DA, Dole N, Herring AH, Thorp JM, Light KC. Patterns of salivary cortisol secretion in pregnancy and implications for assessment protocols. Biol Psychol. 2007 Jan;74(1):85-91. Epub 2006 Sep 18.
- Hede K. 2006. [New biorepository guidelines raise concerns](#). Journal of the National Cancer Institute. 98(14): 952-4.

- Hobcraft J. 2006. [The ABC of demographic behaviour: How the interplays of alleles, brains, and contexts over the life course should shape research aimed at understanding population processes](#). Population Studies 60:153–87.
- Holland NT, Smith MT, Eskenazi B, Bastaki M. 2003. [Biological sample collection and processing for molecular epidemiological studies](#). Mutation Research 543: 217–34.
- Holland NT, Pflieger L, Berger E, Ho A, Bastaki M. 2005. [Molecular epidemiology biomarkers – sample collection and processing considerations](#). Toxicology and Applied Pharmacology 06: 261–8.
- International Society for Biological and Environmental Repositories (ISBER). 2005. [Best Practices for repositories I: collection, storage, and retrieval of human biological materials for research](#). Cell Preservation Technology 3: 5–48.
- Knudsen EI, Heckman JJ, Cameron JL, Shonkoff JP. 2006. [Economic, neurobiological, and behavior perspectives on building America's future workforce](#). PNAS: Proceedings of the National Academy of Sciences of the United States of America. 103(27):10155-62.
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- National Health and Nutrition Examination Survey (NHANES). [Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey \(NHANES III, 1988-94\)](#). 1996. Hyattsville, MD: NCHS. 754 p.
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- Weisberg HF. 2005. [The total survey error approach](#). Chicago: University of Chicago Press. p 5–28, 225–57. (Chapters 1, 2 and 10)
- Wilcox AJ. 1995. [Molecular epidemiology: Collision of two cultures](#). *Epidemiology* 6: 561–2.

#### **RELATED MATERIALS AND WEBSITES**

##### [BioSpecimen Processing \(BSP\) Facility](#)

The UNC BSP Facility provides laboratory support for investigator-initiated large-scale clinical, epidemiologic, and other studies and functions as a human biospecimen repository. It also serves as a resource for clinicians who wish to store and study samples from unusual or potentially important patients.

##### [CPC Biomedical website](#)

The Biomedical Services core aids Carolina Population Center projects in incorporating biomedical specimen collection and assays into their research.

##### [Manual of Pathology and Laboratory Medicine Clinical Services](#)

A guide to the use of the Clinical Laboratory and Anatomic Pathology Services available at the University of North Carolina Hospitals. Includes the [McLendon Clinical Laboratories Safety Manual](#).

[International Society for Biological and Environmental Repositories](#) (ISBER) provides information on logistics and storage of specimens

National Cancer Institute [Office of Biorepositories and Biospecimen Research](#)

UNC-CH's Office of Environment, Health, and Safety has information on safely handling biological specimens, and requirements for shipping biological specimens:

[Laboratory Safety Manual](#)

[Biological Safety Manual](#)

Saf-T-Pak is one of several companies that sell packaging materials for shipping biological samples. Under "Links" their website provides links to many of the regulatory requirements for such shipments. (<http://www.saftpak.com/>)

### **Ethics and Human Subject Links**

Office of Human Research Ethics (OHRE), UNC-CH

[A Guide to the IRB Process](#)

The Institutional Review Board (IRB) is a committee established to review and approve research involving human subjects. The primary purpose of the IRB is to protect the rights and welfare of the human subjects.

IRB Guidance for [Student Research and Class Projects](#)

The National Institutes of Health [Bioethics Resources on the Web](#) provides a number of annotated web links