Genomics and healthcare:
Will primary care lead or follow?

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Chief, Genomic Healthcare Branch
National Human Genome Research Institute
National Institutes of Health

Outline

• Why primary care and genomics?

• How did we get here?

• Connecting the dots? Not easy…

• Where do we go from here?
“More than 4 million hospitalizations potentially could be prevented each year by improving the quality of primary care...

Billions of dollars could also be saved by avoiding the need to hospitalize patients for health problems that, in most cases, can be prevented or if already present, kept stable by high-quality care in physicians' offices.”

AHRQ News and Numbers, Aug. 2007

*Trends in Potentially Preventable Hospitalizations among Adults and Children, 1997-2004*


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**Chronic disease!**

- More than 90 million Americans live with chronic illnesses.
- Chronic diseases account for 70% of all deaths in the United States.
- The medical care costs of people with chronic diseases account for more than 75% of the nation’s $1.4 trillion medical care costs.
- Chronic diseases account for one-third of the years of potential life lost before age 65.

CDC

http://www.cdc.gov/nccdphp/overview.htm#2
The 10 Leading Causes of Death ‘02

1. Heart disease (28.5% of deaths in ‘02) *
2. Cancer (22.8%) *
3. Stroke (6.7%) *
4. Emphysema (5.1%) *
5. Injury (4.4%)
6. Diabetes (3.0%) *
7. Pneumonia/Influenza (2.7%)*
8. Alzheimer disease (2.4%) *
9. Kidney disease (1.7%) *
10. Blood infection (1.4%)*

Chronic disease!

• All have at least some genetic component

• Occur over a long time, and can usually be treated, but not cured

• Might be avoided (or at least held off) in many cases if we could effectively
  – Assess risk
    – Effectively intervene (individualized prevention, environmental modification, medication)
Can genomics be used to get a handle on chronic disease?
Why google wants your genes

The Telegraph 6/10/07

DNA fingerprinting could turn the titian of web-searching into a medical behemoth, says Emma Hartley

As if gauging the nation’s receptiveness to new technology, Lord Justice Sedley suggested recently that the UK’s whole population and its visitors should have their DNA added to a Home Office database that already holds genetic information about four million people – five per cent of the UK population, and the highest proportion of any state in the world.

Sedley is known for his progressive views and has a record on the bench of upholding civil liberties, so this was electrifying stuff. Not only would the measure confer obvious advantages on the police, while getting around the objection by civil libertarians that ethnic minorities are disproportionately represented on the database, it also promised a practical use for a technology so new that the four million sets of data were collected before most of us even knew it was happening.

Ever since the completion of the Human Genome Project in 2003, in which the first whole set of human chromosomes was decoded into its constituent bases, scientists and biotech businesses have been agog at the possibilities. Spying an opportunity, a group of new companies has begun offering to "mine" your genes for information about your ancestors.

One is Oxford Ancestors (oxfordancestors.com), started by Prof Brian Sykes of Oxford University, which will tell you from which of 36 geographically located "tribes" your ancestors originated, all for £180. Cambridge University offers a similar service for £10 less.

But the decoding of the human genome promises much more – just ask a geneticist. An entire history of life on Earth is buried within the cells of our bodies if you possess the skill to interpret it, as is information about our collective longevity, degeneration and ultimate demise. The big question, though, is "What does
1.1 Billion Ambulatory Visits in 2004 in the U.S.

CDC data

Primary Care: 48%
Med Specialist: 16%
Surg Specialist: 10%
ER: 8%
Clinic: 18%
Primary Care

“If you knew there was a genetic disorder already present in your immediate family, with what or whom would you be most likely to consult to learn about the possibility of inheriting it?”

- 71% chose their PCP

1998 AMA survey of 1000 U.S. Adults

Access to genetic services

NSGC web site and places I’ve lived + 50 miles:

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Jim receiving his own personal genome sequence on a DVD

May 31, 2007
Cumulative Pace of Disease Gene Discovery 1981-2005

Number of Genes Associated with Disease

Year

Source: Online Mendelian Inheritance in Man
Gene Discoveries for Common Complex Diseases

NIH Research Initiatives

* Breast CA, type 1 DM, obesity…
Progress in Genotyping Technology

Continued Progress in Genotyping Technology
<table>
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<tr>
<td>2007</td>
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A common variant associated with prostate cancer in European and African populations

Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24

Multiple regions within 8q24 independently affect risk for prostate cancer

Genome-wide association study of prostate cancer identifies a second risk locus at 8q24
A Genome-Wide Association Study Identifies IL23R as an Inflammatory Bowel Disease Gene

Richard H. Duerr,1,2 Kent D. Taylor,1,2 Steven R. Brant,2,3,4 John D. Rioux,2,3,5 Mark S. Silverberg,6,7 Mark J. Daly,8,9,10 A. Hilary Steinhardt,1,2 Clara Abraham,1 Miguel Regueiro,1,2 Anne Griffiths,1,2 Themis Dassopoulos,1,2 Alan Biston,13 Huiying Yang,1,2,3,4,8 Stephan Torguson,6,10,11 Lisa W. Datta,1 Emily O. Kistner,1,2,3,4,8,9,12 L. Philip Schумen,15 Annette Lee,16 Peter K. Gregersen,17 M. Michael Barnard,1 Jerome L. Rotter,1,4 Dan L. Nicholas,1,1,2,3 Judy H. Cho,1

A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity

Timothy M. Frayling,1,2,3 Nicholas J. Timpson,1,2,3 Michael N. Weedon,1,2,3 Eleftheria Zeggini,1,2,3 Rachel M. Freathy,1,2,3,4 Cecilia M. Lindgren,1,2,3,4 John R. B. Perry,1,2,3 Katherine S. Elliott,1 Hana Lango,1,2 Nigel W. Rayner,1,2,3 Beverley Shields,1,2 Lorra W. Harries,2 Jeffrey C. Barrett,2,3 Ian Sander,2,3 Christopher J. Groves,1 Bridget Knight,1 Ann-Marie Patch,2,6 Andrew R. Ness,2 Shah Ebrahim,1 Debbie A. Lawlor,1 Susan M. Ring,1 Yoav Ben-Shlomo,1 Marjo-Riitta Jarvelin,10,11 Ulla Sovio,10,11 Amanda J. Bennett,1 David Melzer,1,3 Luigi Ferrucci,3,13 Ruth J. F. Loos,1,14 Inês Barroso,1,4 Nicholas J. Wareham,1 Fredrik Karpe,3 Katharine R. Owen,1 Leo R. Cardon,1 Mark Walker,15 Graham A. Hitman,17 Colin S. A. Palmer,18 Alex S. F. Doney,19 Andrew D. Morris,19 George Davey-Smith,1 The Wellcome Trust Case Control Consortium,20 Andrew T. Hattersley,1,21,22 Mark I. McCarthy,1,23

Crohn’s Disease

Obesity
A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott, Karen L. Mobliha, Len L. Bonnerca, Cristina L. Wilke, and Yan Li

Identifying the genetic variants that predispose to type 2 diabetes is a critical step in understanding the disease. This study used a genome-wide association approach to identify multiple susceptibility variants associated with type 2 diabetes in a Finnish population. The results provide insights into the genetic basis of diabetes and may aid in the development of targeted therapies.

Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini, Michael N. Neale, Cecilia A. Lindgren, Timothy R. Frayling, Katherine S. Elliott, and John R. B. Perry

The replication of genome-wide association signals in the UK population has revealed additional risk loci for type 2 diabetes. This finding highlights the importance of international collaborations in genetic research and the potential for these findings to inform personalized medicine approaches.

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease


This study identified a common allele on chromosome 9 that is associated with coronary heart disease. The findings suggest new therapeutic targets for cardiovascular diseases and highlight the importance of genetic variants in disease susceptibility.

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction


This study identified a common variant on chromosome 9p21 that affects the risk of myocardial infarction. The findings suggest that this variant plays a role in the development of cardiovascular disease and may inform future genetic and clinical research.

Type 2 Diabetes

Heart Disease
**Genome-wide association study identifies novel breast cancer susceptibility loci**

Douglas F. Easton1, Karen A. Pooley2, Alison M. Dunning2, Paul D. P. Pharoah3, Deborah Thompson1, Dennis G. Ballantine4, Jeffrey P. Strauss3, Jonathan Morrison1, Helen Field4, Robert F. Heden5, Nicholas Wareham2

A genome-wide association study identifies alleles in **FGFR2** associated with risk of sporadic postmenopausal breast cancer

**Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor–positive breast cancer**

Simon N Stacey1, Andrei Manolescu1, Patrick Soulen1, Thorunn Rafnar1, Julius Gudmundsson1, Sigurjun A Gudjonsdottir1, Giödi Masson1, Margret Jakobsdottir1, Steinunn Thorlacius1, Agnar Helgason1, Katja K Aher1,2,3, Luc J Stroebel1, Marijo T Albers-Akare2, Doraine W Swindells5, Brian E Henderson5, Lawrence N Kolonel7, Luc Le Marchand8, Esther Millenstaedt, Baq Al Andro8, Javier Godina8, Maria Dolores Garcia-Prieto8, Eduardo Poh2, Alejandro Tore9, Magali Mony9, Jona Saemundsdottir10, Valgerdur H Backman2, Lucas Gudmundsson1, Kristjana Kristjansdottir1, Jon T Bergthorsson2, Jelena Kostic11, Michael J Frigge1, Frank Geller1, Daniel Gudbjartsson1, Helgi Sigurdsson1, Thea Jonsson12, Jon Hrafnsdottir1, Jakob Johannsson1, Thorarinn Svetaisson1, Gudrun Myrdal1, Hildur Niels Grimsson1, Thorvaldur Jonsson1, Susanna von Hau1, Barbro Werelius13, Sara Margolina14, Anna Lindblom15, Jose I Mayo16, A. Christopher A Hattersley17, Lambertus A Kiemeneij18, Oskar Th Johannsson15, Jeffrey R Golberger1, Umut Therese Widjodottir1, Augustine Kong1 & Karl Stefansson1

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**Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes**

John A Todd1, Neil M Walker1,9, Jason D Cooper9,10, Deborah J Smyth9,10, Kate Downes1, Vincent Flanagan1, Rebecca Bailey1, Sergey Nejentsev1, Sarah F Field1, Felicity Payne1, Christopher E Love1, Jeffrey S Szeiuku1, Jason P Haffner1, Brian Zeitz1, Jennifer H M Yang1, Adrian Vella1,2, Sarah Nuttall1, Helen E Stevens1, Helen Schultenbarg1, Gillian Coleman1, Meeta Masaria1, William Meadoos1, Luc J Smink1, Barry Healy1, Oliver S Burren1, Alex A C Lam1, Nigel R Ovington1, James Allen1, Ellen Adami1, Hsin-Tak Leung1, Chris Wallace1, Joanna M M Howson1, Cristian Guja1, Constantin Ioinescu-Tirgoviste1, Genetics of Type 1 Diabetes in Finland1, Matthew J Simmonds3, Joanne M Heward3, Stephen C L Gough3, The Wellcome Trust Case Control Consortium4, David B Dunger3, Linda S Wicker1 & David G Clayton1

**Type 1 Diabetes**
Alzheimer’s Disease

GAB2 Alleles Modify Alzheimer’s Risk in APOE 44 Carriers

Neuron 54, 713-720, June 7, 2007

Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma

Asthma
Atrial fibrillation

2007: The Year of GWA Studies?
Consistently replicated associations found for:
• 10 Jun 2007: Celiac disease
• 1 Jul 2007: Atrial fibrillation
• 8 Jul 2007: Colorectal cancer
• 15 Jul 2007: Gallstones
• 18 Jul 2007: Periodic limb movements in sleep
• 19 Jul 2007: HIV viral setpoint
• 26 Jul 2007: Childhood asthma
• 29 Jul 2007: Multiple sclerosis
• 1 Aug 2007: Amyotrophic Lateral Sclerosis
• 9 Aug 2007: Exfoliation glaucoma
• 2 Sep 2007: Height
• 5 Sep 2007: Rheumatoid arthritis

Variants conferring risk of atrial fibrillation on chromosome 4q25
Daniel F. Gudbjartsson1, David O. Arnar2, Anna Helgadottir1, Solveig Gretarsdottir1, Hilma Holm2,
Asgáir Sigurðsson1, Adalbjorg Jonasdottir1, Adam Baker1, Gudmar Thorleifsson1, Kristleifur Kristjansson1,
Arnar Palsson1, Thorarinna Blondal1, Patrick Sulem1, Valgerdur M. Backman1, Gudmundur A. Hardarson1,
Ebbja Paludottir1, Agnar Helgason1, Ruma Sigurjonsdottir1, Jon T. Sverrisson1, Konstantinos Kostulas1,
Maggle C. Y. Ng2, Larry Baum2, Wing Yee So2, Ka Sing Wong2, Juliana C. N. Chan2, Karen L. Furie2,
Steven M. Greenberg6, Michelle Sale6, Peter Kelly6, Calum A. MacRae6, Eric E. Smith6, Jonathan Rosand6,
Jan Hillert6, Ronald C. W. Ma6, Patrick T. Ellmore6, Gudmundur Thorsteinsson7, Jeffrey R. Gulcher1, Augustine Kong1,
Unnur Thorsteinsdottir1 & Kari Stefansson1
Following from GWAS

- **Drug discovery** – novel pathways
- **Disease risk prediction** – panels of markers
- **Treatment selection** – “right drug, right dose”
- **Prognosis** – how will the disease affect you

Translating Genomics…

- Genomic discoveries relevant to common disease diagnosis and management are coming at an increasing rate.
- Basic discoveries are leading to the development of clinical applications.
- Ergo, improved healthcare is around the corner!
Translating Genomics…

- Genomic discoveries relevant to common disease diagnosis and management are coming at an increasing rate.
- Basic discoveries are leading to the development of clinical applications.

Mind the gap!

- Ergo, improved healthcare is around the corner!

“The bulk of this {healthcare} spending growth, however, appears to result not from increasing disease prevalence but from the development and diffusion of new medical technologies and therapies.”

Orszag PR, Ellis P.  NEJM Nov. 1 2007
Filling the gap

» Does the application **address** a clinical need?
» Does the application **meet** a clinical need?
» Is the application acceptable to patients?
» Is the application acceptable to health care providers?
» Is the application acceptable to insurers?
» Is the application acceptable to society?
» How are patients best educated about the application?
» How are providers best educated about the application?

Who will (**pay to**) fill the gap?
Bench Scientists
Clinical Scientists
Clinicians
Patients

Multiplex Genetic Susceptibility Testing:
A prototype for applied research to inform personalized medicine

Colleen M. McBride, PhD. & Larry Brody, Ph.D.

Research Partners:
National Human Genome Research Institute
Henry Ford Health System
Group Health Cooperative
Cancer Research Network (NCI)
ClinSeq: A translational research project in clinical genomics

NIH Intramural Sequencing Center

NIH Clinical Center

Medical & Statistical Genetics

NHLBI

Health Professionals’ Understanding of Human Genetic Variation Study

Vence Bonham, JD
Associate Investigator
Social and Behavioral Research Branch
Principal Investigator
Can health care providers become genetically literate in time?

Key Obstacles to Genetic Literacy in Primary Care

- Climate
- Time
- Money
Climate

“Unless there are changes in the broader health care system and within the specialty, the position of family medicine in the United States will be untenable in a 10- to 20-year time frame.”


Time:

Patient priorities

Physician priorities

Insurer priorities

Other priorities
Time:

- 1996 USPSTF Guidelines
- 2500 patients
- 1773 hours or 7.4 hours every working day for a year!
- Average pt is due for 25 guidelines!
- Getting worse not better!

Money:

Lack of adequate value/reimbursement for E/M codes is a major barrier to primary care taking on the management of genetic topics.

alcohol abuse vs. colonoscopy
Money:

Aside from infrastructure development, should much be spent on moving genetics up in the agenda of current primary care, given competing priorities? May 3, 2006 JAMA

Education:

- Genetics community has been reaching out for years with varying degrees of success
  - Genetests/Geneclinics
  - March of Dimes education modules
  - NEJM genetics articles
  - NCHPEG
  - Meeting presentations
Genetics in Primary Care (GPC)
Training Program Curriculum Materials

Wylie Burke, Kelly Frye-Edwards, and Linda E. Finsky, eds.
Revised and updated, September, 2001
Education:

- Why might efforts have failed?
  - Top down approach
  - Not very evidence-based
  - Mechanism/theory driven
  - Subject fatigue
  - Lack of maturity of genetics in areas of interest to primary care
  - Preaching to the converted
Family history is still the cheapest, most accessible, most time-tested way to get a rough estimate of the genetic component of disease risk.

Family History may change how your doctor may screen or treat you for:

- Breast Cancer
- Cardiomyopathy
- Colon Cancer
- Coronary Artery Disease
- Developmental Delay
- Diabetes
- Dyslipidemia
- Emphysema
- Gastric cancer
- Hearing Impairment
- Heart failure
- Hip Dysplasia
- Kidney Cancer
- Hypertension
- Iron Def Anemia
- Liver Cancer
- Osteoporosis
- Pancreatitis
- Prostate Cancer
- Syncope
- Thromboembolism
- Thyroid Cancer
- Thyroid Disease
- Urticaria
- Visual Impairment

From Alan Guttmacher, MD address 10/11/04
Family History
Mother, father, brother, sister, child affected:

• Type 2 diabetes – 2-6X risk increase
• Hypertension – 2-3X risk increase
• Coronary heart disease – 2X risk increase

Web-Based Family History
Tool Available in English and Spanish

www.surgeongeneral.gov/familyhistory/
Do YOU know Vanessa?

Vanessa, 35, just finished walking with her daughter and feels great. These walks are now part of their daily routine, and her health care provider tells her she won't need medication for her diabetes in the foreseeable future.

But for a thorough primary care provider, Vanessa's outlook may not have been so good. All too often, diabetes goes undiagnosed for years while high blood sugars silently attack vulnerable organs like the eyes, kidneys and heart. By the time symptoms appear, organ damage has already occurred.

Luckily for Vanessa, her health care provider asked about her family history at her last visit. Her mother, aunts and grandmother all developed diabetes in their mid-40s. Vanessa's fasting blood sugars were in the diabetic range.

One year later, thanks to changes in diet and exercise, Vanessa's sugars are nearly normal and she is helping the rest of her family adopt a healthy lifestyle.

The next time you see a "Vanessa," take the time to obtain a complete family history. She—and her family—will thank you.

The U.S. Surgeon General's My Family Health Portrait Tool can help your clients gather and organize their family history before visiting your office. Direct them to it at www.surgeongeneral.gov/familyhistory/
Evaluating Family History for Preventive Medicine and Public Health

Family history is known to be a risk factor for many chronic diseases—including coronary heart disease, cancer, and diabetes—but its use in preventive medicine has been de-emphasized compared with modifiable risk factors such as smoking and diet. Although clinicians are trained to collect family histories, they often fail to do so because of lack of time, inadequate reimbursement, and a lack of skill in interpreting family history information. According to the HealthDay's 2004 survey, 96% of Americans believe that knowing their family history is important to their health, yet only 3% have ever tried to gather and organize their family health history.

Most common diseases result from the interactions of multiple genes with multiple environmental factors in complex patterns that, despite progress in sequencing the human genome, are unlikely to be understood fully in the near future. In the meantime, a person's family health history can be used as a low-cost, low-tech "genomic tool" with which to capture the interactions of genetic, environmental, and behavioral factors in determining that person's disease risk. Recognizing the importance of family history for disease prevention and health promotion, the National Office of Public Health Genomics (NOPHG) at the Centers for Disease Control and Prevention (CDC) began CDC's Family History Public Health Initiative in 2005.

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Evidence Report/Technology Assessment
Number 159

Collection and Use of Cancer Family History in Primary Care

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Guadalupe Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 250-02-0020

Prepared by:
McMaster University Evidence-based Practice Center, Hamilton, ON
EMR and Genomics

- Risk stratification by expert systems

- Point of care patient/physician education

- Tracking and integration with other health care
American Health Information Community

Personalized Health Care Workgroup Recommendations

Douglas E. Henley
American Academy of Family Physicians

John Glaser
Partners HealthCare

July 31, 2007

Family Health History

Recommendation 3.0:
A multi-stakeholder workgroup, including the private sector, federal health care providers, and federal Public Health Service agencies, should be formed to develop a core minimum data set and common data definition available for primary care collection of family health history information.
Genomics and Healthcare

**Promise**
- Well educated providers
- Understands genetic and environmental risk
- Tests appropriately, proactively takes proven steps to mitigate risk
- New, effective, cost-saving therapies are developed based on genomic insights

**Pitfall**
- Poorly educated providers
- Over- or under interprets genetic and environmental risks
- Gets tests and fails to act, or acts on unproven interventions
- Minimally effective therapeutics developed and effectively marketed for “pseudo-disease”
Multiple Marker Testing: A Disruptive Technology?

- What will the business model be ultimately?
- What position will the FDA take on this type of testing?
- What will be the fate of the data?
  - In the company’s domain?
  - In the patient’s domain?
  - In the doctors domain?
- Where will the costs and benefits accrue?

Should medical societies (especially primary care societies) review and or take a position on this type of testing?
THANKS!

Slides courtesy of:

Leslie Biesecker, NHGRI
Francis Collins, NHGRI
Alan Guttmacher, NHGRI
Teri Manolio, NHGRI
Colleen McBride, NHGRI