INTRODUCTION TO GENETIC EPIDEMIOLOGY

(EPID0754)

Prof. Dr. Dr. K. Van Steen

CHAPTER 1: SETTING THE PACE

1 Course Responsible

Contact details

2 Administrative Issues

Course details and examination methods

3 Exploring the Scene

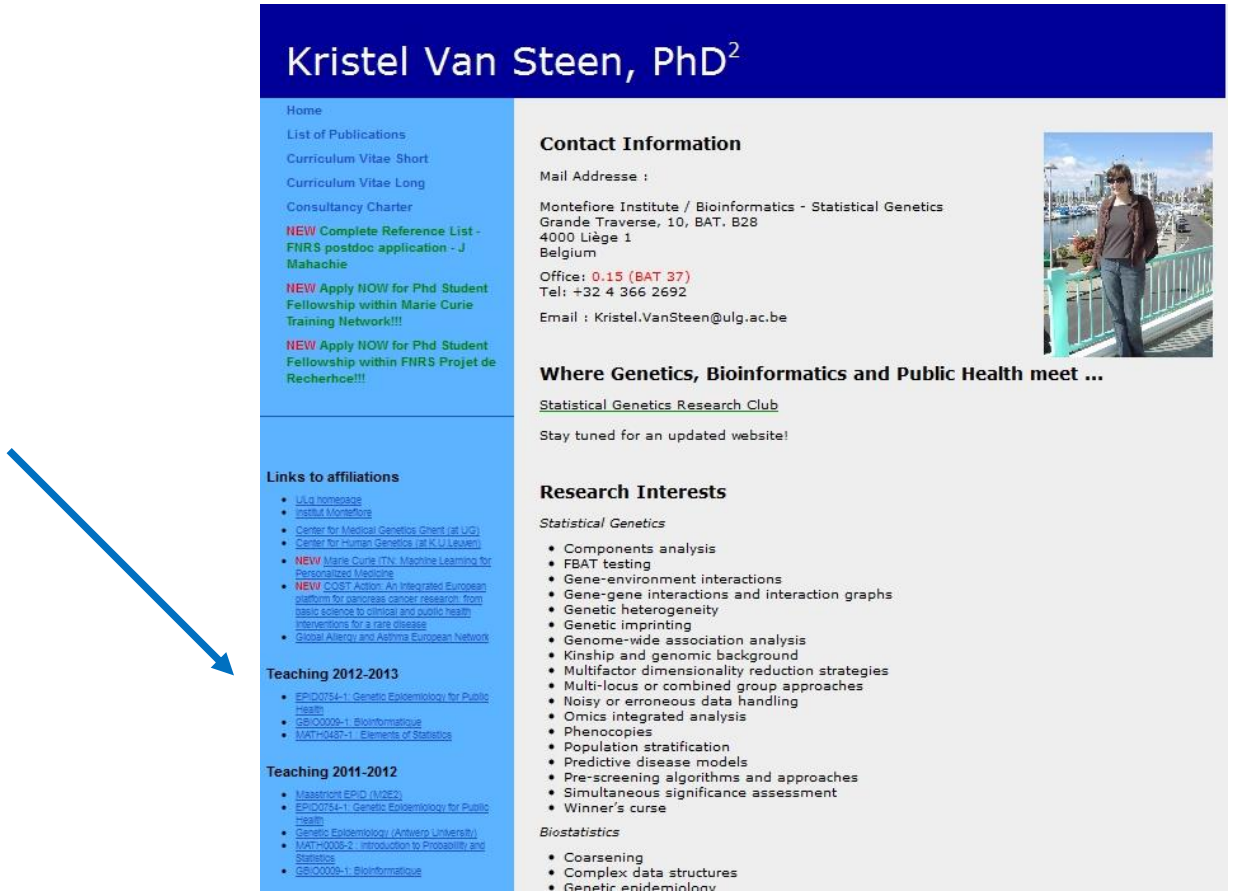
Expectations

4 Background Information: Medical Genomics

Recent evolutions in medical genomics

5 Workshop Papers

1 Course Responsible



Kristel Van Steen, PhD[2]

Home
List of Publications
Curriculum Vitae Short
Curriculum Vitae Long
Consultancy Charter
NEW Complete Reference List - FNRS postdoc application - J Mahachie
NEW Apply NOW for Phd Student Fellowship within Marie Curie Training Network!!!
NEW Apply NOW for Phd Student Fellowship within FNRS Projet de Recherhce!!!

Links to affiliations
- ULg homepage
- Institut Montefiore
- Center for Medical Genetics Ghent (at UG)
- Center for Human Genetics (at K.U.Leuven)
- NEW Marie Curie ITN: Machine Learning for Personalized Medicine
- NEW COST Action: An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease
- Global Allergy and Asthma European Network

Teaching 2012-2013
- EPID0754-1: Genetic Epidemiology for Public Health
- GBIO0009-1: Bioinformatique
- MATH0497-1 : Elements of Statistics

Teaching 2011-2012
- Maastricht EPID (M2E2)
- EPID0754-1: Genetic Epidemiology for Public Health
- Genetic Epidemiology (Antwerp University)
- MATH0008-2 : Introduction to Probability and Statistics
- GBIO0009-1: Bioinformatique

Contact Information

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Where Genetics, Bioinformatics and Public Health meet ...

Statistical Genetics Research Club

Stay tuned for an updated website!

Research Interests

Statistical Genetics
- Components analysis
- FBAT testing
- Gene-environment interactions
- Gene-gene interactions and interaction graphs
- Genetic heterogeneity
- Genetic imprinting
- Genome-wide association analysis
- Kinship and genomic background
- Multifactor dimensionality reduction strategies
- Multi-locus or combined group approaches
- Noisy or erroneous data handling
- Omics integrated analysis
- Phenocopies
- Population stratification
- Predictive disease models
- Pre-screening algorithms and approaches
- Simultaneous significance assessment
- Winner's curse

Biostatistics
- Coarsening
- Complex data structures
- Genetic epidemiology

Contact details via

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Use “genetic epidemiology” in subject title when sending a mail to ask questions or to make a face-to-face appointment for a meeting

2 Administrative Issues

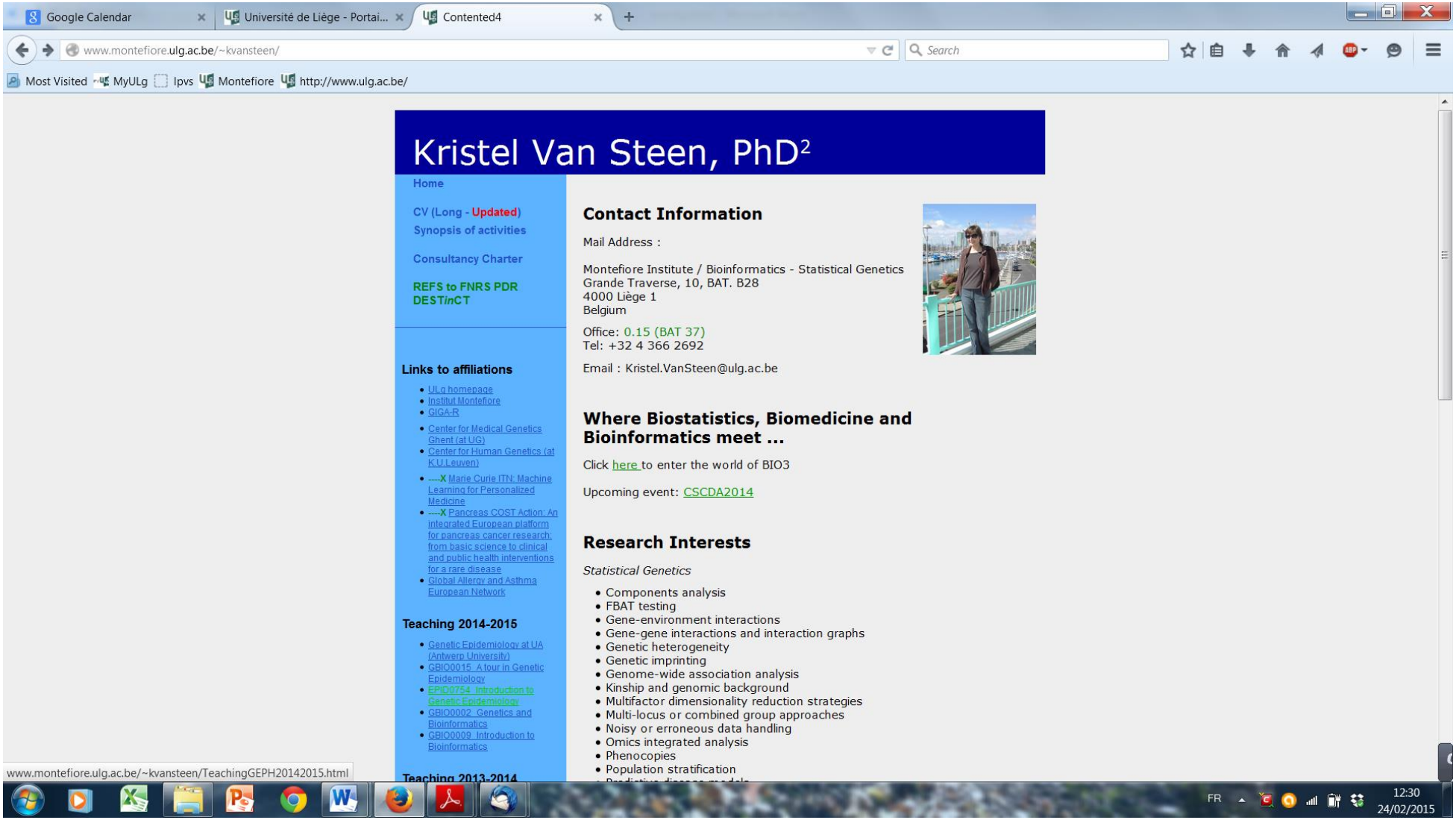
Learning outcomes

- Basic knowledge about themes in genetic epidemiology
- Basic knowledge about concepts that are relevant in genetic epidemiology as seen in class
- Awareness about pros and cons of study designs and analytic techniques related to subtopics within genetic epidemiology, with an emphasis to
  - Aggregation
  - Segregation
  - Association
- "List of thematic questions": when appropriately addressed, the learning outcomes are met …

Public health (PH)

- Work load
  - 20T: concepts
  - 20Pr: presentations
  - 4 credits ~120 hours
- Homeworks:
  - papers around topics or themes are presented and discussed in class
  - two presentation rounds (presentation and report are marked)
  - exam is oral: organized around “list of thematic questions”

Course website



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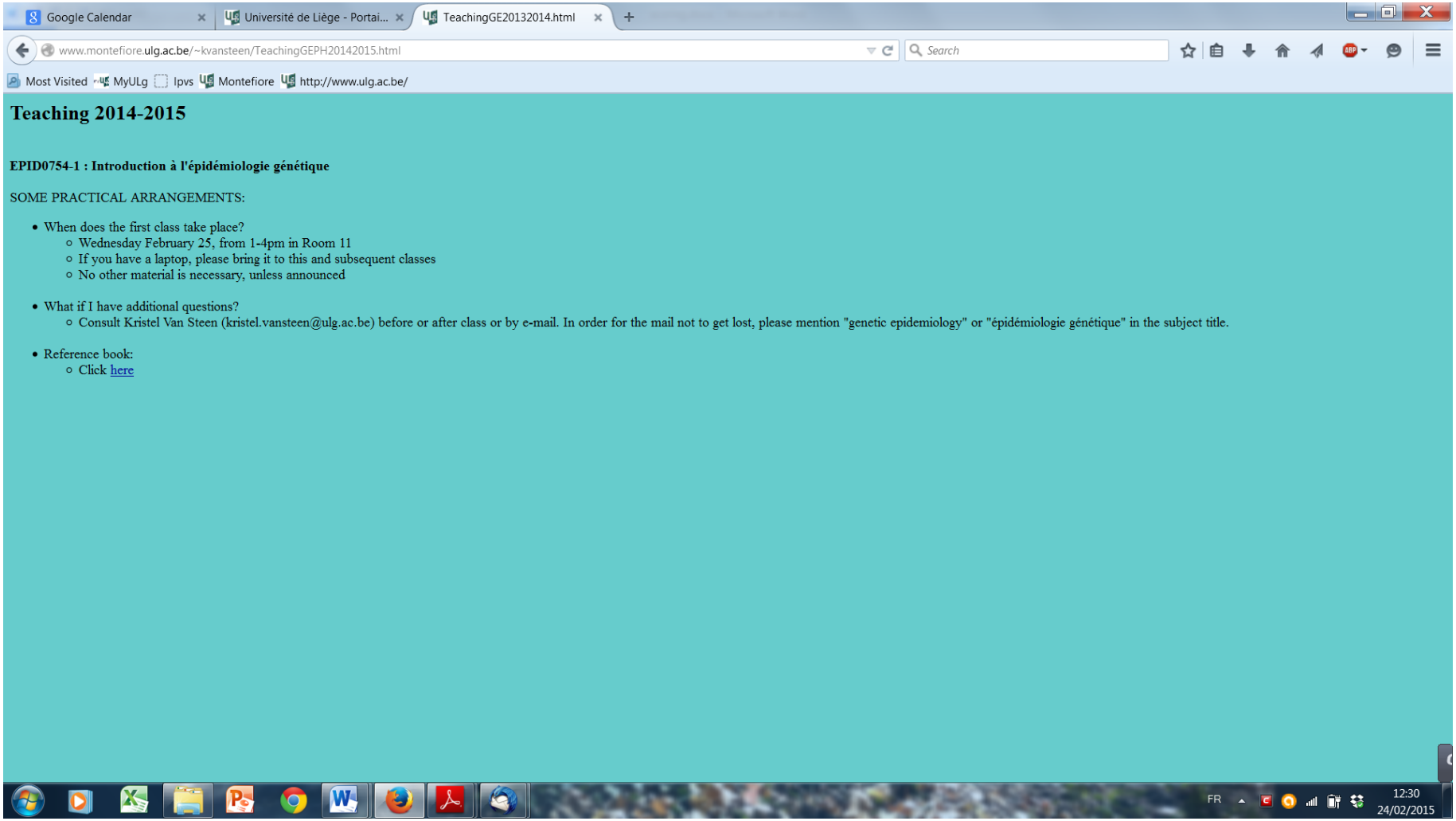


Course organization

	HW1	HW2	Particip. in discussions	Oral Exam (*)	Total
Max	**30 (presentation + slides/ report)**	**30 (presentation + slides/report)**	**20**	**20 (no final report)**	**100**

(*) “themes” (see course website); 2-4 questions / themes (negotiable)

Course topics

CHAPTER 2: INTRODUCTION TO GENETICS

1 Basics of molecular genetics

2 Overview of human genetics

CHAPTER 3: DIFFERENT FACES OF GENETIC EPIDEMIOLOGY

1 Basic epidemiology

2 Relevant questions in genetic epidemiology

CHAPTER 4: FROM POPULATION GENETICS TO MAPPING GENES

1 Aggregation

2 Segregation

3 Selection

4 HWE

CHAPTER 5: GENOME-WIDE ASSOCIATION STUDIES

1 LD as the basic underlying concept

2 Components of a genome-wide association analysis

- Quality control
- Tests of association
- Population stratification
- Multiple testing
- Validation and replication

3 How to read a genome-wide association study?

4 Meta-analysis: more data is better?

CHAPTER 6: INCORPORATING EXTRA LEVELS OF COMPLEXITY – the environment

1 The role of the environment in different streams of genetic epidemiology

2 The role of the environment to define strata

3 The role of the environment as an effect modifier

4 Epigenetics

CHAPTER 7: INCORPORATING EXTRA LEVELS OF COMPLEXITY – systems biology

1 Beyond main effects: GxE interactions

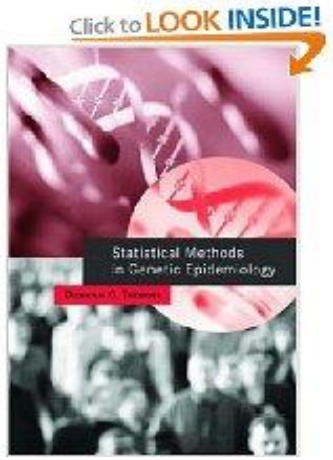
2 Multifactor Dimensionality Reduction techniques

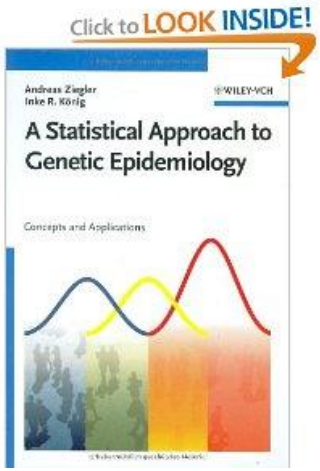
3 Functional follow-up analyses

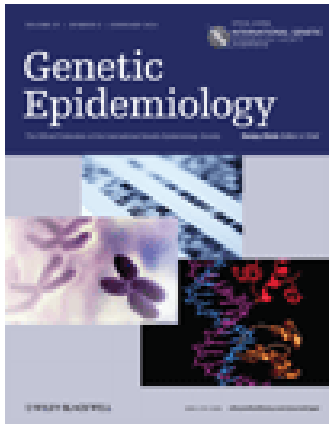
4 Integrated analyses

Course material / References

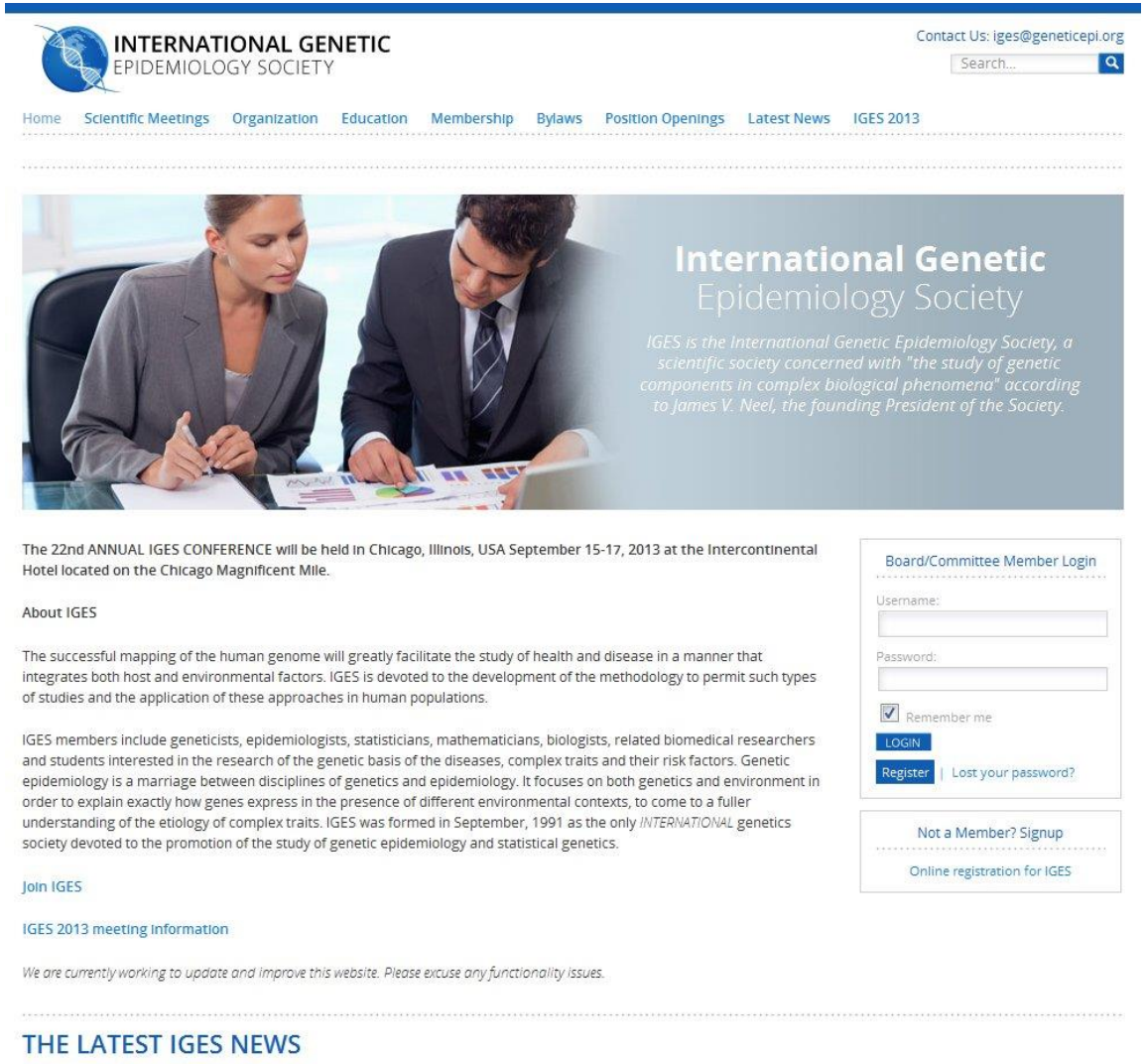
- Check out course website for slides and assignments
- These slides are comprehensive enough for the subset of material that will be covered in class
- For those who are interested, key references are included on the course website and below







IGES (http://www.geneticepi.org/)



3 Exploring the Scene

Round-Table Discussion

Q1: What is your background? What is your thesis about? What do you want to achieve in your professional life?

Q2: Have you analyzed data before? How? Which tools have you used? What was the most difficult part? Data manipulation? Interpretation? Implementation?

Q3: What is epidemiology?

Q4: What do you think genetic epidemiology includes? Personalized medicine? Genetic testing?

Q5: What are your expectations of this course? What would you really like to do / achieve in this course?

4 Our context: Medical Genomics

Bridges the gap between bioinformatics and medical informatics

What is covered by "medical genomics"?

The Mayo staff have authored several articles that will be useful for anyone developing a thorough understanding of medical genomics. These articles have been published as a series in the Mayo Clinic Proceedings journal. The following sections have been copied from their website:

http://mayoresearch.mayo.edu/mayo/research/grc/proceedings.cfm

Genomics Primer from Mayo Clinic Proceedings

Part I: History of Genetics and Sequencing of the Human Genome

Cindy Pham Lorentz, MS; Eric D. Wieben, PhD; Ayalew Tefferi, MD; David A. H. Whiteman, MD; and Gordon W. DeWald, PhD

The first part of this overview gives an account of the history of genetics that spans from humankind's first attempts at understanding and influencing heredity, to the early scientific work in the field of genetics, and then to the advancements in modern genetics. The second part summarizes the Human Genome Project (HGP) from inception to the publishing of the "first draft" of the human genome sequence.

Part II: Background Principles and Methods in Molecular Genetics

Ayalew Tefferi, MD; Eric D. Wieben, PhD; Gordon W. DeWald, PhD; David A. H. Whiteman, MD; Matthew E. Bernard, MD; and Thomas C. Spelsberg, PhD

In this second part of an educational series in medical genomics, selected principles and methods in molecular biology are recapped, with the intent to prepare the reader for forthcoming articles with a more direct focus on aspects of the subject matter

Part III: Microarray Experiments and Data Analysis

Ayalew Tefferi, MD; Mark E. Bolander, MD; Stephen M. Ansell, MD, PhD; Eric D. Wieben, PhD; and Thomas C. Spelsberg, PhD

Genomics has been defined as the comprehensive study of whole sets of genes, gen products, and their interactions as opposed to the study of single genes or proteins. Microarray technology is one of many novel tools that are allowing global and high-throughput analysis of genes and gene products. In addition to an introduction on underlying principles, the current review focuses on the use of microarrays in gene expression analysis. … The current review should serve as an introduction to the subject for clinician investigators, physicians and medical scientists in training, practicing clinicians, and other students of medicine.

Part IV: Expression Proteomics

Animesh Pardanani, MD, PhD; Eric D. Wieben, MD; Thomas C. Spelsberg, PhD; and Ayalew Tefferi, MD

Proteomics, simply defined is the study of proteomes. The three broad areas are expression proteomics, which catalogues the relative abundance of proteins; cell-mapping or cellular proteomics, which delineates functional protein-protein interactions and organelle-specific protein distribution; and structural proteomics, which characterizes the 3-dimensional structure of proteins. This articles reviews the area of expression proteomics.

Part V: Bioinformatics

Peter L Elkin, MD

Bioinformatics is the discipline that develops and applies informatics to the field of molecular biology. Although a comprehensive review of the entire field of bioinformatics is beyond the scope of this article, I review the basic tenets of the field and provide a topical sampling of the popular technologies available to clinicians and researchers. These technologies include tools and methods for sequence analysis (nucleotide and protein sequences), rendering of secondary and tertiary structures for these molecules, and protein fold prediction that can lead to rational drug design. I then discuss signaling pathways, new standards for data representation of genes and proteins, and finally the promise of merging these molecular data with the clinical world (the new science of phenomics).

Part VI: Genomics and Molecular Genetics in Clinical Practice

Stephen M. Ansell, MD, PhD; Michael J. Ackerman, MD, PhD; John L. Black, MD; Lewis R. Roberts, MD, PhD; and Ayalew Tefferi, MD

An important milestone in medical science is the recent completion of a "working draft" of the human genome sequence. The identification of all human genes and their regulatory regions provides the framework to expedite our understanding of the molecular basis of disease. This advance has also formed the foundation for a broad range of genomic tools that can be applied to medical science. These developments in global gene and gene product analysis as well as targeted molecular genetic testing are destined to change the practice of modern medicine.

…

Despite these exciting advances, many practicing clinicians perceive that the role of molecular genetics, especially that of genomics, is confined primarily to the research arena with little current clinical applicability. The aim of the article is to highlight advances in DNA/RNA-based methods of susceptibility screening, disease diagnosis and prognostication, and prediction of treatment outcome in regard to both drug toxicity and response as they apply to various areas of clinical medicine.

Part VII: The Evolving Concept of the Gene

Eric D. Wieben, PhD

The draft sequence of the human genome was reported 2 years ago, and the task of filling gaps and polishing the sequence is nearing completion. However, despite this remarkable achievement, there is still no definitie assessment of the number of genes contained in the human genome. In part, this uncertainty reflects our growing understanding of the complexity and diversity of gene structure. Examples of complex gene structure are considered in the context of the discussion about the evolution of our understanding of gene structure and function.

Part VIII: Essentials of Medical Genetics for the Practicing Physician

Regina E. Ensenauer, MD; Shanda S. Reinke; Michael J. Ackerman, MD, PhD; David J. Tester; David A. H. Whiteman, MD; and Ayalew Tefferi, MD

After the mapping and sequencing of the human genome, medical professionals from essentially all specialties turned their attention to investigating the role genes play in health and disease. Until recently, medical genetics was considered a specialty of minor practical relevance. This view has changed with the development of new diagnostic and therapeutic possibilities. It is now realized that genetic disease represents an important part of medical practice. Achievements in cancer genetics, in the field of prenatal diagnostics (including carrier testing for common recessive disorders), and in newborn screening for treatable metabolic disorders reinforce the rapidly expanding role of genetics in medicine.

…

Diagnosing a genetic disorder not only allows for disease-specific management options but also has implications for the affected individual's entire family. A working understanding of the underlying concepts of genetic disease with regard to chromosome, single gene, mitochondrial, and multifactorial disorders is necessary for today's practicing physician. Routine clinical practice in virtually all medical specialties will soon require integration of these fundamental concepts for use in accurate diagnosis and ensuring appropriate referrals for patients with genetic disease and their families.

Part IX: Scientific and Clinical Applications of DNA Microarrays -- Multiple Myeloma as a Disease Model

John Shaughnessy, Jr., PhD

Multiple myeloma (MM) is a poorly understood and uniformly fatal malignancy of antibody-secreting plasma cells. …

This review discusses progress made in the development of molecular-based diagnostics and prognostics for MM through the dissection of the transcriptome of plasma cells from healthy individuals and patients with MM and other plasma cell dyscrasias.

Part X: Gene Therapy

Stephen J. Russell, MD, PhD; and Kah-Whye Peng, PhD

Gene therapy is defined as any therapeutic procedure in which genes are intentionally introduced into human somatic cells. Both preclinical and clinical gene therapy research have been progressing rapidly during the past 15 years; gene therapy is now a highly promising new modality for the treatment of numerous human disorders. Since the first clinical test of gene therapy in 1989, more than 600 gene therapy protocols have been approved, and more than 3000 patients have received gene therapy. However, at the time of writing this article, no gene therapy products have been approved for clinical use.

…

This article explains the potential clinical scope of gene therapy and the underlying pharmacological principles, describes some of the major gene transfer systems (or vectors) that are used to deliver genes to their target sites, and discusses the various strategies for controlling expression of therapeutic transgenes. … This review should serve as an introduction to the subject of gene therapy for clinician investigators, physicians and medical scientists in training, practicing clinicians, and other students of medicine.

Genetic epidemiology:

Bridges the gap between public health and personalized medicine

5 Background Information

- On the course website, "**background information**" is for your information only. It is up to you to what extent you consult this information
- This is NOT EXAM MATERIAL

- In contrast, "**workshop papers**" do provide complementary information to the course slides and may help in better understanding certain concepts or may be used as reference material for your presentations and reports
- The idea of workshop papers is to see concepts applied to relevant (other) contexts and to grow awareness about pros and cons of certain strategies
- Therefore, this material is also useful when preparing the EXAM (cfr. "list of thematic questions")

6 Workshop papers

Workshop paper : to be compared with future (recent) course material; revisit during last class

European Journal of Epidemiology **18**: 607–616, 2003.

REVIEW

Prospects of genetic epidemiology in the 21st century

Marieke C.J. Dekker & Cornelia M. van Duijn
Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands

Accepted in revised form 14 April 2003

Abstract. Genetic epidemiology is a young but rapidly developing discipline. Although its early years were largely dedicated to family-based research in monogenic disorders, now genetic–epidemiologic research increasingly focuses on complex, multifactorial disorders. Along with the development of the human-genome map and advances in molecular technology grows the importance of genetic–epidemiologic applications. Large-scale population-based studies, requiring close integration of genetic and epidemiologic research, determine future research in the field. In this paper, we review the basic principles underlying genetic–epidemiologic research, such as molecular genetics and familial aggregation of disease, as well as the typical study approaches of genome screening and candidate-gene studies.

Key words: Familial aggregation, Genetics, Genetic epidemiology, Polymorphisms, Study design