Genetic and Genomic Medicine: An Essential Part of Primary Care and the Medical School Curriculum-
Message from the National Human Genome Research Institute (NHGRI) of NIH

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Disclaimers

• The presenter has no potential or actual conflicts of interest and no relevant financial relationships.

• This presentation does not necessarily represent the views of the National Human Genome Research Institute (NHGRI) of the National Institutes of Health or Nova Southeastern University College of Osteopathic Medicine.
“It's one of the major landmarks that rank up there with going to the moon. Obviously people think I could be a little biased, but I think historians will agree with me,” Francis Collins, MD, PhD, Director, National Human Genome Research Institute (NHGRI) when the genome was mapped (now Director of NIH).

• Since the final mapping of the human genome April 14, 2003, the field of medical genomics has rapidly evolved. It will soon change the entire complexion of medicine and health care.
Objectives of NHGRI: Primary care physicians must be able to:

- Advise patients about genetic and genomic manifestations of diseases and disorders.
- Acquire a family tree providing information about diseases for which they are at risk.
- Make a determination as to when to refer patients to medical geneticists.
- Be among the advocates of including genomic medicine in medical schools.
Background: Genetics vs. Genomics

- Medical genetics is the study of individual genes and how they impact relatively rare single gene disorders.

- Medical genomics is the study of all genes in the human genome together, including their interaction with each other, the environment, and the influence of other psychosocial and cultural factors.
Building healthcare providers’ genomic competencies

• All healthcare providers must acquire competency in genomics to provide services appropriate for their scope of practice.

• Genomics needs to be integrated into the curricula of health professional education programs, as well as the licensing and accrediting processes.
Because of the pervasive effects of one gene, single-gene disorders may be expressed regardless of the environment, whether cellular or external (i.e., genetics). Others require specific stimuli, for example, phenylalanine in PKU, or many agents for the hemolytic anemia of G6PD deficiency.
• In complex diseases their expected expression is influenced by products of multiple genes interacting with environmental factors throughout development, maturation, and aging (i.e., genomics).

• Epigenetics: the study of how environmental factors over time can alter the way genes work and influence development and health.
The expected expression of complex diseases is influenced by products of multiple genes interacting with environmental factors throughout development, maturation, and aging (i.e., genomics).

Epigenetics looks at how the environment overtime can affect how genes work and influence development and health. *(Blending nature and nurture)*
• Common disorders generally are more amenable to treatment than single gene disorders. In single gene disorders the damage often occurs early in development and is often resistant because of the severity and pervasiveness.
• Although the impact of common diseases often is quite severe, such diseases generally develop gradually, throughout the life span, often presenting in middle age.

• The practitioner often can improve and sometimes prevent symptoms by modifying contributing environmental factors (e.g., diet, exercise, medication, or counseling).

• Some common diseases also are amenable to early intervention, such as the removal of precancerous lesions.
• By understanding environmental contributions to complex disease through education, we can begin to eliminate them or dilute their impact.

• An environment can be created where the remaining major contributions to disease are those resulting from variants in the human genome.
“Sequencing an affected individual's entire "exome"; that is, all of the genes that carry instructions for producing proteins, can reveal critical genes that when mutant, cause inherited disorders.”  
*American Journal of Human Genetics, July 29, 2011*
Every physician has patients where something “runs in the family” (i.e., breast cancer). The clinical availability of personal genome analysis through sequencing the whole exome allows the ordering of a single test that gives information on all genes, including ones known to be linked to breast cancer.

Hulik P. Genomic medicine: personal genome analysis in the doctor’s office. Family Practice News.; November 1, 2011
• Complex diseases such as cancer, heart disease, diabetes, and mental illness are the major contributors to morbidity and mortality in developed and developing countries alike.

• Single-gene disorders are individually rare (generally), and even in the aggregate constitute a much smaller burden of disease and death than do complex diseases.
With the Shortage of Medical Geneticists and Genetic Counselors, What Should be the Primary Care Clinician’s Role in Genomics?

Curricular objectives: Regarding genomics, primary care clinicians should be able to:

• Acquire and interpret a multigenerational family history.

• Employ the genomic basis of health and illness as a part of the process of prevention, diagnosis, and care (e.g., diabetes, colorectal cancer, and cardiovascular disease).
• Give advice on how genetics and genomics affect health. This includes diet, environment, lifestyle and how to identify genetic risks from relatives, close and distant.

• Address the ethical issues involved in genetics and genomics. Five percent of the annual budget of the NHGRI is dedicated to examining ethical, legal and social implications (ELSI) related to human genome research, incorporating specific recommendations into the activities of NHGRI and providing guidance to policymakers and the public.
A focus on the genetic, developmental, and environmental components of disease, and their unique combination in a given individual, will require that health care increases emphasis on prevention.

By establishing a genetic susceptibility to a complex disease, providers will have the alternative of prevention to help patients use environmental factors that can avoid provoking disease or adopt regimens of self examination to detect early indications of illness.
The Challenge

• Genetic/genomic medicine is and will likely continue to be a rapidly evolving discipline.

• We need to prepare future physicians, many of whom will be future primary care providers, to be able to integrate genomic medicine in clinical practice.
NIH/NHGRI Formula for Primary Care Providers Taking on Responsibilities in Genomics*

Do’s

A significant emphasis of the National Human Genome Research Institute meeting was on the extreme importance of integrating genetics and genomics into primary care education rather than relying on individual unconnected courses.

*Developing a Blueprint for Primary Care Physician Education in Genomic Medicine; June 8-9, 2009
Don'ts

Creating didactic courses in genetic and genomic medicine is especially inefficient in trying to achieve the objective of integrating genetic and genomic knowledge and concepts into primary care clinical practice.
Do’s

• Create a generation of primary care providers who incorporate modern genetic/genomic concepts and skills into practice.

• Using **active learning** is most effective to facilitate the learning of clinical genetics/genomics.
The National Human Genome Research Institute (NHGRI) of NIH advises that providing genetic/genomic medicine instruction by organizing a course offered during the medical school curriculum is not as effective as integrating information, concepts, and skills as a “thread” that runs through the curriculum.
Small Group Learning
Scenario

A 32 year old overweight female in a primary care practice office complains of a “sore throat” for the past two days. On quick examination she has what appears to be a non-complicated upper respiratory infection without fever. However, in a questionnaire she completed there is a multigenerational history of diabetes in her family (mother, grandmother, and older brother).
Examples of Questions for Facilitators to Ask

• What are the genomic implications for this patient?

• What steps can you take to further determine her risk of acquiring diabetes?

• What type of follow-up may lessen her risk for acquiring diabetes or delaying its onset?
Pitfalls to be Addressed

1. Will the results of personal genome analysis have meaningful impact on patient care and management?
2. Can a patient opt out of knowing particular results (e.g., genes associated with an increased risk of Alzheimer’s disease)?
3. How will data be stored (including privacy issues)?
Whole-Genome Sequencing

• Within a decade (or less) whole-genome sequencing will be used to help prevent many medical conditions from developing.

• In whole-genome sequencing, a patient’s blood sample or other source of genetic material is used to examine the 20,000 to 25,000 genes making up an individual’s genome.

• Standard genetic testing examines only individual genes (e.g., genes for sickle cell anemia, hemophilia). As a result, physicians often must order multiple tests to get needed genetic information.
• Whole-genome sequencing will enable specialists to identify variations in people’s genetic code that increase their genetic risk of developing such conditions as Alzheimer’s disease, cancer, diabetes and schizophrenia.

• It may reveal the cause of undiagnosed symptoms, provide possible preventive actions, and determine the specific medication likely to be effective (pharmacogenomics).
• Primary care physicians will be able to assess whole-genome sequence results and create preventive care plans for conditions individuals are at risk of developing as part of medical care provided from birth to old age.
By employing genomic medicine in clinical practice:

“Medicine will go from a field where we are reactive to one in which we can prevent symptoms and signs from ever occurring.”

(Robert Marion, MD, Chief Division of Genetics and Child Development, Department of Pediatrics, Children’s Hospital at Montefiore and the Albert Einstein College of Medicine in New York)
Ethical Concerns

• Uncertainties and ethical concerns about whole-genome sequencing need to be resolved before it becomes a standard procedure used by physicians.

• Among the chief worries is what to do with the large number of variants in genes associated with human disease that can show up in a patient’s sequencing.
• “The genome is so complex and some of our understanding of various mutations is so shaky that it’s hard to tell which information is meaningful and which isn’t.” (Robert C. Green, MD, MPH, Associate Professor of Medicine in the Division of Genetics at Brigham and Women’s Hospital and Harvard Medical School in Boston)
There still are no guidelines on:

- Which findings from whole-genome sequencing should be passed on to patients?
- Who should have access to the findings, such as a patient’s employer?
- Should there be access to relatives who could share some of the same genes?

This will alter the way we care for people.

(Robert Marion, MD, chief division of genetics and child development, Dept. of Pediatrics at the Children’s Hospital at Montefiore and the Albert Einstein College of Medicine in New York)
Informing patients about their genetic predispositions

- The human genome contains about 3 billion DNA base pairs, the chemical building blocks forming the two DNA strands. About 3 million such bases vary between individuals. Most of the variations do not affect a person’s health; some indicate a medical risk.
Physicians will have to determine which risks to report to patients. This could lead to unnecessary anxiety, medical tests, and procedures. Patients should have access to their whole-genome sequencing results if they are put into perspective and delivered sensitively. (Paul R. Billings, MD, PhD, internist/clinical geneticist, Carlsbad, Ca)
A patient’s family history may help determine which results to provide to the individual. For example, if a patient’s family history predisposes the patient to diabetes and breast cancer, it is suggested telling the individual, “We will only look at the breast cancer genes and the diabetes genes. We’re not going to look at anything else.”
• Some patients may want to see results for all the genes that could impact their health. It needs to be made clear to patients that a genetic predisposition to a disease doesn’t mean that a patient will necessarily acquire that disease. Or physicians could tell patients, “We absolutely know how to prevent this.”
Personalized Medicine

• From information primary care physicians receive, they will use the whole-genome sequencing results to develop personalized, preventive care plans for a patient (more recently referred to as “precision medicine”).

• Creating personalized treatment plans that target factors such as diet and exercise, will allow doctors to keep symptoms of many conditions from appearing.

(Charis Eng, MD, PhD, Professor and Founding Chair of the Genomic Medicine Institute and Founding Director of the Center for Personalized Healthcare at Cleveland Clinic)
American Medical Association policy says genomic-based personalized medicine will play an increasingly important role in patient care. The AMA is developing educational resources and point-of-care tools to help doctors implement genomic-based medicine.
Privacy Issues

• It is important for the health care community to keep patients’ whole-genome sequencing results private. Patients probably will need to tell relatives about genetic variations (e.g., mutation in the breast cancer gene that could impact those family members).

(Bioethicist Jeffrey Kahn, PhD, MPH, Professor of Bioethics and Public Policy at Johns Hopkins Berman Institute of Bioethics in Baltimore)
• The Genetic Information Nondiscrimination Act of 2008 prevents discrimination by health insurers and employers of people who have known genetic variations that might impact their health. Recent discussions talk about whether the Americans with Disabilities Act provides workplace protection for people with known genetic predisposition for a health condition.
Genomics is Coming- Rapidly

“Primary care physicians should know that genomics is coming. It will be part of their practices.”

(Robert C. Green, MD, MPH, Associate Professor of Medicine in the Division of Genetics at Brigham and Women’s Hospital and Harvard Medical School in Boston)
Evolving Examples of the Implications of Genomic Medicine on Primary Care
New genetic data will be available to any researcher around the world studying Alzheimer's disease (AD). The hope is that the data will help to better understand how genes cause and are affected by physiological changes associated with AD.
• The sequencing of the human genome and the introduction of new technologies have made it possible to analyze multiple genes simultaneously, rather than one at a time.
Pharmacogenomics

• The study of how variations in the human genome affect the response to medications.

• Pharmacogenomics describes such large-scale, often genome-wide approaches.
• **Pharmacogenomics** may permit drugs to be tailor-made for individuals and **adapted to each person's own genetic makeup**.

• Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an **individual's genetic makeup** is thought to be the key to **creating personalized drugs** with greater efficacy and safety.
Pharmacogenomics will make it easy to pick up a side effect of a drug. Every common drug should have genomic data, and every developing drug that looks like it's going to wind up in clinical use should incorporate a genomic-embedded program, so we know who the drug works on and if there are serious side effects. We should be able to predict when to preempt the use of a drug, so we don't use it through trial and error, which doesn't work very well!

Eric J. Topol, MD, Director Scripps Translational Science Institute and Professor of Translational Genomics at The Scripps Research Institute, La Jolla, California
At the end of the day, it is the patients' stories that really affect you the most, more than a bioassay on a certain drug. For example, seeing this child prone on the ground, face down, unable to get up, and then with genomic information they give this child a drug and she is dancing with her sister. That's what I'll remember 4 or 5 years from now, not the 50 loci that were found with type 1 diabetes. For certain people, genomic medicine makes a huge difference.

Bradley A. Patay, MD, Assistant Professor of Medicine at the Scripps Clinic in La Jolla, California Scripps Translational Science Institute, and head of the section of internal medicine at the Scripps Clinic in La Jolla, California