

INSTRUCTOR: Stephanie M. Engel, PhD

Department of Epidemiology

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Office Hours by Appointment

Mailbox located in 2102, 2nd floor of McGavran-Greenberg in the Epidemiology wing.

TIME & PLACE: Fridays 11:15-1:10 McGG 2305

OBJECTIVE: Biomarkers are increasingly used in population-based research, with varying success. On the plus side, they tend to be quantitative and relatively objective measures of an important exposure, covariate, or intermediate marker of disease. However, their pitfalls are often poorly appreciated, and frequently ignored. This course surveys the major issues relevant to the application of biomarkers in epidemiological research, including the logistical hurdles in biospecimen collection and storage, a critical assessment of biomarker quality, the interpretation of quantitative estimates, and the resultant analytic issues that often arise in statistical analyses.

After taking this course, students should understand the important issues to consider in planning a molecular epidemiological study, and be able to critically assess the literature linking biomarkers to health endpoints.

CLASS EXPECTATIONS: This will be an interactive course, drawing from the literature, local expertise, and hands-on manipulation of data to develop an appreciation for the challenges of using biomarkers in population-based research. Active classroom participation will weigh heavily into the final course grade (10%). The class is ideally suited to students considering using biomarker data in their graduate research work, or who have an interest in developing ideas for future research involving biomarkers. Familiarity with basic data management techniques of creating new variables and visualizing distributions is recommended. Datasets will be provided in SAS.

Grading: In consideration of students who meet the assigned deadlines, 10% will be deducted for each day late except in extraordinary circumstances to be determined by instructor. No late assignments will be accepted after 5 days.

Readings: Assigned articles published in professional journals will be available through Medline. Readings from textbooks will be provided on Sakai. **Bolded readings should be completed in preparation for the lecture.** Other listed readings may be completed after lecture, or if listed as "optional"

For the following 2 assignments, you are asked to form groups of 3-4 students to work jointly on the project. If you are unable to find a group, please see Dr. Engel.

Group Assignment #1: Imagine that you are conducting a community-based study on exposures among migrant farm workers. Develop a collection, aliquoting and storage protocol for urine. 2-3 page maximum. **Due 5pm Feb 20th by email to Stephanie.Engel@unc.edu.** 20% of grade

Group Assignment #2: Imagine that you are conducting a hospital-based study on multiple prenatal factors related to preterm delivery. 2-3 page maximum. Develop a collection, aliquoting and storage protocol for maternal prenatal peripheral blood. **Due 5pm March 27th by email to Stephanie.Engel@unc.edu. 20% of grade**

Individual Project: Students will have three options for their individual project. A 1 paragraph abstract should be submitted to Dr. Engel for approval by 5pm on Feb 6th describing the student's intentions. Students are encouraged to select a project that is relevant to their future dissertation/thesis research. Semi-final projects will be presented to the class. Final projects are due to Dr. Engel by 5pm on April 27th. **50% of the course grade**

Option 1: Write a review paper on a chosen biomarker. The choice of the biomarker is up to the student, but it should be something that is measurable in urine, blood, tissue, DNA, saliva, or other biological matrix (e.g. meconium, feces). The focus of the review should be on collection, measurement, storage, reliability and validity issues of a chosen biomarker. Alternatively, students may focus on a specific methodological issue common to multiple biomarkers, e.g. handling limits of detection in analysis or issues related to matrix dilution. **The focus of the review SHOULD NOT be on the relation of that biomarker to any given disease.** An example might be a critical review of cortisol measures and how they related to questionnaire-based assessments of stress—such a paper might discuss diurnal variability in cortisol, reliability of biomarker over a period of time, comparisons of blood and saliva measures, or the like. Papers should focus on the molecular epidemiological features of the biomarker, how stable it is in any given matrix, identifying any gaps in our understanding of the suitability of measuring the biomarker in stored specimens. Relevant literature should be cited. *Formatting: Arial 10, 1 inch margins, double spaced, 6 page limit not including references or Tables.*

Option 2: Conduct a data analysis of the reliability and/or validity of any biomarker. **The focus of the analysis SHOULD NOT be on the relation of that biomarker to disease.** Few students may have access to acceptable data for this option, so be sure to check with Dr. Engel before proceeding. Allowable projects include analyses of biomarker stability and reliability over time, comparison of a biomarker level to a Gold Standard assessment of the exposure in question (e.g. cortisol to self-reported stress), investigation of different approaches to accounting for matrix dilution or variability in limits of detection, or an investigation of storage or collection issues on biomarker stability. *Formatting: Arial 10, 1 inch margins, double spaced, 6 page limit not including references or Tables.*

Option 3: Report on one of the following ethical issues: Enrolling vulnerable populations into biomarker research; reporting results of biomarker studies back to populations; or dealing with the impact of potentially stigmatizing biomarker levels on research participants. Reports should include a description of the ethical problem and statement of impact, a case study of its relevance (ideally drawing from the published scientific literature or popular press), and recommendations for addressing this concern in future studies. *Formatting: Arial 10, 1 inch margins, double spaced, 6 page limit not including references or Tables.*

Course Schedule

Date	Topic	Lecturer	Readings
Jan 9	Introduction to Biomarker Studies	Stephanie Engel, PhD Associate Professor of Epidemiology Stephanie.Engel@unc.edu	Gallo V et al., PLOS Medicine, 2011 PMID 22029945 (Focus on Boxes 1-5) Chapter 9, pages 285-297. "Principles of exposure measurement in epidemiology" Second Edition. White, Armstrong & Saracci
Jan 16	Logistical & Ethical Issues in Fielding a Biomarker Study	Stephanie Engel, PhD Associate Professor of Epidemiology Stephanie.Engel@unc.edu	Nina T. Holland, Martyn T. Smith, Brenda Eskenazi, Maria Bastaki. "Biological sample collection and processing for molecular epidemiological studies." 2003. Mutation Research 543:217-234. http://biospecimens.cancer.gov/bestpractices/elp/ (start with Page 30) http://cebp.aacrjournals.org/content/16/12/2521.full
Jan 23	Maintaining a Biosample Repository	Patricia Basta, PhD Director, UNC BioSpecimen Processing Facility UNC School of Public Health Patricia_Basta@unc.edu	Peakman T, Elliott P. Current standards for the storage of human samples in biobanks. Genome Med. 2010 Oct 5;2(10):72. PMID: 20923579 <i>Optional:</i> Hallmans G, Vaught JB. Best practices for establishing a biobank. Methods Mol Biol. 2011;675:241-60. PMID: 20949394
Jan 30	Effects of storage and transport conditions on biomarker stability	Stephanie Engel, PhD Associate Professor of Epidemiology Stephanie.Engel@unc.edu	Dvinge H, Ries RE, Ilagan JO, Stirewalt DL, Meshinchi S, Bradley RK. Sample processing obscures cancer-specific alterations in leukemic transcriptomes. Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):16802-7. PMID: 25385641. Peplies J et al. "Influence of sample collection and preanalytic sample processing on the analyses of biological markers in the European multicenter study IDEFICS" Int J Obes 2011. PMID 21483409 Peakman TC, Elliott P. The UK Biobank sample handling and storage validation studies. Int J Epidemiol. 2008 Apr;37 Suppl 1:i2-6. PMID: 18381389 PLEASE BRING LAPTOP TO CLASS & DOWNLOAD DATASET FROM SAKAI PRIOR TO CLASS
Feb 6 Abstract due by 5PM	Quality assurance and quality control in biomarker studies (Validity and Reliability)	Stephanie Engel, PhD Associate Professor of Epidemiology Stephanie.Engel@unc.edu	Hofmann JN, Yu K, Bagni RK, Lan Q, Rothman N, Purdue MP. Intra-individual variability over time in serum cytokine levels among participants in the prostate, lung, colorectal, and ovarian cancer screening Trial. Cytokine. 2011;56(2):145-8. PMID: 21764327 TwoRoger SS, Spentzos D, Grall FT, Liebermann TA, Hankinson SE. Reproducibility of proteomic profiles over 3 years in postmenopausal women not taking postmenopausal hormones. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1480-5. PMID: 18559564.

Feb 13	Urinary biomarkers: collection & analysis	Stephanie Engel, PhD Associate Professor of Epidemiology Stephanie.Engel@unc.edu	Best practices for Urine Sample Storage and Processing (see sakai) Waikar SS, Sabbisetti VS, Bonventre JV. Normalization of urinary biomarkers to creatinine during changes in glomerular filtration rate. <i>Kidney Int.</i> 2010 Sep;78(5):486-94. Epub 2010 Jun 16. PubMed PMID:20555318 Pearson MA, Lu C, Schmotzer BJ, Waller LA, Riederer AM. Evaluation of physiological measures for correcting variation in urinary output: Implications for assessing environmental chemical exposure in children. <i>J Expo Sci Environ Epidemiol.</i> 2009 Mar;19(3):336-42. PMID: 18841168.
Feb 20 <i>*Assignment 1 DUE</i>	Example of biospecimen collection in large population-based cohort study GULF	Lawrence Engel, PhD Associate Professor of Epidemiology Larry.Engel@unc.edu	Goldstein BD, Osofsky HJ, Lichtveld MY. "The Gulf oil spill". NEJM 2011; 364(14):1334-48. PMID 21470011 Savitz DA, Engel LS. "Lessons for study of the health effects of oil spills." Ann Intern Med 2010; 153(8):540-1.
Feb 27	SNOW DAY		
March 6	Tissue biomarkers: collection & analysis	Melissa Troester, PhD Associate Professor of Epidemiology Troester@unc.edu	Sherman ME, Howatt W, Blows FM et al. "Molecular Pathology in Epidemiologic Studies: A Primer on Key Considerations". CEBP 2010; 19:966-972 Ogino S, Beck AH, King EE et al. "Ogino et al. Respond to "The 21 st Century Epidemiologist". <i>AJE</i> August 30, 2012 PMID 22935516 Kuller LH, "Invited Commentary: The 21 st Century Epidemiologist—A need for different training?" <i>AJE</i> Aug 30 2012 PMID 22935514 Ogino S, King EE, Beck AH, Sherman ME et al. "interdisciplinary Education to Integrate Pathology and Epidemiology: Towards Molecular and Population-Level Health Sciences." <i>Aug 30 2012, PMID 22935517</i>
March 13	SPRING BREAK		
March 20	Blood biomarkers: collection & analysis	Stephanie Engel, PhD Associate Professor of Epidemiology Stephanie.Engel@unc.edu	Vaught JB. Blood collection, shipment, processing, and storage. <i>Cancer Epidemiol Biomarkers Prev.</i> 2006 Sep;15(9):1582-4. PMID: 16985016. Elliott P, Peakman TC; UK Biobank. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. <i>Int J Epidemiol.</i> 2008 Apr;37(2):234-44. PMID: 18381398. Schisterman EF, Whitcomb BW, Louis GM, Louis TA. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environ Health Perspect. 2005 Jul;113(7):853-7. PMID: 16002372

<p>March 27 Assignment 2 due</p>	<p>Limits of Blank, Detection and Quantification in biomarker studies.</p> <p>Demonstrating the impact of LOD values on analyses.</p>	<p>Jessie Buckley, PhD Postdoctoral Fellow Department of Epidemiology</p>	<p>Lubin JH, Colt JS, Camann D, Davis S, Cerhan JR, Severson RK, Bernstein L, Hartge P. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ Health Perspect. 2004 Dec;112 (17):1691-6. PMID: 15579415.</p>
<p>April 3</p>	<p>HOLIDAY</p>		
<p>April 10</p>	<p>Special Topics: The Microbiome</p>	<p>Andrea Azcarate-Peril Director, Microbiome Core Facility</p>	<p>Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012 Jun 13;486(7402):207-14. PMID: 22699609</p>
<p>April 17</p>	<p><i>STUDENT PRESENTATIONS</i></p>	<p>Class</p>	<p><i>Each student will have 10 minutes to present a summary of their individual project. The format of the presentation is up to the student. The class will have the opportunity to ask questions, or provide feedback to the student. Individual projects should be revised to reflect class feedback.</i></p>
<p>April 24</p>	<p><i>STUDENT PRESENTATIONS</i></p>	<p>Class</p>	<p><i>Each student will have 10 minutes to present a summary of their individual project. The format of the presentation is up to the student. The class will have the opportunity to ask questions, or provide feedback to the student. Individual projects should be revised to reflect class feedback.</i></p>