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 UNIVERSITY OF MICHIGAN



2008 PATIENTS AND POPULATIONS
August 7-29, 2008

MEDICAL GENETICS COMPONENT

SEQUENCE DIRECTOR

Thomas D. Gelehrter, M.D.
Professor Emeritus of Human Genetics and Internal Medicine
Department of Human Genetics

LECTURERS

David Ginsburg, M.D.
James V. Neel Distinguished University Professor, and
Warner-Lambert/Parke-Davis Professor of Medicine
Professor of Internal Medicine and Human Genetics

Stephen Gruber, M.D., Ph.D., M.P.H.
H. Marvin Pollard Professor of Medicine
Associate Professor of Internal Medicine, Epidemiology, and Human Genetics

Michael Imperiale, Ph.D.
Professor of Microbiology and Immunology

Elizabeth Petty, M.D.
Associate Professor of Internal Medicine and Human Genetics
Associate Dean - Student Programs

Wendy Uhlmann, MS, CGC
Genetic Counselor, Molecular Medicine and Genetics Clinic
Clinical Instructor, Human Genetics

TEACHING ASSISTANTS

Grant Rowe

Matt Vasievich

OVERVIEW

The growing awareness of the central role of genetic factors in the causation of human disease has made genetics one of the most rapidly developing fields in medicine. Much of this progress has been propelled by advances in the area of molecular genetics and genomics, advances that, in turn, have been applied directly to the diagnosis and management of disease. The **objective** of

this course is to present the **basic principles of medical genetics** and their **application to clinical medicine**, with the intent of providing students the necessary background **to understand ongoing developments in genetics** and their **application to clinical problems**. The elucidation of the human genome, and the genomes of multiple other organisms, will change the way medicine is practiced. In order for physicians to understand these developments and utilize them for the benefits of their patients, they will have to be **conversant with molecular genetic technologies** and the **technologies for acquiring, organizing, and interpreting new information**.

An understanding of the genetic basis of disease would be incomplete without a discussion of how DNA is organized and how information flows from genes through RNA and into gene products. Therefore, we will discuss the structure of DNA, how it is organized into genes and chromosomes, how it is replicated, how it might rearrange, how mutations arise and how they are repaired, how the DNA is transcribed, how the transcripts are processed, and how mRNA is translated into protein. New advances in understanding epigenetic regulation, which involves chromatin modification, and in the role of microRNA's will also be presented. We will also look at the prospects for using genes and RNA's to correct disease.

Genetics proposes a significant change in the way in which we view disease. Rather than viewing the body as a machine and disease as a specific problem with the workings of the machine that can be fixed, a genetic view of medicine sees the individual as a product of evolution and of individual development and experience. In this paradigm, disease is seen as a mismatch between variable homeostatic mechanisms and equally variable environmental experiences. The implications of this model, beyond a better understanding of the nature of disease, are that management can be directed to those variables, whether biological or social or cultural, that are most amenable to change. The intent of medical care is to enable the individual's homeostatic mechanisms to regain a steady state in which disease is minimized. This view of disease allows the physician to focus on the individual rather than the disease.

A genetic approach to medicine provides opportunities to predict susceptibility to disease and to intervene where appropriate to prevent or avoid the consequences of genetic disease. A critical aspect of dealing with a genetic risk is educating both patients and their physicians to understand the fundamental notion that **risk is not equivalent to certainty**. Environmental modification, for example of life style or diet, can play an important role in modifying, either minimizing or enhancing genetic risk of disease. Thus, understanding the principles upon which genetic tests are based will be critical to being able to interpret test results, choosing appropriate tests, and advising patients appropriately.

The applications of genetic screening programs, directed at populations, and genetic testing for disease susceptibility, directed at individuals, are becoming an increasingly important part of medical care. The ability to predict genetic risk raises a number of important medical and public health issues. A host of critical ethical issues are also raised, including individual autonomy, confidentiality, and issues such as duty to (or right to) contact family members at risk. Many of these issues, both medical and ethical, are not unique to genetics, but are important aspects of medical care in all areas.

A number of clinical examples will be used during this course to illustrate genetic principles, and we will try to use certain diseases repeatedly, because they illustrate several aspects of medical genetics. There will also be three **MDC/Patient Presentations**, at which attendance is mandatory. As physicians and students, we owe a great debt to our patients, for they are ultimately our teachers. These patients are, without recompense, giving of their time and of themselves. Please dress and act accordingly. It is appropriate to ask them questions, but please be sensitive.

The Genetics Component will also include three **Small Group Sessions**. Attendance at these sessions is required and will constitute 10% of your course grade. The first session will provide practice dealing with interpretation of pedigree information and assessment of risk to family members, and the second with the interpretation of genetic screening and diagnostic testing information. These sessions are for your benefit, to help you understand important concepts and apply them to solve clinical problems. Please study the problems before the SGD's, and be prepared to discuss them. Annotated answers to (most of) the questions will be provided after the sessions so that you can assess your ability to handle these questions. We hope you will attend prepared to discuss the issues, help your classmates with understanding the concepts, and/or improve your own understanding.

The final SGD on August 28 will deal with genetics and ethics and provide the opportunity to discuss actual cases raising important ethical issues, and to discuss the interplay of ethical, cultural, as well as scientific issues.

There will be one **Online Exercise** on breast cancer genetics that will review concepts of cancer genetics and introduce a few of the growing number of genetic tools available on the web. This exercise will not be scored but **must be completed** by 5PM on Thursday, August 29, 2008.

RECOMMENDED TEXTBOOK

The **recommended** (NOT required) **text** is the **2nd edition** of **Principles of Medical Genetics** by Gelehrter, Collins, and Ginsburg; Lippincott, Williams and Wilkins, Baltimore, 1998. Note that the chapter titles bear an astonishing resemblance to many of the lecture titles! We hope that you will read the relevant chapters of the text. We plan to use the class time to cover basic concepts, to try to clarify difficult points, update areas in which there have been new advances since publication of the book, and focus on the most interesting aspects of these topics.

For those desiring more readings in the area of molecular medicine and medical genetics, we **recommend** the following:

Strachan and Read, Human Molecular Genetics, 3rd ed., Wiley-Liss, 2004, presents an experimentally-based, detailed exposition of current technology applied to human genetics.

Emery and Rimoin's Principles and Practice of Medical Genetics, 5th ed., Rimoin, Connor, Pyeritz and Korf (eds.), Churchill Livingstone, 2006, and

The Metabolic and Molecular Bases of Inherited Disease, 8th ed., Scriver, Beaudet, Sly, and Valle (eds.), McGraw-Hill, 2001, are excellent, comprehensive reference books. New online edition (OMMBID) launched in 2007.

The Genetic Basis of Common Diseases, 2nd ed., King, Rotter, and Motulsky (eds.), Oxford University Press, 2002, is a detailed exposition of the genetics of common complex diseases.

For Dr. Imperiale's lectures, the **recommended texts** are:

Alberts, et al., Molecular Biology of the Cell, 5th ed., Garland Science, 2007. ... OR

Lodish, et al., Molecular Cell Biology, 5th edition, 2007.

Alternatively, most any up-to-date molecular biology textbook that covers DNA replication and gene expression should suffice.

WEBSITES

GeneClinics <http://www.geneclinics.org/> is an extremely useful site for clinical genetics. It includes almost 400 authoritative, current reviews of a large number of genetic disorders including information on available genetic testing for almost 1500 diseases, as well as links to relevant laboratories. There is also information on patient resources and physician resources, and there are educational resources. We use this site on a regular basis!

The National Human Genome Research Institute of the National Institutes of Health (<http://www.nhgri.nih.gov/>) is another site with educational resources, as well as further information on genetics and genomics research and on the Ethical, Legal and Social Implications (ELSI) Program.

Wendy Uhlmann has prepared a very useful listing of web resources in genetics, published in JAMA this year. Uhlmann WR, Guttmacher AE: Key internet genetics resources for the clinician. JAMA 299 (11) 1356-58, 2008

TEACHING ASSISTANTS

We are very fortunate to have **Grant Rowe** and **Matt Vasievich** as our **teaching assistants** this year. Both are MSTP students who have survived an earlier version of Medical Genetics. Grant has served as Teaching Assistant in this course for the past two years, and Matt is starting his rookie season. Office hours will be held by appointment to try to accommodate better the student's schedules. Students, either as individuals or groups, should contact the TA's, preferably by e-mail, to set up appointments:

REQUIRED EXPERIENCES

In the Medical Genetics Component of Patients and Populations, there are several required experiences. In the RARE circumstance where a student cannot attend, the student must contact their class counselor in advance (or as soon as possible in an emergency) to request a deferral. (Please do NOT contact sequence directors with requests for or explanations of deferrals.) Absences will be approved or denied by class counselors based on the same guidelines used for Quiz and Exam deferrals. Should you obtain a deferral from your class counselor, make up instructions for the required experiences (found below) should be followed.

1. Students who miss a Patient Presentation/MDC with an EXCUSED absence must remediate the exercise by watching the video of the presentation (and signing in the book at the LRC Help Desk saying you had done so), and submitting a written paragraph discussing three major points made in the presentation.
2. Students who miss the Genetics and Ethics Small Group Discussion with an EXCUSED absence must remediate the exercise by reading the cases presented, selecting one case, and writing a paragraph discussing three important points regarding ethics made by the case.

All remediation must be completed and submitted to Dr. Gelehrter before 5 pm on Thursday August 29, 2008.

Students who miss a mandatory exercise without an excuse will have a letter placed in their file regarding professional behavior.

GRADING

Grading is Satisfactory/Fail. In order to pass the **Patients and Populations Course**, you must pass each of the three components of this course (Medical Genetics, Medical Decision-Making, and Pathology). Passing requires a minimum score of 75% in each component.

The grade for the Medical Genetics Component will be distributed as follows:

| | |
|-----------------------------------------|-----|
| Final examination | 50% |
| Quizzes (there will be two quizzes) | 40% |
| Small group attendance/On-line exercise | 10% |

EVALUATIONS

Finally, we would sincerely appreciate your feedback on the course and hope you will make the effort to fill out the on-line **evaluations** thoughtfully and critically. We especially welcome your specific written comments. We take these comments seriously and use them in planning the following year's course. We would especially appreciate written comments on your SGD's and SGD instructors