

Graduate School of Public Health
Educational Policies and Curriculum Committee
Agenda for March 2, 2017

1:30-3:30pm
4128 Parran Hall

A. New Business:

1. Course Modification Re-Visit EPIDEM 2610 *Molecular epidemiology – tools and techniques*, Jennifer Adibi (at 1:30pm)
2. HUGEN bulk course description updates, John Shaffer
3. Updates from the Associate Dean for Education, Robin Leaf for Eleanor Feingold/ Jessie Burke
4. Approval of February Meeting Minutes, All
5. Follow-up from February Council Meeting, Patricia Documet and Robin Leaf
6. Update on EPCC Web Form, Robin Leaf
7. Scheduling Summer Meetings, All
8. Course Modification HPM 2055 *Health Systems Engineering Seminar*, Wes Rohrer and Barry Ross (at 2:15pm)

Next meeting: April 6, 1:30-3:30pm, 4128 Parran Hall

Course Meeting Day(s) and Time(s) **TBD**

Class Locations

Lectures: TBD

Lab-based classes: Crabtree A720 and Parran Annex 3001

Computer lab classes: TBD

Credit Hours **3**

Term/Academic Year **Fall 2017**

Principal Instructor: Dr. Jennifer J. Adibi MPH, ScD

Department of Epidemiology

Office Location: Parran Hall 5132, 130 Desoto Street, Pittsburgh, PA 15261

Tel. 412-624-1913, adibij@pitt.edu

Office Hours: By appointment

Co-Instructor: Dr. Allison L. Kuipers, PhD

Department of Epidemiology

Office Location: Crabtree Hall A543, 130 DeSoto Street, Pittsburgh PA 15261

Tel. 412-624-2781, kuipers@pitt.edu

Office Hours: By appointment

Laboratory Assistant: Yaqi Zhao, Parran Annex 3001, 130 Desoto Street, Pittsburgh, PA 15261, Tel. 412-383-7083, yaz64@pitt.edu

Office Hours: TBD

Course Description

There is a steady stream of new methods and technologies entering the biomedical sciences that can be used to generate high-quality, quantitative data on the molecular and biochemical aspects of health and disease. There is tremendous value in applying these methods in epidemiologic studies to interrogate the molecular underpinnings of associations within populations, generate hypotheses on the mechanisms involved, to monitor the effects of interventions and to increase confidence in causal inferences. This course will be an opportunity for students to be exposed to methods for measuring the biologic processes that are relevant to DNA variation in populations, and to exposure effects that impact RNA and protein (and other molecule) expression. This course will go beyond the standard level of awareness of how to receive and analyze data from a laboratory. We will engage students in rigorous thought on how to pose questions on the underlying biology, conduct biomarker selection, design assays, and analyze and interpret data. We will spend ~50% of the time exposing students to hands-on experimentation at the laboratory bench. While, we will discuss 'omics' and high-dimensional methods in lectures, the hands-on work will be limited to single molecule analyses.

Course Prerequisites

Prerequisites include Molecular Epidemiology (EPID 2600), Epidemiology Methods I (EPID 2180), and Introduction to SAS (EPID 2185), or instructor permission.

Learning Objectives

1) to conceive of DNA, RNA and protein biomarkers as methods used in epidemiologic research;

2) to carry out DNA, RNA, and protein measurements using single molecule assays: genotyping, quantitative and non-quantitative polymerase chain reaction, western blotting, immunostaining, ELISA, EpiTect Methyl II DNA Restriction.

3) to make use of the knowledge gained to design a biomarker protocol that incorporates methods for sample handling and storage, setting up an assay, matrix extraction, pipetting, inspecting raw data, evaluating QC measures and reproducibility, accuracy, and reliability, normalization, and quantitation.

3) to analyze data on DNA variation, and RNA and protein expression. Using different types of software, we will learn data processing and cleaning steps, quality assessment, outlier evaluation, normalization of biomarkers by internal controls, data merging, analysis of biomarkers in relation to exposures and endpoints, and data visualization.

Teaching Philosophy

We have come to these topics through our own research experience in identifying pathways by which exposures and genetics can contribute to chronic disease risk in human populations. We seek to provide an engaging and practice-oriented experience for students of epidemiology, who may or may not have ever stepped into a lab. We want Epidemiology students to understand how biomarker data are generated, what they are indicators of, how to analyze them, and how to correctly interpret them in the larger context of human health. We will teach based on our experience and using protocols that we have developed, with some reference to the published literature and examples of how others have rigorously and effectively tested hypotheses related to the molecular underpinnings of disease and health. For some students, we expect this experience may be their only one in the lab and they will walk away with a richer understanding and appreciation of future datasets that they will design and receive from collaborating labs. For other students, we may spark interest in going deeper into developing their own skills in laboratory-based research.

Required Textbooks/Articles/Readings

There are no required texts. Required reading (journal articles, protocols) will be posted on the CourseWeb site by the beginning of the semester.

CourseWeb/BlackBoard Instruction

Revisions to this document, schedules, readings, and assignments will be posted to CourseWeb (Blackboard). All students are required to log on weekly and check CourseWeb.

Required or Recommended Software

We will use SAS and R for teaching and for assignments in this class. SAS is available to students (<http://technology.pitt.edu/software/for-students-software.html>) and R can be downloaded at no cost (<https://www.r-project.org/>). Students should also have Microsoft Excel on their personal computers.

Class Expectations/ Behavior and Ground Rules

We expect students to turn off cell phones while in class. Class attendance and participation are required. A single missed lecture class is allowed. Missed lab classes cannot be made up.

Grading Scale

97.0-100%	A+	93.0-96.9%	A	90.0-92.9%	A-
87.0-89.9%	B+	83.0-86.9%	B	80.0-82.9%	B-
77.0-79.9%	C+	73.0-76.9%	C	70.0-72.9%	C-
< 70.0%	F				

Student Performance Evaluation

Final grades will be based on: 75% attendance and active participation; 25% final project. Attendance and participation are critical to success in this course. You may only miss one class (please let us know in advance). Any other absences must be excused by an instructor. Participation must include active engagement in lecture and class discussions, hands-on manipulation of wet lab experiments and individual work on computer lab assignments. You will be expected to maintain a lab notebook. We

understand that experiments do not always work on the first try and will not use success of any in class wet-lab assay to determine your participation grade.

Assignments and Descriptions

Students will be required to do course readings weekly, review protocols, maintain a lab notebook, and watch assigned videos. Class attendance and participation are the most critical assignment and, accordingly, make up 75% of the final grade, combined.

For a final project, we will ask students to develop a Methods section of a grant that will measure one or more types of biomarker (DNA, RNA, protein, or epigenetic). The biomarkers can be proposed as exposures, mediators, or endpoints to test a hypothesis. It is important that students think of ways to either confirm or refute their associations using complementary, but independently measured biomarkers. For example, they might measure in the same sample set a related biologic molecule such as a protein encoded by an RNA to see how it correlates with the primary biomarker and also with exposure and/or outcome. Students will write 5-7 pages giving:

- 2-4 Specific Aims;
- Rationale for biomarker selection in relation to an exposure, a health outcome, or both;
- Preliminary data: students can download raw data from PubMed or request assistance from instructors in obtaining a dataset;
- Detailed research methods (biomarkers only): how samples will be processed and stored, how the biomarkers will be measured, QC steps, internal controls, normalization quantitation, minimize batch-to-batch variability;
- Statistical methods: analysis of the biomarker data to test the proposed Aims;
- Sample size calculations: given estimates of effect size and variability in their measures, how many subjects are needed to refute the null hypothesis;
- A detailed section on potential problems with the assays that you have chosen and alternative approaches to solve them.

Schedule of Sessions and Assignments

N	Topic	Format	Teacher
1.	<p>1) Introduction: Navigating the molecular biomarkers available to epidemiologists: DNA, RNA, protein, epigenetic markers, metabolites</p> <p>2) DNA sequence and Genetic epidemiology</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Describe in a broad context how measures of DNA variation and RNA and protein expression are used in epidemiologic research; • Restate where application of these types of measures have increased our knowledge of causes and prevention of disease risk in the population; • Compare and contrast family vs. unrelated; and cohort vs. case-control study designs; • List factors important for biospecimen sample collection and storage <p><u>In-Class:</u> Become comfortable with pipetting</p> <p><u>Readings:</u> Am J Hum Genet. 2015 Aug 6;97(2):199-215. Toxicol Appl Pharmacol. 2005 Aug 7;206(2):261-8.</p> <p><u>Optional Videos:</u> https://www.youtube.com/watch?v=bVk0twJYL6Y (Genetic Intro) https://www.youtube.com/watch?v=YUlcSPkLNB8 (Genetics in Health)</p>	Lecture	J. Adibi, A. Kuipers
2	<p>DNA Analysis I: Human DNA Extraction</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Describe the principles of DNA extraction; • Employ basic lab techniques of pipetting, elution, centrifugation, decanting, incubation and recording notes; • Explain the principles underlying DNA quality and quantity assessment using spectrophotometry, and Restriction Fragment Length Polymorphism (RFLP) assay design. <p><u>In-class:</u> Extract your own DNA from saliva and check the quality and quantity using spectrophotometry.</p> <p><u>Readings:</u> Review Laboratory Protocol for DNA extraction Cancer Epidemiol Biomarkers Prev. 2006 Sep;15(9):1585-7.</p> <p><u>Optional Videos:</u> https://www.youtube.com/watch?v=LzvdoVVUUDI (DNA Extraction) https://www.youtube.com/watch?v=xHQM4BbR040&feature=iv&src_vid=pxC6F7bK8CU&annotation_id=annotation_360342 (DNA Spec)</p>	Wet lab	A. Kuipers
3	DNA Analysis II: Human DNA Genotyping and Sequencing	Wet lab	A. Kuipers

	<p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Compare and contrast RFLP, TaqMan, and other modern genotyping methodologies; • Explain the main idea behind Polymerase Chain Reaction methods to perform DNA amplification; • Describe the theory behind current sequencing platform options; • Compare the strengths and limitations of big genomic data collection and genomic imputation; • Compare and contrast when to gather genotyping vs. sequencing data based on study question <p><u>In-class:</u> Run RFLP and TaqMan Genotyping with class DNA</p> <p><u>Readings:</u> Review Laboratory Protocols for RFLP and TaqMan Nature. 2015 Oct 1;526(7571):68-74.</p> <p><u>Optional Videos:</u> https://www.youtube.com/watch?v=RSVenfEUiol (PCR first 4min) https://www.youtube.com/watch?v=sjGj7OkRpQA (TaqMan genotype) https://www.youtube.com/watch?v=sjGj7OkRpQA (TaqMan genotype) https://www.youtube.com/watch?v=IVG04dAAyVY (Chip arrays) https://www.youtube.com/watch?v=jFCD8Q6qSTM (Sanger seq) https://www.youtube.com/watch?v=MvuYATh7Y74 (Next gen seq)</p>		
4	<p>DNA Data Analysis: Analysis of DNA genotype data and application to an epidemiologic question</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Demonstrate an ability to calculate MAF, genotype frequencies and test for violations from HWE; • Describe the concepts for implementing thresholds for genetic data analysis quality control and diagnostic statistics; • Employ SAS to calculate genotype statistics and to test for association between genotypes and trait of interest <p><u>In-class:</u> Work through a worksheet related to genotype data analysis including calculating genotype frequencies, HWE and SAS analysis of genetic data.</p> <p><u>Homework:</u> Complete the worksheet if not completed during class time and prepare for next week’s lecture.</p> <p><u>Readings:</u> http://www.nature.com/scitable/definition/hardy-weinberg-equilibrium-122 Cold Spring Harb Protoc. 2012 Mar 1;2012(3):297-306.</p> <p><u>Optional Videos:</u> https://www.youtube.com/watch?v=-QfLyy4-VIM (Stat gen) https://www.youtube.com/watch?v=LBn_zsd7-4 (1000 genomes)</p>	Computer lab	A. Kuipers

<p>5</p>	<p>Coding and non-coding RNAs, and their applications in epidemiology</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Explain the basics of gene regulation and RNA synthesis; • Outline key distinctions between the different categories of coding and non-coding RNAs; • Discuss examples of how RNA biomarkers have been studied in relation to exposures and to health outcomes. <p><u>Readings (Hand-outs):</u></p> <ol style="list-style-type: none"> 1. Chapter 1. Overview: What is Gene Expression. In Mechanisms of Gene Regulation. Eds. Carlberg and Molnar. Springer : New York. 2014. Pp. 5-24. 2. Chapter 1. Introduction. In <u>Non-coding RNAs and Cancer</u>. Ed. Fabbri. Springer: New York. 2014. Pp. 3-15. 3. Exposure and mRNA: Danitsja et al. 2008. EHP PMID: 19057705 4. Outcome and miRNA: Nair et al. 2014 AJE PMID: 24966218 <p><u>Optional videos:</u> https://youtu.be/tMr9XH64rtM (Eric Lander on transcription 8 min)</p>	<p>Lecture</p>	<p>J. Adibi</p>
<p>6</p>	<p>RNA quantitation I: mRNA analysis</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Decide in which settings to pursue single RNA analysis methods vs. transcriptome analysis; • Address in study design issues related to selection of biomarker, assay, validity, primer design, internal controls, quantitation, sources of and ways to assess technical and biologic variability, normalization. • Isolate RNA from human tissue. <p><u>In-class assignment.</u> Homogenize placental tissue sample and isolate RNA.</p> <p><u>Readings (Hand-outs):</u></p> <ol style="list-style-type: none"> 1. Chapter 3. Detecting Noncoding RNA Expression: From Arrays to Next Generation Sequencing In <u>Non-coding RNAs and Cancer</u>. Ed. Fabbri. Springer : New York. 2014. Pp. 25-44. 2. Chapters 3, 5. In <u>Molecular Epidemiology: Principles and Practices</u>. Ed. Schulte and Perera. Academic Press: New York. 1993. Pp.79-107; 109-135. 3. mRNA Biomarker validation: Adibi et al. 2009 Environmental Health. PMID: 19389254; Santiago and Postashkin 2015 PNAS PMID: 26566043 4. Qiagen RNAEasy Protocol: https://www.qiagen.com/us/resources/resourcedetail?id=14e7cf6e-521a-4cf7-8cbc-bf9f6fa33e24&lang=en <p><u>Optional videos:</u> https://www.youtube.com/watch?v=fkUDu042xic (Taqman) https://youtu.be/2c3t3tDEmsU (microarray vs. sequencing, 7 min)</p>	<p>Wet lab</p>	<p>J. Adibi</p>

<p>7</p>	<p>RNAs quantitation II. mRNA analysis by qPCR</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Assess assess quality and quantity of total RNA; • Reverse transcribe RNA to cDNA; • Set up a qPCR reaction; • Evaluate the raw data from a qPCR experiment. <p><u>In-class assignment:</u> Set up reverse transcription reaction, set up a qPCR experiment, retrieve data at the end of the experiment.</p> <p><u>Readings (Hand-outs):</u></p> <ol style="list-style-type: none"> 1. Chapters 3, 6. Protocol for QuantStudio https://www.thermofisher.com/content/dam/LifeTech/migration/files/pcr/pdfs.par.36605.file.dat/4470935b.pdf <p><u>Optional videos:</u> https://youtu.be/kvQWKcMdyS4 (real-time quantitative PCR, 6 min) https://www.thermofisher.com/us/en/home/life-science/pcr/real-time-pcr/real-time-pcr-instruments/quantstudio-12k-flex-real-time-pcr-system.html (QuantStudio instrument, 4min)</p>	<p>Wet lab</p>	<p>J. Adibi</p>
<p>8</p>	<p>RNA data analysis. Analysis of RNA data, application in epidemiologic research</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Discuss the difference between absolute quantitation, relative quantitation and the delta-delta ct method. • Carry out the pre-modeling steps of qPCR data analysis: quantitation, sources of and ways to assess technical and biologic variability, normalization. • Write a basic program in SAS to analyze a qPCR data set. • Explain to someone else the steps in the pre-processing and analysis of a microarray data set. <p><u>In-class assignment:</u> Import raw qPCR data into SAS, write a program to evaluate and analyze the data. Using a qPCR data set, estimate the association of placental gene expression with gestational age and fetal sex. Plot the raw data and the modeled data.</p> <p><u>Readings (Hand-outs):</u></p> <ol style="list-style-type: none"> 1. Johnson et al. 2014. Methods Mol Biol PMID 24740217 2. Chapter 5. Data analysis. In Gene Expression Studies: Using Affymetrix Microarrays. Ed. Gohlmann and Talloen. CRC Press: New York Pp 113-233. 	<p>Computer lab</p>	<p>J. Adibi</p>
<p>9</p>	<p>Protein biomarkers as products of synthesis and predictors of cellular function</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Outline basic steps in protein synthesis and protein function; • Explain types of protein regulation (translation, post-translational modifications, metabolism, degradation); 		<p>Adibi and/or guest lecture</p>

	<ul style="list-style-type: none"> • Give an overview of the different methods used to measure proteins (circulating, tissue level, single molecule, proteome); • Give examples of how protein biomarkers are used effectively in epidemiology. <p><u>Readings (Hand-outs):</u></p> <ul style="list-style-type: none"> • TBD <p><u>Optional videos:</u> -video on protein synthesis, protein regulation</p>		
10	<p>Protein analysis I. measurement of circulating proteins and protein products</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Describe options to measure a circulating molecule; • Try a protein quantification method such as an ELISA; • Give a brief background on multiplexing methods (Luminex, MSD platform). <p><u>In-class:</u> work in groups to do an ELISA assay. Receive an introduction to the HPLC and GC/MS instruments.</p> <p><u>Readings (Hand-outs):</u> -protocols; TBD</p> <p><u>Optional videos:</u> -https://www.youtube.com/watch?v=RRbuz3VQ100 (ELISA, 2 minutes) http://www.youtube.com/watch?v=kz_eqMtdnL4 (HPLC, 5 minutes)</p>	Wet lab	J. Adibi
11	<p>Protein analysis II. Measurement of tissue level proteins</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> • Describe options to measure a protein within tissue; • Try a technique: quantitative western blot, immunostaining and/or imaging. <p><u>In-class:</u> work in groups to load a gel for a western blot experiment, transfer proteins to a membrane, set up for overnight antibody incubation. While waiting for the above, we will learn about immunostaining of tissue to localize and visualize proteins. We will try phase contrast and fluorescent microscopy with already prepared samples.</p> <p><u>Readings (Hand-outs):</u> -protocols; TBD.</p> <p><u>Optional videos:</u> TBD</p>	Wet lab	J. Adibi

12	<p>A survey of epigenetic biomarkers</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> To describe different types of epigenetic regulation (methylation, non-coding RNA, chromatin modification); List epigenetic biomarker analysis methods that can accommodate large sample size data; Critique examples of their application in an epidemiologic study. <p><u>Readings (Hand-outs):</u> TBD</p> <p><u>Optional videos:</u> -TBD</p>	Lecture	Dr. Jeremy Martinson, IDM
13	<p>Quantitation of methylation, and application to an epidemiologic question</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> Carry out a single epigenetic marker assay called EpiTect; Manipulate raw methylation data and normalize for use in statistical analyses; Conduct an analysis to relate epigenetic data with expression data, an exposure, and an outcome. <p><u>In-class:</u> Do an EpiTect II Methylation Assay on the same sample that was used to determine genotype. Use R/Bioconductor code to analyze methylation status in relation to genotype and gene expression, using a raw data set provided.</p> <p><u>Readings (Hand-outs):</u> TBD</p> <p><u>Optional videos:</u> -TBD</p>	Scaife teaching lab/ Computer lab	Dr. Jeremy Martinson, IDM
14	<p>Bringing it all together: the analysis of an exposure, a biomarker of effect, and an outcome</p> <p><u>Learning Objectives:</u></p> <ul style="list-style-type: none"> Restate course concepts including key points of DNA, RNA and protein regulation and molecular analysis; Describe new technologies and the future of the field; Evaluate the course. <p><u>Readings (Hand-outs):</u> -protocols; TBD</p>	Lecture	Adibi, Kuipers
15	Final class: group presentations	Lecture	Adibi, Kuipers

Accommodation for Students with Disabilities

If you have any disability for which you may require accommodation, you are encouraged to notify both your instructor and the Office of Disability Resources and Services, 140 William Pitt Union (Voice or TTD 412-648-7890) as early as possible in the term.

Academic Integrity Statement

All students are expected to adhere to the school's standards of academic honesty. Any work submitted by a student for evaluation must represent his/her own intellectual contribution and efforts. The Graduate School of Public Health's policy on academic integrity, approved by EPCC on 10/14/08, which is based on the University policy, is available online in the Pitt Public Health Academic Handbook (www.publichealth.pitt.edu/home/academics/academic-requirements). The policy includes obligations for faculty and students, procedures for adjudicating violations, and other critical information. Please take the time to read this policy.

Students committing acts of academic dishonesty, including plagiarism, unauthorized collaboration on assignments, cheating on exams, misrepresentation of data, and facilitating dishonesty by others, will receive sanctions appropriate to the violation(s) committed. Sanctions include, but are not limited to, reduction of a grade for an assignment or a course, failure of a course, and dismissal from the school.

All student violations of academic integrity must be documented by the appropriate faculty member; this documentation will be kept in a confidential student file maintained by the Office of Student Affairs. If a sanction for a violation is agreed upon by the student and instructor, the record of this agreement will be expunged from the student file upon the student's graduation. If the case is referred to the Pitt Public Health Academic Integrity Hearing Board, a record will remain in the student's permanent file.

Diversity Statement

Graduate School of Public Health supports learning environments that are inclusive and respectful of all individuals. Every member of our community is expected to be respectful of the individual perspectives, experiences, behaviors, worldviews, and backgrounds of others.

Copyright Notice

Course material may be protected by copyright. United States copyright law, 14 USC section 101, et sec., in addition to University policy and procedures, prohibit unauthorized duplication or retransmission of course materials. See [Library of Congress Copyright Office](#) and the [University Copyright Policy](#).

Health Sciences Library and Pitt Public Health Librarian

We encourage students to access the HSLS Molecular Biology online resource for more in-depth information on molecular biology methods, <http://www.hsls.pitt.edu/molbio/>. They offer regular workshops and tutorials on technologies and data analysis methods.

Pitt Public Health
EPCC | Template for Bulk Course Description Submission

Department: Human Genetics

Date of Submission: February 22, 2017

Course Number	Course Title	Current Course Description	Proposed New Course Description	Reason for Update	Semester when update will take effect
HUGEN 2022	Human Population Genetics	Deals with general principles of population genetics, especially those applicable to human populations.	This survey course covers the principles of population genetics as applicable to human populations, including (1) the laws of inheritance that govern the organization of the genomes in populations, (2) the evolutionary forces and phenomena that impact genetic diversity in human populations, and (3) the foundational concepts of genetic epidemiology and gene discovery.	To provide a more detailed description of the course	Fall 2017
HUGEN 2026	Special Studies Human Genetics	This course is designed to provide advanced undergraduates and graduate students with directed, intensive training in laboratory, statistical or clinical research methods relevant to human genetics. These will be specialized skills not available through regularly taught courses in the university. Each special study is designed in consultation with an individual member of the human genetics faculty. Course performance will be judged by the preparation of a written final report to the supervising faculty member.	This course is designed to provide advanced undergraduates and graduate students with directed, intensive training in laboratory, statistical or clinical research methods relevant to human genetics. These specialized skills are not available in regularly taught courses in the university. Each special study is designed in consultation with an individual member of the human genetics faculty.	Clarify language. The course may use other means of assessment.	Fall 2017

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HUGEN 2028	Human Genetics Journal Club and Peer Review	Human genetics journal club and peer review meets once per week for one hour and provides students and faculty with an opportunity to present exciting research in an informal format. The purpose of the course is to hone students' oral and written critical evaluation skills via oral presentations of published literature, as well as a written review of a manuscript. Upon completion of the course, students will be able to orally critique a paper from the literature and also critically review a manuscript for publication.	Human genetics journal club provides students and faculty with an opportunity to present and discuss exciting research in an informal format. The purpose of the course is to hone students' oral and written critical evaluation skills.	Simplify description.	Spring 2018
HUGEN 2029	Introduction to Gene Mapping	This course presents a literature-based approach to understanding and interpreting results from gene mapping papers in the field of human genetics. Traditional and state-of-the-art linkage analytic methodologies will be explored. Students should have a basic knowledge of biostatistics principles, molecular genetics, and population genetics. Short summaries will be given of each analytic technique, followed by student-led critiques of representative papers from the current literature and discussion of study design issues, results, interpretations, and shortcomings of each paper.	This course presents a literature-based approach to understanding and interpreting results from gene mapping papers in the field of human genetics. Traditional and state-of-the-art genetic mapping methodologies will be explored.	Updating language, remove details of course implementation.	Fall 2017
HUGEN 2034	Biochemical and Molecular Genetics of Complex Diseases	This course provides students with an understanding of the molecular and biochemical genetic approaches to understanding genetically determined susceptibility to common disease. This will be presented using selected examples of complex human diseases	This course provides students with an overview of the molecular and biochemical genetic approaches to determine the underlying genetic architecture of common diseases that account for a large portion of the public health burden of disease. The	Simplify language. Choice of specific diseases to be discussed as examples may change.	Spring 2018

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		(cardiovascular disease, neurodegenerative diseases, diabetes, lupus, age-related macular degeneration, cancer and osteoporosis). Risk of common, complex diseases is determined by genotypes at multiple genetic loci and the complex interaction of genetic variation and environmental exposures. Risk of almost every common disease is influenced by genes, but the relationship between genotype and disease phenotype is weak compared to that observed with rare Mendelian traits. However, understanding the contribution of genes to common disease susceptibility is important to public health.	genetic, environmental and epigenetic factors that influence susceptibility to common disease will be illustrated using selected examples, such as cardiovascular disease, neurodegenerative diseases, mental health diseases, autoimmune diseases and eye diseases.		
HUGEN 2035	Principles of Genetic Counseling	Provides basic training in genetic counseling with particular reference to its applications in public health programs.	This course addresses fundamental concepts important to genetic counseling principles and practice.	To better reflect the content of the course.	Fall 2017
HUGEN 2036	Genetic Counseling Internship	Provides practical applications of the fundamentals of genetic counseling. Involves both the observation of and participation in at least 50 counseling sessions in the medical genetics departments of children's, Magee-Women's and West Penn hospitals. Literature review and searches pertinent to each patient will be necessary for adequate preparation. Weekly case presentations and/or lectures will also be included.	For this course, students will participate in supervised genetic counseling clinical rotations in a variety of specialty areas. The lectures that are part of the course will address topics relevant to clinical genetics and counseling.	To better reflect the content of the course.	Fall 2017

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HUGEN 2039	Risk Calculation Genetic Counseling	Provides training in calculating risk of disease, or carrier status, in a variety of genetic counseling situations by learning to identify the sources of risk in the counselee's personal and family history and to analyze and synthesis a single overall risk of disease from these competing risks.	This course provides hands-on training in calculating risk of disease or carrier status in a variety of typical genetic counseling situations, as well as discussion of the limitations of those calculation methods.	Clarify language.	Spring 2018
HUGEN 2040	Molecular Basis of Human Inherited Disease	This course will provide an up-to-date overview of the most common and biologically informative human inherited disorders and will integrate clinical descriptions with recent genetic, molecular genetics and biochemical insights. Disorders covered include lysosomal storage disorders, neuromuscular diseases, organic acidopathies, amino-acidopathies, neurofibromatosis, cystic fibrosis, neurodegenerative and ophthalmic disorders. Current techniques of gene mapping, cloning, transfer, and expression will be integrated into the overviews.	This course will provide an overview of selected human inherited disorders and integrate clinical descriptions with recent genetic, molecular genetics and biochemical insights. Current state of the art molecular genetics methodologies will be integrated into the overviews.	Simplify language. Remove list of specific diseases to be discussed as these examples may change.	Fall 2017
HUGEN 2049	Introduction Public Health Genetics	This graduate level course focuses on public health genetics. The goal of this course is to educate the student about the basic principles of genetics and their application to public health practice and research. Public health genetics is the application of advances in genetics and molecular biotechnology to improve public health and prevent disease. This course will provide the knowledge necessary to apply genetic concepts to public health practice.	This course provides a framework in which to assess how advances in genomics may be applied to public health practice and policies that affect both individuals and society. In addition, the ethical, legal, and social consequences of historical, current, and future interventions are considered.	Simplify language.	Fall 2017

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HUGEN 2050	Public Health Genetics Practicum	The practicum, through a structured and educationally supervised placement at an approved site with an experienced professional is aimed at providing a means to identify and to apply a variety of theories and skills discussed and demonstrated in the classroom to the real-life experiences to which the student is assigned in the field under professional supervision. The choice of practicum site is determined by the mph degree director and the director of graduate studies for the department of human genetics. The MPH degree requirements and career goals of the student influence the choice of the practicum assignment.	The practicum is a short term field placement (minimum 200 hours of public health oriented work) with an organization or agency that is relevant to the student's area of interest. Each placement must be agreed upon by the student and the MPH program advisor.	Simplify language, remove unnecessary details.	Fall 2017
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NOTE: When the course descriptions are approved by EPCC the department's student services staff will prepare the paperwork and submit to the Office of Student Affairs for submission on a semester by semester basis when the Registrar's Office will accept the changes.

Educational Policies and Curriculum Committee
Graduate School of Public Health
University of Pittsburgh
(Revised: 9/22/2015)

REQUEST FOR APPROVAL OF NEW COURSES AND COURSE CHANGES

1. **General Instructions:**

- a. Faculty should submit this form and the associated syllabus following the Pitt Public Health Syllabus Guidelines and the Syllabus Checklist (on pages 4 and 5) **by e-mail** to Patricia Documet, Chair (pdocumet@pitt.edu) and Robin Leaf, EPCC Staff Liaison (ral9@pitt.edu). If you choose not to include all the information detailed on the Syllabus Guidelines in your course syllabus for distribution to students, please attach this information to the proposal.
- b. The initiating Department is asked to submit one hard copy of this completed form with the proper signatures, syllabus and other materials (if any) to Robin Leaf in Student Affairs **at least one week prior** to the EPCC meeting. If this target date is not met, the proposal will be deferred for consideration at the next meeting scheduled.
- c. You will be contacted by the EPCC Chair or the EPCC Staff Liaison to schedule a presentation and discussion of your program/course proposal with the Committee, if possible at the next scheduled EPCC meeting.

2. **Review based on the following (check all which apply):**

- | | |
|--|---|
| <input checked="" type="checkbox"/> New course, not previously approved (<i>as for-credit</i>) | <input type="checkbox"/> Course modification (major) |
| <input type="checkbox"/> Course title change | <input type="checkbox"/> Special topics course content |
| <input type="checkbox"/> Cross-listing only | <input type="checkbox"/> Pitt Public Health Core Course |
| (Specify academic unit & course number): _____ | <input type="checkbox"/> Practicum, internship, field placement |

3. **Course designation:**

Course Number HPM 2050 Title: Seminar in Contemporary Health System Engineering Issues Credits: 1

4. **Cross-listing:**

If you want to cross-list this course in any other Pitt Public Health department or any other school of the University, specify which department(s) and School(s) and provide brief justification.

Already cross-listed as IE 2110 as this is a required course for the Certificate in Health Systems Engineering co-sponsored by the Departments of HPM and Industrial Engineering, Swanson School of Engineering

5. **Course Instructors:**

(Indicate type of Pitt Public Health faculty appointment,* and percentage of total course time/effort anticipated. For any instructor who does not hold a Pitt Public Health faculty appointment, indicate title and affiliation.)

* The principal instructor for any Pitt Public Health course must have a primary, secondary or adjunct appointment in the school.

- a. Principal instructor: Barry Ross, PhD, Adjunct Instructor, HPM and IE (50%)
- b. Co-instructors (if any): Wesley M. Rohrer, PhD, Associate Professor, HPM (50%)

6. **Statement of the course for *Course Inventory*.** Include purpose of course; summary of prerequisites, if any; general course content; and method of conducting course (e.g., lecture, laboratory, field work, etc.).

This survey course will focus on contemporary issues confronting the U.S. health care system and the opportunities for health systems engineering to address and mitigate them. The intent is to sensitize those embarking on health care management careers to better comprehend and be prepared for what is happening in the health care industry. The rationale for the course to be offered to HPM and IE graduate students is that the disciplines represented in these two Departments are symbiotically intertwined in the world of practice to effect and sustain continuing performance improvement. This course provides IE student with a greater understanding of the complexities of the health care system while affording MHA students an opportunity to develop the analytical skills and methods associated with process engineering and control systems.

The course will be conducted as a seminar with guest expert presenters with the expectation of a high level of student participation in discussions. Each student will also be required to present a summary of findings of a written paper focused on a targeted literature review.

7. **Student enrollment criteria/restrictions:**

- a. Indicate any maximum or minimum number of students and provide justification for this limitation.

The minimum number of students is five given the commitment of external speakers and the emphasis on active in-class participation.

- b. If admission is by permission of instructor, state criteria to be applied.

Students outside the HPM and IE Departments may be admitted with permission.

- c. Provide a brief description of any prerequisite skills or knowledge areas that are necessary for students entering this course, including any specific course prerequisites or equivalents.

No specific prerequisites other than being enrolled in a graduate level program in Pitt Public Health or the Swanson School of Engineering.

8. **Course schedule and allocation of hours:**

- a. Number of course hours per session: 2 Sessions per week: 1 Weeks per academic term: 7-8

- b. Approximate allocation of class time (hours or %) among instructional activities:

Lectures ___ Seminars __80%__ Recitations _____ Field work _____ Laboratory _____
 Other (specify): Student discussion and presentations: 20%

- c. Term(s) course will be offered: Fall X Spring _____ Summer Term _____ Summer Session _____

9. **Grading of student performance:**

Indicate the grading system to be used (A, B, C, etc.; H, S, U); provide statement justifying use of system other than letter grade.

Standard letter grading (A-F)

10. **On-line course delivery:**

Indicate the extent to which you will be using on-line instructional methods in teaching this course by checking all of the options below which apply:

I plan to use the course management aspects of CourseWeb/ Blackboard (or equivalent), e.g., grade book, announcements.

I plan to use the interactive features of CourseWeb/Blackboard (or equivalent), e.g., discussion board, etc.

I have designed the course for remote (off-site) learning with little/no classroom attendance required.

I do not plan to use on-line instruction methods for this course (briefly explain)

11. **Relevance of course to academic programs and curricula:**

- a. Describe how this course contributes to learning objectives specified for the curriculum of one or more Pitt Public Health degree or certificate programs. Indicate whether course is required for any specified degree or certificate.

This seminar is required as the portal for the Certificate in Health Systems Engineering and provides the opportunity for non-Certificate students from both Pitt Public Health and the Swanson School of Engineering to gain an overview of the domain of Health Systems Engineering, the relevant literature, models and current issues.

- b. Describe how this course addresses public health issues involving diversity (gender, race, ethnicity, culture, disability, or family status).

Diversity is addressed within the context of applications of technology and process improvement that increase access, lower cost and insure patient safety for all those seeking health care services including minority and underserved populations.

12. **Signature and date of principal faculty member (include department/program) making request:**

Name/Title: Shah M. Ahmed Date: 2-27-2017
Vice-Chair for Education & Assoc. Professor

13. **Signature and date of endorsement of department chairperson:**

Name/Title: [Signature] Date: 2/27/17

14. (For cross-listing only)

Signature and date of endorsement of department chairperson:

Name/Title: _____ Date: _____

**Educational Policies and Curriculum Committee
 Graduate School of Public Health
 University of Pittsburgh
 (11/19/2013)**

SYLLABUS CHECKLIST FOR NEW AND REVISED COURSES

Addendum to REQUEST FOR APPROVAL OF NEW COURSES AND COURSE CHANGES FORM

Objective to assist faculty to ensure syllabus contains the required and necessary elements to provide students with clear expectations of the course.

NOTE: * indicates a required element of the syllabus. If N/A is checked or this element is not included complete the information detailed on page two for all instances.

Syllabus Area	Recommended Detail * Required	Included in Your Syllabus?					
<i>Heading</i>	Course Number*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Course Title*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Course Meeting Time/Day of Week*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Classroom Location*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
<i>Faculty Information</i>	Office Location*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Office Hours*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Phone Number*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Email Address*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Teaching Philosophy	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Teaching Assistant Contact	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input checked="" type="checkbox"/>
<i>Student Expectations in Classroom</i>	Behavior/ Ground Rules (cell phones off, laptops off, etc.)	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Recording of Lectures	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
<i>Course Summary</i>	Course Description*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Learning Objectives*	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
<i>Materials</i>	Required Textbooks/ Articles/Readings	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Required Software	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input checked="" type="checkbox"/>
	Required Equipment (including use of CourseWeb/Blackboard)	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Recommended Material	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input type="checkbox"/>
	Availability of Software for Purchase and/or Use	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>	N/A	<input checked="" type="checkbox"/>

Departments of Health Policy & Management and Industrial Engineering
HPM 2050/IE 2110 Seminar in Contemporary Health Care System Issues
Syllabus and Course Schedule
Version: February 27, 2017

Course Identification

- Graduate School of Public Health and Swanson School of Engineering
- Departments of Health Policy and Management (HPM) and Industrial Engineering (IE)
- Course Number and Title: HPM 2050/IE 2110 – Seminar in Contemporary Health System Engineering Issues
- Credit Hours: 1
- Term/Academic Year: Fall semester
- Class location: Benedum Hall, Room T/B/D
- Class schedule (Day/time): Monday, 1:00 pm – 3:00 pm. Class is held the first 8 weeks of the Fall Term with adjustments for University holidays and breaks

Faculty Information

- Faculty: Barry Ross, PhD and Wesley Rohrer, PhD, MBA
- Support Staff: Jessica Dornin, A688, Crabtree Hall
- email address: BRoss@pitt.edu, and wrun@pitt.edu
- Phone number: 412-624-2743 (Wes Rohrer)
- Office: Room 1022 Benedum Hall (Ross); Room A649 Crabtree Hall (Rohrer)
- Office hours: By appointment

Summary and rationale

This survey course will focus on contemporary issues confronting the U.S. health care system and the opportunities for health systems engineering to address and mitigate them. The intent is to sensitize those embarking on health care management careers to better comprehend and be prepared for what is happening in the health care industry.

The rationale for the course to be offered to HPM and IE graduate students is that the disciplines represented in these two Departments are symbiotically intertwined in the world of practice to effect and sustain continuing performance improvement. This course provides IE student with a greater understanding of the complexities of the health care system while affording MHA students an opportunity to develop the analytical skills and methods associated with process engineering and control systems.

The course provides students the opportunity to benefit from and dialogue with University-based and external subject experts on the topics scheduled.

Teaching/Learning Objectives

Upon completion of this course, the students will/should

1. Be exposed to current trends and issues in health care services relevant to health systems engineering methods, tools and applications
2. Be encouraged to pursue completion of the HSE Certificate having been presented with the benefits of the Program for their professional and career development
3. Broaden the scope of their knowledge of the U.S. health care system and the application of IE models and processes beyond their disciplinary base
4. Develop base-line knowledge of the domain of HSE in order to benefit fully from the required and elective courses completed in pursuing the HSE Certificate
5. Benefit from the expertise and experience of scholars and professionals with insights about health care systems management, process engineering and control systems.
6. Understand the various career track opportunities available to students within the HSE realm.

Teaching Philosophy

The faculty ground their teaching approach and methods on the assumption that the students are adult learners who will make a reasonable investment in course preparation to enable them to participate regularly and effectively in in-class discussion, by sharing experiences and perspectives and in presenting their projects competently.

Relationship to CAHME Requirements

This is a required course for the Master of Health Administration (MHA) Program which is accredited by the Commission on Accreditation of Healthcare Management Education (CAHME) This course addresses the following CAHME accreditation curricular requirements:

CAHME Competencies

This course will address the following CAHME competencies.

HPM/CAHME Management Competency Model	Target Level of Competency Attainment	Teaching Methods	Assessment Methods
Cross Cutting			
Communication	Basic	Lecture and Discussion	Written assignment and oral participation
Systems Thinking	Basic	Lecture and Discussion	Written assignment and oral participation
Self-Actualization			
Professionalism	Basic	Active participation	Written assignment

			and oral participation
Self-Development	Intermediate	Active participation	Written assignment and oral participation
Management			
Performance Measurement and Process Improvement	Basic	Lecture and Discussion	Oral participation

Learning Methods (i.e., Teaching & Assessment)

	Lower-Level Methods	Higher-Level Methods
Specify which methods you will employ to <u>teach</u> students:	Lectures, readings, in-class discussion	Project presentations, written assignments, etc.
Estimated % of Course Time Devoted to these Teaching Methods:	__ 80 __ %	__ 20 __ %
Specify which methods you will employ to <u>assess</u> student performance:	Active Participation	Written paper; class presentation
Estimated weight Given to these assessment methods	__ 50 __ %	__ 50 __ %

Texts: No required text book will be assigned. However, one or more readings from the relevant literature will be assigned for each session. Tentative assigned readings are listed below in the Schedule of Sessions.

Performance Expectations: It is expected that students will put in the time and effort to make the presented information as meaningful as possible to them. To this end, the following items are expected of students:

1. Students will be provided materials relevant to the topic of the week beforehand to read and will come prepared to actively engage in the class discussion.
2. A five (5) page paper reflecting the synopsis of a presented topic based on relevant articles (6-8) identified through a focused literature review.
3. The student will present an in-class summary of findings and conclusions.
4. Students must attend a minimum of six (6) sessions, arrive punctually and participate actively in class discussions.

Class Conduct: Professional and mature behavior will be expected including punctuality, notifying faculty of unavoidable absences, and readiness to participate. The use of cell phones and equivalent electronic devices are discouraged except for emergencies.

Lectures and discussions may be recorded only with the permission of the faculty and guest presenter.

Student Performance Evaluation (Factors and Weights)

Student evaluation will be based on the following factors:

- Attendance and Participation 50%
 - A minimum attendance of 6 classes is required.
 - Demonstration that student has done assigned readings, contributions to class discussions, etc.
- Paper assignment and Class Presentation 50%
 - Relevance, quality and clarity of written paper
 - Professionalism in oral presentation

Except for true emergencies or other extenuating circumstances, papers submitted beyond the deadline will be subject to a discounted grade.

Grading Scale:

The following grading scale will be used:

90-100%	A
80-89%	B
70-79%	C
60-69%	D
< 60%	F

As appropriate, letter grades may be refined using + and -.

CourseWeb/BlackBoard Instruction will be used in this course. **Course Web Page:**
<http://courseweb.pitt.edu>

Accommodation for Students with Disabilities

If you have any disability for which you may require accommodation, you are encouraged to notify both your instructor and the Office of Disability Resources and Services, 216 William Pitt Union (412-648-7890) during the first two weeks of the term.

Academic Integrity Statement

All students are expected to adhere to the school's standards of academic honesty. Any work submitted by a student for evaluation must represent his/her own intellectual contribution and efforts. The GSPH policy on academic integrity, approved by EPCC on 10/14/08, which is based on the University policy, is available online at <http://www.publichealth.pitt.edu/interior.php?pageID=126>. The policy includes

obligations for faculty and students, procedures for adjudicating violations, and other critical information. Please take the time to read this policy.

Students committing acts of academic dishonesty, including plagiarism, unauthorized collaboration on assignments, cheating on exams, misrepresentation of data, and facilitating dishonesty by others, will receive sanctions appropriate to the violation(s) committed. Sanctions include, but are not limited to, reduction of a grade for an assignment or a course, failure of a course, and dismissal from GSPH.

All student violations of academic integrity must be documented by the appropriate faculty member; this documentation will be kept in a confidential student file maintained by the GSPH Office of Student Affairs. If a sanction for a violation is agreed upon by the student and instructor, the record of this agreement will be expunged from the student file upon the student's graduation. If the case is referred to the GSPH Academic Integrity Hearing Board, a record will remain in the student's permanent file.

**Health Systems Engineering (HSE) Seminar
Schedule of Topics (Tentative)
Fall Term 2017**

<u>Session</u>	<u>Topic</u>
1	<p>Overview: Content and Expectations History of and Outlook for HSE</p> <p>Readings:</p> <ul style="list-style-type: none">❖ <i>A Brief History of Health Systems Engineering</i>, B. Ross and B. Bidanda, 2014❖ <i>Report to the President – Better Health Care and Lower Costs: Accelerating Improvement through Systems Engineering</i>, President’s Council of Advisors on Science and Technology, May 2014❖ <i>Industrial and Systems Engineering and Health Care: Critical Areas of Research</i>, University of Wisconsin, 2009
2	<p>Global Perspective of Health Systems</p> <p>Reading:</p> <ul style="list-style-type: none">❖ EMR Adoption Model (EMRAM) (https://app.himssanalytics.org/emram/emram.aspx)❖ Adoption of Electronic Health Record Systems among U.S. Non-federal Acute Care Hospitals: 2008-2013 (https://www.healthit.gov/sites/default/files/oncdatabrief16.pdf)
3	<p>HSE: Real Life Application – VAPHS</p> <p>Reading:</p> <ul style="list-style-type: none">❖ http://www.pittsburgh.va.gov/verc/index.asp
4	<p>Meaningful Use</p> <p>Readings:</p> <ul style="list-style-type: none">❖ <i>An Aging Nation: The Older Population in the United States, Population Estimates and Projections</i>, by Jennifer M. Ortman, Victoria A. Velkoff, and Howard Hogan, May 2014, P25- 1140)❖ https://www.healthit.gov/providers-professionals/meaningful-use-definition-objectives
5	<p>Big Data/Data Analytics Applications</p> <p>Readings:</p> <ul style="list-style-type: none">❖ <i>Big Data in Health Care: Separating the Hype from the Reality</i> (https://www.healthcatalyst.com/healthcare-big-data-realities)
6	<p>Healthcare Reform . . . Where Are We Now?</p>

- ❖ Brill, Steven. (2015). America's Bitter Pill: Money, Politics, Backroom Deals & The Right to Fix our Broken Healthcare System. New York: Random House.
- ❖ Emanuel, Ezekiel. (2014). Reinventing American Health Care. New York: Public Affairs.
- ❖ Health spending growth rate surges to 5.3% under ACA
ModernHealthcare

7 **IT Impact on Clinical Practitioners**

- ❖ Readings to be determined

8 **Oral Presentations; seminar wrap-up and feedback (*if additional session is required*)**