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

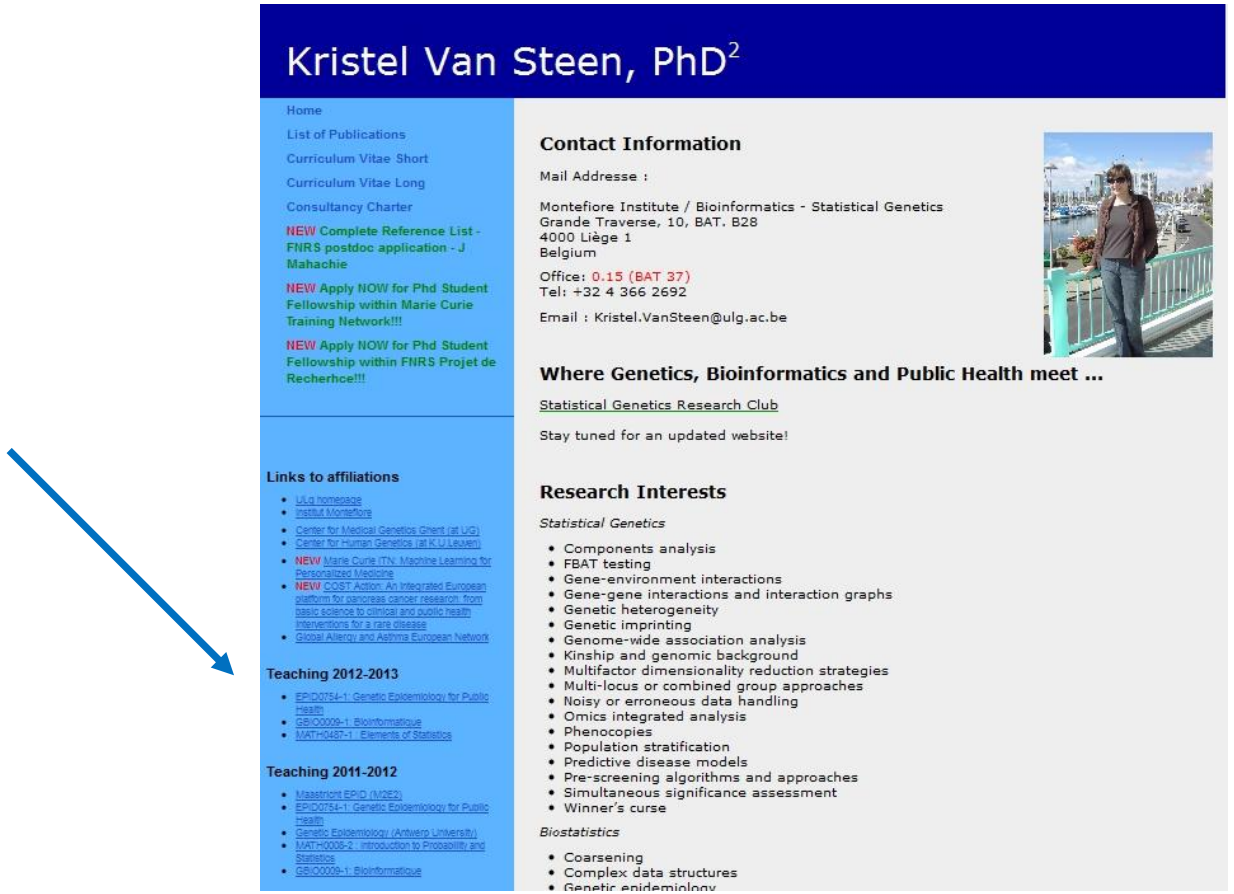
Expectations

4 Resource: Medical Genomics

Recent evolutions in medical genomics

5 Supporting documents

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

www.montefiore.ulg.ac.be/~kvansteen

Questions or remarks via e-mail

kristel.vansteen@ulg.ac.be or the TA jessmahachie@yahoo.co.uk

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

Old learning outcomes are revised ~last year's organization

Acquis d'apprentissage (objectifs d'apprentissage) du cours	Learning outcomes of the course
Familiariser les étudiants avec les différentes facettes de l'épidémiologie génétique, avec une emphase à la génétique statistique.	To familiarise students with the different facets of genetic epidemiology, with an emphasis on statistical genetics.
Prérequis et corequis / Modules de cours optionnels recommandés	**Prerequisites and co-requisites/ Recommended optional programme components**
Connaissance de base de concepts de statistiques. Les termes génétiques seront répresentés.	Basic knowledge of statistical concepts. Genetic terms will be re-introduced.
Activités d'apprentissage prévues et méthodes d'enseignement	**Planned learning activities and teaching methods**
Travail personnel par l'intermédiaire des tâches de lecture, homeworks et plus grands projets, à l'aide principalement des outils de Bioconductor dans le logiciel libre R. Les informations seront disponibles sur la page www.montefiore.ulg.ac.be/~kvansteen/	Personal work through tasks set during lectures, homework and larger projects, with the help primarily of Bioconductor tools using the 'R' open source software. Further information is available at www.montefiore.ulg.ac.be/~kvansteen/
Mode d'enseignement (présentiel ; enseignement à distance)	**Mode of delivery (face-to-face ; distance-learning)**
2eme semestre. Le cours sera interactif dans anglais/français. Slides en anglais. Devoirs peut être en français. Les examens ont organisés en français. Toutes les modalités pratiques du cours seront disponibles sur la page www.montefiore.ulg.ac.be/~kvansteen/	2nd semester. The course will be interactive in English/French. All course notes are in English. Homeworks can be handed in in French. Examination will be in French. All practical details about the course will be available at www.montefiore.ulg.ac.be/~kvansteen/
Lectures recommandées ou obligatoires et notes de cours	**Recommended or required readings**
Slides en anglais (www.montefiore.ulg.ac.be/~kvansteen/)	English-language slides via www.montefiore.ulg.ac.be/~kvansteen/

Course website

Teaching 2012-2013

EPID0754-1 : Introduction à l'épidémiologie génétique (website under construction -final version end of the day)

SOME PRACTICAL ARRANGEMENTS:

- When does the first class take place?
  - Wednesday February 13
  - If you have a laptop, please bring it to the classes.
  - No other material is necessary.
- When do the next classes take place?
  - Click here for an updated course schedule

    Updated ()
- Where do the classes take place?
  - room 11 (B23 RDC)
- What about homeworks?
  - Click here for some guidelines
  - Click here for NEW guidelines
- What if I have additional questions?
  - Consult Kristel Van Steen (kristel.vansteen@ulg.ac.be) before or after class or by e-mail. In order for the mail not to get lost, please mention "genetic epidemiology" in the subject title.

Course website

INFORMATION BY CLASS:

13 February 2013 - CLASS 1 : 1pm-5pm

- Course notes:
  - Chapter 1: Logistics
  - Chapter 2: Molecular Biology Revisited
  - Downloading instructions R and Bioconductor: Follow this link
  - Information on using R:
    - Working with the R software
    - Part 1: R manuals
    - Part 2: Basic Commands !!!
    - Part 3: An introduction to R
    - Part 4: Advanced
    - Part 5: A few illustrative examples in R
- Workshop papers: Some motivations for genetic epidemiology
  - Paper 1: Prospects of genetic epidemiology in the 21st century
  - Paper 2: Investigative genetics
- Background reading:
  - Basic epidemiology

20 February 2013 - CLASS 2 : 1pm-5pm

- Course notes: Chapter 3: Relevant questions in genetic epidemiology
- Workshop papers:
  - Paper 1: Heritability: concepts and misconceptions
  - Paper 2: Key concepts in genetic epidemiology
- Identification of "topics" of interest for homeworks and final project
  - Examples from last year
- Homework assignment 1 (due March 20):
  - Questions by group (from last year)

  Updated ()

Course organization

	HW1	HW2	Participation in discussions	Written /Oral Exam	Total
Max	**20**	**30**	**10**	**40**	**100**

Written = exam project, combining HW1-2 (using feedback from class disc.)

Oral = starting from written exam project and "themes"

("themes" are posted on course website)

Course outline

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 Genetic epidemiology

3 Phenotypic aggregation within families

4 Segregation analysis

5 Genetic epidemiology and public health

CHAPTER 4: BASIC POPULATION GENETICS

1 What is means and doesn't mean

2 How does evolution take place?

3 Distributions of genotypes in human populations

4 Natural selection revisited

5 Inbreeding

6 Fitness

CHAPTER 5: POPULATION BASED ASSOCIATION STUDIES

CHAPTER 6: TRAVELLING THE WORLD OF INTERACTIONS

1 Beyond main effects: GxG interactions

2 Multifactor Dimensionality Reduction techniques

3 Challenges: GxE interactions, omics integration

CHAPTER 7: BIOLOGICAL INTERPRETATION OF DATA

1 What is the purpose of giving biological interpretations?

2 Which resources are available to allow giving a biological interpretation?

3 How can biological knowledge be integrated in different studies of genetic epidemiology?

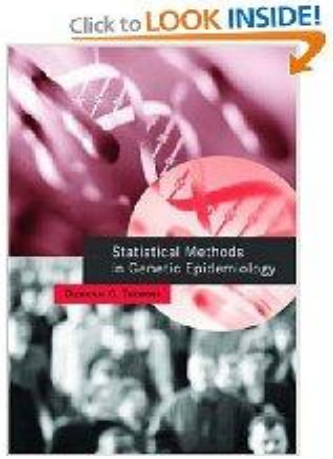
Course schedule

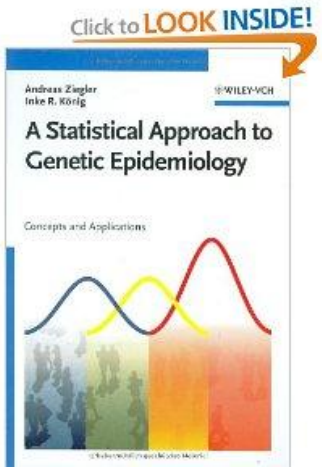
Courses in « genetic epidemiology » in 2012-2013 **11/02/2013**

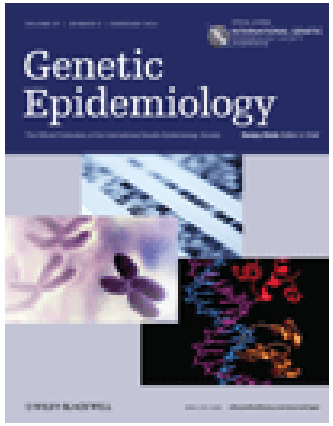
Course Name	Date	Class	Topic
PH20-20	13/02/2013	COURSE PH1+2 Formation of groups	Intro, setting the pace, homeworks and projects, concepts in molecular biology revisited
PH20-20	20/02/2013	COURSE PH3+4	Genetic epidemiology; what is it and what is it not? Assignment 1 (due 20/3)
BIOINF15-15	*05/03/2013*	*COURSE 1+2* *Assignments: split up the work and generate one report per group*	*Intro, setting pace, **epidemiology** in R –concepts in epidemiology (finding resources), highlight the variation in available tools such as the FBAT **software**, R SNPassoc and GenABEL, PLINK Assignment1: e.g., what are the key properties of these software packages*
PH20-20	06/03/2013	COURSE PH5+6	Basic concepts in population genetics, primer on genetic association studies
UA	18/03/2013	CLASS 1	Intro in genetic epidemiology
BIOINF15-15	*19/03/2013*	*COURSE 3+4*	*Quality control: genome-wide association studies, confounders, environmental effect modificators (i.e., quality control of environmental constructs) Assignment 2: Compare*

Course material / References

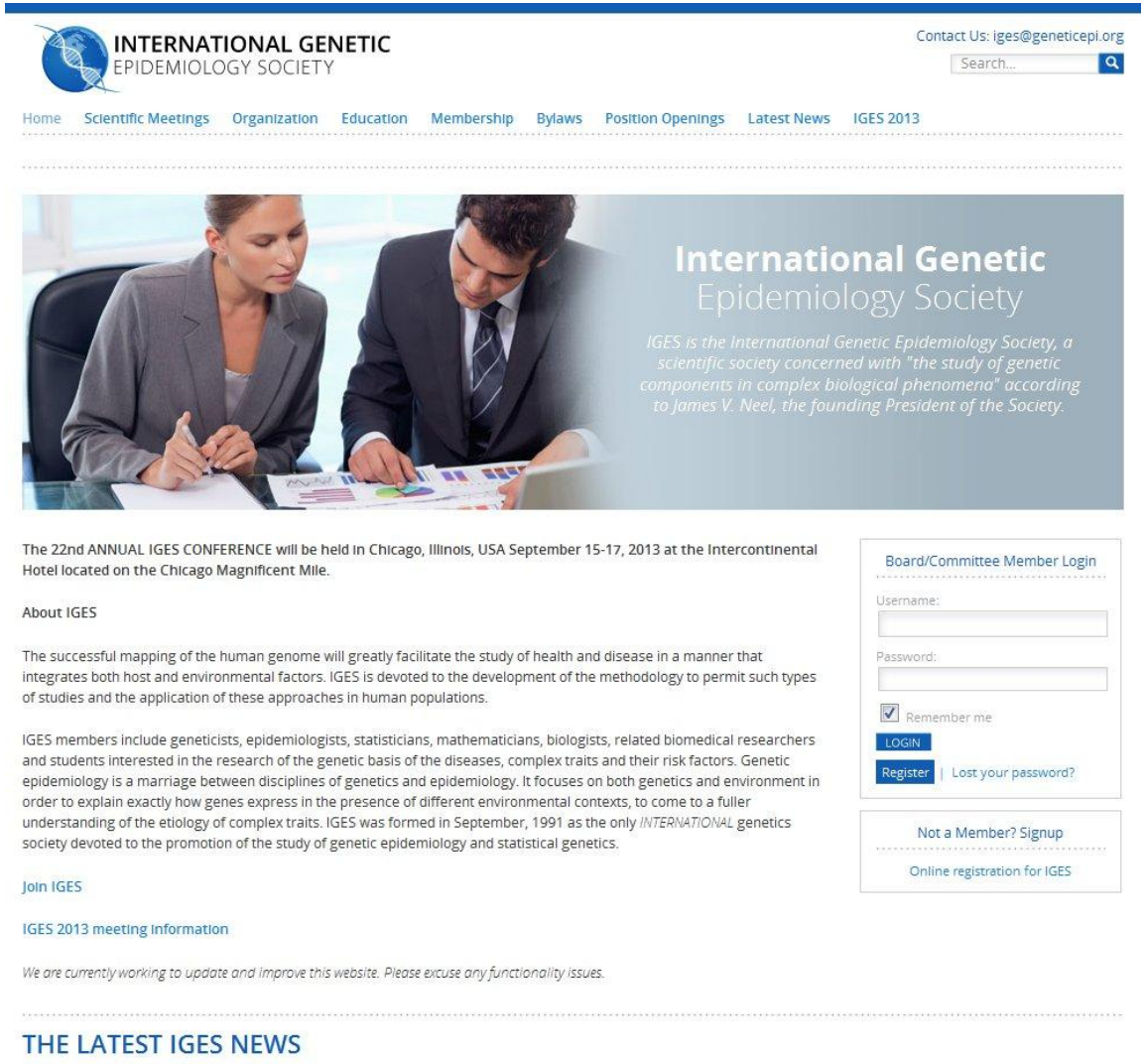
- Check out course website for slides and assignments
- These slides are comprehensive enough for the subset of material that will be covered in class
- For those who are interested, key references are provided as well.







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?

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

4 Resource: Medical Genomics

Genomics Primer from Mayo Clinic Proceedings

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

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. Safety issues regarding clinical use of gene therapy are explored, and the most important technical challenges facing this field of research are highlighted. 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.

5 Supporting documents

Workshop papers

- To have additional information on key concepts discussed in class
- To see concepts applied to relevant contexts
- To grow an awareness on pros and cons or potentials of certain approaches

→ considered to be exam material

Background information

- To have additional information on key concepts discussed in class
- Supplementary, not mandatory reading

→ NOT considered to be exam material

Workshop paper 1

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

Workshop paper 2

Janssens and van Duijn *Investigative Genetics* 2010, **1**:10
http://www.investigativegenetics.com/content/1/1/10

Investigative Genetics

OPINION Open Access

An epidemiological perspective on the future of direct-to-consumer personal genome testing

A Cecile JW Janssens*, Cornelia M van Duijn

Abstract

Personal genome testing is offered via the internet directly to consumers. Most tests that are currently offered use data from genome-wide scans to predict risks for multiple common diseases and traits. The utility of these tests is limited, predominantly because they lack predictive ability and clear benefits for disease prevention that are specific for genetic risk groups. In the near future, personal genome tests will likely be based on whole genome sequencing, but will these technological advances increase the utility of personal genome testing? Whole genome sequencing theoretically provides information about the risks of both monogenic and complex diseases, but the practical utility remains to be demonstrated. The utility of testing depends on the predictive ability of the test, the likelihood of actionable test results, and the options available for the reduction of risks. For monogenic diseases, the likelihood of known mutations will be extremely low in the general population and it will be a challenge to recognize new causal variants among all rare variants that are found using sequencing. For complex diseases, the predictive ability of genetic tests will be mainly restricted by the heritability of the disease, but also by the genetic complexity of the disease etiology, which determines the extent to which the heritability can be understood. Given that numerous genetic and non-genetic risk factors interact in the causation of complex diseases, the predictive ability of genetic models will likely remain modest. Personal genome testing will have minimal benefits for individual consumers unless major breakthroughs are made in the near future.