Looking Through a Genetic Lens Broadly

David L. Brown, M.D.
Chair, Anesthesiology Institute
Cleveland Clinic

Looking Through a Genetic Lens Broadly

David L. Brown, M.D.
Conflicts: None
Daily practice: POA
"Plain old anesthesiologist"

Looking Through a Genetic Lens Broadly

1. Benefits of genomic advances
2. Risks of these advances
3. Disease and genomics
4. Safeguards

Looking Through a Genetic Lens Broadly

1. **Benefits of genomic advances**
2. Risks of these advances
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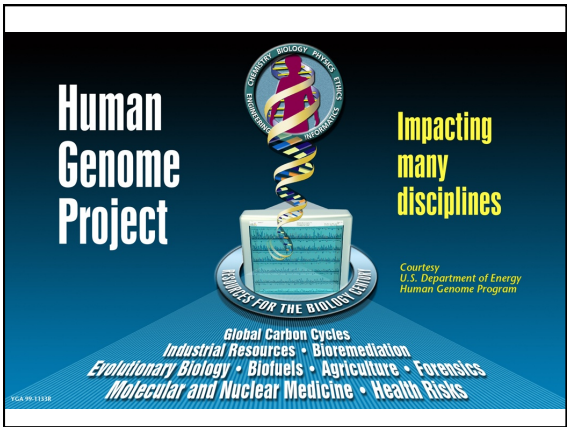
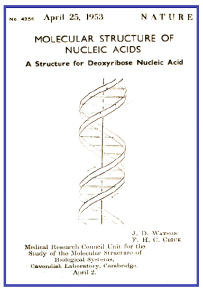
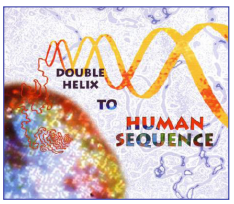
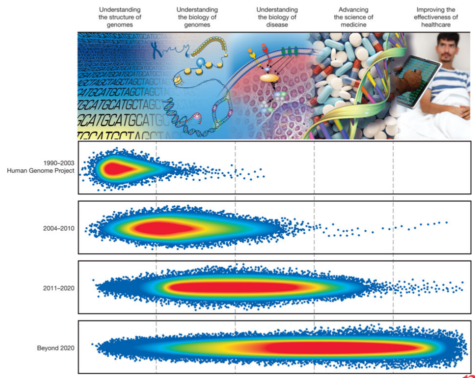


April 1953 → April 2003

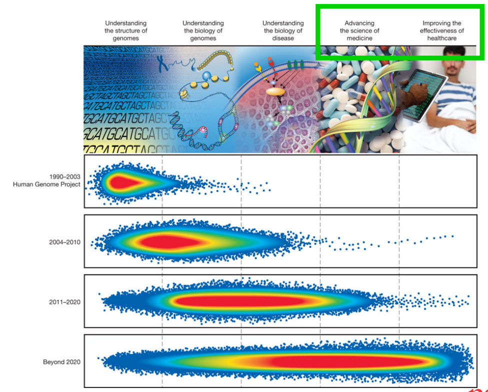




Francis Collins 2008



E D. Green *et al*. *Nature* **470**, 204-213 (2011) doi:10.1038/nature09764



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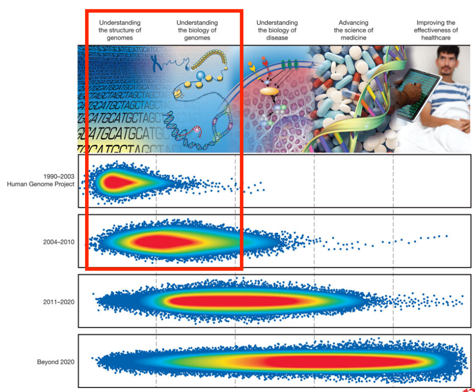

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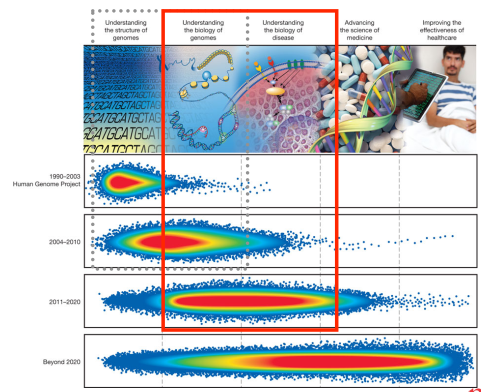


E D. Green *et al*. *Nature* **470**, 204-213 (2011) doi:10.1038/nature09764

Today

Disease with Genetic Component

Identify Genetic Risk Factors

Accelerated by Human Genome Project and HapMap

Diagnostics

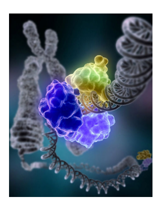
Pharmacogenomics

Preventive Medicine

Therapeutic Developments

- Gene Therapy
- Drug therapy

Time



Human Genome mapping was completed in 2003 via use of technology developed by **Applied Biosystems** and others.

March 9, 2011 had US regulators approve *Benlysta*®, the first new drug for lupus in 52 years developed by **Human Genome Sciences**

In September, 2010 **Santaris Pharma** began trial of Hepatitis C drug that blocks the activity of genetic material needed by the virus to grow in the liver.

Gene sequencing machines, typically costing between $80,000 and $700,000, help researchers analyze strings of chemical codes that turn into proteins, enzymes, and other molecules.

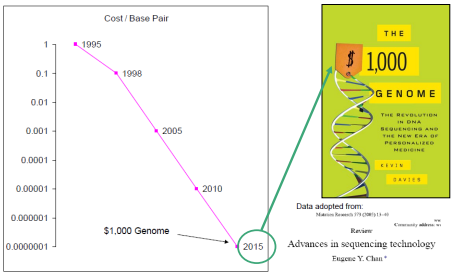
Genomic startups have funding increased 23% since 2007, even while biotech funding decreased 31% overall. There was $261 Million in 2010 of venture capital funding for genomic startups.

Bloomberg Business Week, March 21, 2011

About five years ago, DNA sequencing of an individual's genome cost about $1 million. Three years ago, that price tag had dropped to about $10,000, and the number continues to fall.

New tools and technologies are emerging to reduce the cost of DNA sequencing so that, ultimately, it can be a routine part of both research and medicine. Experts say the threshold for making that happen is the **$1,000 genome**. ("Dr. Stephen Turner: Creating DNA Sequencing Solutions").

Cost of DNA Sequencing



Sandy Aronson
Executive Director of Information Technology
Harvard Medical School – Partners HealthCare
Center for Genetics and Genomics

With a simple saliva sample we'll help you gain insight into your traits, from baldness to muscle performance. Discover risk factors for 95 diseases. Know your predicted response to drugs, from blood thinners to coffee. And uncover your ancestral origins.

Plus, get alerts as new discoveries are made about **your DNA**!*

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Broad societal focus on personal autonomy and control over "nature" encourages genomic advances

Personal Observation: DL Brown, 2011

Looking Through a Genetic Lens Broadly

Largest risk to advances in genomic research is that those leading these efforts over promise the upside, and negatively impact long term governmental research funding

Personal Belief: DL Brown, 2011

PERSPECTIVE

Nature 2011

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[2] & National Human Genome Research Institute*

There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

PERSPECTIVE DRINKING FROM THE FIRE HOSE — STATISTICAL ISSUES IN GENOMEWIDE ASSOCIATION STUDIES

STATISTICS AND MEDICINE

Drinking from the Fire Hose — Statistical Issues in Genomewide Association Studies

David J. Hunter, M.B., B.S., and Peter Kraft, Ph.D.

Related article, page 443

"The past 3 months have seen ating the need for guessing which The main problem with this strategy is that because of the

"There have been few, if any, similar bursts of discovery in the history of medical research…"

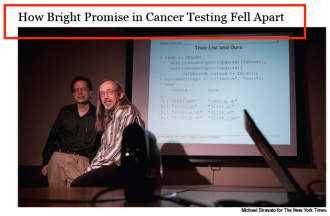
ost studained in samples ower to

and in this issue of the Journal, lated to the disease. Some of these In addition, most variants identified recently have been associated coronary artery disease (reported associations have been found in with modest relative risks (e.g., by Samani et al., pages 443–453). regions not even known to har- 1.2 for heterozygotes and 1.6 for These genomewide association bor genes, such as the 8q24 re- homozygotes), and many true as- studies have been able to exam- gion, in which multiple variants sociations are not likely to exceed ine interpatient differences in in- have been found to be associat- P values as extreme as 10^{-7} in an herited genetic variability at an ed with prostate cancer.[2] Such initial study. On the other hand, unprecedented level of resolution, findings promise to open up new a "statistically significant" finding thanks to the development of mi- avenues of research, through both croarrays, or chips, capable of as- the discovery of new genes rele-

Hunter DJ and Kraft P: N Engl J Med 2007

How Bright Promise in Cancer Testing Fell Apart

The New York Times



Michael Stravato for The New York Times

Keith Baggerly, left, and Kevin Coombes, statisticians at M. D. Anderson Cancer Center, found flaws in research on tumors.

By GINA KOLATA
Published: July 7, 2011

"The Duke saga began when a prestigious medical journal, ***Nature Medicine***, published a paper in 2006 by Anil Potti, a cancer researcher at Duke University; Joseph Nevins, a senior scientist there; and their colleagues. The described genomic tests that looked at molecular traits of cancerous tumors and figured out which chemotherapy would work best"

NYT; July 7, 2011

Joseph Nivens,Ph.D.

Anil Potti, M.D.

How Bright Promise in Cancer Testing Fell Apart

The New York Times

The situation finally grabbed the cancer world's attention – not because of Baggerly and Coombes – but because a trade publication, The Cancer Letter, reported the lead researcher, Dr. Potti, had falsified parts of his resume; claiming among other things that he had been a Rhodes scholar.

"Th… medical journal, ***Nature Medicine***, pub… Potti, a cancer researcher at Duke University; Jose… scientist there; and their colleagues. The described geno… tests that looked at molecular traits of cancerous tumors and figured out which chemotherapy would work best"

NYT; July 7, 2011

Looking Through a Genetic Lens Broadly

An equally large risk to advances in genomics work is fear that "my" individual genetic information will adversely impact "my" insurability, future health care, or employment.

Personal Belief: DL Brown, 2011

People are Afraid

- NIH research with families at risk for hereditary colorectal cancer has shown that the number one concern regarding genetic testing is the fear of losing health insurance.
- Even health care providers are vulnerable to these fears. A survey of the personal attitudes of cancer genetics specialists showed that 68% of respondents would not bill their own insurance companies for cancer-related genetic testing due to fears of discrimination, and 26% said they would use an alias when being tested.

Non-Discrimination Legislation: A 13 Year Effort

- Efforts to pass federal legislation protecting all Americans from discrimination based on their genetic information began in 1995, with 14 different bills introduced over the years
- Entrenched opposition by employers, lesser difficulty with the insurance industry

- "The first major new civil rights bill of the new century"

Senator Edward Kennedy
April 24, 2008

GINA Becomes Law!

May 21, 2008

110th CONGRESS
1ST SESSION

S. 1053

S.358

H.R.493

AN ACT

To prohibit discrimination on the basis of genetic information with respect to health insurance and employment.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Genetic Information Nondiscrimination Act of 2003".

"GINA"

Chronic illness: Hepatitis C
Personal story

- Military practice - **onset asymptomatic**
- 35-year history
- **Uninsurable** outside large group (life, health, disability)
- ***Extras*** not available
- VA – service connected

What is GINA?

- A federal law that prevents health insurers and employers from discriminating based on an individual's genetic information
- The bill is intended to allow Americans to take advantage of the benefit of genetic testing without fear of losing their health insurance or their jobs

MK Holohan, J.D.; National Human Genome Research Institute, 2008

What will GINA do?

- Prohibits group and individual health insurers from using a person's genetic information in determining eligibility or premiums
- Prohibits an insurer from requesting or requiring that a person undergo a genetic test
- Prohibits employers from using a person's genetic information in making employment decisions such as hiring, firing, job assignments, or any other terms of employment
- Prohibits employers from requesting, requiring, or purchasing genetic information about a person or his or her family members

MK Holohan, J.D.; National Human Genome Research Institute, 2008

What will GINA do?

- Prohibit health insurers from requiring genetic information or using it in decisions regarding coverage, rates, or preexisting conditions
- Prohibit employers from requiring genetic information or using it for decisions regarding hiring, firing, or any terms of employment

MK Holohan, J.D.; National Human Genome Research Institute, 2008

What GINA does not do

Does not prevent health care providers from recommending genetic tests to their patients

Does not mandate coverage for any particular test or treatment

Does not prohibit medical underwriting based on current health status

Does not cover life, disability, or long-term care insurance

Does not apply to members of the military

Does not preempt state law

MK Holohan, J.D.; National Human Genome Research Institute, 2008

What GINA does not do

Hepatitis C – Personal Experience

Does not prevent health care provide… genetic tests to their patients

Does not ma… any particular test or treatment

Do… …ot medical underwriting based on current health status

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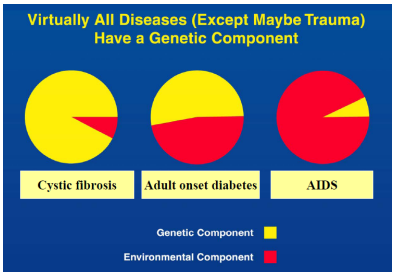
Getting Personal: Genomic Medicine is Near
By Alison Davis
April 28, 2010

Imagine the future … It is 2030, and at a routine visit to the doctor you hand over your personal DNA chip to the receptionist along with your credit card for that visit's co-payment. On the chip is a key component of your medical record: the readout of all of the genes that you inherited from your parents.

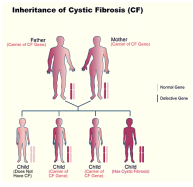
That's all 23,000 of the DNA-based words — your genes — in one place. Because each person's DNA is as unique as her/his actual fingerprint, the field of study known as genomic medicine offers the chance for treatment strategies tailored specifically to individuals.

By 2030, research will have told us what our genes can tell us about our health, and what they can't. Likely, scientists will have defined several signatures of genetic risk that give you and your doctor important information to help you stay healthy, or to take concrete preventive steps to keep disease away. But the DNA chip can't replace common sense about some basic things: You don't need a DNA chip to know that you shouldn't smoke, that you should maintain a healthy diet, and that you should get off the couch for regular exercise.

What will it take to get to this day when personalized medicine becomes routine, as opposed to the "one-size-fits-all" medicine of today? **The pace of genomic research and related technology development has been so quick that it's difficult to digest the new knowledge and what it all means.**

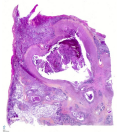


Francis Collins 2008

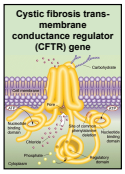


autosomal recessive

Cystic Fibrosis



Mucous plug and bronchiectasis



This predisposition is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, resulting in:

- the absence of CFTR-mediated Cl^- **secretion** and regulation of epithelial Na^+ channel (ENaC) function;
- the sole dependence on extracellular ATP to rebalance these ion transport processes through P2 purinoceptor signaling.

International researchers, co-led by a Swiss team, have discovered three genes in the DNA of HIV-infected patients that offer protection against the virus.

The EuroChavi consortium, coordinated by Amalio Telenti, sifted through data collected from more than 30,000 patients.

They arrived at 486 patients who had had multiple blood tests documenting viral loads after infection and before they started receiving antiretroviral treatment.

Patients involved in the study came from Switzerland, Italy, Britain, Australia, Spain and Denmark. The genetic analysis was performed at the universities of Lausanne and Geneva, and Duke University in the US.

Telenti's team spent 18 months tracking the genes (Keystone)

"We found three genes that were very powerful against the virus. If you have the good luck to have these gene variants, they will protect you from the virus," Amalio Telenti of Lausanne University's institute of microbiology told swissinfo.

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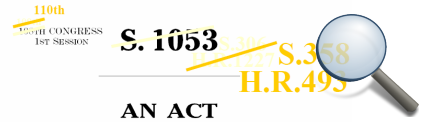

MK Holohan, J.D.; National Human Genome Research Institute, 2008

Personal autonomy and control over "nature"

Where is balance point?

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SCIENTIFIC AMERICAN™

Genetic education: Reflections on Berkeley's student gene-testing program

Geneticist Jasper Rine reflects on a controversial gene-testing programme.

September 21, 2010 By Zoë Corbyn

An ethical storm hit the University of California, Berkeley, earlier this year after it invited more than 5,000 incoming students to receive a personal genetic analysis of three genes associated with how they metabolize lactose, alcohol and folic acid. Privacy fears led to a public outcry and a bill in the California legislature to block the program. That effort failed, but the California Department of Public Health has since ruled that federal law prohibits the university from giving students their individual results.

You have put a lot of yourself into the program--even having your own genes tested for a range of diseases to present the results to the students--what has driven you to get so involved?

We all have a fundamental right to know about ourselves. That right needs to be coupled with the **means of understanding**, and that is an important role for universities. Ignorance is never illuminating. The **importance of the issues surrounding personal genetic information are obvious**, and knowledge trumps fear, but it sometimes takes a while.

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Genetic education: Reflections on Berkeley's student gene-testing program

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Societal Outrage

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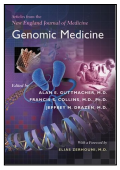

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Karen Lu: Cancer is an expanding field for genetic counselors

THE BROADENING SCOPE OF MEDICAL GENETICS OFFERS A RANGE OF CAREER OPPORTUNITIES, FROM JUNIOR FACULTY POSITIONS TO SENIOR LEADERSHIP ROLES, AND STRONG BASIC SCIENCE KNOWLEDGE IS AN INTEGRAL REQUIREMENT FOR MANY EMPLOYERS. "THERE'S A BIG DEMAND AT THE MOMENT FOR CLINICAL GENETICISTS WHO SPEND A SIGNIFICANT COMPONENT OF THEIR TIME IN RESEARCH," SAYS DARRYL WAGGONER, MEDICAL DIRECTOR OF HUMAN GENETICS AT THE UNIVERSITY OF CHICAGO MEDICAL CENTER.

ONE PARTICULAR GROWTH AREA IN THE JOB MARKET IS **GENETIC COUNSELLING**. "AS GENETICS LOOKS MORE INTO SUBTLE GENETIC SUSCEPTIBILITIES TO MORE COMMON DISEASES, THERE'S GOING TO BE A HUGE ROLE FOR GENETIC COUNSELLORS TO INTERPRET WHAT'S HELPFUL TO KNOW AND WHAT'S NOT," SAID THEREASA RICH, A GENETIC COUNSELLOR AT THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER IN HOUSTON. THERE IS ALSO AN INCREASING NEED FOR MORE SPECIALISED COUNSELLORS. **"THE CANCER FIELD IS PROBABLY THE LARGEST GROWING JOB MARKET," SAYS KAREN LU, CO-DIRECTOR FOR CLINICAL CANCER GENETICS AT MD ANDERSON CANCER CENTER.**

ACGME

Medical Genetics Training

1. 52 ACGME accredited programs
2. 207 trainee positions approved in these programs
3. 88 trainees appointed in programs

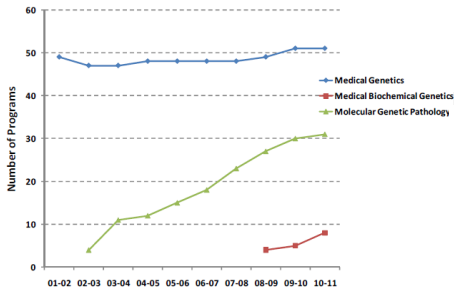
Medical Genetics Training

- Clinical medical geneticists are physicians who provide comprehensive diagnostic, management, treatment, risk assessment, and genetic counseling services for patients who have or are at risk for having genetic disorders or disorders with a genetic component.
- A residency in clinical medical genetics may be accredited to provide **two and/or four years of graduate medical education.**

Medical Genetics Training

Molecular Genetic Pathology (MGP) is the subspecialty of Medical Genetics and Pathology in which the principles, theory, and technologies of molecular biology and molecular genetics are used to make or confirm clinical diagnoses of Mendelian genetic disorders, disorders of human development, infectious diseases and malignancies, to assess the natural history of those disorders, and to provide the primary physician with information by which to improve the ability to provide optimal care for individuals affected with these disorders.

Number of Programs Trends



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Largest risk to advances in genomic research is that those leading these efforts **over promise the upside**, and **negatively impact long term funding**

Personal Belief: DL Brown, 2011

Looking Through a Genetic Lens Broadly

Largest risk to ...omic research ...hese efforts **over promise the upside**, and **negatively impact long term funding**

THANKS

Personal Belief: DL Brown, 2011