What genomics decision support tools are needed for health practice?

DCCPS PHG Lecture Series
5/27/09

Greg Feero, M.D., Ph.D.
Chief, Genomic Healthcare Branch
National Human Genome Research Institute
National Institutes of Health

WE (or at least I) DON'T KNOW!

But feel free to stay for the rest of the talk anyway…

The most important advance in U.S. public health genomics in the last five years was:

A. The passage of GINA.
B. The passage of MIPPA.
C. The advent of GWAS.
D. The creation of EGAPP.
E. The creation of GappNet.
F. The Federal prohibition against the use of acronyms.

The Medicare Improvements for Patients and Providers Act (MIPPA)

July 15, 2008

"MIPPA 2008 (Section 101) gives authority to DHHS Secretary to consider additional preventive services benefits (e.g., those with an "A" or "B" rating from US Preventive Services Task Force) through Medicare NCD process"

Barry M. Straube, MD SACGHS Meeting March 12, 2009

Outline

- **A bit of context.**
- **Three “easy” steps.**
- **One of many challenges ahead.**
- **Conclusions.**

The Health of Our Society

- **$2.26 trillion dollars spent on health care in the U.S. in 2007 (16% GDP)**
- **About equal to the total GDP of France, Italy or the U.K.**

OECD "Amenable Mortality"

United States

- Nolte, Health Affairs, Jan. 2008

Jim Watson receiving his own personal genome sequence on a DVD

May 31, 2007

Douglas Kamerow

Waiting for the genetic revolution

“The sequencing of the human genome was completed in 2003. Since then we’ve been told that we’re living in the "genomic era"—the biggest revolution in human health since antibiotics, some say, and the beginning of scientific, personalised medicine. In the United States we’ve spent about $4bn (£2bn; 2.8bn) since 2000 to fund the National Human Genome Research Institute, so it seems fair to ask what we’ve got for our money.”

BMJ 2008;336:22 (5 January)

“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

http://www.hcup-us.ahrq.gov/reports/statbriefs/sb36.pdf

Top 10 Causes of Death 06

1. **Diseases of heart** *
2. **Cancer** *
3. **Stroke** *
4. **Chronic lower respiratory diseases** *
5. **Accidents (unintentional injuries)**
6. **Alzheimer's disease** *
7. **Diabetes mellitus** *
8. **Influenza and pneumonia** *
9. **Kidney disease** *
10. **Septicemia** *

CDC 2008

Can genomics be used to get a handle on chronic disease?

Diseases and Traits with Published GWA Studies (n = 93, 3/30/09)

- Macular Degeneration
- Exfoliation Glaucoma

- Lung Cancer
- Prostate Cancer
- Breast Cancer
- Colorectal Cancer
- Bladder Cancer
- Neuroblastoma
- Melanoma
- Basal Cell Cancer
- *TP53* Cancer Pred'n
- Ac/Ch Lym. Leukemia
- Thyroid Cancer
- Myeloprolif. Synd.

- Infl. Bowel Disease
- Celiac Disease
- Gallstones
- Hirschsprung Disease
- Cleft Palate

- QT Prolongation
- Coronary Disease
- Coronary Spasm
- Atrial Fibrill'n/Flutter

- Stroke
- Intracranial Aneurysm
- Hypertension
- Hypt. Diuretic Rsp.
- Periph. Artery Disease
- Lipids/Lipoproteins
- Warfarin Dosing
- Ximelegatran Adv.Rsp.

- Parkinson Disease
- Amyotrophic Lat.Scler.
- Multiple Sclerosis
- MS Interferon-β Rsp.
- Prog. Supranuc. Palsy
- Tauopathies
- Alzheimer's Disease
- Var. Creutzfeldt-Jakob
- Cognitive Ability
- Memory
- Hearing, Otosclerosis
- Restless Legs Synd.
- Essential Tremor
- Nicotine Dependence
- Methamphet Depend.

- Pain
- Panic Disorder
- Neuroticism
- Schizophrenia
- Sz. Iloperidone Rsp.
- Bipolar Disorder
- Family Chaos
- Narcolepsy
- ADHD
- Personality Traits

- Rheumatoid Arthritis
- RA Anti-TNF Rsp.
- Syst. Lupus Erythem.
- Juv. Idiop. Arthritis
- Osteoarthritis
- Psoriasis
- Kawaski Disease
- Sarcoidosis
- Pulmonary Fibrosis
- COPD/Lung Function
- CF Severity
- Asthma
- Chr. Rhinosinusitis
- HIV Viral Setpoint

- Type 1 Diabetes
- Type 2 Diabetes
- Diabetic Nephropathy
- End-St. Renal Dis.
- Obesity, BMI, Waist
- IR, Metabolic Traits
- Height
- Osteoporosis
- Age at Menarche
- Male Patt. Baldness

- Fetal Hemoglobin
- Platelet Mass/Volume
- Transferrin Levels
- C-Reactive Protein
- ICAM-1 Levels
- Eosinophil Numbers
- Total IgE Levels
- Urate Levels, Gout
- Protein Levels
- Folate Path. Vitamins
- β-Carotene Levels
- Recombination Rate
- Pigmentation

Following from GWAS

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

http://www.genome.gov/26525384

TIME's Best Inventions of 2008

Invention of the Year

Next ▸

1. The Retail DNA Test

By Anita Hamilton

ARTICLE TOOLS

Print

Email

Sphere

AddThis

RSS

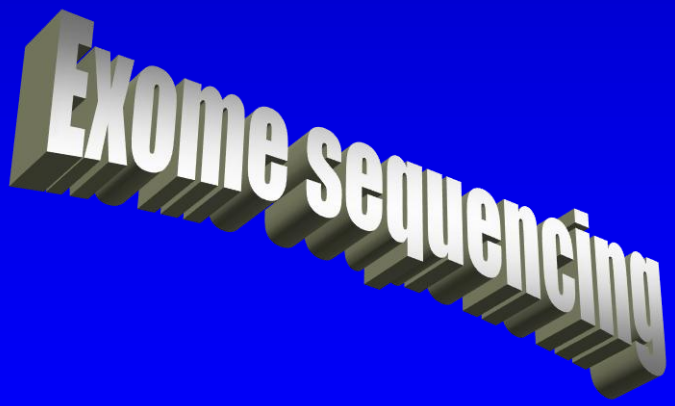
Yahoo! Buzz

Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin, and she went to Yale. But after an hour chatting with her in the small office she shares with co-founder Linda Avey at 23andMe's headquarters in Mountain View, Calif., I know some things no Internet search could reveal: coffee makes her giddy, she has a fondness for sequined shoes and fresh-baked bread, and her unborn son has a 50% chance of inheriting a high risk for Parkinson's disease.

Learning and sharing your genetic secrets are at the heart of 23andMe's controversial new service — a $399 saliva test that estimates your predisposition for more than 90 traits and conditions ranging from baldness to blindness. Although 23andMe isn't the only company

Genome-wide scans

Single gene testing

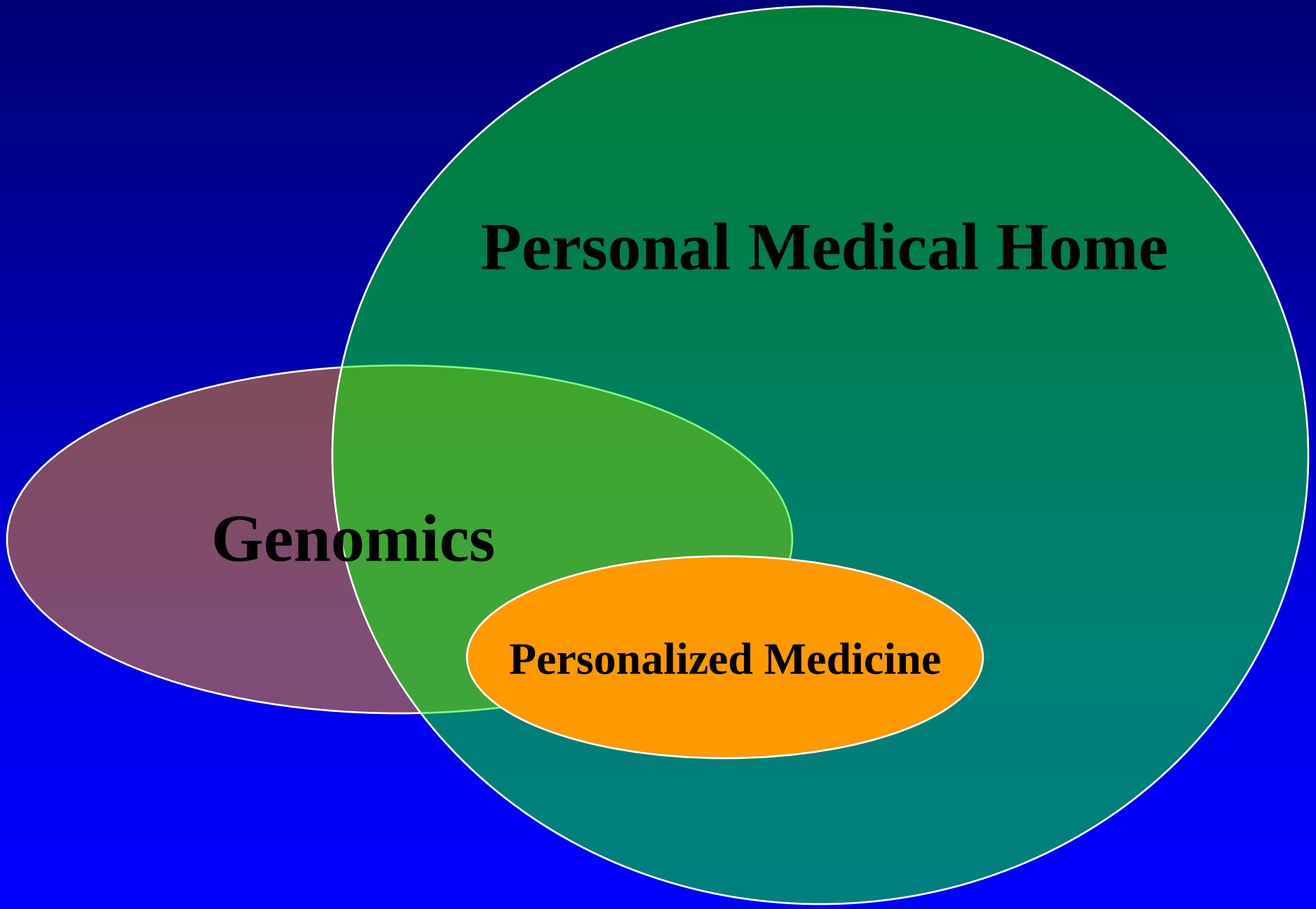


Expression profiling

Personalized Medicine

The Personalized Health Care Initiative will improve the safety, quality and effectiveness of healthcare for every patient in the US. By using "genomics", or the identification of genes and how they relate to drug treatment, personalized health care will enable medicine to be tailored to each person's needs.

http://www.hhs.gov/myhealthcare/index.html


Personal Medical Home
Genomics
Personalized Medicine

Conclusions:

1. Make genetics reasonably profitable.

2. Prove clear patient benefit.

3. Make the process as unobtrusive as possible.

MD geneticists represent 0.18% of the 700,000 physicians in the U.S.

ACMG testimony before SACGHS, Nov. 2007

"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

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OMB Leadership Bios

Peter Orszag, Director

Peter Orszag served as the Director of the Congressional Budget Office from January 2007 to December 2008, overseeing the agency's work in providing objective, nonpartisan, and timely analyses of economic and budgetary issues -- supervising the numerous analytical papers and cost estimates that the agency produces and, to present the results, frequently testifying before the Congress. Under his leadership, the agency significantly expanded its focus on areas such as health care and climate change. In previous government service, Orszag served as Special Assistant to the President for Economic Policy and as a staff economist and then Senior Advisor and Senior Economist at the President's Council of Economic Advisers. Orszag was the Joseph A. Pechman Senior Fellow and Deputy Director of Economic Studies at the Brookings Institution. While at Brookings, he also served as Director of The Hamilton Project; Director of the Retirement Security Project; and Co-Director of the Tax Policy Center, a joint venture with the Urban Institute. Orszag graduated summa cum laude in economics from Princeton University and obtained a Ph.D. in economics from the London School of Economics, which he attended as a Marshall scholar. He has coauthored or coedited a number of books, including *Protecting the Homeland 2006/7* (2006), *Aging Gracefully: Ideas to Improve Retirement Security in*

Conclusions:

1. Make genetics reasonably profitable.

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"We identified only 1 RCT of a genetic testing intervention for a common condition that measured a clinical outcome."

- Scheuner et al., JAMA 2008

Evaluation of Genomic Applications in Practice and Prevention

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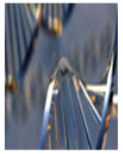


Evaluation of Genomic Applications in Practice and Preventi
systematic process for evaluating genetic tests and other geno
public health practice in the United States.

The EGAPP Working Group was established in 2005 to support
evidence regarding the validity and utility of rapidly emerging genetic tests for cli
and selects tests, reviews CDC-commissioned evidence reports and other contextu
on appropriate use of genetic tests in specific clinical scenarios.

What's New

EGAPP Working Group Releases First Recommendation Stater
recommendation statement.*

December 2007 · Vol. 9 · No. 12

EGAPP recommendation statement

Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**

This statement summarizes the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendations regarding CYP450 genetic testing in adult patients beginning treatment with selective serotonin reuptake inhibitors (SSRIs), and the supporting scientific evidence. EGAPP is a project developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention to support a rigorous, evidence-based process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States. A key goal of the EGAPP Working Group is to develop conclusions and recommendations regarding clinical genomic applications and to establish clear linkage to the supporting scientific evidence. The Working Group members are nonfederal experts in genetics, laboratory medicine, and clinical epidemiology convened to establish methods and processes; set priorities for review topics; participate in technical expert panels for commissioned evidence reviews; publish recommendations; and provide guidance and feedback on other project activities.

Summary of Recommendation

The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.

Rationale: The EGAPP Working Group found no evidence linking testing for CYP450 to clinical outcomes in adults treated with SSRIs. While some studies of a single SSRI dose in healthy patients report an association between genotypic CYP450 drug metabolizer status and circulating SSRI levels, this association was not supported by studies of patients receiving ongoing SSRI treatment. Further, CYP450 genotypes are not consistently associated with the patient outcomes of interest, including clinical response to SSRI treatment or adverse events as a result of treatment. No evidence was available showing that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes, or was useful in medical, personal, or public health decision-making. In the absence of evidence supporting clinical utility, it is not known if potential benefits from CYP450 testing will outweigh potential harms. Potential harms may include increased cost without impact on clinical decision making or improvement in patient outcomes, less drugs

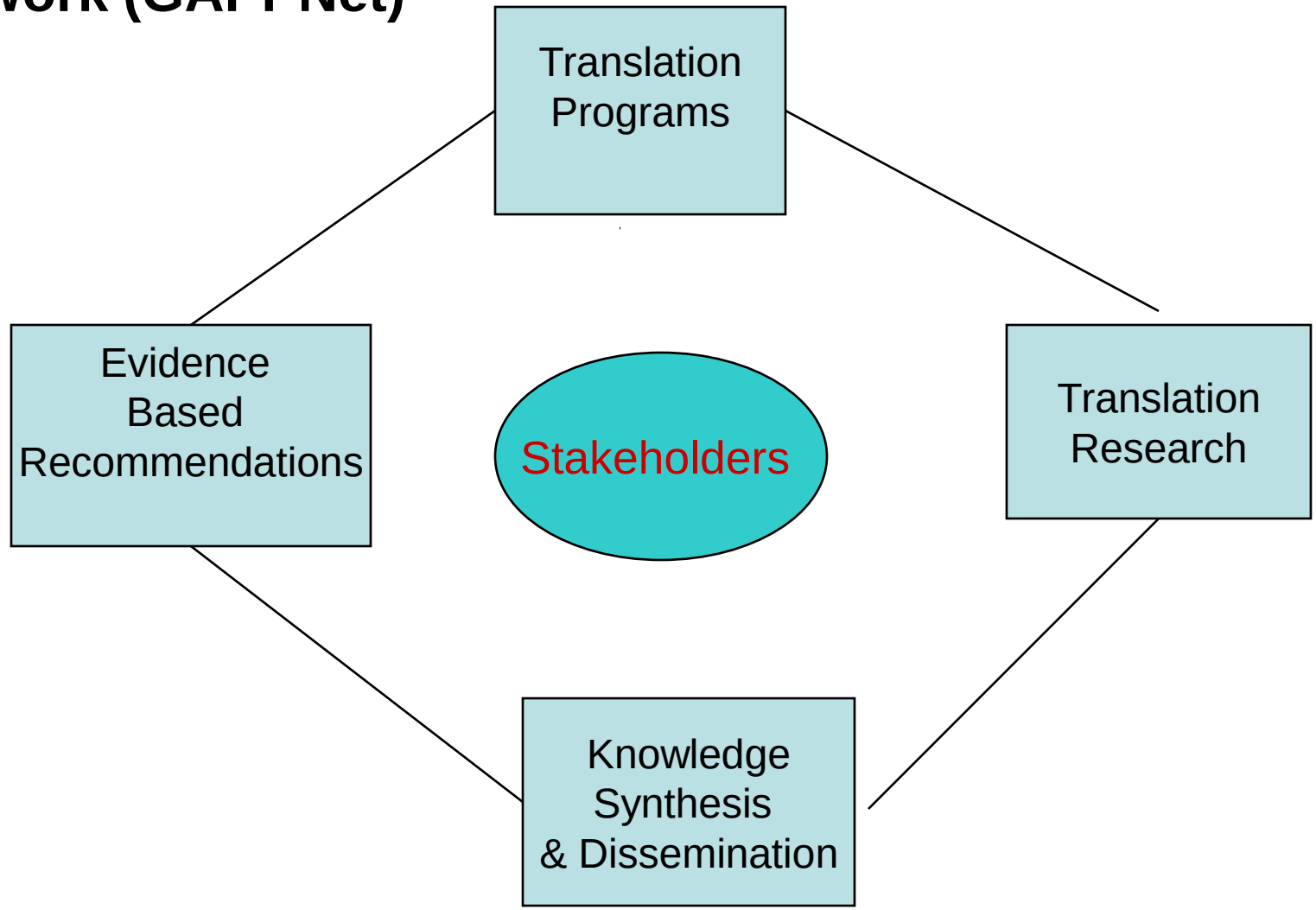
December 2007 · Vol. 9 · No. 12

commentary

Evidence based medicine meets genomic medicine

Jim Evans, MD, PhD[1], and Muin J. Khoury, MD, PhD[2]

The Genomic Applications in Practice and Prevention Network (GAPPNet)



In press: *Genetics in Medicine*

Conclusions:

1. Make genetics reasonably profitable.

2. Prove clear patient benefit.

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Education!

We all are trying.

Table 2
Provider types and knowledge scores

Provider type	No. to consult provider Type *N* (% of 5915)	Respondents' ratings of providers' knowledge of the genetics of the condition in their family		
		Poor	Average	Good or excellent
Family practice/primary care	3179 (53.7%)	39%	27%	34%
Pediatrician	2530 (42.7%)	27%	25.3%	47%
Cardiologist/electrophysiologist	2062 (35%)	22%	22%	56%
Neurologist	1885 (31.8%)	21%	23%	56%
Ophthalmologist/retinal specialist	2060 (34.8%)	22.6%	22.4%	55%
Pulmonologist	923 (15.6%)	20.2%	21%	58.8%
Endo				
Hema				
Derm				
Gastr				
Surge				
Psych				
Ortho				
Gynec				
Neph				
Speech-language pathologist	1546 (26%)	32.7%	25.4%	41.9%
Rheumatologist	341 (5.8%)	38.6%	20.2%	41.2%
Nutritionist	1191 (20%)	36.8%	24.1%	39.1%
Otolaryngologist	869 (14.6%)	29.5%	24.9%	45.7%
Physical therapist	1949 (33%)	31.4%	24.8%	43.8%
Urologist	693 (11.7%)	34%	20.9%	45.1%
Occupational therapist	1726 (29%)	31.2%	26.6%	42.2%
Allergist/immunologist	815 (13.8%)	52.1%	22.5%	25.4%
Social worker	965 (16%)	42.8%	24.7%	32.5%
Emergency physician	1100 (18.6%)	62%	20.6%	17.4%

The 25 provider types listed here represent 95% of all providers identified by respondents in the management of their condition.

Table 2 Provider types and knowledge scores
From: Harvey: Genet Med, Volume 9(5):May 2007.259-267

Over 50% of IM/FP/Peds/OBGyns rated as having a poor or average knowledge of genetics of conditions in their family….

Harvey et al., Genet Med. May 07

Statistics/risk communication:

- Risk communication to patients by family physicians (300 providers in Massachusetts)
  - 93% agreed qualitative risk communication was important, 87% were confident that they could do so.
  - 76% felt quantitative risk communication was important, **36%** were confident that they could do so.
  - **One in ten** considered themselves ineffective in communicating risk!

Gramling et al. J Am Board Fam Pract. 2004 Nov-Dec;17(6):473.

Primary care providers are not well prepared to make rational decisions regarding the current round of genetic tests for common complex conditions.

Except perhaps to ignore the issue…

Create guidelines!

Clinical guidelines:

- Widely accepted as a way to standardize and improve practice
- Serve as a basis for P4P programs
- Numerous (perhaps too many) organizations promulgate guidelines
- In U.S. largely elective*, in other developed nations may be mandatory

* The legal system acts largely as an enforcer

Clinical guidelines:

- Adherence to guidelines with an excellent evidentiary base remains sub-optimal
  - Secondary risk reduction for ACS is an excellent example
- Knowledge of guidelines is necessary but not sufficient (access to downstream services, adherence, time to counsel, tools for education etc)

Guidelines continued:

Attitudes of primary care providers toward clinical practice guidelines – meta-analysis of 17 qualitative studies from U.S. and Europe.

Carlsen et al., British Journal of General Practice, Sept. 2007

Guidelines continued:

1. Guideline quality and applicability
2. Personal experience
3. Doctor-patient relationships - rationing
4. Professional responsibility – risk avoidance
5. Practical issues - time to access and negotiate
6. Guideline format – keep it simple

Can ‘personalized medicine’ occur without electronic clinical decision support?

USPSTF and Family History: Breast Cancer

The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for *BRCA* testing. B recommendation

Family Health History - Welcome - Mozilla Firefox

File Edit View History Bookmarks Tools Help

My Family Health Portrait

A tool from the U.S. Surgeon General

Using *My Family Health Portrait* you can:

- Enter your family health history.
- Create drawings of your family health history to share with family or health care worker.
- Use the health history of your family to create your own.

Talking with your health care worker about your family health history can help you stay healthy!

Learn more about *My Family Health Portrait*

Create a Family History

Open a Saved History File

Health Care Providers: Learn how *My Family Health Portrait* can improve the health of all Americans.

My Family Health Portrait is compatible with most browsers and operating systems. Please see our compatibility statement for more information. *My Family Health Portrait*
Click here if you would like a printable version of *My Family Health Portrait*.

Done demo.5amsolutions.com

Evaluating risk of hereditary cancer syndromes- Harvard-Partners

Value

- My Family Health Portrait data can be imported into clinical systems that run risk analyses

Example:

- Data can be pulled into **HughesRiskApps**
  - Import data
  - Edit data
  - Risk analyses

Risk Assessment

Patient Name: **Annie Harvard Proband** Unit Number: **99999990** Date Of Birth: **01/11/1971**

Breast / Ovarian | Colorectal | OMIM Syndromes

Genetic Testing

Guideline	Consider testing a relative
Clinician's Recommendation	Consider testing a relative
Patient's Preference	agrees with recommendation

Synthesis of Mutation Risk:

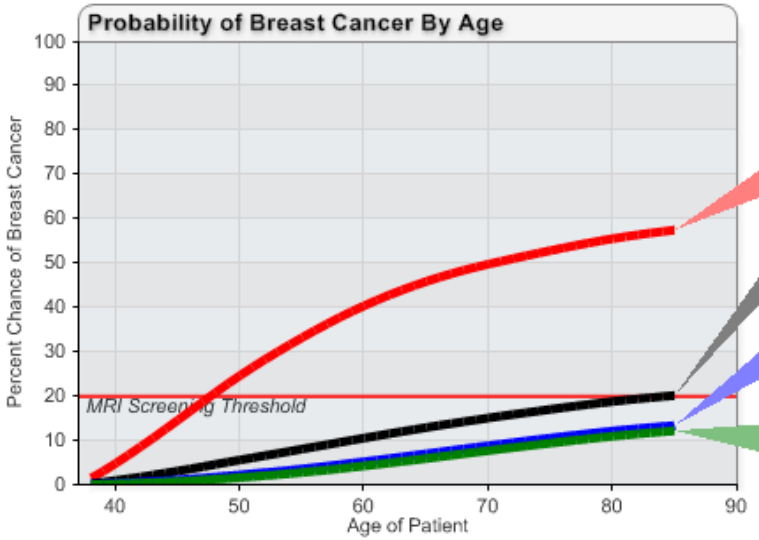
Probability Of Mutation: 18 %

BRCAPRO: 18%

Myriad: 12.2%

Pedigree | BRCAPRO | Gail | Claus | Myriad (Non-Ashkenazi Table) | Additional Information

Breast | Ovary



Lifetime Risk	Risk of Mutation	Interventions: MRI	Mammo	Chemo-Prevention	Prophylactic Mastectomy
If BRCA1 Positive					
58%	100%	Yearly	Yearly	Tamoxifen	Consider
Based on Current Synthesis of Risk					
20%	**18%**	**Yearly**	**Yearly**	**Tamoxifen**	**Consider**
If BRCA1 and BRCA2 Negative					
13%	3%	No	Yearly	No	No
Average Population					
12%	0%	No	Yearly	No	No

Exit | < Back | Next >

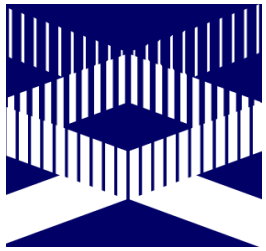
In 10,000 cases tested for BRCA 1 and BRCA 2 mutations…

- 1,129 deleterious mutations (424 unique) in BRCA 1 and BRCA 2 genes
- 970 ‘variants of unknown significance’
- 505 individuals reclassified over time from VUS to polymorphism or deleterious!

Frank TS et al. J Clin Oncol 20:1480-1490.

The ClinSeq Project: A Pilot Approach to Clinical Genomics

NHLBI



Medical & Statistical Genetics

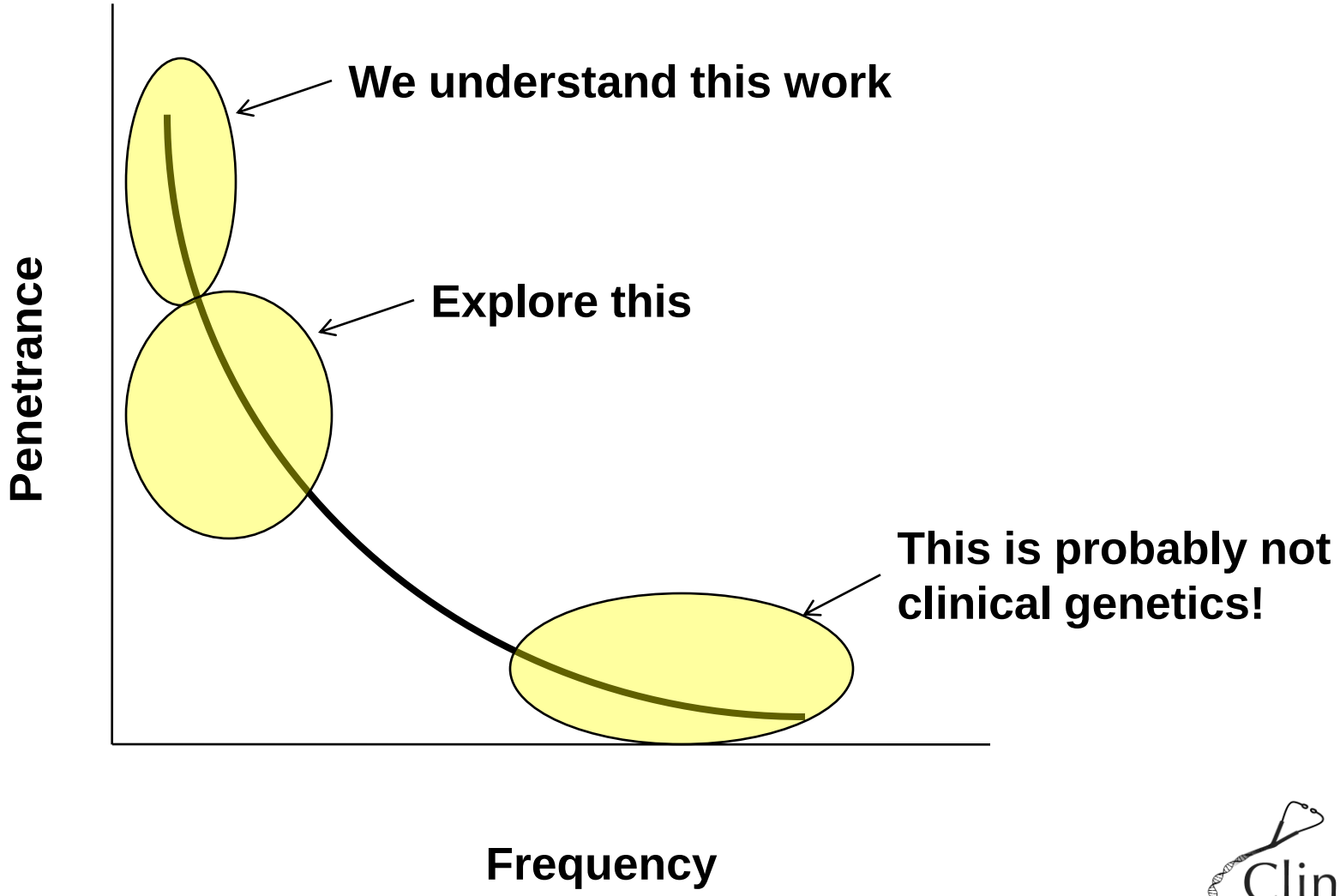
NIH Intramural Sequencing Center

Large Scale Medical Sequencing (LSMS)

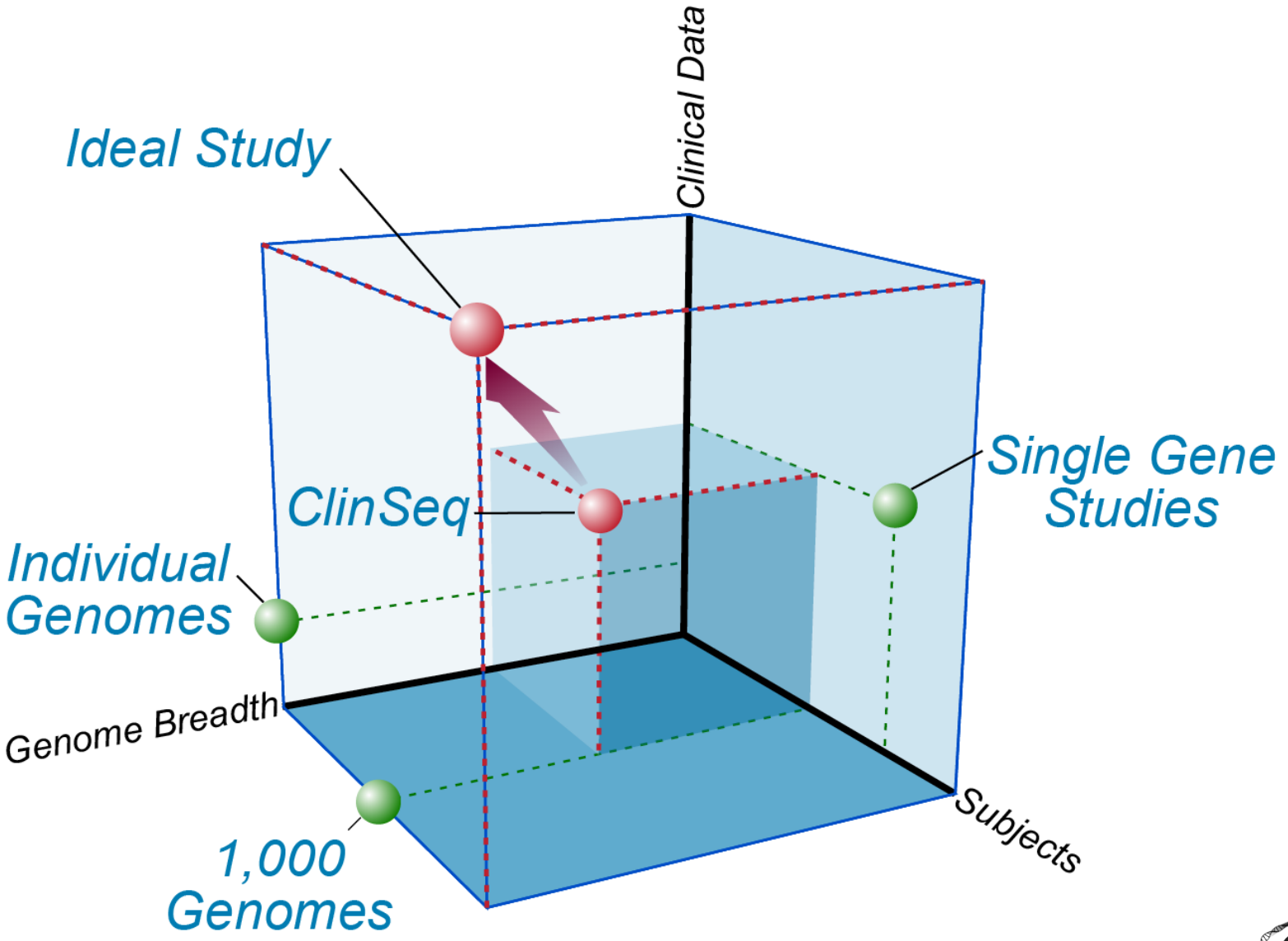
- **Detects rare and common variants**
- **Hypothesis generator**
  - **Few *a priori* assumptions that limit variants to be detected**
- **Technologic developments coming *rapidly***

ClinSeq™

Penetrance & frequency



Clinical genomics research space



ClinSeq™

Approach

- **Initial target phenotype: Atherosclerosis**
  - **Phenotype 1,000 subjects**
    - **Coronary calcium, lipidemia, & related indices**
  - **Sequence 200-400 candidate genes**
  - **Follow-up studies**
    - **Bioinformatic & bench**
  - **Interpret variants and validate *some***
  - **Return results**

ClinSeq™

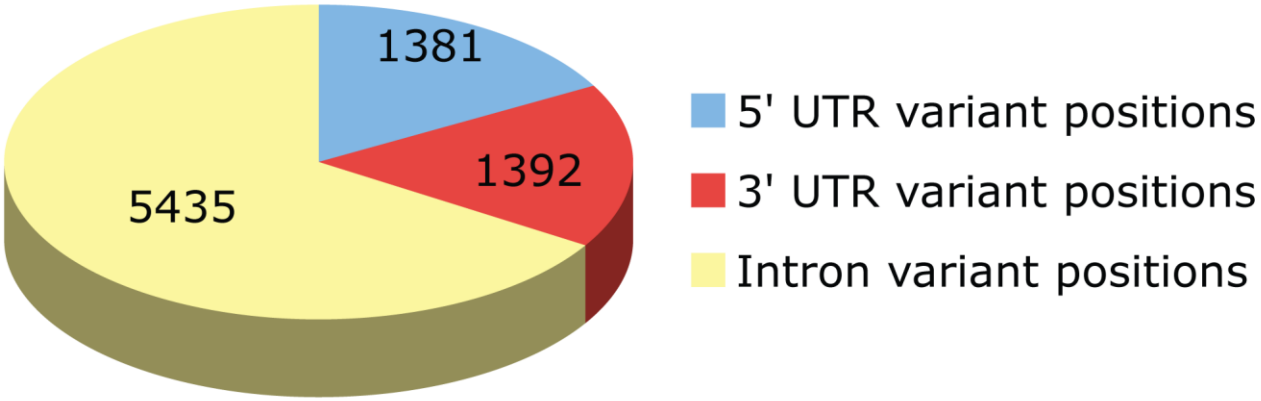
Progress – the numbers

- **Enrollment began January, 2007**
- **>625 patients enrolled May, 2009**
- **354 DNAs sequenced – PCR/3730**
  - **326 ClinSeq subject samples**
  - **28 HapMap samples**
- **219 genes**
  - **3,500 genomic target sequences**
- **> 1.7 M sequence reads to date**

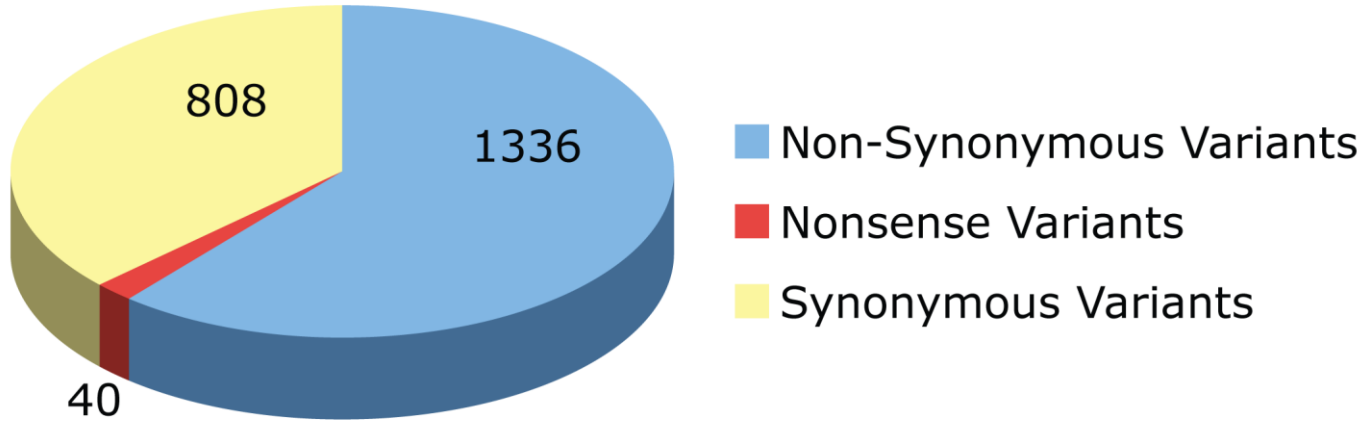
  ~825,000,000 bp of bidirectional genomic sequence

ClinSeq™

8,208 Non-exon novel variants

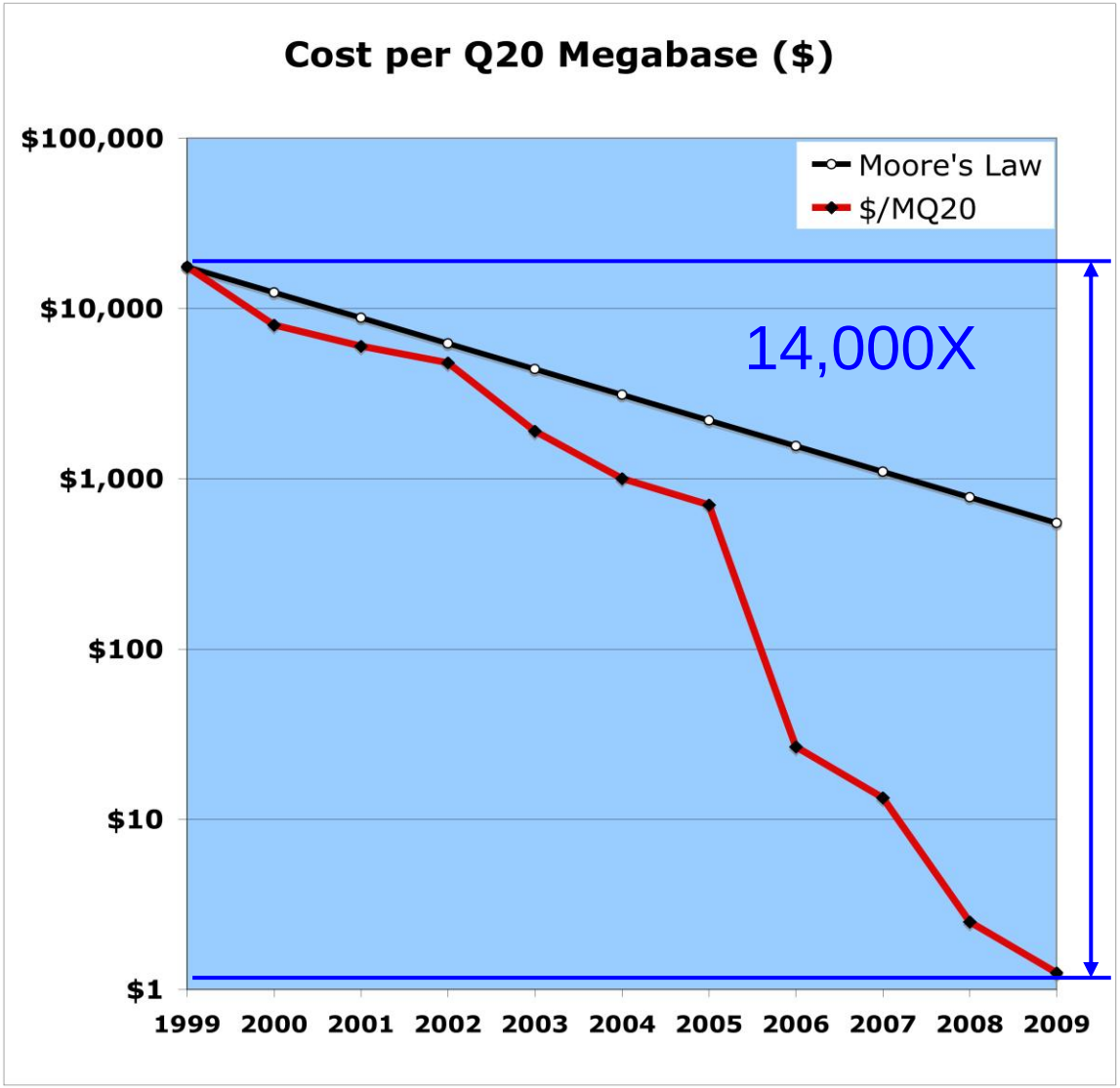


2,185 Exonic novel variants



Hold on to your hats!

Moore's Law put to shame



Courtesy of Eric Lander, Broad Institute

Knome offers sequencing of all of your protein-coding genes for $24,500

Category: exome sequencing • knome • personal genomics
Posted on: May 18, 2009 10:15 AM, by Daniel MacArthur

Personal genomics is a rapidly evolving game, with a clear end goal in sight: offering consumers an **accurate, affordable and complete genome sequence**, and providing them with tools to dig out the useful nuggets of information contained therein. That goal remains out of reach, and while DNA sequencing technology continues to mature companies in the personal genomics space are offering products at various points on the trade-off curve between information content and cost.

At the low-information/low-cost end, companies such as 23andMe and deCODEme offer **cheap (sub-$1000) genome scans looking at between 500,000 and a million sites of common variation throughout the genome**. These provide insight into a small fraction of your genome, but include the variants we know the most about (due to the recent explosion of genome-wide association studies, which look for common genetic variants associated with complex disease risk).

Meanwhile, at the other end of the spectrum we have the boutique service offered by Knome - **sequencing of the entire human genome, or at least the 85-90% of it that can be reached with current short-read technologies, for the princely sum of close to $100,000**. It's difficult to justify this cost given the interpretable information currently obtainable from a genome sequence, but a full genome sequence does offer the possibility of getting insight into rare, severe disease-causing variants lurking in your genome that are largely invisible to genome scans.

Now Knome has launched a new product that provides a substantial chunk of the information value of a whole genome sequence at a quarter of the cost, by focusing exclusively on the 2-3% of the genome that codes for proteins:

> Unlike low-priced SNP-based genotyping, which captures genetic changes known as common variants by taking a sample of less than 0.05% of the genome, comprehensive gene sequencing

Conclusions

- **Careful science dictates a serial approach to developing support tools for health professionals. Real life doesn't.**
- **Much research needs to go into the science of supporting health professional decision making:**
  - **Build it well**
  - **Build it well and they may not come**
  - **If they come they may not agree**
  - **If they come and agree they may not act**
  - **If they come, agree, and act it might not improve outcomes**
- **If you are interested in the area of electronic CDS consider joining the Government CDS Collaboratory: CDSGovtCollaboratory@hhs.gov**

THANKS

Slides courtesy of:

Les Biesecker, NHGRI

Francis Collins, address unknown

Alan Guttmacher, NHGRI

Muin Khoury, CDC

Teri Manolio, NHGRI