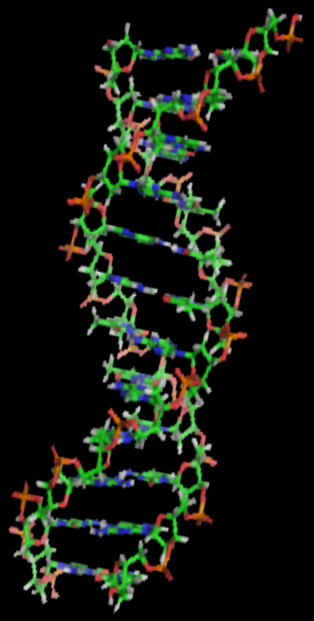
Realizing the Promise of Genomic Medicine

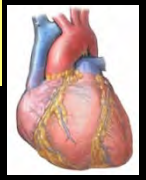


Smithsonian Institution
Natural History Museum

13 June 2013

Jim Evans MD, Ph.D
UNC Chapel Hill

The Human Genome is Big



- ~1/1,000,000th of the Human Genome
- Interspersed with genes
- Polymorphisms
  - Many meaningless
  - Some influencing traits
  - or medically important characteristics
- Occasional rare mutations that greatly influence health

Near to Midterm Practical Applications of Massively Parallel Sequencing

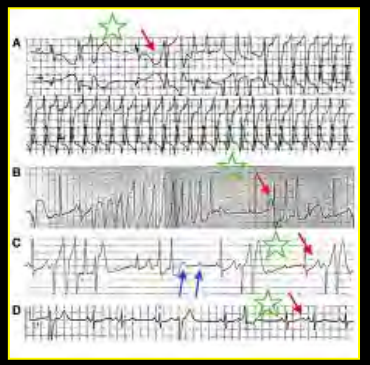
What are the appropriate “nails” for the hammer of Massively Parallel Sequencing?

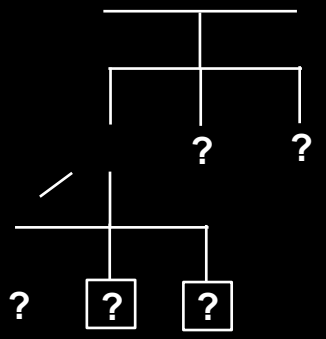
In sick people and healthy people

Sick People

MPS as a Clinical Diagnostic Tool

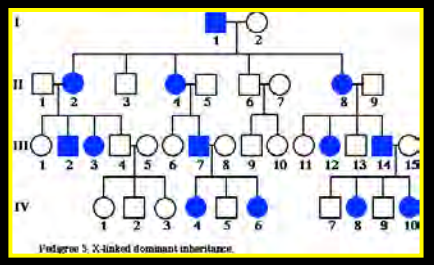
- 47 yo female with sudden cardiac arrest
- Resuscitated successfully
- EKG reveals Long QT Syndrome
  - High risk for sudden death
  - Treatable
  - Knowledge of which gene is mutated affects Rx of choice & prognosis
  - Dozens of genes implicated
- Application of MPS to detect mutation
  - By sequencing a panel of genes
- Guiding patient's treatment
- And prevention of death in family members



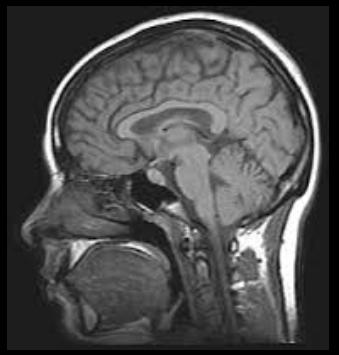


NHGRI is funding multiple efforts to harness its use in the clinic

Which Patients Will Benefit from it's Application?



- Like any complex medical test will be used optimally if applied in a thoughtful & targeted fashion
- MPS of entire genomes or gene panels (real or virtual) will benefit a *subset* of patients
  - Those with disorders that can be caused by mutations in many different genes
  - Those with enigmatic conditions & clues suggesting a primarily genetic etiology, e.g.
    - Familial conditions
    - Progressive neurological disorders
    - Children with multiple malformations
  - Eventually informing our approach to common disease



Genomic Analysis of Cancer

- For over a century we've defined cancer by its appearance under the microscope and its tissue of origin
- Genome-scale sequencing of tumors offers a new means of *functional* characterization
  - Defining the specific mutations that drive its growth
  - Guiding Rx by identifying the Achilles heel of each tumor
- Eventually tumor classification will rely as much upon genotype as on tissue of origin and microscopic appearance

The Cancer Genome Atlas is characterizing tumors on an unprecedented level

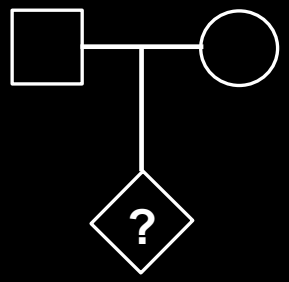
Applying Genomics to the Healthy

- Healthy people have more to lose than sick people
- Different relationship between provider & recipient
  - The individual isn't typically seeking us out
- Benefits are less obvious
  - “You didn't get sick!”
- The downsides are easy to see
  - All interventions have downsides
- Implementation & policy issues are orders of magnitude more difficult

Healthy People

Public Health Genomics

- Pre-emptive delineation of select variants that influence an individual's response to drugs
- As an adjunct to newborn screening
  - NHGRI will soon fund a consortium of such studies to investigate its potential in this context
- Pre-conceptual carrier screening
  - MPS permits comprehensive screening of prospective parents for the risk of severe genetic disease in their children



Healthy People

New born screening for adults

- ~1% of the population harbors mutations that lead to a very high risk of preventable disease
  - e.g. Lynch syndrome
    - 1/400 individuals at >80% risk for CRC
    - Highly preventable if risk is known
    - Currently identified only after they or family members develop cancer
- MPS may allow population screening for high-risk, preventable disorders
  - e.g. cancer syndromes, certain cardiac diseases, vascular catastrophe, etc.
- Potentially benefitting millions in the US

A new NHGRI funded project at UNC will investigate the feasibility of such an approach

Challenges to Harnessing MPS in Clinical Medicine & Public Health

- Accuracy
  - 99.99% accuracy x 3 billion nucleotides
  - = 300,000 errors *per patient*
- Interpretation of the variants we find
- Storage and access in the medical record
  - We each have ~4 million variants
- Education of patients, providers & public
- Crafting policy regarding use of genomics
  - Especially in realm of reproductive issues
- The human genome isn't the only important genome in your body
  - You are only about 10% human
- Incidental information…

NHGRI funded efforts like EMERGE are exploring this issue and an upcoming special issue of Genetics in Medicine will be devoted to this challenge

Challenges to Clinical Genomics

Incidental Information

- Your genome is an unpredictable – and not necessarily friendly - place
- Upon genomic sequencing we discover many things we weren't looking for
  - Some are trivial or indeed beneficial
  - Some are problematic
    - We will occasionally discover dramatic risk of lethal, untreatable late onset conditions
- Some wish to know such information; others do not

If you carry a mutation that essentially guarantees that you will develop a serious *but highly preventable* disease would you wish to know?

1. Yes
2. No
3. I'm not sure

A few serious but preventable diseases that can be highly genetic …

- Colorectal cancer
- Breast cancer
- Thyoid cancer
- Aortic Aneurysm

If you carry a mutation that essentially guarantees that you will develop a severe, *unpreventable & untreatable* neurological disease would you wish to know?

1. Yes
2. No
3. I'm not sure

A few really bad & unpreventable & untreatable genetic diseases…

- Alzheimer Disease
- Fatal Familial Insomnia
- Spinocerebellar Ataxia
- Huntington Disease
- CADASIL

A Few Social Challenges

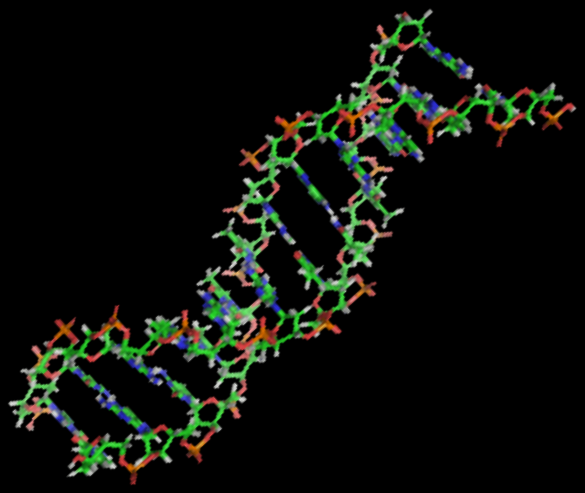
- Genetic Discrimination
  - In the US GINA now protects against medical insurance discrimination
    - But no protection in the realm of LTCI, disability, life insurance
- The threat of "allelism"?
- Gene Patenting
  - ~20% of our genes have patent claims on them
- Privacy Issues
  - Genomic information is digital and easy to distribute… and hack
  - "Privacy is dead, deal with it,"
  - Bankruptcy of a major DTC Genomics company
- We will require an educated public to succesfully grapple with how to handle this new flood of information about ourselves

"We envision a new type of community where people will come together around specific genotypes…"

Sun MicroSystems
CEO Scott McNealy

Thank You

jpevans@med.unc.edu



Proposed outline of topics to consider:
Jim's role is high-level presentation of clinical issues

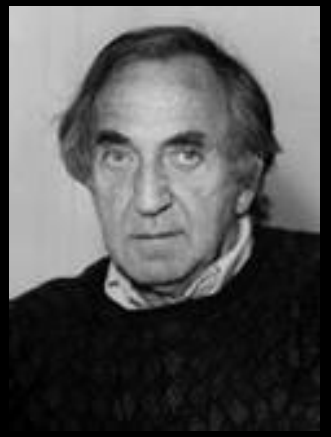
- A vision of what personalized medicine will look like in the near future
    1. What are the benefits?
    2. What are the challenges to instituting genomic science in medical care?
        a. Reimbursement
        b. Electronic medical records
        c. Physician ability to use this information
- What is already happening in the clinic and how will genomic sciences likely become common in medical care. In other words, when will this happen and will it be gradual or sudden?
- What are some of the things that the genomics research field is doing to solve the problems getting genomics into medical care, such as:
    1. Clinical Sequencing Exploratory Research program, CSER – Jim has a CSER grant. So talk about ….
    2. eMERGE – the Electronic Medical Records and Genomics Network
    3. Genome Variation studies – please make sure there is some focus on common disease and not just rare inherited illnesses.
        a. 1000 Genomes
        b. GWAS
    4. Mendelian Sequencing Centers goal of finding the genetic cause of all inherited illnesses – what is the vision of doing that? How does learning about rare or inherited illnesses impact dx and rx of common diseases? Note Lipitor example.
- CANCER – TCGA and the expectation that knowing the genetics of cancer will revolutionize dx and rx. Jim resists hype, but he does think genomics will be revolutionary in cancer application … highlight that. We will look at cancer and dx and rx in a new way in the next decade.
- Human Microbiome – Larry to get some forward looking material from Lita Proctor, the HMP program director.

MPS of the Whole Genome to Solve a Diagnostic Dilemma

- 36 yo female with dx of progressive spastic paraplegia since age 6
- Many different genetic lesions can cause such symptoms and thus WES was pursued
- As part of NCGENES, a mutation was found in Dopa-Responsive Paraplegia gene, *GTPCH1*
  - Identifying specific and highly effective Rx
- Diagnosis will often not provide specific Rx, but -
  - Ends diagnostic odyssey
  - Offers important information to families
  - Provides intangible benefits of a diagnosis
  - Provides the basis for future progress in Rx

Challenges to Clinical Genomics

Storage in the EMR



- We each have ~4 million variants
- Do we want or need to keep them all?
- Your 2015 WGS will be much better (and cheaper) than your 2013 WGS
- Our current medical record system is highly fragmented
- Orgel's second law of evolution: "Evolution is cleverer than you are"
  - We already have ready access to a cheap storage medium for genetic information
- The DNA in 10 ml of blood contains ~3.75 petabytes of data storage capacity
  - ~400 x the amount of information in the library of congress

Insert something about CSER

Add back in storage slide

Mention Mendelian

microbiome

Pre-conceptual carrier screening

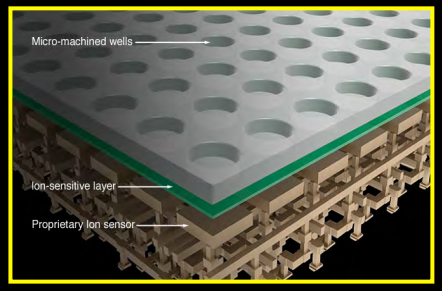
- Currently PCCS is recommended for a few specific disorders
  - Based solely upon mutation prevalence
    - We (by necessity) have recommended screening for a few conditions like CF or Tay Sachs because it is practical
    - Not what couples would like to really know
- MPS eliminates this arbitrariness
  - Potentially profound and welcome impact on family planning
  - Highly actionable information to some
  - Ethically problematic for others
    - Making formulation of policy variable and difficult for this application

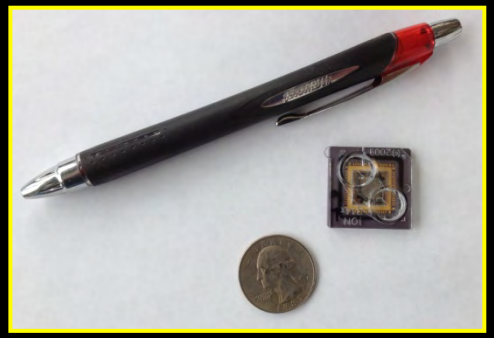
MPS of the Whole Genome to Solve a Diagnostic Dilemma

- 36 yo female with dx of progressive spastic paraplegia since age 6, wheelchair bound
- Movement disorders are highly heterogeneous and thus WES was pursued
- As part of NCGENES, a mutation was found in Dopa-Responsive Paraplegia gene, *GTPCH1*
  - Identifying specific and highly effective Rx
- Diagnosis will usually not provide specific Rx, but -
  - Ends diagnostic odyssey
  - Offers important information to parents about recurrence risk
  - Provides intangible benefits of a diagnosis

DNA Sequence Analysis by Multi-Tasking

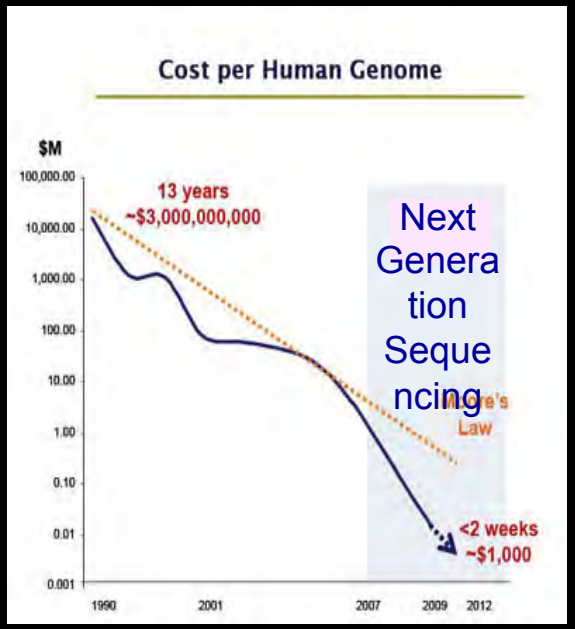
- A variety of chemical and physical strategies have existed for years
- Biggest limitation has been the need to carry out such approaches one fragment at a time
- Massively Parallel Sequencing takes advantage of miniaturization to carry out millions of reactions simultaneously
- Sophisticated computer analysis allows “assembly” of a given sequence

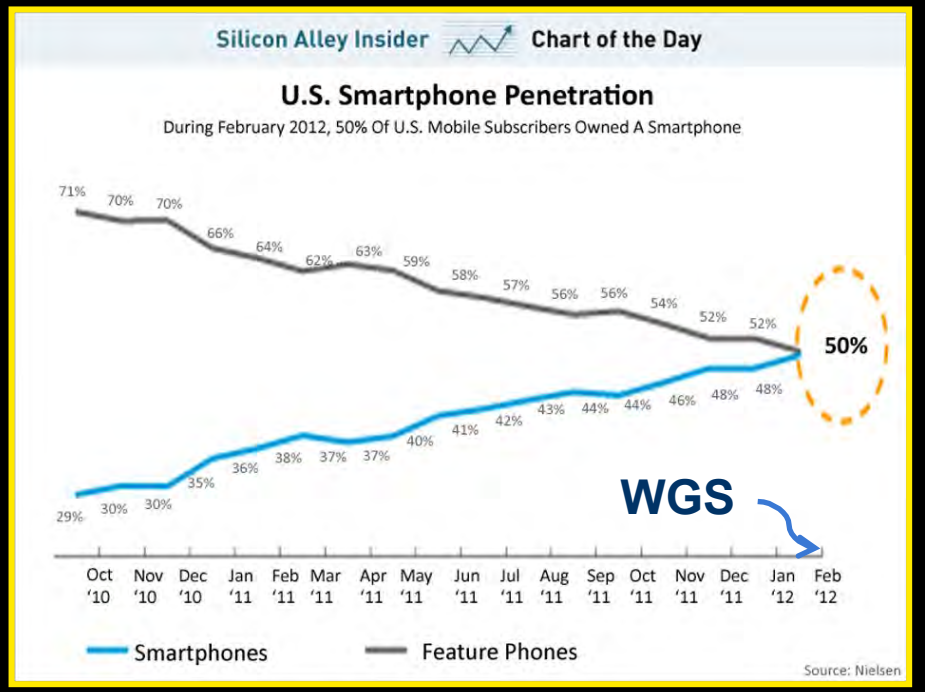




Accelerating Technology, Plummeting Cost & Penetration to the Individual

$795 in 1977 (=$2,800 in current $)





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- Different relationship between provider & recipient
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- Benefits are less obvious
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- The downsides are easy to see
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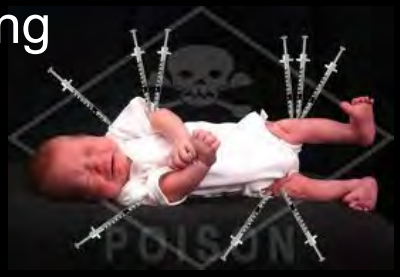
- Applications are implemented *en masse*
  - All have a say
    - Including the ill-informed & those who are simply wrong
- Policy issues are orders of magnitude more difficult



Healthy People

Prevention of Common Disease

- Genetics is only one (small) component of common diseases
  - Inherent ceiling on utility of parsing risk
- Relative risks provided by genomic analysis are usually much too small to matter clinically
- Provision of genetic information has limited ability to alter behavior
- Confusing absolute and relative risk

Risk assessment is valuable when the identified risks are high

One Possible Binning Scheme

Genes							
Criteria:	***Loci with Clinical Utility***		***Loci with Clinical Validity***			***Loci with Unknown Clinical Implications***	*Loci with important reproductive implications*
Bins:	**Bin 1** Genes, which when mutated, result in high risk of clinically actionable condition	**Bin 2A** Low risk incidental information	**Bin 2B** Medium risk incidental information	**Bin 2C** High risk incidental information		**Bin 3** All other loci	**Bin R** Carrier status for severe AR disease
Examples:	*BRCA1/2* *MLH1, MSH2* *FBN1* *NF1* Loci with proven PGx clinical utility	PGx variants and common risk SNPs with no proven clinical utility	*APOE*, genes associated with Mendelian disease for which no firm clinical recommendations exist	Huntington disease Prion diseases *SCA, PS1, PS2, APP*			Tay Sachs, Familial Dysautnomia, CF, etc.
Estimated # of genes/loci	Dozen(s)	~20 (eventually 100s – 1000s)	100	Dozen(s)		>20,000	Hundreds

Alleles that would be reportable (YES) or not reportable (NO) in a clinical context

Variants						
Known deleterious	YE	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]	YES
Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]	YES
VUS	NO	N/A [3]	NO	NO	NO [4]	NO
Presumed benign	NO	N/A [3]	NO	NO	NO	NO
Known benign	NO	NO	NO	NO	NO	NO

Adapted from Berg, Khoury, Evans; GIM, June 2011

Sick People

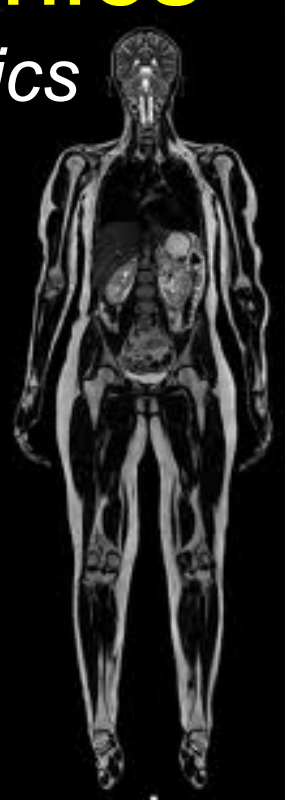
Genomic Diagnostics in the Clinic

- Making a primary diagnosis has long been the lynchpin of medicine
  - Guiding prognosis, treatment and enabling medical progress
- Diagnosis provides tangible benefit
  - Ending the "diagnostic odyssey"
    - Saving both anxiety and resources
  - Informing reproductive decisions for parents of an affected child
  - Affording preventive strategies to family members for some disorders
  - Delivering to patients & families an explanation for their malady

MPS is a new diagnostic tool that will greatly facilitate the diagnosis of disorders whose etiology is primarily genetic

Challenges of Clinical Genomics

The Rise of Direct-To-Consumer Genomics

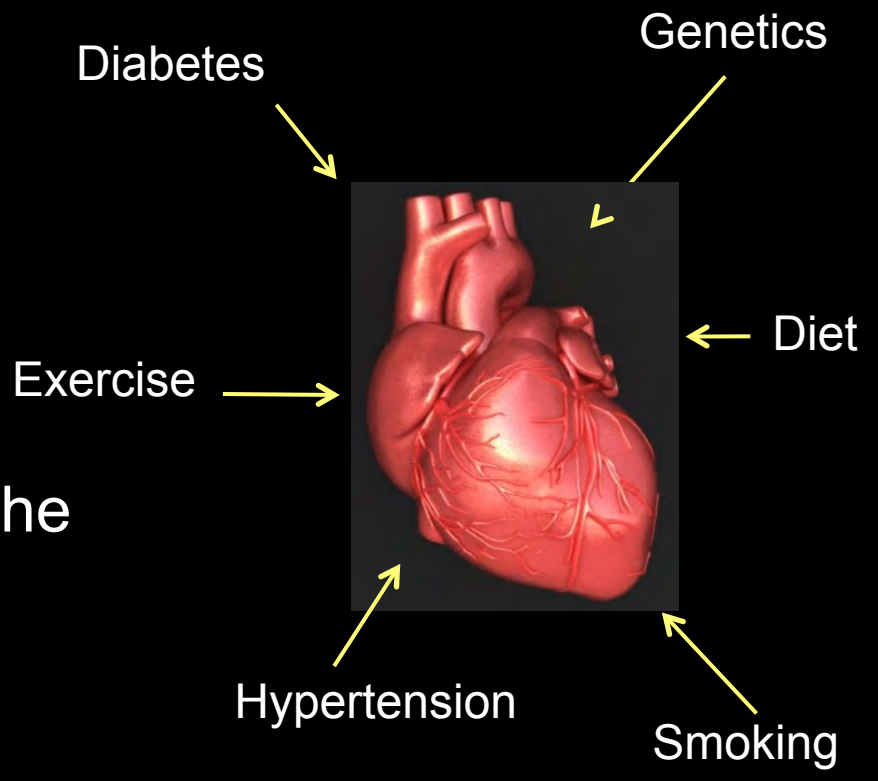


- Multiple companies now offer DTC genomic analysis, including WGS
  - Complex medical test with the power to help, harm and confuse
  - Often marketed with unrealistic claims or as entertainment
- I'm concerned that aggressive marketing of complex medical tests does no one any favors
  - The individual
  - Society & Medicine
- Regulation of such products

Focus on Prevention of Common Diseases?

A Problematic Nail

- The hope that through refining risks for diseases like HTN, CAD, DM, etc. we can decrease morbidity
- Common diseases have many etiologic factors
  - Of which genetics is only one & usually relatively small
- Placing an inherent ceiling on the utility of germline genetic information



And Predictive Power is Feeble

The Problem of Relative Risk

- Numerous risk alleles identified
  - The vast majority of RR ~1-2
    - What do I ***do*** with such information?
  - From a clinical standpoint the information is so lacking in robustness that it is of no clinical utility
- Few data to suggest that knowledge of one's genomic status is effective in changing behavior
  - And if it does that could be a problem…

Example variant	Closest gene	Odds ratio (per allele)*
rs1801282 (P12A)	*PPARG*	1.14 (1.08–1.20)
rs5215 (E23K)	*KCNJ11*	1.14 (1.10–1.19)
rs7901695	*TCF7L2*	1.37 (1.31–1.43)
rs4430796	*TCF2*	1.10 (1.07–1.14)
rs10010131	*WFS1*	1.11 (1.08–1.16)
rs1111875	*HHEX–IDE*	1.15 (1.10–1.19)
rs13266634	*SLC30A8*	1.15 (1.12–1.19)
rs10946398	*CDKAL1*	1.14 (1.11–1.17)
rs10811661	*CDKN2A–2B*	1.20 (1.14–1.25)
rs4402960	*IGF2BP2*	1.14 (1.11–1.18)
rs8050136	*FTO*	1.17 (1.12–1.22)

Pepe MS et al. (2004). American Journal of Epidemiology. 159 (9):882

Confusing Relative and Absolute Risk

I Know What You're Going to Die Of…

- For common diseases, what does it really mean to be at a *relatively* reduced risk?
  - The absolute risk for common diseases is high
  - Thus, we're all at increased risk for these maladies - regardless of our relative risk
  - Many at "decreased risk" for heart disease will still die of heart disease

Risk assessment will be valuable when the identified risks are high

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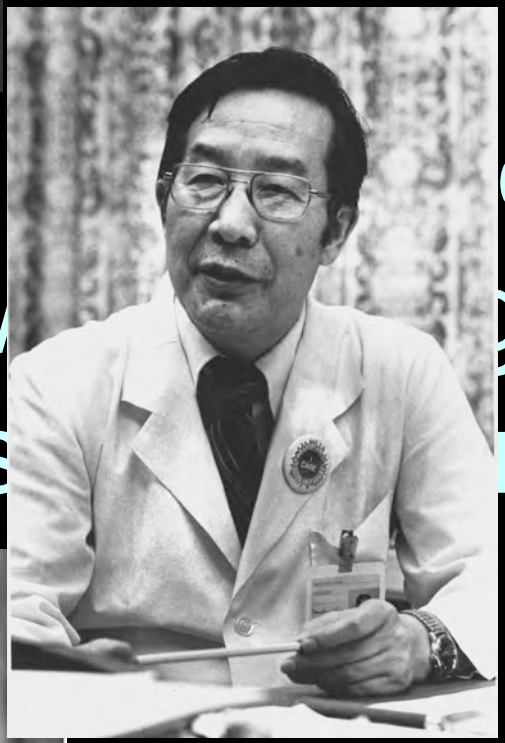
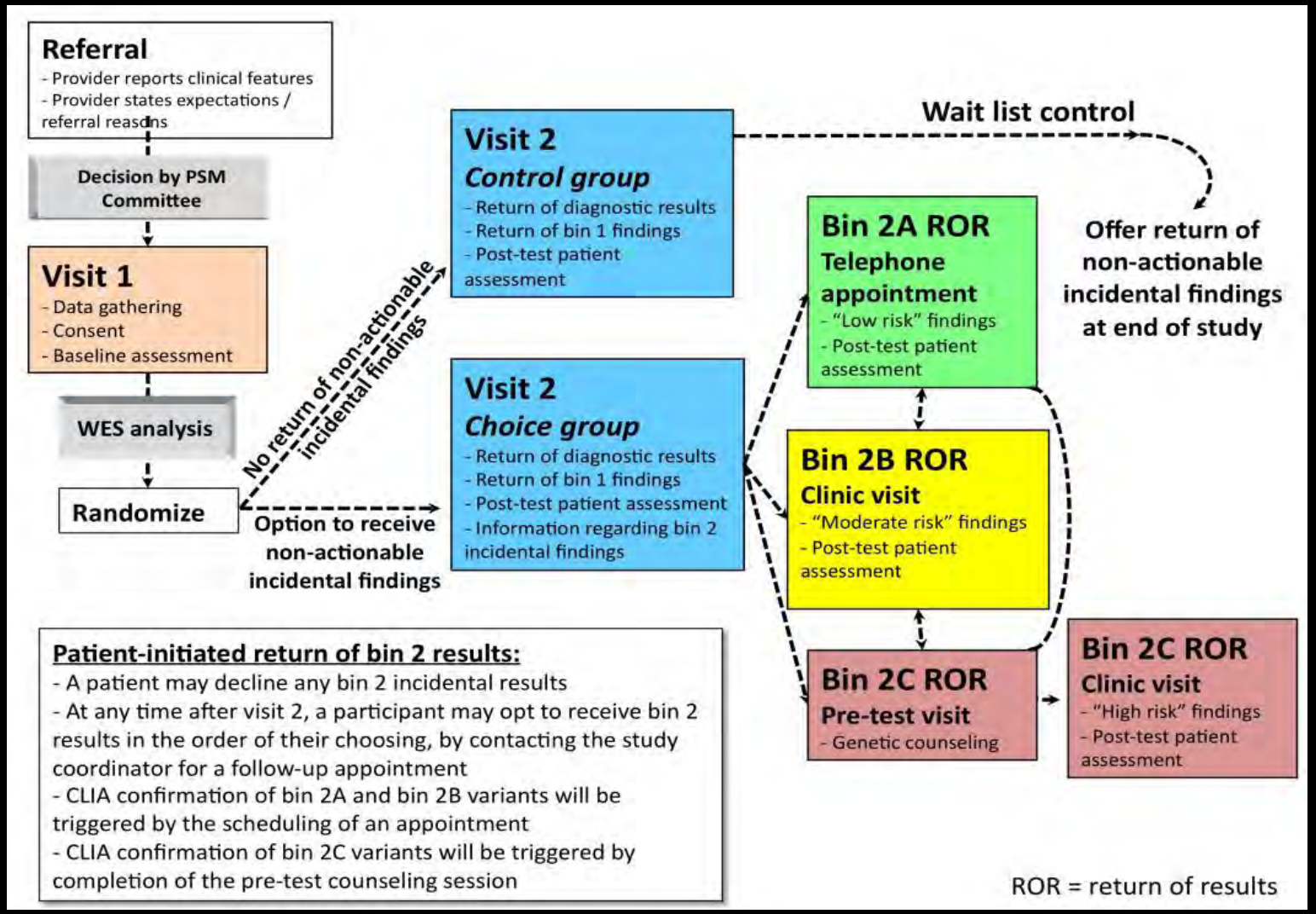


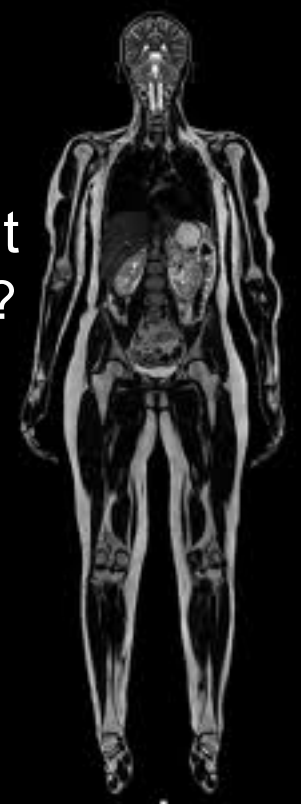
Randomization Scheme to Study Return of IF in Adults



Challenges of Clinical Genomics

The Rise of Direct-To-Consumer Genomics

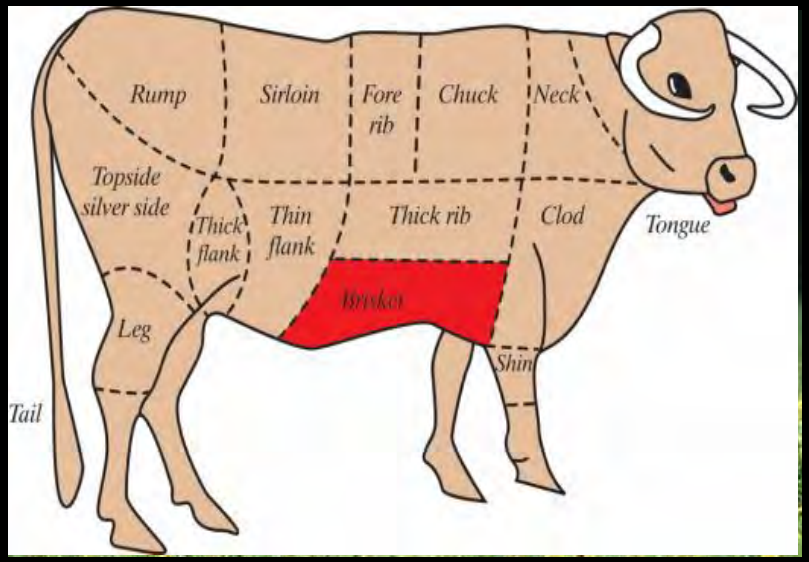
- Multiple providers now offer DTC genomic analysis, including WES/WGS
- Genomic sequencing is a complex medical test with the power to help, harm and confuse
- Often marketed with unrealistic claims or as entertainment
  - Is marketing a good reason to have a complex medical test?
- The misuse of complex medical tests harms everyone
  - Because none of us pays for our own medical care
- Stakes are high and information is complex
  - Regulation is needed regarding testing & interpretation



Binning by Loci

Cutting Up the Cow

- WGS is often thought of as a “test”
- In reality it is 3 billion highly heterogeneous tests
- We can’t swallow it whole
- We need to carve it up into manageable bits if we are to derive any utility from it
- Save the good parts and toss the rest
- Do so informatically



Dealing with Lots of Data

- Each of us has ~4 million variants
- How do we decide what to analyze, store, report?
- The significance of the vast majority of genomic variants will be utterly unknown
  - Are thus clinically inconsequential and do not mandate reporting
  - Don't waste valuable clinical effort on data that is inherently highly uncertain
  - Indeed we have no *business* reporting them
    - Clinical action when we don't really know what we're doing is harmful
      - PSA, HRT, etc.
- A few will be tangibly useful to subjects
  - Report those with established evidence of health benefit
- Accomplish this by taking a locus-based approach to categorization of potential results

Saved by our Ignorance

The Challenges of Public Health

- Healthy people have less to gain and more to lose than sick people
- Different relationship between provider and recipient
  - The individual isn't typically seeking us out
  - No one-to-one relationship
- Benefits are less obvious
  - “Good news: you didn't get sick!”
- The downsides are easy to see
  - And all interventions have downsides
- The ratio of benefit to harm must be much greater in the population setting than in the clinical setting
  - Difficult since our tools for intervention in medicine are blunt
  - Why behavioral modification is appealing in public health
    - But hard to do
- Applications are implemented *en masse*
  - Making policy issues orders of magnitude more difficult
  - All have a stake and a say
    - Including those with views that are simply wrong

Rare is the New Common

Realizing the Promise of Genomic Medicine

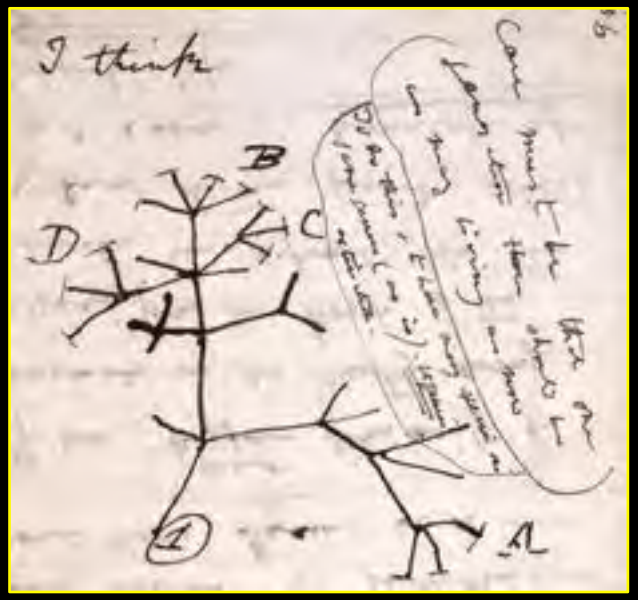
Arno Motulsky Lecture

28 September 2012

Jim Evans

University of North Carolina at Chapel Hill

Another of My Heroes



AN

ESSAY

ON THE

PRINCIPLE OF POPULATION,

AS IT AFFECTS

THE FUTURE IMPROVEMENT OF SOCIETY.

WITH REMARKS

ON THE SPECULATIONS OF MR. GODWIN,

M. CONDORCET,

AND OTHER WRITERS.

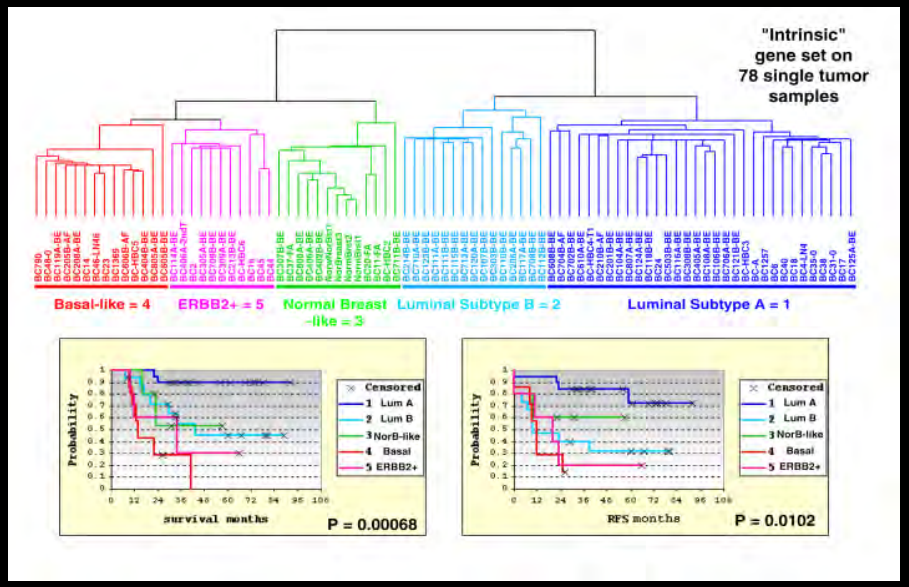
LONDON:

PRINTED FOR J. JOHNSON, IN ST. PAUL'S CHURCH-YARD.

1798.

Somatic Genomic Analysis in Cancer Offers Unique Opportunities

- Cancer is fundamentally a genetic disease
- Genome-scale sequencing of tumors offers opportunities to parse complex phenotypes & target Rx to tumor genotypes
- Chemotherapeutic agents are toxic and thus excellent targets for the application of PGx



Genomics for the Healthy

- Public health involves a different set of challenges and rewards than does clinical medicine
- The most significant gains in medicine have been in the context of public health
- The historical benefit through such intervention is dramatic
  - The chance to benefit millions
  - Prevention is better than curing
- Historic examples
  - Vaccines
  - Fluoridated water
  - New born screening for preventable conditions

The Challenges of Public Health

- Healthy people have less to gain and more to lose than sick people
- Different relationship between provider and recipient
  - The individual isn't typically seeking us out
  - No one-to-one relationship
- Benefits are less obvious
  - “Good news: you didn't get sick!”
- The downsides are easy to see
  - And all interventions have downsides
- The ratio of benefit to harm must be much greater in the population setting than in the clinical setting
  - Difficult since our tools for intervention in medicine are blunt
  - Why behavioral modification is appealing in public health
    - But hard to do
- Applications are implemented *en masse*
  - Making policy issues orders of magnitude more difficult
  - All have a stake and a say
    - Including those with views that are simply wrong

Public Health Genomics

Finding the Right Nails

- The field's focus has thus far been on common diseases
  - With the hope that by assessing risk for disorders like HTN, DM, Cancer, CVD we can decrease morbidity and mortality
- Even small progress in decreasing common diseases could have big payoffs
- The hope that we can use genomics to assess risk and productively alter our approach to common disease

Prevention of Common Disease Through Genomic Risk Assessment

- The current status of screening in medicine
  - Relatively little benefit
  - Actual harm to some
  - Tremendous waste of resources

We now have the ability to analyze the individual's genome deeply and define statistically significant variation

However, applying genomic tools to common diseases has thus far been disappointing…

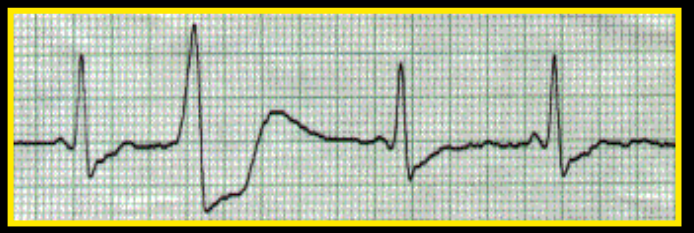
A Plea for Evidence-Based Genetic Medicine

Medical Science ≠ Medical Practice

- Medical Science is the indispensible foundation of Practice
- But is far more complex
- More variables
    - Including tremendously complex variables like differing values
- Time-line for practical translation is long
  - And not guaranteed by scientific understanding
- Its application is far more expensive than the underlying science
- The stakes are much higher in medical practice
  - Because the power to harm is real and potent
- Theory alone is insufficient to guide practice

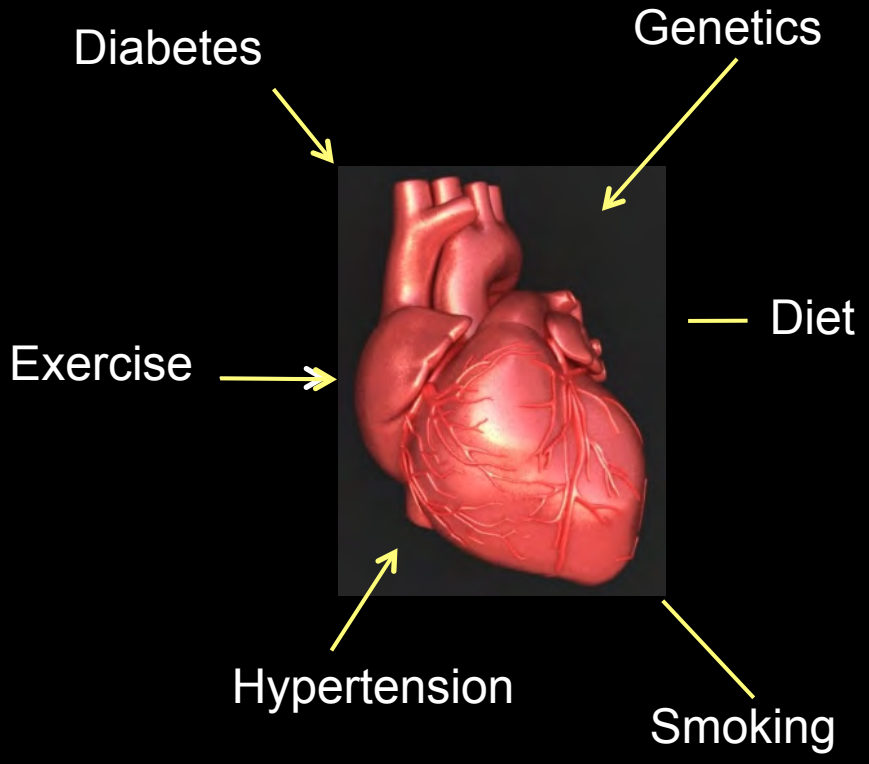
Good Ideas Are Insufficient to Guide Practice

- Reflexic HRT after menopause
- Anti-arrhythmics for PVCs
- Sleeping Babies & prevention of SIDS
- Beta-Carotene supplements to prevent cancer
- Coronary stents do not prolong life
- Excessively strict glucose control in diabetes
- Routine use of PSA screening



Common Diseases Have Many Etiological Components

- The genetic component is one of many & typically small
- Placing an inherent ceiling on the utility of germline genetic analysis in these disorders



Predictive Power is Feeble

The Problem of Relative Risk

- Many risk alleles identified for common diseases
- RR are typically 1-2
  - What do I *do* with such information?
  - Little practical utility for the individual
    - Or at the population level
- Few data indicate that knowledge of one's risk changes behavior
  - And if it does, that could be a problem

Example variant	Closest gene	Odds ratio (per allele)*
rs1801282 (P12A)	PPARG	1.14 (1.08–1.20)
rs5215 (E23K)	KCNJ11	1.14 (1.10–1.19)
rs7901695	TCF7L2	1.37 (1.31–1.43)
rs4430796	TCF2	1.10 (1.07–1.14)
rs10010131	WFS1	1.11 (1.08–1.16)
rs1111875	HHEX–IDE	1.15 (1.10–1.19)
rs13266634	SLC30A8	1.15 (1.12–1.19)
rs10946398	CDKAL1	1.14 (1.11–1.17)
rs10811661	CDKN2A–2B	1.20 (1.14–1.25)

Little Added Value for Combinations of Variants Thus Far

Year	Researchers	Disease	Genetic variant	AUC	Δ AUC
2005	Lyssenko et al.	Type 2 diabetes	3 establ. variants	0.68	+0.00
2006	Podgoreanu et al.	MI after surgery	3 (out of 48)	0.70	+0.06
2007	Humphries et al.	CHD	4 (out of 12)	0.66	+0.04
2007	Morisson et al.	CHD	11 (out of 116)	0.76	+0.01
2008	Vaxillaire et al.	Type 2 diabetes	3 (out of 19)	0.82	+0.00
2008	Zheng et al	Prostate cancer	5 (out of 16)	0.61	+0.02
2008	Kathiresan et al.	CVD	9 (out of 11)	0.80	+0.00
2008	Lango et al.	Type 2 diabetes	18 establ. variants	0.78	+0.02
2008	Van Hoek et al.	Type 2 diabetes	18 establ. variants	0.66	+0.02
2008	Meigs et al.	Type 2 diabetes	18 establ. variants	0.90	+0.00
2008	Lyssenko et al	Type 2 diabetes	11 establ. variants	0.74	+0.01

Janssens & van Duijn *Hum Mol Genet* 2008

Confusing Relative and Absolute Risk

I Know What We're All Going to Die Of…

- For common diseases, what does it really mean to be at a *relatively* reduced risk?
  - The absolute risk for common diseases is so high that we're all at significant risk for these maladies regardless of our relative risk
    - Even if you are at a "decreased risk" for heart disease you stand a good chance of dying from heart disease
  - All will benefit from population measures to reduce CVD, obesity, etc.

Risk assessment will be most valuable when the identified risks are high

A New Opportunity for Public Health Genomics

Embrace the 1%!

- We now have the capacity to identify those at high risk of preventable disease
- ~0.2% of US population carries a Lynch Syndrome mutation (>600,000 individuals)
  - At very high risk of colon & uterine cancer
    - highly preventable
  - We currently identify such people only after they and numerous family members develop cancer or die

– MPS allows population screening for such disorders
– Rare > Common
– ~1% (~3 million) of population carries mutations that predispose to similar serious but preventable disease

Public Health & Rare Diseases?

- New Born Screening
- Targeting rare diseases can yield tremendous public health benefits if certain conditions are met
  - Serious disease with a clinically silent latent period
  - Detection possible during latent phase with an affordable, effective test
  - Acceptable and effective preventive measures exist
  - Sufficient aggregate prevalence to make screening worthwhile

New born screening for adults

A Proposal

- Explore the potential of Multiplex MPS of a selected panel of genes that meet these criteria
- Pilot study of MPS of 10,000 healthy adults to study:
  - Acceptability, uptake & outcomes
  - Prevalence of deleterious mutations for candidate conditions & the true penetrance of such disorders
  - Optimal target ages to screen
  - Cost of screening & possible economic benefits
  - Informatics needs & approaches
  - Ethical, Legal and Social Implications, including
    - How such information is understood & used
    - Informed consent
    - Privacy issues
    - etc.

Challenges to Implementing Public Health Genomics

- Setting criteria for calling & reporting mutations
  - Focus on clearly deleterious mutations
    - e.g. truncating mutations & known deleterious mutations
    - Ignoring other variants will sacrifice some sensitivity
      - But is necessary to minimize false positives
        - » Cannot tolerate high numbers of FPs at a population level
        - » Lack of an ability to adjudicate VUS
- Accuracy of MPS platforms is poor
  - Need for confirmation at present
- Insurance coverage is necessary to ensure access to prevention
  - e.g. colonoscopy for those with Lynch-associated mutation
- Ensuring good understanding by population
  - e.g. not having a Lynch mutation doesn't mean you're at decreased risk for CRC

What I Am *Not* Calling For

- This is a call to investigate the potential of *targeted* MPS in a *highly selected* set of genes at the population level
- It is not a call to "perform WGS in everyone"
- No need
  - We don't understand most of what we'd find
  - 98% of us have boring genomes
  - ~1% of us have useful nuggets of information
    - Which can be efficiently targeted by sequencing
- Your genome is not necessarily a friendly place
  - Surprise!

If you harbor a mutation that essentially guarantees you will develop a severe untreatable neurological disease by 65 would you want to know?

1. Yes
2. No
3. I'm not sure

A few examples of really bad genetic diseases…

- Alzheimer Disease
- Fatal Familial Insomnia
- Spinocerebellar Ataxia
- Huntington Disease
- CADASIL
- etc…

- Little point in looking for such things except on a highly individualized basis

Targeted analysis of a panel of carefully selected genes in the broad population could yield substantial benefits

How Do We Select Candidate Genes To Target?

- Transparent process by which candidates are judged by specified criteria
- Representatives from
  - Genetics
  - Public health
  - General and specialty medicine
  - Medical economics
  - The public
- Iterative process with ongoing review in light of new knowledge regarding prevention, testing, etc.
- Again, we can learn from NBS community

One Possible Selection Strategy

Characteristics of Threat & Rx		Score	*MSH2*	*BRCA1*
Nature of threat	Possible Death	2	2	2
	Significant Morbidity	1		
	Minor Morbidity			
Likelihood of Disease (Penetrance)	>50%	2	2	2
	5-50%	1		
	<5%	0		
Effectiveness of Intervention	Highly Effective	2	2	2
	Moderately Effective	1		
	Minimally Effective			
Acceptability of Intervention	Highly Acceptable	2	2	1
	Moderately Acceptable	1		
	Minimally Acceptable			
Knowledge Base	High	2	2	2
	Moderate			
	Low			
			10	**9**

A Possible List of Genes to Target

Gene	Disease	US Mutation Prevalence

Total Population Prevalence: **~0.5-1%**

Cost of Such a Pilot

- The cost of a 5 year pilot with ~10,000 adults
  - Sequencing costs with multiplexing at ~$200/sample = $2 million
  - Implementing informatic analysis upon existing infrastructure
    - ~$1 million
  - Recruitment, education, consent, follow-up, including ELSI investigations
    - ~$2 million
- Possible funding sources:
  - NIH/NHGRI
  - NCI
  - Private (health) insurers

Rare is the New Common

Coming Full Circle in Medical Genetics

- Medical Genetics has historically been focused upon rare diseases, it's work directly applicable only to a few
- Now new technology provides us with efficient means of finding them
  - Making them relatively common in aggregate
- Ironic that through embracing our expertise in rare diseases we can potentially help improve the health of millions in the near term

We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time

TS Eliot, 1942

Little Gidding

A Possible List of Genes to Target

Gene	Disease	US Mutation Prevalence

Total Population Prevalence: **~1%**

How Can Next Generation Sequencing Be of Benefit in the Near Term?

- Sick People:
  - Diagnosing otherwise enigmatic diseases with a predominately genetic etiology
- Healthy People:
  - Finding those individuals at high risk of preventable disease
  - Enabling a variety of reproductive decisions

A Proposal

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- Pilot study of MPS of 10,000 healthy adults to study:
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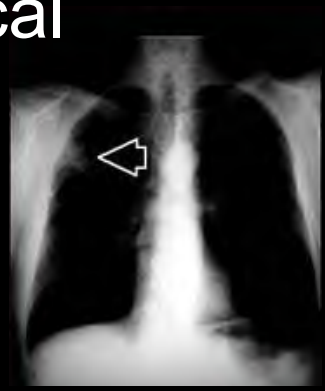
What About DTC WGS?

- The tsunami may not materialize
- Available data thus far suggest little uptake by public
- Some / many will have their genomes analyzed outside of traditional venues
- A coming shift from DTC genotyping
  - Largely worthless and thus largely benign
- To DTC WGS
  - Sometimes medically informative but with much higher stakes
  - With occasional client receiving potentially devastating information
    - Lynch vs. BRCA1/2 vs. APP & FFI
- Stakes are sufficiently high that stricter regulation will (should) exist regarding such testing
- Interpretation will be complex enough so that expert (clinician) interpretation will be necessary

Uncertainties in Clinical Genomic Analysis

Obligatory Reporting

- When WGS is performed are we obligated to examine some genes regardless of the clinical indication for sequencing?
  - Doing so entails increased effort and expense
  - But can offer life-saving information to some
- Not a new problem
- A minimum set of obligatorily scrutinized genes
  - e.g. Lynch Syndrome, *BRCA1*, *RET*
- Informatics approaches to limited scrutiny of such genes should not be prohibitively expensive
- >0.5% of patients will have such IFs for which detection & reporting could be life-saving



Uncertainties in Clinical Genomic Analysis

Maintaining Privacy

- Genomic information is inherently identifiable
- Our ability to protect privacy of those sequenced has steadily eroded
- “Privacy is Dead. Deal with it.”
- Most people want some degree of privacy protection
- Clear guidelines are needed
  - With real penalties for violation

Sun MicroSystems CEO Scott McNealy

Identifying Personal Genomes by Surname Inference

Melissa Gymrek,[1,2,3,4] Amy L. McGuire,[5] David Golan,[6] Eran Halperin,[7,8,9] Yaniv Erlich[1*]

A Few Final Uncertainties

- Gene Patenting
  - ~20% of human genes have patent claims upon them
  - How will this influence widespread genomic analysis?
- The threat of "allelism"?
- Genetic Discrimination
  - In the US GINA now protects against discrimination in the context of health insurance
    - But no protection exists in the realms of LTCI, Life Insurance and disability insurance

"We envision a new type of community where people will come together around specific genotypes…"

- Anne Wojcicki
Co-founder of 23andMe

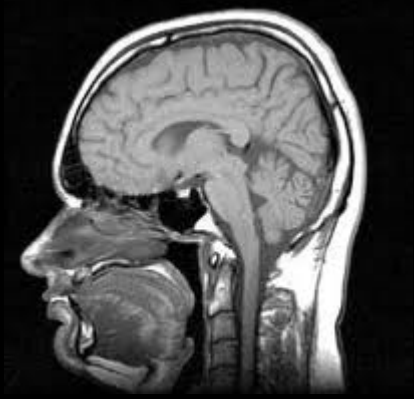
We must work together as a community of experts to reduce harmful uncertainties that hold the field and our patients back

x

Massively Parallel Sequencing as Just Another Medical Test

With both potential & limitations

- Claims are often made that "soon everyone will have their genome sequenced"
  - Typically predicated upon high perceived utility and low cost
  - Even if "free", the perceived low cost is an illusion
    - The misapplication of medical tests is very expensive
      - Morbidity/mortality to individuals
        - » Think routine screening PSAs
      - Expense to society
- I suspect it will be applied as are other medical tests
  - When and if the situation warrants



The Central Challenges of Clinical Genomic Analysis

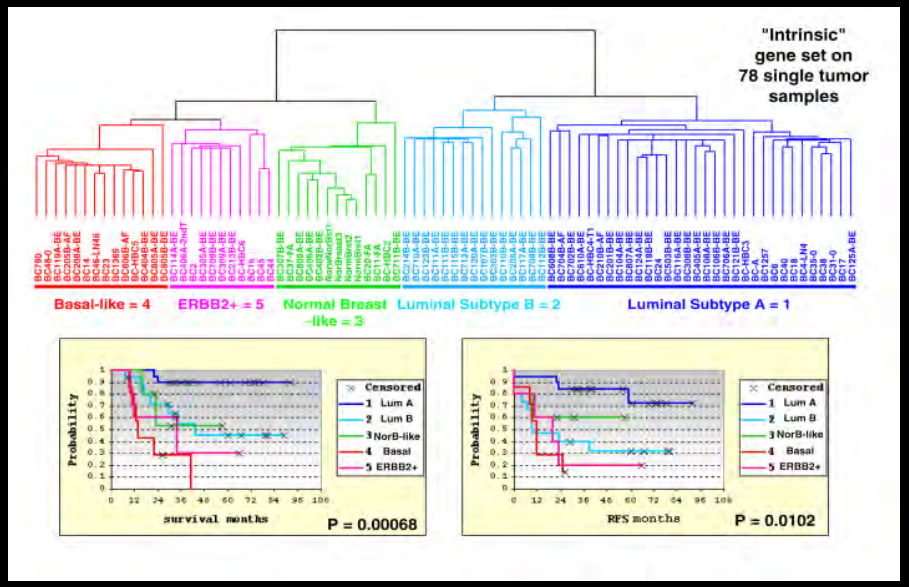
Dealing with Surprises

- The advent of robust genomic analysis inevitably leads to surprises
- Not necessarily a bad thing
  - Some such information will prove highly useful to participating individuals
  - Most is neutral or its impact is unknown
  - Some is overtly harmful

- IFs and all their attendant dilemmas are not new to medicine
- Deal with large amounts of data and surprises by taking a locus-based approach to categorization of potential results

Somatic Genomic Analysis in Cancer Offers Unique Opportunities

- Cancer is fundamentally a genetic disease
- Somatic analysis of tumors offers opportunities to parse complex phenotypes & improve Rx
- Chemotherapeutic agents are toxic and thus excellent targets for the application of PGx



How Will Genomics Affect the Central Endeavors of Clinical Medicine & Public Health?

- Prevention
- Diagnosis
- Treatment

How Much Added Value?

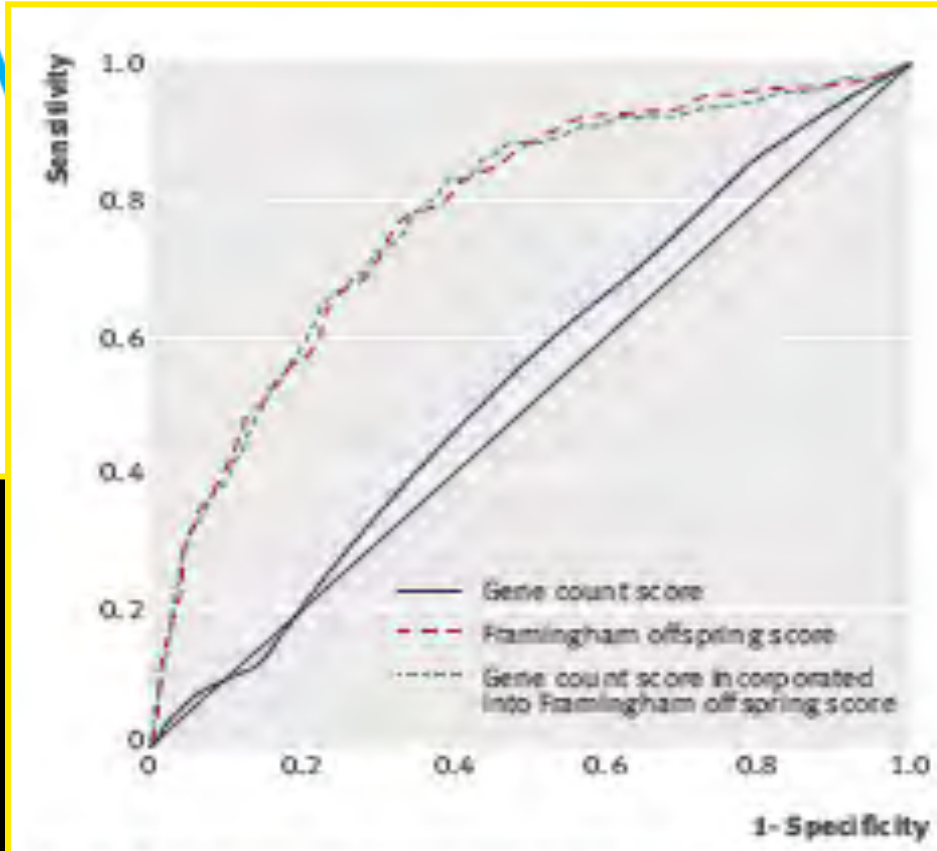


Fig 1| Receiver operating characteristics curves for gene count score alone (area under curve 0.54, 95% CI 0.50 to 0.58), Framingham offspring risk score (area under curve 0.78, 0.75 to 0.82), and gene count score incorporated into Framingham offspring risk score (area under curve 0.78, 0.75 to 0.81)

Cite this as: *BMJ* 2010;340:b4838
doi:10.1136/bmj.b4838

Risk Assessment is a Moving Target

Condition	23andMe Risk Susannah Wedgewood	DeCODE Risk Susannah Wedgewood
Age-Related Macular Degeneration	0.623	0.25
Breast Cancer	1.13	1.16
Celiac Disease	0.471	0.38
Colorectal Cancer	0.99	1.149
Crohn's Disease		
Heart Attack		
Multiple Sclerosis		
Obesity		
Prostate Cancer		
Restless Leg Syndrome		
Rhematoid Arthritis		
Type 1 Diabetes		
Type 2 Diabetes	0.808	0.76
Venous Thromboembolism	0.976	0.88

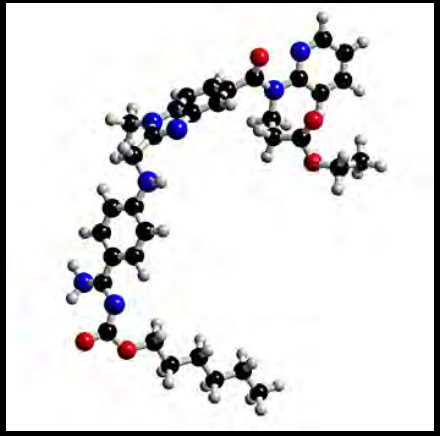
Contradictory Risk Predictions for Prostate Cancer and Hypertension

Gender	Age	Condition	Company 1	Company 2	Company 3	Company 4
Male	49	Prostate cancer	Average	Average	Below average	Above average
		Hypertension	Average	Below average	Above average	Not tested

Source: GAO.

Medical Treatment and the Genome

- Improved treatment will eventually result from:
  - Parsing the underlying heterogeneity of disease
  - Identification of new drug targets
    - Allowing us to short circuit biochemistry & physiology
  - The time line is long for implementation
- PGx will make near-term contributions to care:
    - Some current utility
      - e.g. abacavir, tamoxifen, clopidogrel(?), warfarin(?)
    - Will not be applicable to all drugs
      - Disorder in question must be severe and available drugs must be problematic
        - » e.g. chemotherapy
    - Incorporation must hinge on case by case demonstration of improved efficacy, safety or cost
    - Working against PGx is the short market $t_{1/2}$ of most drugs



dabigatran

The Central Challenges of Clinical Genomic Analysis

Dealing with Lots of Data

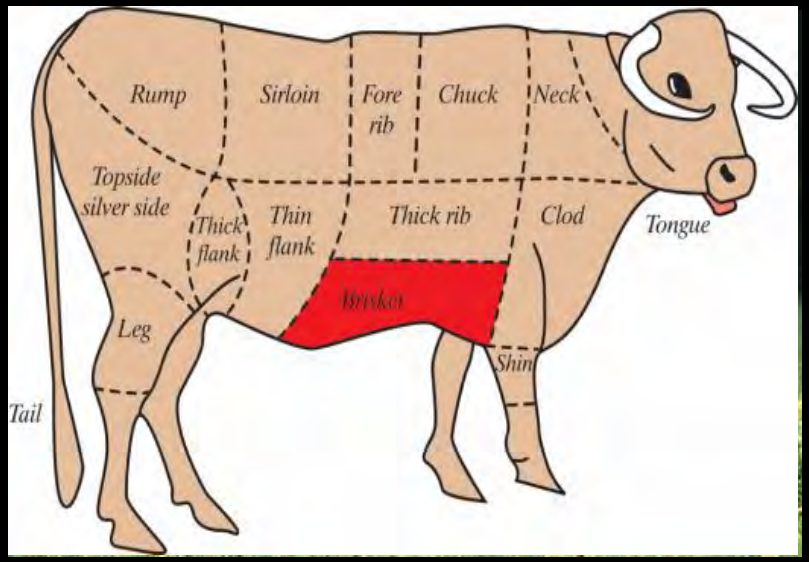
- Each of us has ~4 million variants
- Undue pessimism regarding analytic challenges
- The novel feature is quantitative, not qualitative
- The coming deluge is manageable
- The significance of the vast majority of genomic variants will be utterly unknown
  - Are thus clinically inconsequential and do not mandate reporting
  - Indeed we have no business reporting them

Saved by our Ignorance

Binning by Loci

Cutting Up the Cow

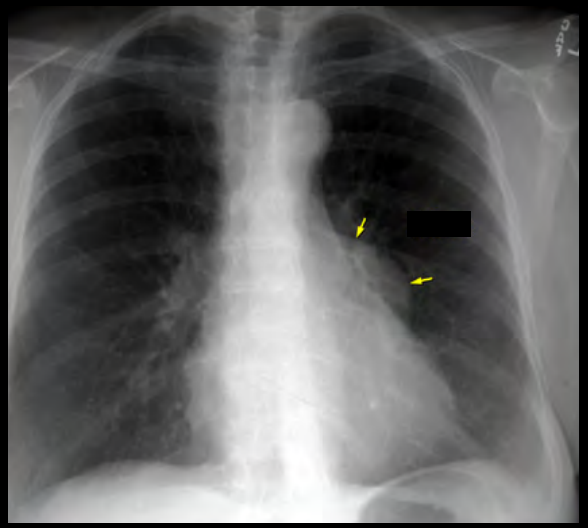
- WGS is often thought of as a “test”
- In reality it is 3 billion tests
- We can’t swallow it whole
- We need to carve it up into manageable bits if we are to derive any utility from it
- Save the good parts and toss the rest
- Do so informatically



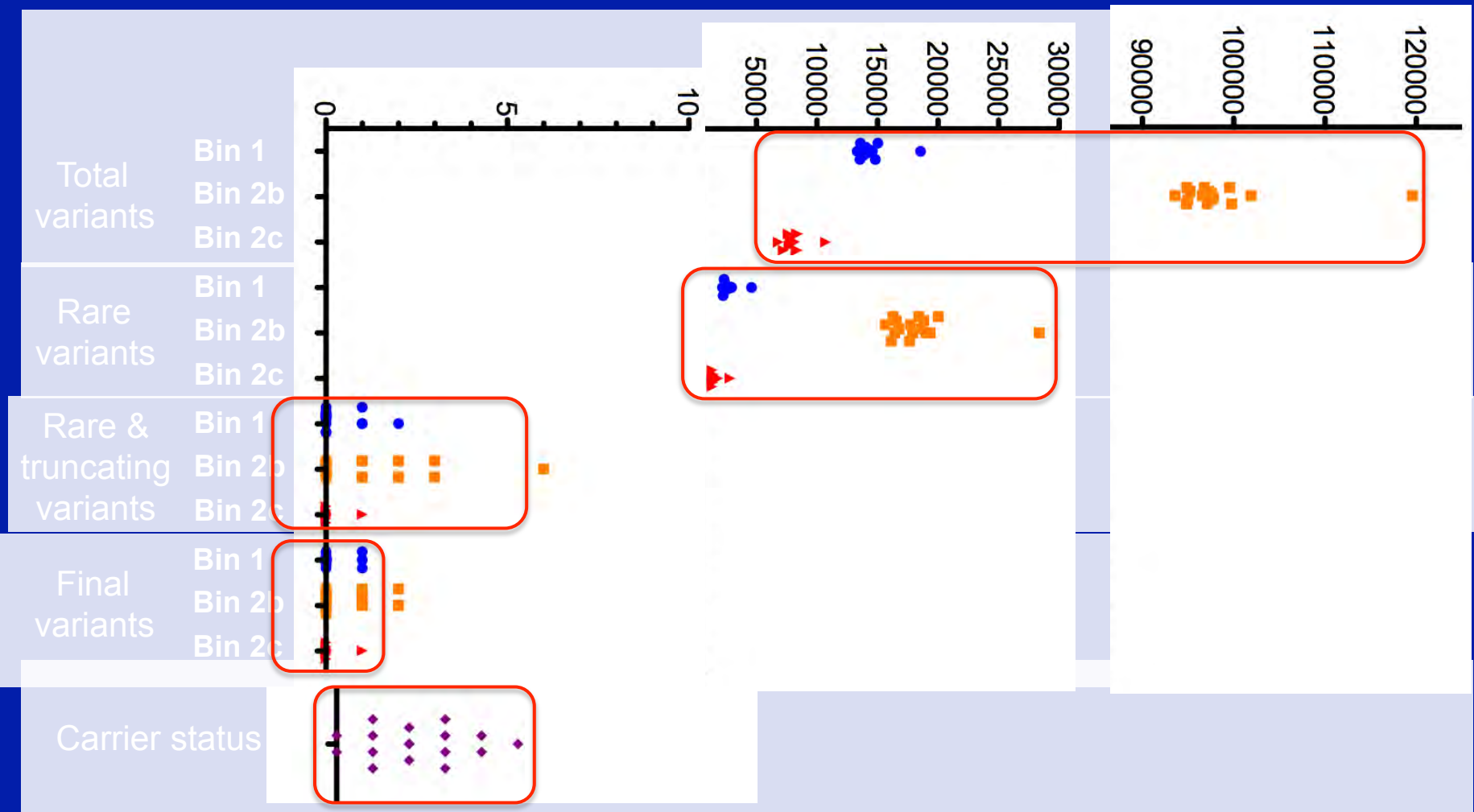
Binning of Data / Results

Facilitates Analysis, Reporting, Storage and Patient Choice

- Classification by evidence of clinical utility (especially actionability) can guide reporting of IFs
  - Bin 1:
    - Actionable
      - Obligatorily reported
  - Bin 2:
    - Clinical validity only
    - Return can be tailored to patient desires
    - Categorically driven pretest counseling & delivery
  - Bin 3:
    - Of no known significance
      - Obligatorily ignored



Binning results



Sensitivity & Specificity – Striking the Right Balance

- Most serious analytic concern in the clinical setting is a crippling number of false positives
- The bar for calling a mutation deleterious must be high
  - Nonsense, frame-shift, known missense, canonical splice site, etc.
    - Cannot rely on predictive models in the clinical context
- Initially sensitivity will suffer
  - But such mutation categories represent the majority of mutations in most human disease genes
  - Not a new problem
  - Sensitivity will rise as our databases and predictive abilities improve

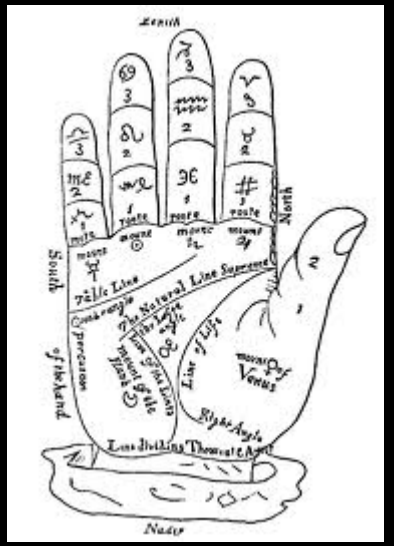
Challenges to Realizing Genomic Medicine

How do we formulate the bin structure?

- Too big of a job for each practitioner
- Inclusion / exclusion by a formalized aggregate of stakeholders & experts
  - Using evidence-based criteria
  - With ongoing study
  - Focus on clinical utility & *actionability*
  - Extant guidelines by professional organizations regarding actionability
  - Must be iterative
    - Today's bin 3 locus is tomorrow's bin 1
- Process must be evidence-based

Assigning Loci to Bins

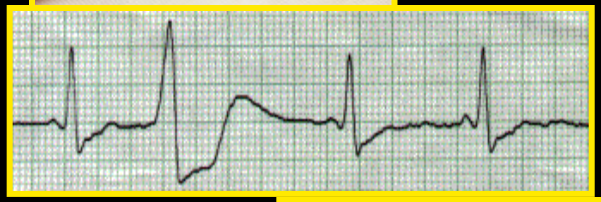
- Must be based on evidence of clinical actionability
  - Guidance from existing recommendations
- "Personal utility" not an argument for disclosure in the clinical setting
  - It varies in unpredictable ways and does not necessarily possess objective validity
  - The mission of clinical (and research) endeavors is not to satisfy individual's curiosity
    - That's what DTC Genetic testing companies and astrologists are for



The Case for Evidence

Good ideas are not sufficient to guide medical practice

- Hormone Replacement Therapy
- Sleeping Babies & prevention of SIDS
- Anti-arrhythmics for PVCs
- Beta-Carotene supplements to prevent cancer
- Bed rest for back pain
- Coronary stents do not prolong life
- Excessively strict glucose control in diabetes
- PSAs may cause more harm than good



Challenges to Realizing Genomic Medicine

Evidence

- Science ≠ Medicine
- Clinical medicine is messy
- Good ideas are insufficient to guide medical practice
- We need evidence of health benefit before incorporating new practices
- Can't demand RCTs for everything
  - We need novel approaches to evidence generation

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell BMJ VOLUME 327 20–27 DECEMBER 2003 bmj.com

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Challenges to Realizing Genomic Medicine

Dissemination of Genetic Information to Providers

- Providers and the public are ill-equipped to grapple with genomic medicine
- Nothing succeeds like success
  - Demonstrate utility and doctors will take interest
    - Genomics must be pulled into medicine, not pushed
- Genetics involves every specialty - but only in limited ways
  - It's easier to train oncologists to use the genetics they need than to train geneticists to be oncologists
  - Tremendous role for GCs, nurses, PA's
  - Just-in-time / point-of-care technologies
- Pay structures which reward interpretation and shared decision making at all levels (e.g. GCs)

Challenges to Realizing Genomic Medicine

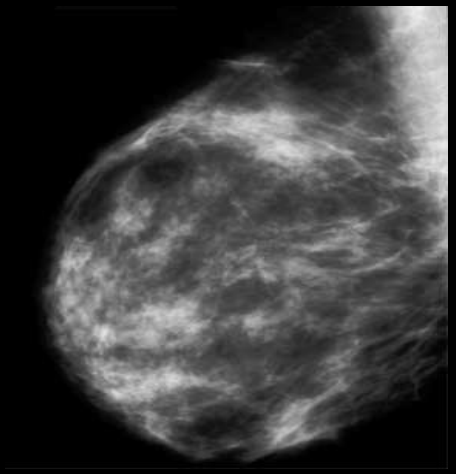
The Electronic Medical Record

- A functional EMR is an absolute necessity for both exploring and using genotype/phenotype relationships as we accelerate WGS
- Data requirements will be large
  - But greatly attenuated by small number of variants that mean anything
  - Re-analysis of the sample may ultimately be optimal approach
- We will regularly uncover sensitive data
  - But this is no different from the current medical record
  - *All* medical records require protection
- In the realm of clinical medicine there's *nothing* exceptional about genomic information

Challenges to Realizing Genomic Medicine

"Genetic Tests are Different from Other Tests"

- Genetic tests affect others
  - Infectious Disease
- Provide probabilistic information to asymptomatic
  - Cholesterol
- Our genome cannot be changed
  - Nor can much of what we discover medically
- Insurance discrimination
  - Actually *better* for genetics than the rest of medicine
- Unexpected results, FPs/FNs
  - Are a routine part of all clinical care
- DNA is "uniquely identifiable"
  - Zip code + DOB + spouse's first name



Social Challenges

- Genetic Discrimination
  - In the US GINA now protects against medical insurance discrimination
    - But no protection in the realm of LTCI, disability, life insurance
- The threat of "allelism"?
- Gene Patenting
  - ~20% of our genes have patent claims on them
  - How will this influence widespread genomic analysis?
- Privacy Issues
  - Genomic information is digital and easy to distribute
  - "Privacy is dead, deal with it,"
  - Bankruptcy of DeCode
- Who will control and have access to this information?

"We envision a new type of community where people will come together around specific genotypes…"

- Anne Wojcicki
Co-founder of 23andMe

Sun MicroSystems
CEO Scott McNealy

How Will NGS Affect the Central Endeavors of Clinical Medicine & Public Health?

- Prevention
  - By identifying the small % of individuals who harbor highly penetrant disorders for which proven preventive modalities exist
  - Allowing comprehensive preconception (and prenatal?) screening
- Diagnosis
  - For the minority (but still significant) proportion of diseases having a primarily genetic etiology
- Treatment
  - Preemptive delineation of certain useful PGx variants
  - Somatic parsing of genetic signatures, especially in cancer & ID
  - (Long Term) identification of drug targets and improved understanding of disease

Realizing Genomic Medicine

- It's not an insurmountable task
- Keep a focus on clinical utility
- Creation of a centralized, evidence-based, iterative process to define clinically significant genomic findings
- Better assessment of environment
- Maintain a sober (but not strangling) focus on evidence

Life is short, the art long,
opportunity fleeting,
experience delusive,
judgment difficult

Gene Patents

- ACLU *vs*. Myriad decision recently announced by CAFC
- Mixed signals
  - 101 claims upheld 2-1
  - Broad method claims denied
- Next step likely SCOTUS
- Will it matter?
  - Expiration
  - Will the problem be solved by the world simply ignoring gene patents?

Hey Jim 8/3/2011

What do you think will happen with the Myriad lawsuit? The recent reversal is causing a lot of buzz. We are getting a new barrage of cease and desist letters from companies with patents on various genes for which we do clinical testing.

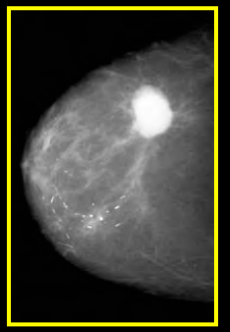
Have to meet with the lawyers and clinical lab admin folks next week to decide what to do. Since there is relatively new McLendon lab leadership (Herb Whinna and hospital admin person), we are going to have to start from scratch. What a royal(ty) pain in the ass!

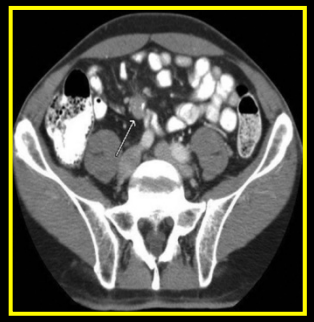
Challenges to Realizing Genomic Medicine

Ultimately Re-Evaluate Informed Consent

- Tests with devastating implications, FPs/FNs, unexpected & ambiguous results are the norm in medicine
  - We routinely handle with shared decision making
  - When is IC really needed?
  - When is it actively counterproductive to care?
  - A category-based approach can facilitate patient education and more informed consent

WBC	6.7 K/uL	4.0-12.0 K/uL
LYM	31.8 %L	25.0-45.0 %L
MID	5.9 %M	0.1-15.0 %M
PMN	62.3 %G	35.0-55.0 %G
RBC	3.53 M/uL	4.00-5.30 M/uL
HGB	7.8 g/dL	11.5-14.5 g/dL
HCT	24.7 %	33.0-43.0 %
MCV	70.0 fL	76.0-90.0 fL
MCH	22.1 pg	25.0-31.0 pg
MCHC	31.6 g/dL	32.0-36.0 g/dL
RDW	19.4 %	11.5-15.0 %
PLT	473 k/uL	150-450 K/uL





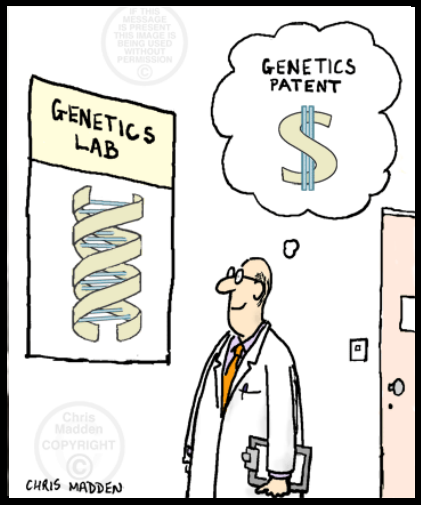
Comprehensive Metabolic Panel (w/ EGFR)

			Fasting Reference Interval
Glucose	89		65 - 99 mg / dL
Urea Nitrogen (BUN)	19		7 - 25 mg / dL
Creatinine		1.35 H	0.78 - 1.34 mg / dL
eGFR Non-Afr.American		57 L	> or = 60 mL/min/1.73m2
eGFR African American	>60		> or = 60 mL/min/1.73m2
BUN / Creatine Ratio	14		6 -22 (calc)
Sodium	140		135 - 146 mmol / L
Potassium	4.5		3.5 - 5.3 mmol / L
Chloride	105		98 - 110 mmol / L
Carbon Dioxide	22		21 - 33 mmol/L
Calcium	9.4		8.6 - 10.2 mg/dL
Protien, Total	7.0		6.2 - 8.3 g/dL
Albumin	4.7		3.6 - 5.1 g/dL
Globulin	2.3		2.1 - 3.7 g/dL (calc)
Albumin / Globulin Ratio	2.0		1.0 - 2.1 (calc)
Bilirubin, total	1.0		0.2 - 1.2 mg/dL
Alkaline Phosphatase	50		40 - 115 U/L
AST	24		10 - 40 U/L
ALT	32		9 -60 U/L

Consider the following few slides if I want to address drivers of hype

Drivers of the Misuse of Science

- Naïve enthusiasm and hope
- Scientists are human (really!)
  - We want promotion, attention, better salaries
    - Funding is (always) tight – and getting tighter
- Ideology
- Profit motives
  - Amplified by intertwining of industry and academia
  - Envisioning science primarily as an engine of economics



Scientific Illiteracy among the public and policy makers

Avoiding Scientific Misuse

- We will never abolish the motives that lead to the misuse of science
  - Appropriate regulation
  - An insistence that "scientific" claims be founded on good science
  - Transparency
    - e.g. links among academia and industry must be visible
  - Grooming a scientifically literate society

Creating a Scientifically Literate Society

Statistical literacy

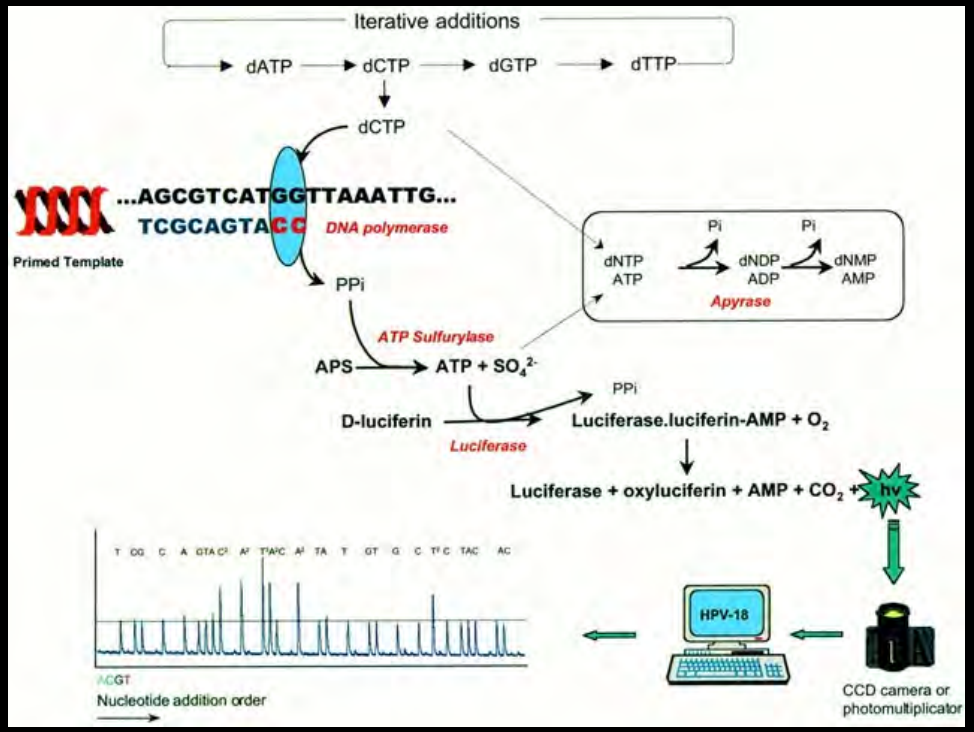
- The single educational reform that would accomplish the most
  - Profoundly neglected at all levels of education
  - Useful to all
    - The public
      - Regardless of their focus in life
    - Policy makers
    - The press
- "Statistics are boring and dry…"

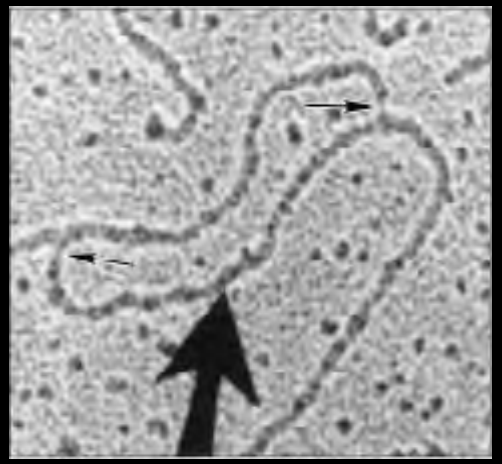
Creating a Scientifically Literate Society

An Emphasis on Beauty

- A firm grounding in science is as necessary as the humanities to fully appreciate the beauty of our world
- Sheer pleasure in the act of understanding
- Amplifying awe and wonder

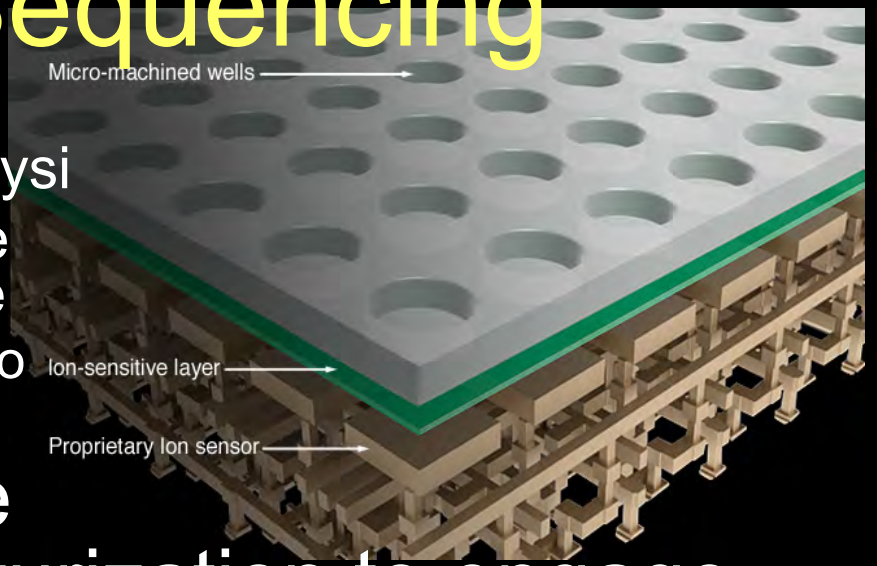
Sequencing DNA





- A variety of approaches now exist
- The biggest limitation to sequencing is that the genome is big and prior technologies proceeded one base at a time on one DNA strand at a time
  - So carrying out these reactions for an entire genome is slow and expensive

DNA Sequencing



- A variety of chemical and physi
- The biggest limitation has be place one fragment at a time
  - So carrying out these reactio and expensive
- Next Generation Se advantage of miniaturization to engage in massively parallel analysis
  - Essentially carrying out millions of sequencing reactions simultaneously in each of 10 million tiny wells
- Sophisticated computer analysis of huge

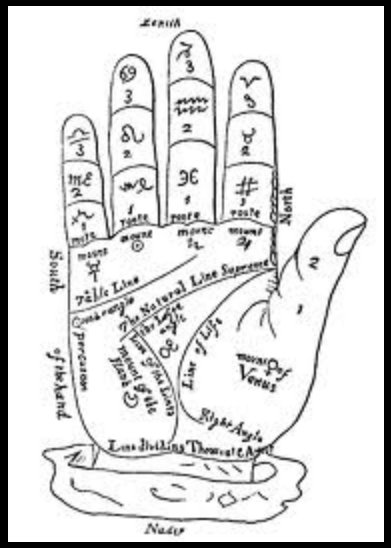
What About DTC WGS?

- The tsunami may not materialize
- Available data thus far suggest little uptake by public
- Some / many will have their genomes analyzed outside of traditional venues
- Interpretation will be complex enough so that expert (clinician) interpretation will be necessary
- Stakes are sufficiently high that regulation will exist regarding how such testing is offered

Thresholds for ROR

Personal Utility is Not Good Enough to Mandate ROR

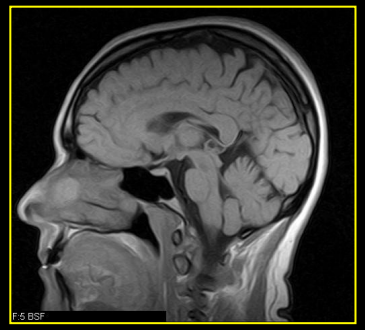
- "Personal utility" can be invoked in any situation
  - It varies in unpredictable ways and does not necessarily possess objective validity
  - Is thus not an argument for disclosure in this context
  - Neither is release of information just because "people want it"
    - The mission of clinical (and research) endeavors is not to satisfy individual's curiosity
      - » That's what DTC Genetic testing companies and astrologists are for



Dealing with Lots of Data

- Each of us has ~4 million variants
- The coming deluge is manageable
- The significance of the vast majority of genomic studies will be utterly unknown
  - Are thus clinically inconsequential and do not mandate reporting
  - Indeed we have no business reporting them
- A few will be tangibly useful to subjects
  - Report only those with established evidence of health benefit
- Accomplish this by taking a locus-based approach to categorization of potential results
  - Learn how to manage such results from how we manage imaging and other lab results

Saved by our Ignorance

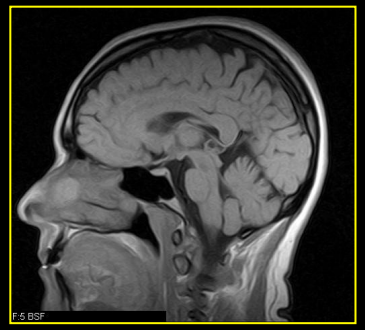


Challenges to Realizing Genomic Medicine

Dealing with vast amounts of information

- The coming deluge is manageable
  - Very few WGS findings will rise to the level of significance soon
  - Reporting all variants to "sequencees" is irresponsible and poor patient care
  - Learn how to manage such results from how we manage imaging and other lab results
  - We must centrally curate meaningful variants and report those to patients

Saved by our Ignorance



What's The Right Nail For Sequencing Technology?

- As a diagnostic tool in enigmatic patients
- As a public health tool to identify those apparently well individuals with dramatically increased risk of preventable disease

Challenges to Harnessing NGS in Clinical Medicine & Public Health

- Accuracy
  - 99.99% accuracy x 3 billion nucleotides
  - = 300,000 errors *per patient*
- Interpretation of the variants we find
- Storage and access in the medical record
- Education of patients and public
- Issues of consent and reporting
- Education of providers

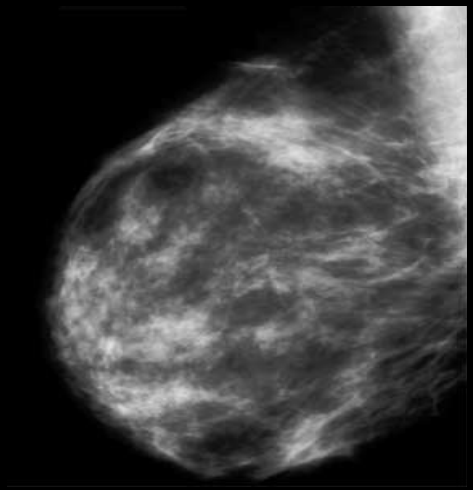
Incidental Information

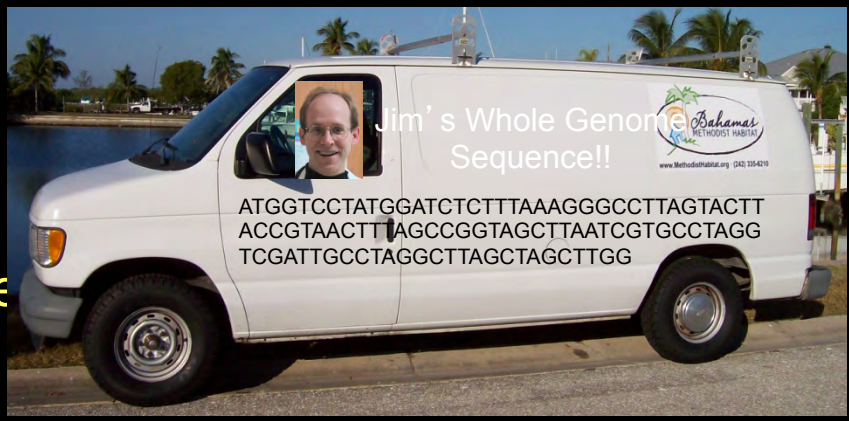
- Upon WGS we discover many things we weren't looking for, which we can do nothing about
  - Some are trivial or indeed beneficial
  - But some are problematic
  - And we will occasionally discover lethal, untreatable late onset conditions
- Some wish to know such information; others do not
- We must grapple with how to inform patients about such informa
  - protect patients fror
    individual autonomy
    and choice

In the Clinical Arena, Genetic Information Presents Few *Qualitatively* New Challenges

Eschewing Genetic Exceptionalism

- Genetic tests affect others
  - Infectious Disease
- Provide probabilistic information to the asymptomatic
  - Cholesterol
- Our genome cannot be changed
  - Nor can much of what we discover medically
- Insurance discrimination
  - Actually better for genetics than the rest of medicine
- Unexpected results, FPs/FNs
  - Are a routine part of all clinical care
- DNA is "uniquely identifiable"
  - Zip code + DOB + spouse's first name





Challenges to Realizing Genomic Medicine

- Creation of a centralized, evidence-based, iterative process to define clinically significant genomic findings
- Thorough health-oriented phenotypic annotation of variants
- Enabling realistic shared decision making among a range of providers, technology interfaces and patients
- Understanding the ethical dimensions, patient preferences & values regarding returning incidental results
- Maintaining a scope focused on evidence

Life is short, the art long, opportunity fleeting, experience delusive, judgment difficult


Jim's Whole
Genome Sequence!!
ATGGTCCTATGGATCTCTTTAAAGGGCCTTAGTACTT
ACCGTAACTTTAGCCGGTAGCTTAATCGTGCCTAGG
TCGATTGCCTAGGCTTAGCTAGCTTGG
Bahamas
METHODIST HABITAT
www.MethodistHabitat.org (242) 335-4210

Potential Examples for Discussion

- BRCA1/2
  - Possesses clinical utility/actionability
    - Bin 1
- FBN1 (Marfan)
  - Possesses clinical utility/actionability
    - Bin 1
      - Other examples: NF1, Lynch-associated genes, LQT
- ApoE
  - Possesses clinical validity but not actionability
  - Some “risk” to patient
  - Bin 2b
    - Return with appropriate patient involvement/counseling
- Risk SNPs for common disease
  - No clinical utility/actionability
  - Questionable clinical validity
  - Little harm
  - Bin 3

Hard Calls (?)

- Factor V Leiden
  - No clear actionability in asymptomatic individuals
  - Professional guidelines discourage screening (and thus reporting of FV status to asymptomatic individuals)
  - Bin 2a
- HFE
  - Easy and safe intervention to avoid potentially serious disease
  - Low penetrance
  - Good chance of diagnosis clinically prior to irreversible manifestations
  - Expert recommendations *not* to screen
  - Bin 2a
- Fragile X premutation male
  - Bin 2b ?
- Fragile X premutation female
  - Bin 2a ?
- Macular degeneration risk SNPs
  - Bin 2a
- Carrier status for lethal AR disease
  - Bin 2b

Potential Examples

Bin 2c

- Reporting the discovery of a Huntington Disease mutation
  - Pros:
    - Determinative (i.e. high RR/penetrance)
      - The information is thus at least valid
    - Would allow for family planning
    - May possess “personal utility” for some
  - Cons:
    - No medical actionability
    - Most (~80%) of those who understand the disease and know they are at risk decline testing
    - Potential harm in the sense of LTC insurance, disability, life insurance

Lack of tangible medical actionability and real risk of psychological harm argue against disclosure

Potential Examples
Bin 2b

- Reporting *APOE* status
  - Pros:
    - Modestly predictive
    - Personal utility for some
    - Highly selected individuals who are motivated to learn of status deal with information well (REVEAL Study)
  - Cons:
    - Not highly predictive (i.e. modest RR/penetrance)
    - No medical actionability

Potential Examples

Bin 2a

- Reporting risk SNPs for Common Diseases
  - Pros
    - Some may perceive personal utility
    - Little potential for psychological harm
  - Cons
    - Poorly predictive
    - No evidence to suggest such knowledge improves outcomes
    - Rapidly shifting terrain

July 22, 2010

DIRECT-TO-CONSUMER GENETIC TESTS

Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices

Contradictory Risk Predictions for Prostate Cancer and Hypertension

Gender	Age	Condition	Company 1	Company 2	Company 3	Company 4
Male	48	Prostate cancer	Average	Average	Below average	Above average
		Hypertension	Average	Below average	Above average	Not tested

Source: GAO.

Potential Examples
Bin 3

- A clearly deleterious mutation in a highly conserved gene of unknown function or medical relevance
  - Pros:
    - ?
  - Cons:
    - We don't understand the gene/ variant or its medical relevance
    - Thus reporting it provides no tangible benefit

Potential Examples
Bin 1

- Clearly deleterious mutation in *BRCA1*
  - Pros:
    - Clear actionability
      - Increased surveillance
      - RR surgery
    - High penetrance
    - Value to family members
    - Professional organizations with recommendations
  - Cons
    - Potential for psychological harms
- Other examples: *NF1, FBN1, MSH2*

Context of delivery is critical to avoid harms

Context of Delivery

- Reported variants must be confirmed in a CLIA lab
  - Funds must be allocated for this
    - Practical and affordable given rarity of this event
- Must be delivered by a clinician
  - Perhaps by telephone - but with offer of personal f/u
- No charge to subject (who is now a patient)

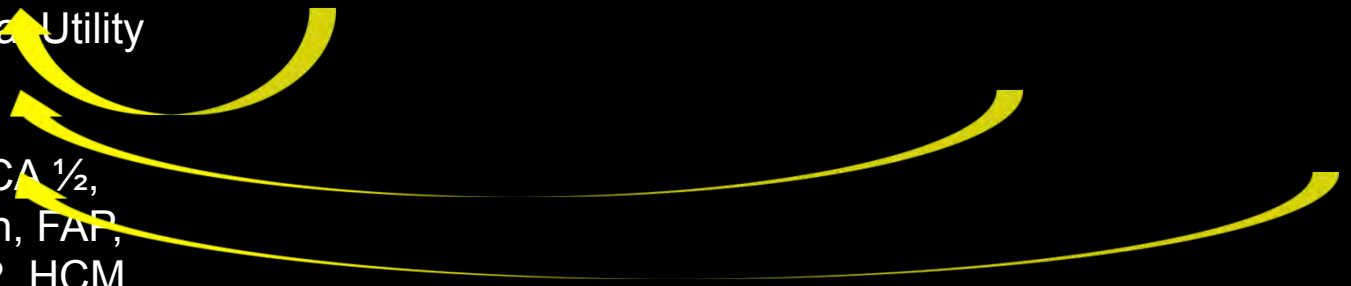
All Genetic Changes Are Not the Same

Variants of Uncertain Significance in Bin 1 Genes

- A given variant must meet a high threshold for likely deleterious nature before reporting
  - Frame shift
  - Nonsense
  - Truncating
  - Missense if previously confirmed to be deleterious
- I would argue against reporting other VUS
  - A low *a priori* chance of being deleterious in a non-clinical population
  - Harm to both subject and research could be significant if false positives are not minimized
    - VUS's are common

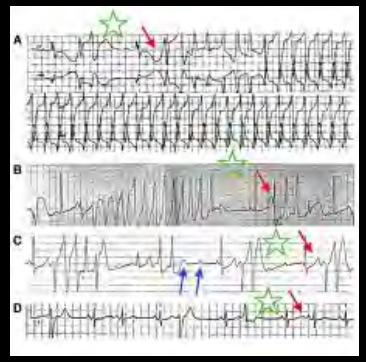
Bin 1

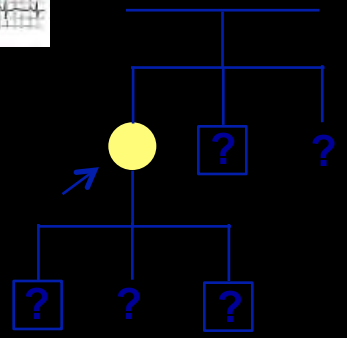
Definition	Clinical Utility
Examples	BRCA ½, Lynch, FAP, MEN2, HCM, Mendelian Diseases actionable PGx loci…
Practice	Integrate into practice now; encourage use
Coverage	Yes



Next Generation Sequencing as a Clinical Diagnostic Tool

- 47 yo female with sudden cardiac arrest
- Resuscitated successfully
- EKG reveals “Long QT Syndrome”
  - High risk for sudden death
  - Dozens of genes implicated
- Application of NGS to detect mutation
- Thereby guiding patient’s treatment and prevention of death in family members

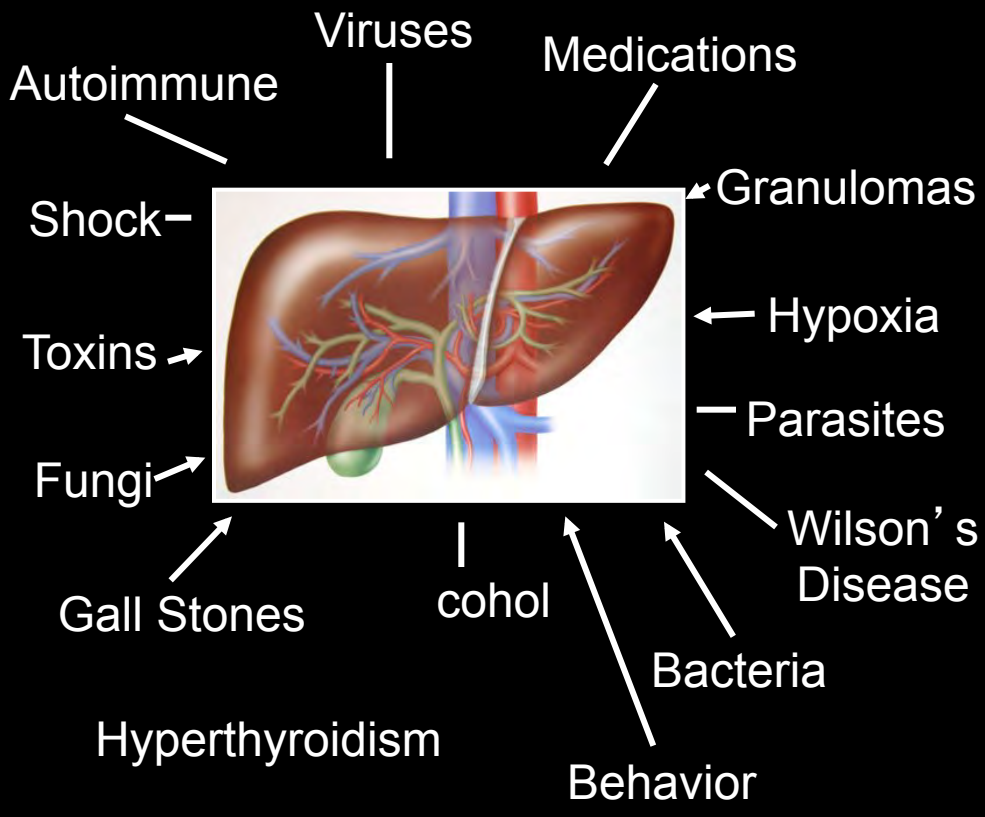




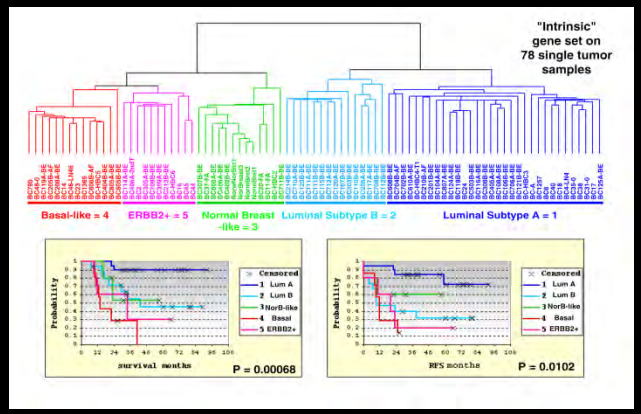
Next Generation Sequencing as a Public Health Tool

- ~0.25% of US women (375,000) carry a mutation in *BRCA1/2*
  - At very high risk of breast and ovarian cancer
    - 85% lifetime breast cancer risk
    - 25-50% lifetime ovarian cancer cancer
- Knowledge of risk allows prevention
  - Currently we only can identify such women once several family members have developed cancer
- NGS allows population screening for high risk preventable disorders
  - Cancer predisposition, cardiac disease, etc.
  - ~1-2% of population carry such mutations
    - 3-6 million individuals in the US with preventable disorders if identified

Limitations of Genomic Diagnostics



- Somatic analysis offers opportunities to parse complex phenotypes & improve Rx
- Germline genomic analysis is unlikely to transform primary diagnosis of most human diseases
  - Simply because the etiology of most diseases have many complex non-genetic components

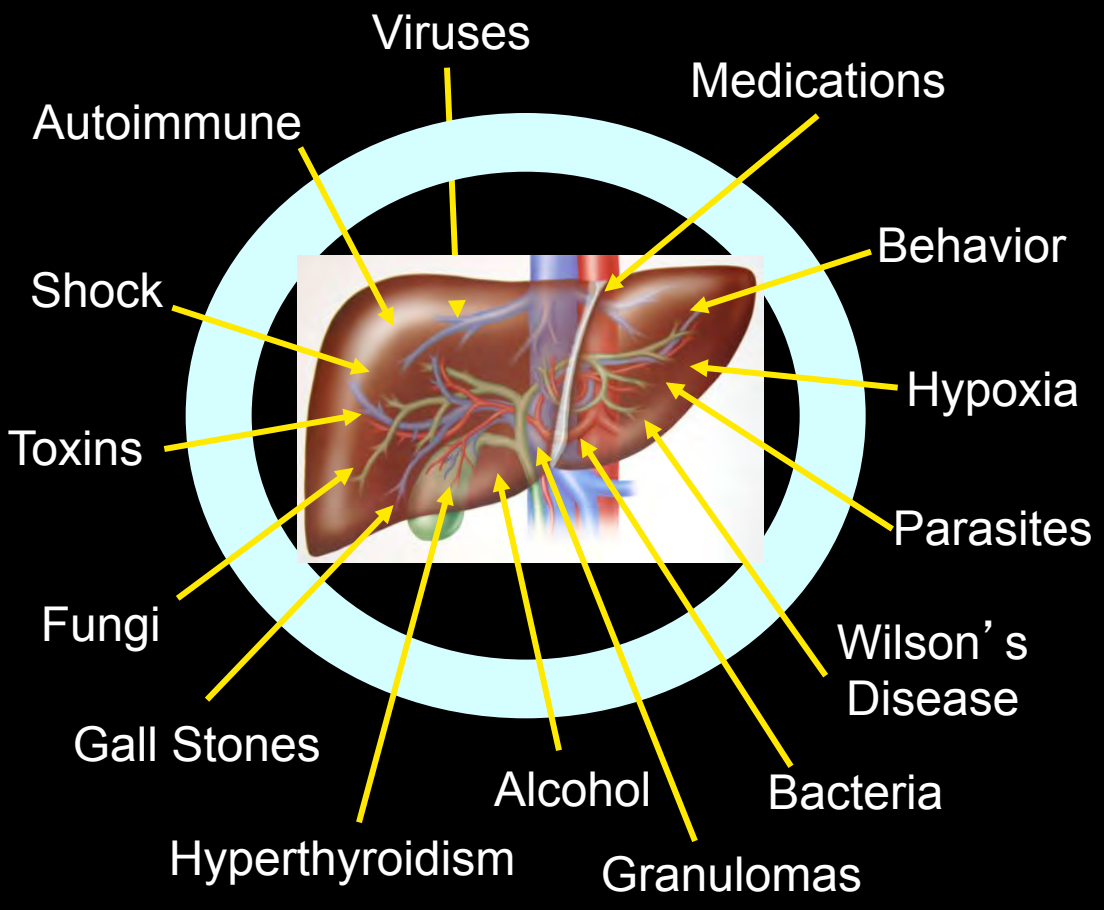


Challenges to Realizing Genomic Medicine

Future Investments

- The genetic component of disease is limited
- But is distributed widely
  - i.e. virtually all other etiologic factors likely interact with it
- We must invest heavily in phenotype/genotype analysis
- And environmental assessment
  - Much more difficult than genetics
  - Analog vs. digital

Understanding the environment is the only way to understand the genetics of disease causation



Little Added Value

Year	Researchers	Disease	Genetic variant	AUC	Δ AUC
2005	Lyssenko et al.	Type 2 diabetes	3 establ. variants	0.68	+0.00
2006	Podgoreanu et al.	MI after surgery	3 (out of 48)	0.70	+0.06
2007	Humphries et al.	CHD	4 (out of 12)	0.66	+0.04
2007	Morisson et al.	CHD	11 (out of 116)	0.76	+0.01
2008	Vaxillaire et al.	Type 2 diabetes	3 (out of 19)	0.82	+0.00
2008	Zheng et al	Prostate cancer	5 (out of 16)	0.61	+0.02
2008	Kathiresan et al.	CVD	9 (out of 11)	0.80	+0.00
2008	Lango et al.	Type 2 diabetes	18 establ. variants	0.78	+0.02
2008	Van Hoek et al.	Type 2 diabetes	18 establ. variants	0.66	+0.02
2008	Meigs et al.	Type 2 diabetes	18 establ. variants	0.90	+0.00
2008	Lyssenko et al	Type 2 diabetes	11 establ. variants	0.74	+0.01

Janssens & van Duijn *Hum Mol Genet* 2008

Genetics and Soccer

"Soccer is the sport of the future in America…

…and it always will be."

Acknowledgements

- Eric Green
- Chris Austin
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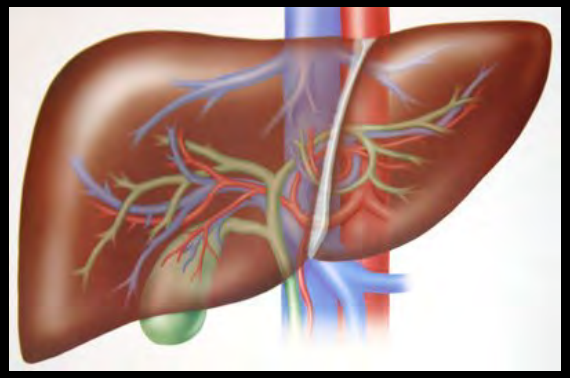
- Greg Feero
- Mark Guyer
- Muin Khoury
- Theresa Marteau
- Howard McLeod
- Eric Meslin
- Clifford Reid
- Marc Williams

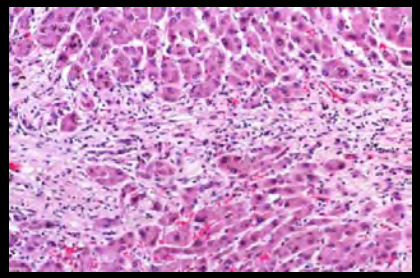
Genomic Diagnosis

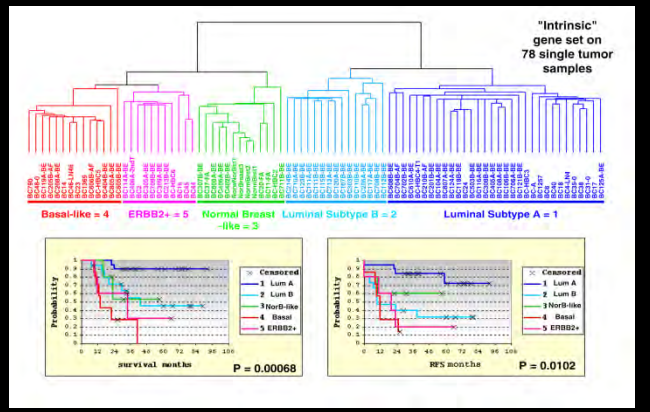
2° Diagnostics

Where Genomics Comes into it's Own

- Secondary diagnostics
  - "What subclassification of a particular disease does my patient have?"
- Powerful because most "diseases" are highly heterogeneous
  - The human body can respond in only a limited number of ways to myriad insults
  - The microscope allowed us to parse 1° diagnoses
    - Better prognosis and treatments
  - By querying those with a given 1° diagnosis at the (typically) somatic molecular genetic level we can further parse an individual's disease
  - Informing prognosis, Rx response, etc.
    - w/o understanding underlying biology







The Paradox of Risk Information

- "Knowledge is Power"…*or is it?*
- It is often maintained that knowledge of one's genetic risk will benefit patients
- Does knowledge of increased risk of obesity, diabetes, CVD lead to improved lifestyle?
- Little evidence that genetic information *per se* is more effective than other types of information in getting people to change their long-term behavior
- And if it is…
  - For everyone I find who is at increased risk, I'll find those at *decreased* risk
    - Will such information give such individuals license to not pursue healthy lifestyles?

Novel Approaches to Evidence Acquisition are Needed

- RCTs supply vital information
  - At great expense
  - Are sometimes not needed
- Other models must be harnessed
  - Innovative study designs
  - Provisional approval by payers
  - With ongoing & post-market data accrual
  - Evidence thresholds can be calibrated to risk of harm

Vast Amounts of Information Will Be Generated

Saved By Our Own Ignorance

- The significance of the vast majority of findings from WGS will be utterly unknown & thus will be clinically inconsequential
  - We can and should disregard them in the clinical arena
    - While they are studied with ongoing phenotyping efforts
  - A few will be useful now
    - Implement those for which evidence exists for health benefit

Bin 1

Definition	Clinical Utility
Examples	BRCA1/2, Lynch, MEN2, Mendelian Diseases, actionable loci
Practice	Integrate into practice
Coverage	Yes

Practical Promises and Challenges of Genomic Based Clinical Care

- Where does future promise lie?
- What are some of the challenges which must be addressed to realize the potential of Genomic Medicine?
- What can be implemented now?

Practical Promises and Challenges of Genomic Based Medical Care

- Medical management revolves around two* primary activities:
  - Diagnosis
  - Treatment

How will genomics affect these central endeavors in caring for the sick patient?

*I will not discuss screening/prevention

Central Challenges to Realizing Genomic Medicine

- Creation of a centralized, evidence-based, iterative process for defining clinically significant genomic findings
- Thorough health-oriented phenotypic annotation of WGS findings
- Better assessment of environment
- Enabling shared decision making between providers, technology interfaces and patients

The Human Genome Project vs. The Hubble Space Telescope

- The public funded the HST because it is interesting and satisfies our fundamental curiosity
  - With some justification by trickle down benefits
    - 0.3% of US budget devoted to NASA
- Health care consumes 17% of the US GDP
  - An expenditure only justified if practical benefits result

The HGP was sold to the public because of its practical promise

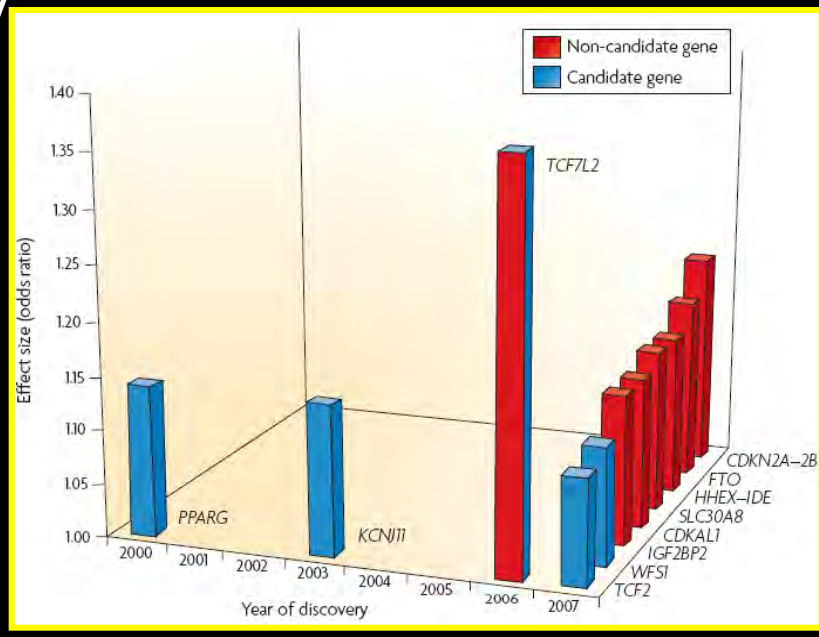
Improved Treatment and the Genome
Pharmacogenomics

- PGx is already a reality for select agents
  - e.g. abacavir, clopidogrel, herceptin
    - warfarin, tamoxifen
  - Will not be applicable to all drugs
    - The determinants of efficacy for many drugs will have little genetic component
    - Wide therapeutic window
    - Redundant elimination
    - The best predictor of any drug's efficacy is compliance
  - PGx will be most useful for agents:
    - With robust genomic component of variability
    - With narrow therapeutic window
    - Used to treat serious disorders
    - For which alternatives exist

Improved Treatment and the Genome

Novel drug targets

- Genomics allows us to short circuit biochemistry & physiology
- GWAS are defining numerous new drug targets
- Little reason to think RR is correlated with promise as drug target
- An infrastructure exists to capitalize on genomic information
  - However, that infrastructure is expensive has a poor absolute success rate and its time-line is long
- New models are needed
  - e.g. TRND & NIH Chemical Genomics Center



Definition of a healthy 85 yo…

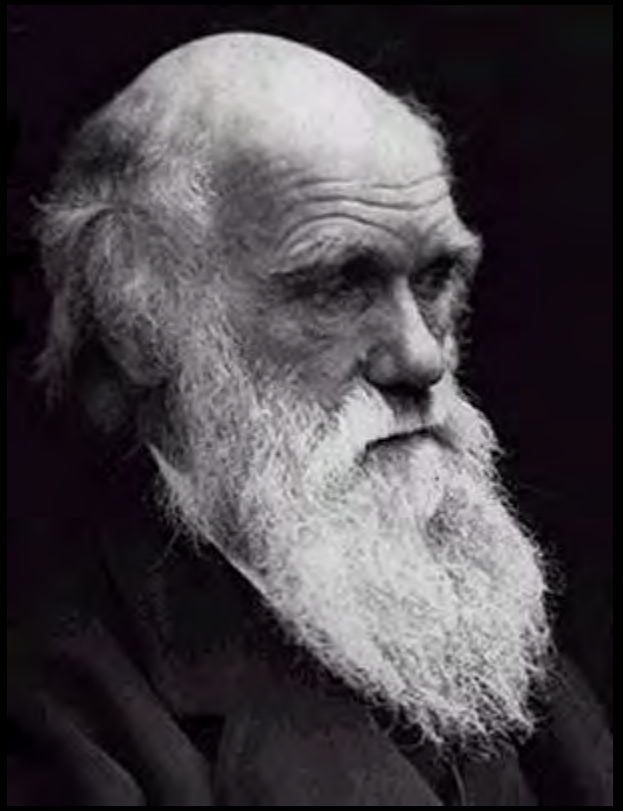
Ancient Roots of Personalized Medicine

"But remember throughout that no external cause is efficient without a predisposition of the body itself. Otherwise, external causes which affect one would affect all…"

The Darwinian Roots of Personalized Medicine

- Darwin overturned "essentialist" thought in biology
  - Fixed species modeled on an archetypical ideal
- He pointed to the importance of individual variation
- This insight lies at the root of "personalized medicine"

Individualized Medicine seeks to exploit such variation for better health



The Promise of Individualized Medicine

Screening, Diagnosis, Management

- The current status of screening in medicine
  - Relatively little benefit
  - Actual harm to some
  - Tremendous waste of resources
- Current drug therapy in medicine
  - Efficacy varies widely
  - Adverse effects are common *and unpredictable*
  - Wasted resources and time

We now have the ability to analyze the individual's genome deeply and define medically important variation

What Should be Our Agenda for Realizing the Promise of Genomic Medicine?

- We should seek to discover which genomic advances can improve patient/ public health
- We must insist on data which demonstrate safety and benefit before implementing what seem like good ideas
  - Such benefit may be in
    - Outcomes
    - Costs
      - For individuals or for populations

How Do We Achieve That Agenda?

- Resist impatience and the seductive power of good ideas
- Maintain an insistence on appropriate data
- Increased funding and incentivize:
  - Comparative Effectiveness Research
  - Translational medicine
  - Comprehensive and integrated databases of reference sequences, variants and phenotypes
  - Appropriate regulatory agencies (e.g. FDA)
- Don't forget to address ELSI challenges
- Innovate with regard to our data demands

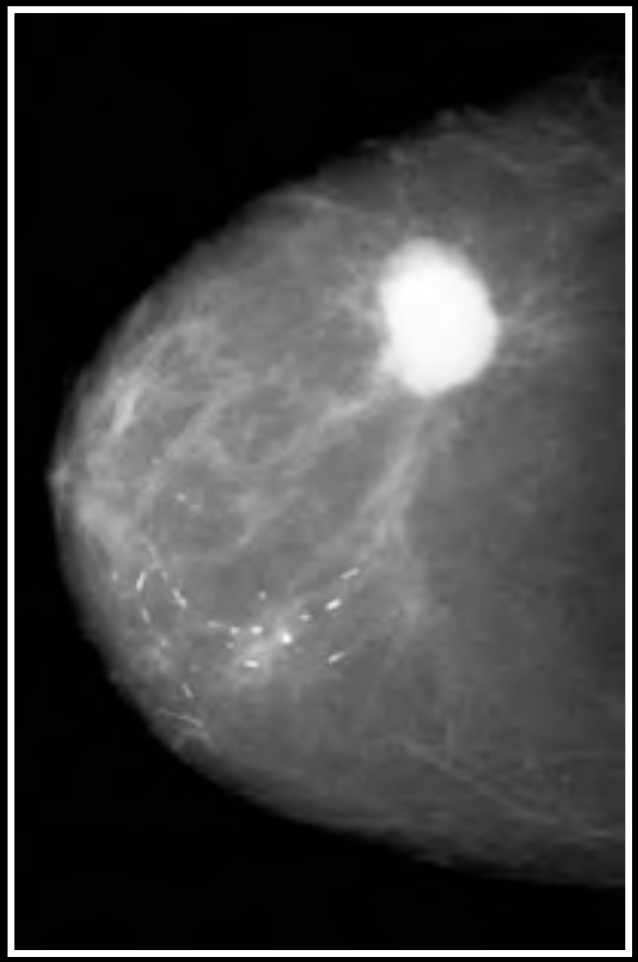
(Multiplex Sequencing or WGS?)

- One can argue for MS instead of WGS given the low number of validated variants with utility
  - Already clinically viable
    - e.g. RP, Lynch Syndrome, HSPP, SCA, etc.
- WGS may be just as cheap (or cheaper)
- WGS may well be done anyway (due to market forces)
  - Making it all the more vital to pursue in the context of careful study
- We don‘t necessarily know enough to decide which multiple genes to sequence in a given patient
- WGS, coupled with appropriate study, phenotypic annotation & follow-up offers an added wealth of data
- Clinical *vs.* public health applications could argue for different approaches
  - MS having the edge in public health context

Thoughtful pursuit of clinical WGS in the form of pilot programs

A Closer Look at Genetic Exceptionalism

- A test with potential for profound medical & psychological implications
  - Might be falsely reassuring
  - Might reveal highly disturbing news
    - e.g. “you have a potentially lethal disease”
  - Frequently results in ambiguous findings
- Is highly imperfect
  - 13% false negative rate
  - 10% false positive rate



Mammography

How Does Medicine Currently Deal With Potentially Toxic Information?

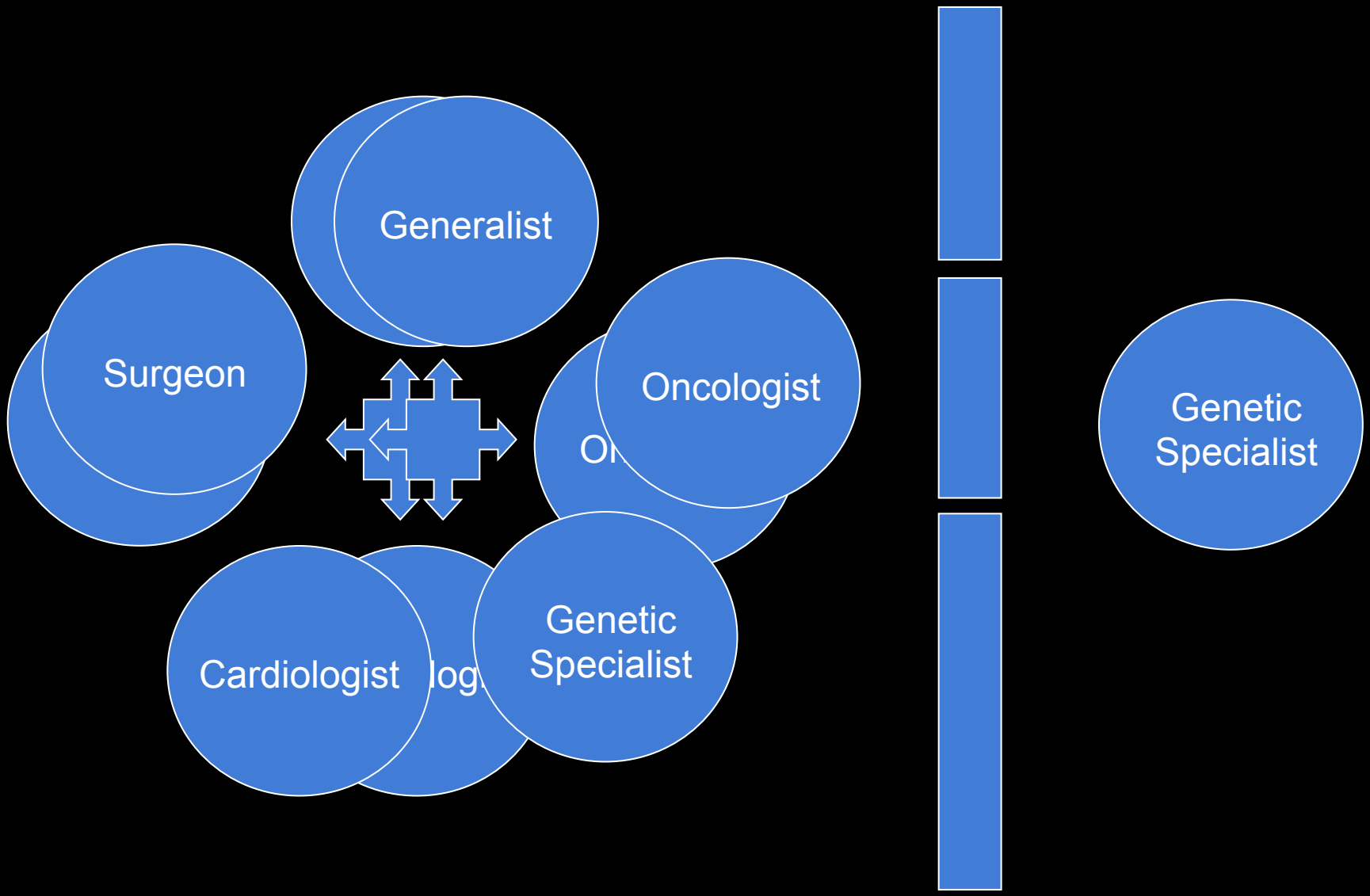
- Recent h/a's
- Subtle neurological finding on exam
- Chance of a brain tumor

- The generalist discusses possibilities with the patient
- Orders a potentially definitive test (e.g. MRI)
- If that reveals a tumor, referral to a specialist (e.g. neurosurgeon and oncologist)
- Necessitates that the generalist is knowledgeable, sensitive and that a measure of trust exists

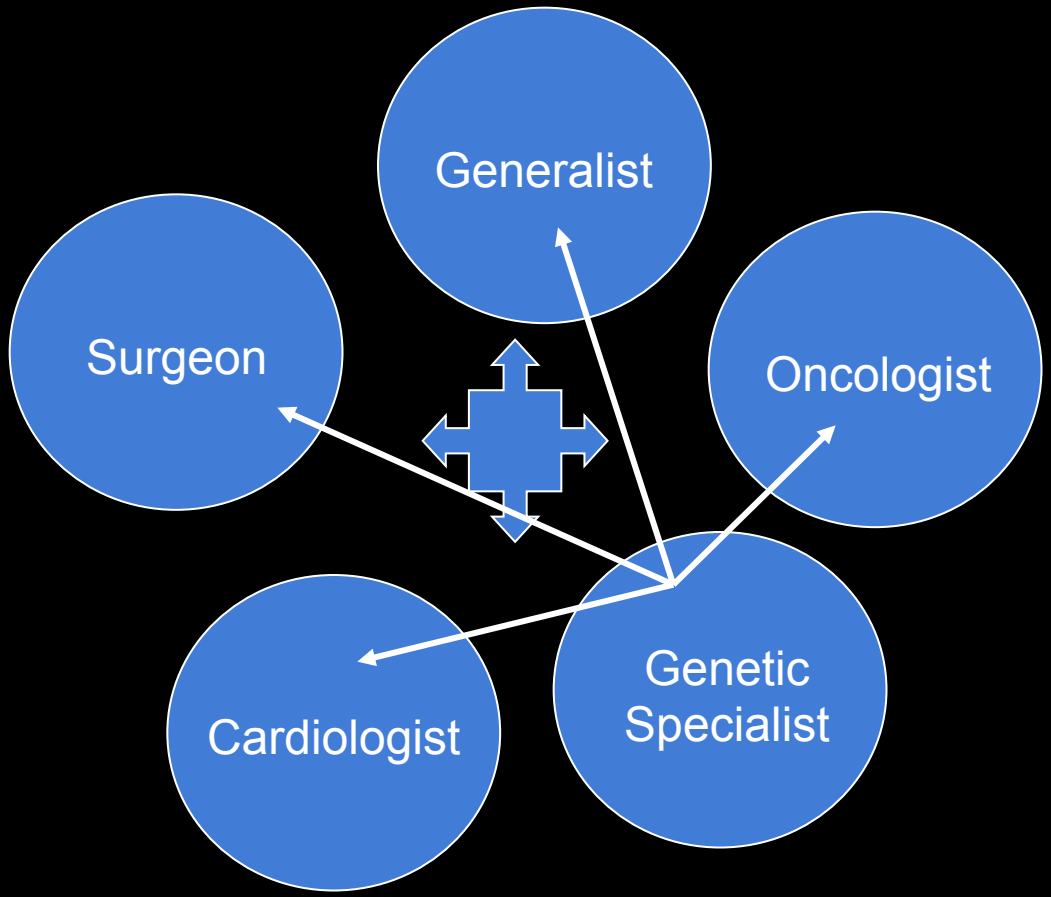
A New / Old Model:
Incorporating Genetics into Medicine's Mainstream

- Referral to a genetic specialist is logical once a suggestion of genetic implications is uncovered
- This is precisely how other specialties work
  - The generalist consults the cardiologist *after* he or she has determined that heart disease may be present
- The fact that "toxic information" might ensue does not necessarily warrant the requirement for informed consent *simply because that information is of a genetic nature*

Genetic Exceptionalism



Genetic Inclusion



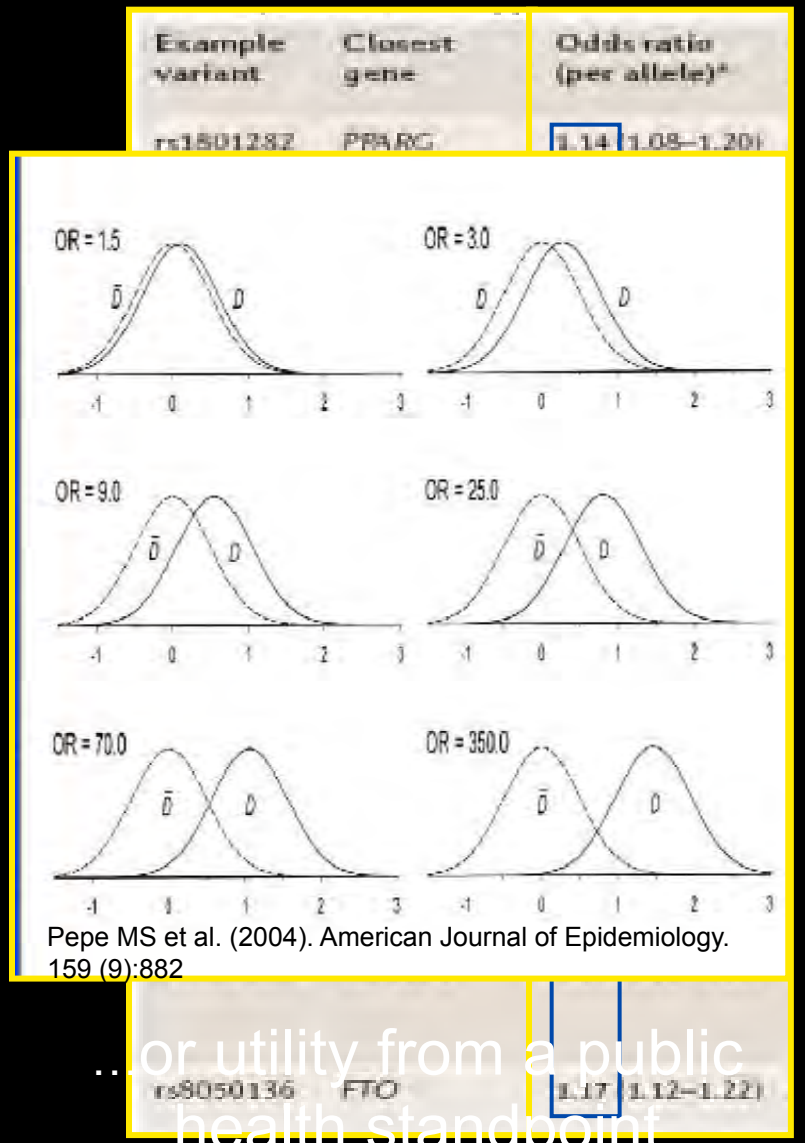
- Requirements for Inclusion
  - Genetics must prove its relevance to patient care
  - Formulation of clear guidelines for referral
  - Adequate # of genetic providers
  - Genetic education of physicians & patients
    - demystification of genetics

The responsibility of the genetics community

What Good is Defining Risks?

The Problem of Relative Risk

- Numerous risk alleles have been identified
  - The vast majority of RR defined by GWAS are between 1-2
    - What do I ***do*** with such information?
  - From a clinical standpoint the information is so lacking in robustness that it is of questionable clinical utility



Pepe MS et al. (2004). American Journal of Epidemiology. 159 (9):882

…or utility from a public health standpoint

Frayling T; Nature Reviews 8:657.2007

How Much Added Value?

Year	Researchers	Disease	Genetic variant	AUC	Δ AUC
2005	Lyssenko et al.	Type 2 diabetes	3 establ. variants	0.68	+0.00
2006	Podgoreanu et al.	MI after surgery	3 (out of 48)	0.70	+0.06
2007	Humphries et al.	CHD	4 (out of 12)	0.66	+0.04
2007	Morisson et al.	CHD	11 (out of 116)	0.76	+0.01
2008	Vaxillaire et al.	Type 2 diabetes	3 (out of 19)	0.82	+0.00
2008	Zheng et al	Prostate cancer	5 (out of 16)	0.61	+0.02
2008	Kathiresan et al.	CVD	9 (out of 11)	0.80	+0.00
2008	Lango et al.	Type 2 diabetes	18 establ. variants	0.78	+0.02
2008	Van Hoek et al.	Type 2 diabetes	18 establ. variants	0.66	+0.02
2008	Meigs et al.	Type 2 diabetes	18 establ. variants	0.90	+0.00
2008	Lyssenko et al	Type 2 diabetes	11 establ. variants	0.74	+0.01

Janssens & van Duijn *Hum Mol Genet* 2008

Risk Assessment is a Moving Target

Condition	23andMe Risk Susannah Wedgewood	DeCODE Risk Susannah Wedgewood
Age-Related Macular Degeneration	0.623	0.25
Breast Cancer	1.13	1.16
Celiac Disease	0.471	0.38
Colorectal Cancer		1.149
Crohn's Disease		2.29
Heart Attack		0.87
Multiple Sclerosis		1.52
Obesity		1.05
Prostate Cancer		0.85
Restless Leg Syndrome		1.6
Rhematoid Arthritis	1.381	2.32
Type 1 Diabetes	0.56	0.46
Type 2 Diabetes	0.808	0.76
Venous Thromboembolism	0.976	0.88

The Illusion of Parsing Risk

- For common diseases, what does it really mean to be at "reduced risk"?
  - Lifetime risk of dying of cancer for a US citizen
    - 28%
  - Lifetime risk for a 50 yo US male of developing heart disease
    - 55%
  - We're ***all*** at increased risk for these maladies - regardless of our relative risk
- For uncommon diseases what does it mean?
  - Risk of developing Crohn's Disease = 5/1,000

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  - Translational medicine
  - Comprehensive and integrated databases of reference sequences, variants and phenotypes
  - Appropriate regulatory agencies (e.g. FDA)
- Don't forget to address ELSI challenges
- Innovate with regard to our data demands

RTCs Are Not the Only Answer

- RTCs supply vital information
  - At great cost
  - At great expense
  - Cannot be the only solution to our insistence on evidence
  - And are sometimes not needed

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell BMJ VOLUME 327 20–27 DECEMBER 2003 bmj.com

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Additional Approaches are Needed

- Other models must be harnessed
  - Innovative study designs
  - Provisional approval by payers with ongoing data accrual
  - Post-market data accrual
  - A common theme will be leverage by payers
  - We must influence payers and incentivize them to seek data

The Coming Deluge

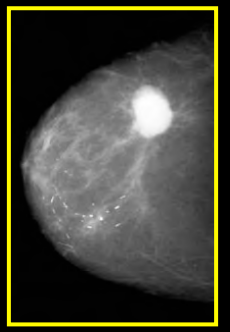
- The $1,000 genome is almost here
- We will be awash in highly complex genetic information
- WGS is the first medical test which will be guaranteed to yield abnormal results in everyone tested
  - We are all mutants
  - We all will have false positive and false negative results
  - There are serious challenges to interpreting its medical implications
- And serious social challenges

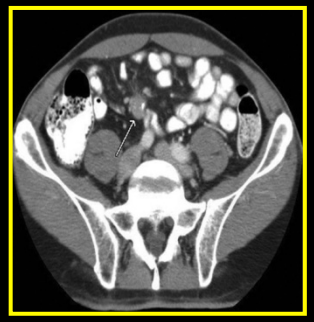
Challenges to Realizing Genomic Medicine

Ultimately Re-Evaluate Informed Consent

- Tests with devastating implications, FPs/FNs, unexpected & ambiguous results are the norm in medicine
  - We routinely handle with shared decision making
  - When is IC really needed?
  - When is it actively counterproductive to care?
  - A category-based approach can facilitate patient education and more informed consent

WBC	6.7 K/uL	4.0-12.0 K/uL
LYM	31.8 %L	25.0-45.0 %L
MID	5.9 %M	0.1-15.0 %M
PMN	62.3 %G	35.0-55.0 %G
RBC	3.53 M/uL	4.00-5.30 M/uL
HGB	7.8 g/dL	11.5-14.5 g/dL
HCT	24.7 %	33.0-43.0 %
MCV	70.0 fL	76.0-90.0 fL
MCH	22.1 pg	25.0-31.0 pg
MCHC	31.6 g/dL	32.0-36.0 g/dL
RDW	19.4 %	11.5-15.0 %
PLT	473 k/uL	150-450 K/uL





Comprehensive Metabolic Panel (w/ EGFR)

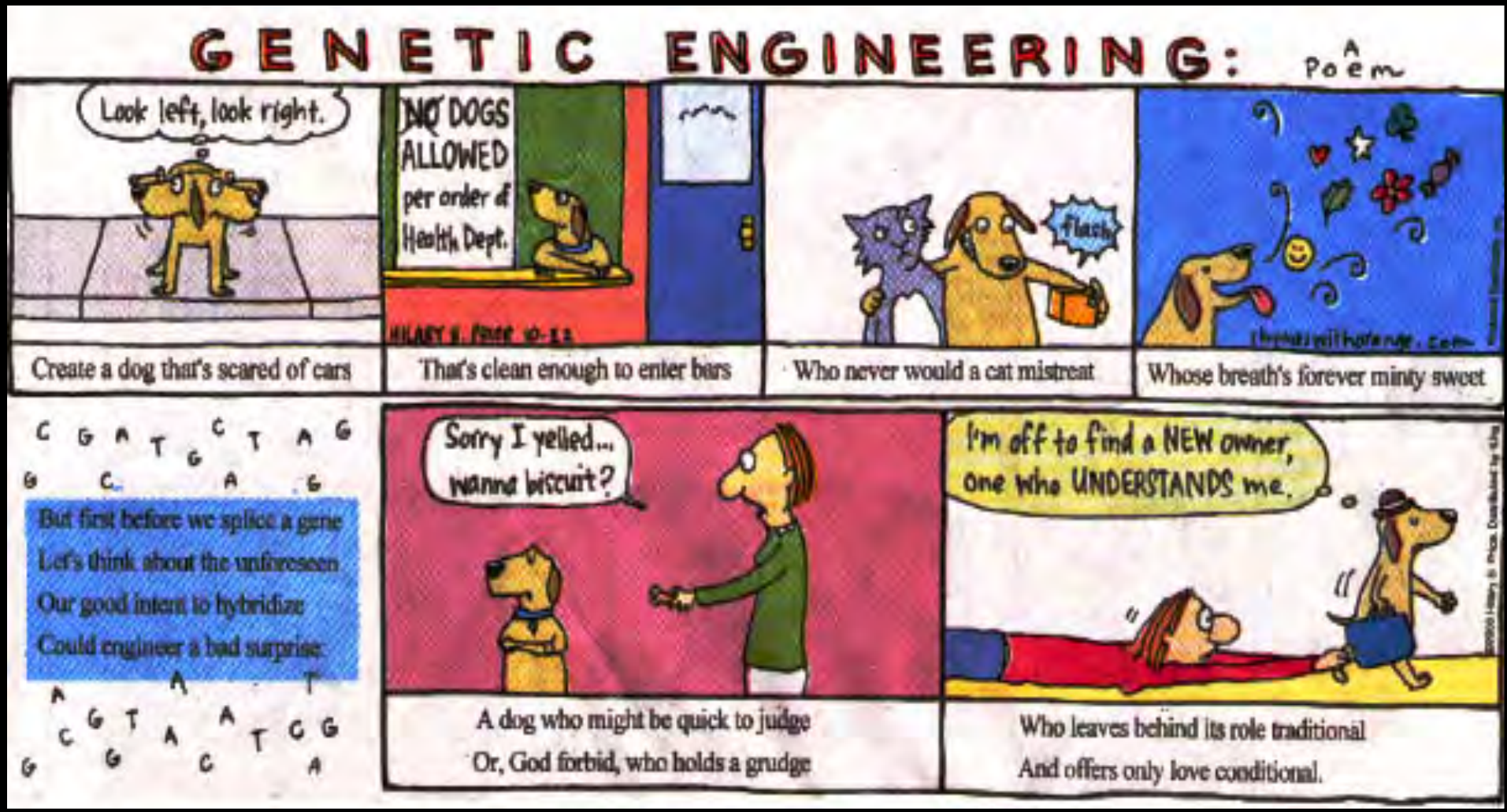
			Fasting Reference Interval
Glucose	89		65 - 99 mg / dL
Urea Nitrogen (BUN)	19		7 - 25 mg / dL
Creatinine		1.35 H	0.78 - 1.34 mg / dL
eGFR Non-Afr.American		57 L	> or = 60 mL/min/1.73m2
eGFR African American	>60		> or = 60 mL/min/1.73m2
BUN / Creatine Ratio	14		6 -22 (calc)
Sodium	140		135 - 146 mmol / L
Potassium	4.5		3.5 - 5.3 mmol / L
Chloride	105		98 - 110 mmol / L
Carbon Dioxide	22		21 - 33 mmol/L
Calcium	9.4		8.6 - 10.2 mg/dL
Protien, Total	7.0		6.2 - 8.3 g/dL
Albumin	4.7		3.6 - 5.1 g/dL
Globulin	2.3		2.1 - 3.7 g/dL (calc)
Albumin / Globulin Ratio	2.0		1.0 - 2.1 (calc)
Bilirubin, total	1.0		0.2 - 1.2 mg/dL
Alkaline Phosphatase	50		40 - 115 U/L
AST	24		10 - 40 U/L
ALT	32		9 -60 U/L

What Good is Defining Risks?

- Identified genomic relative risks are modest
- The illusion of parsing risk
- The paradox of risk information
- Risk assessment is a moving target
- Good ideas aren't sufficient to guide medical practice
- The stakes are high

Actual clinical outcome data are critical

The Dangers of Modern Genetics



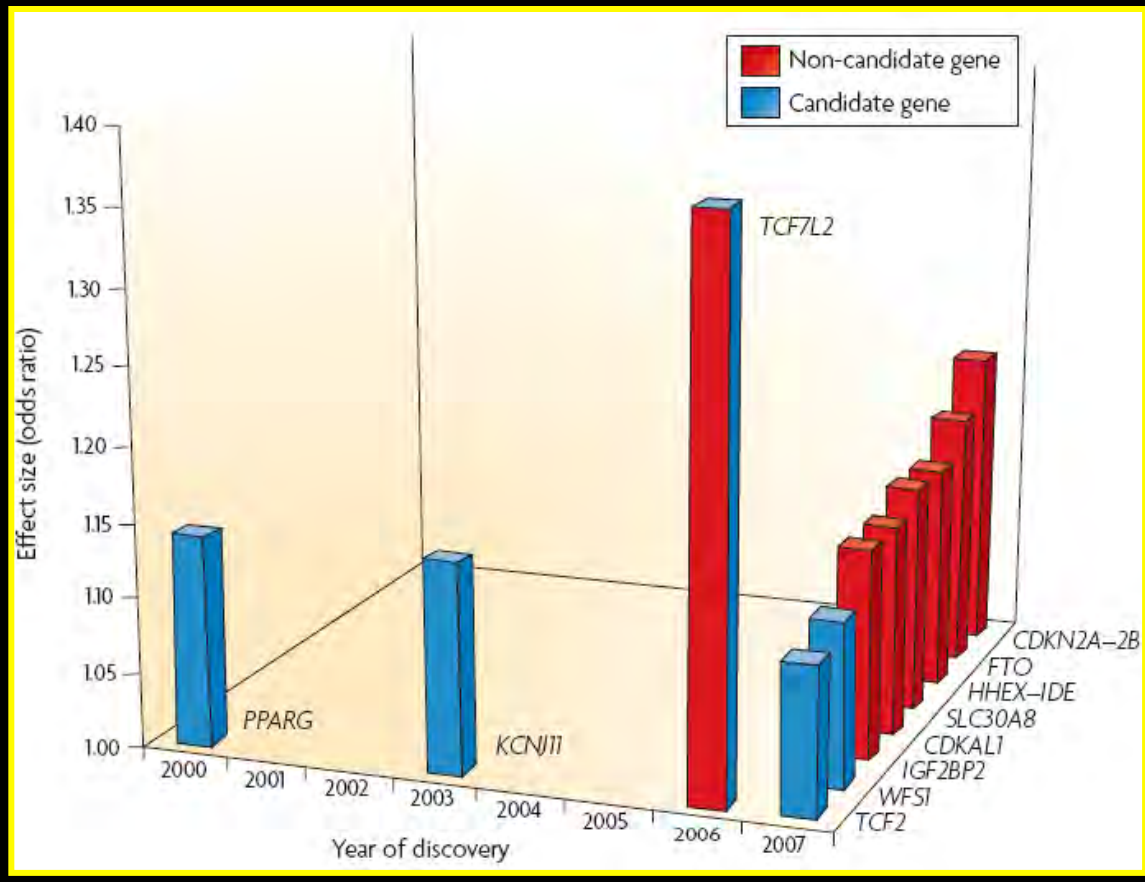
Rhymes with Orange; Hillary Price 1999

Hippocrates of Cos
(*ca*. 460 BC – *ca.* 370 BC)

Life is short, the art long, opportunity fleeting, experience delusive, judgment difficult

There is Tremendous Potential for Advancing *Medical Science*

- Through delineation of novel etiologic genes
  - Without the need for underlying biochemical / physiological knowledge



Such advances will ultimately be the foundation of improved medical care

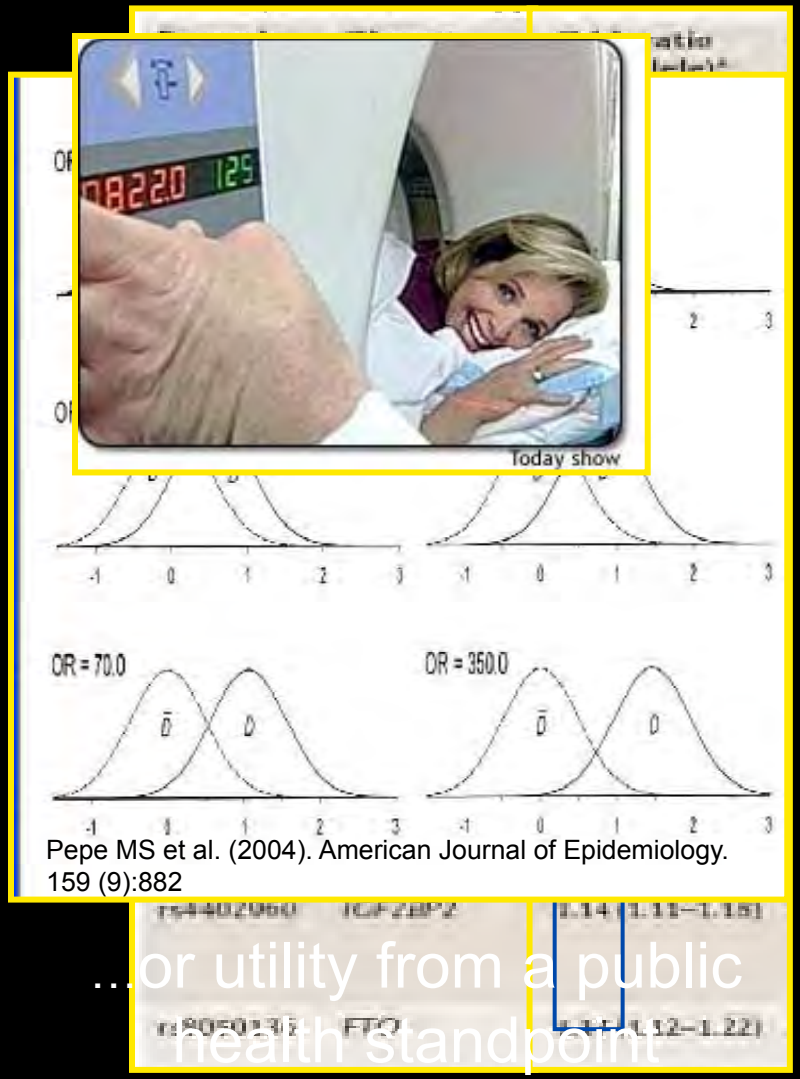
Other Uses for WGS in a Public Health Context

- Pre-emptive delineation of select PGx variants
- As an adjunct to NBS
  - But also illustrates the limitations of genetic *vs*. phenotypic testing
- Pre-conceptual carrier screening
  - Potentially profound impact on family planning with respect to AR diseases
  - Highly actionable information to some
    - Morally problematic for others
      - Making formulation of policy difficult for this application

What About Prevention through Risk Assessment?

The Problem of Relative Risk

- Numerous risk alleles have been identified
  - The vast majority of RR defined by GWAS are between 1-2
    - What do I ***do*** with such information?
  - From a clinical standpoint the information is so lacking in robustness that it is of no clinical utility



Pepe MS et al. (2004). American Journal of Epidemiology. 159 (9):882

…or utility from a public health standpoint

The Illusions of Risk Assessment

Confusing Relative and Absolute Risk

- Few data to suggest that knowledge of one's genomic status is effective in changing behavior
- For common diseases, what does it really mean to be at a relatively reduced risk?
  - The *absolute* risk for common diseases is high
  - Thus, we're all at increased risk for these maladies - regardless of our relative risk
  - Most people who are at "decreased risk" for heart disease will still die of heart disease
- For uncommon diseases what does it mean?
  - Risk of developing Crohn's Disease = ~5/1,000

How Much Added Value?

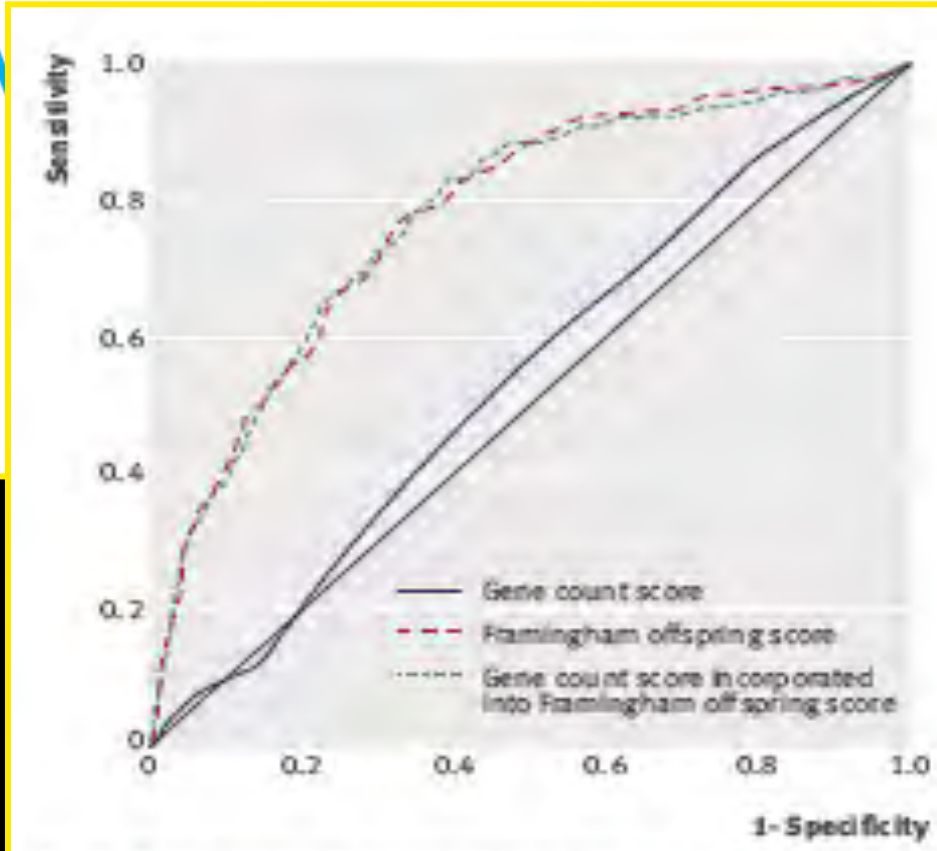


Fig 1| Receiver operating characteristics curves for gene count score alone (area under curve 0.54, 95% CI 0.50 to 0.58), Framingham offspring risk score (area under curve 0.78, 0.75 to 0.82), and gene count score incorporated into Framingham offspring risk score (area under curve 0.78, 0.75 to 0.81)

Cite this as: *BMJ* 2010;340:b4838
doi:10.1136/bmj.b4838

Personalized Medicine is Driven by Accelerating Technology

- In 1997 it took about a day to genotype a one Single Nucleotide Polymorphism
  - Cost was ~$100
- Now in a matter of days one can genotype an individual at >2,000,000 sites
  - At a cost of < $500
    - Reduction in cost of >400,000 fold

$795 in 1977 (=$2,800 in current $

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Risk Assessment is a Moving Target

- We are rapidly discovering more genes influence the risk of disorders
- We have yet to define the majority of the genetic component for these diseases
- We don't know how to calculate aggregate risks
- Future discoveries will shift risk assessments
  - It may eventually make genetic prediction more robust…but…
  - Today's "low risk" genotype may well be tomorrow's "high risk" genotype, and vice versa
  - One lab's high risk is another lab's low risk genotype

What Else Will be Done With Such Information?

deCODE genetics
Delivering on the promise of the new genetics

23andMe

- Numerous companies are now offering "boutique" genotyping
- Heavily covered by the media
- Most genotyping may soon be performed outside of the traditional medical setting
- "Buying is more American than thinking"
- What does one discover with a whole genome scan?

Navigenics

Ancestry

- My ancestors are from Europe
- *Who'd have thought?*

Haplogroup R1b (M343)

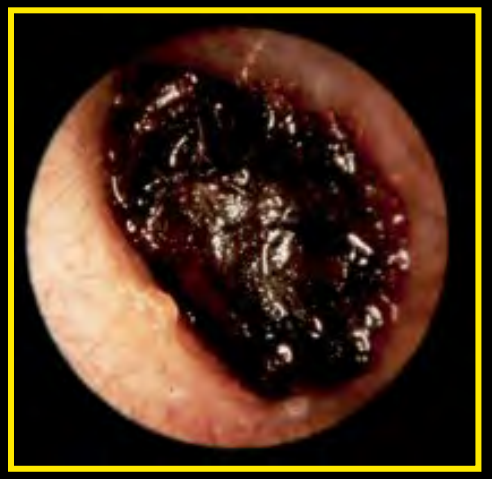
The designations for all twelve loci examined for this purpose are listed here, along with the Short Tandem Repeats (STRs) outcome for each.

393	19	391	439	389-1	389-2	388	390	426	385a	385b	392
13	14	11	11	13	16	12	23	12	11	11	13

July 21, 2005

Traits

- Earwax type
- Alcohol Flush Reaction
- Bitter Taste Perception
  - e.g. Whether you'll like Brussels sprouts
- Eye color
  - DeCode's narrator:
    - "My likelihood of having brown eyes is 67% and of having brown hair is 92%; ***and I do have brown eyes and brown hair!***"



Disease Risk

- Breast Cancer
- Prostate Cancer
- Alzheimer Disease
- Crohn's Disease
- Cardiovascular disease
- Multiple Sclerosis
- Diabetes
- Restless Legs Syndrome
- Venous Thromboembolism
- etc….

What Will We Find Out?

- Things that we already know
  - You are at risk for heart disease and you should exercise and eat right
- Things we're not sure what to do with
  - You're at 30% increased risk for prostate cancer. *Okay…*
- Things we don't want to know.
  - You're at increased risk for Alzheimer Disease
- Things that are fun to know
  - Your ancestry and whether you might like Brussels sprouts
- Things we *think* we know but don't
  - Because of changing risk assessments and discovery of new loci
- Things that are useful to know
  - At least for now a distinct minority of what will emerge from such analyses
  - PGx application to selected agents
  - Dramatically elevated risk for breast cancer & Parkinson Disease
    - Is such knowledge best handled by the individual within a web-based relationship by its purveyors?

A Need to Reconcile Claims with Reality

- Such offerings are designed to appeal directly to health concerns
- A grab-bag of results ranging from entertainment to real medical information with tremendous variation in utility
  - Little or no guidance regarding how to tell the difference
  - Or what to do with that information

"Knowledge is Power"

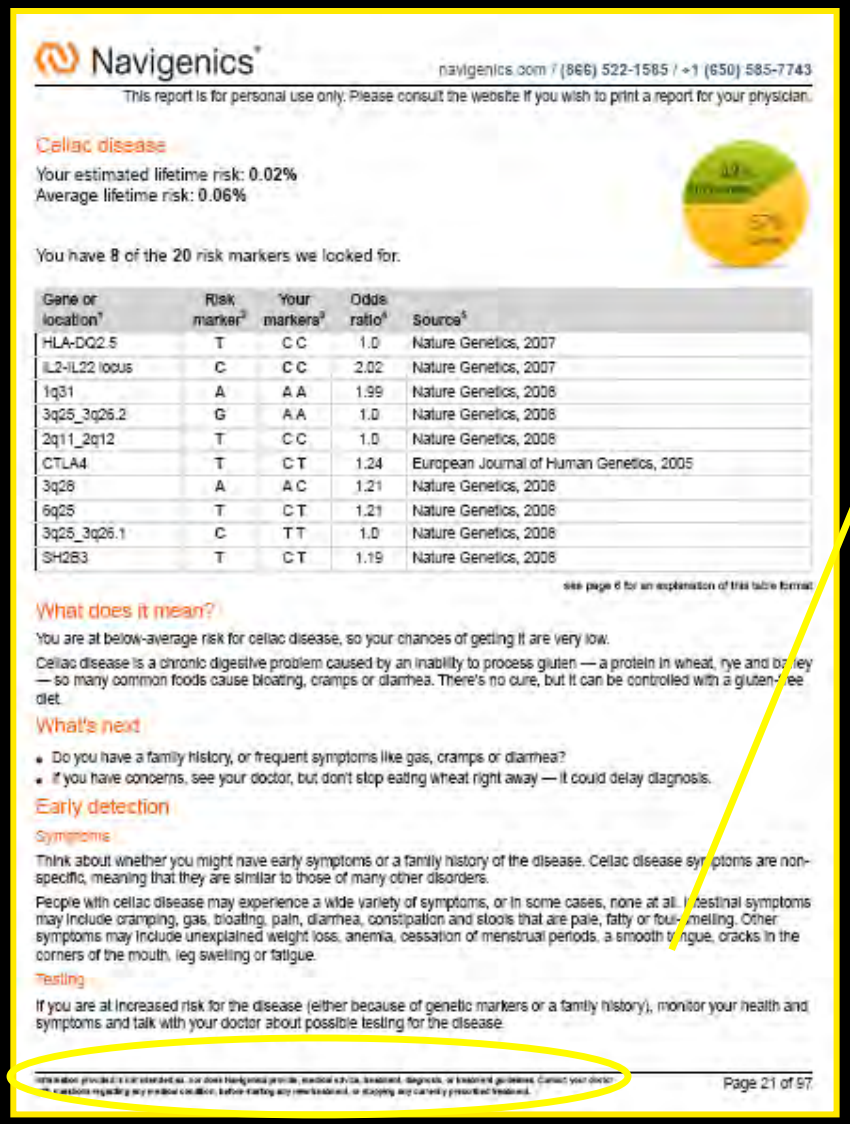
Your risk analyzed for 116 diseases

"revealing your genetic predisposition for important health conditions and empowering you with knowledge to help you take control of your health future"

Calculate genetic risk – Empower prevention

your genes are a road-map to better health

The Fine Print



Navigenics®

navigenics.com / (866) 522-1585 / +1 (650) 585-7743

This report is for personal use only. Please consult the website if you wish to print a report for your physician.

Celiac disease

Your estimated lifetime risk: **0.02%**
Average lifetime risk: **0.06%**

You have **8** of the **20** risk markers we looked for.

Gene or location[1]	Risk marker[2]	Your markers[3]	Odds ratio[4]	Source[5]
HLA-DQ2.5	T	C C	1.0	Nature Genetics, 2007
IL2-IL22 locus	C	C C	2.02	Nature Genetics, 2007
1q31	A	A A	1.99	Nature Genetics, 2008
3q25_3q26.2	G	A A	1.0	Nature Genetics, 2008
2q11_2q12	T	C C	1.0	Nature Genetics, 2008
CTLA4	T	C T	1.24	European Journal of Human Genetics, 2005
3q26	A	A C	1.21	Nature Genetics, 2008
6q25	T	C T	1.21	Nature Genetics, 2008
3q25_3q26.1	C	T T	1.0	Nature Genetics, 2008
SH2B3	T	C T	1.19	Nature Genetics, 2008

see page 6 for an explanation of this table format

What does it mean?

You are at below-average risk for celiac disease, so your chances of getting it are very low.

Celiac disease is a chronic digestive problem caused by an inability to process gluten — a protein in wheat, rye and barley — so many common foods cause bloating, cramps or diarrhea. There's no cure, but it can be controlled with a gluten-free diet.

What's next

- Do you have a family history, or frequent symptoms like gas, cramps or diarrhea?
- If you have concerns, see your doctor, but don't stop eating wheat right away — it could delay diagnosis.

Early detection

Symptoms

Think about whether you might have early symptoms or a family history of the disease. Celiac disease symptoms are non-specific, meaning that they are similar to those of many other disorders.

People with celiac disease may experience a wide variety of symptoms, or in some cases, none at all. Intestinal symptoms may include cramping, gas, bloating, pain, diarrhea, constipation and stools that are pale, fatty or foul-smelling. Other symptoms may include unexplained weight loss, anemia, cessation of menstrual periods, a smooth tongue, cracks in the corners of the mouth, leg swelling or fatigue.

Testing

If you are at increased risk for the disease (either because of genetic markers or a family history), monitor your health and symptoms and talk with your doctor about possible testing for the disease.

Information provided is not intended as, nor does Navigenics provide, medical advice, treatment, diagnosis, or treatment guidelines. Consult your doctor with questions regarding any medical condition, before starting any new treatment, or stopping any currently prescribed treatment.

Page 21 of 97

"Information provided is not intended as, nor does Navigenics provide, medical advice, treatment, diagnosis, or treatment guidelines. Consult your doctor with questions regarding any medical condition, before starting any new treatment, or stopping any currently prescribed treatment."

- People may well deserve access to such information
- But they also deserve an honest accounting of its meaning

Clinical Medicine is Messy

- The application of good ideas to the care of the individual is difficult and fraught with hazard
- This is just as true for genomic risk information as it is for any other type
  - Identified genomic relative risks are modest
  - The illusion of parsing risk
  - The paradox of risk information
  - Risk assessment is a moving target
  - Good ideas aren't sufficient to guide medical practice
    - Because the stakes are high

Actual clinical outcome data are critical

Pharmacogenomics

Lower Hanging Fruit

- PGx has already become standard of care for selected agents
  - Abacavir and *HLA-B*570* for prediction of hypersensitivity reaction
- Likely to become standard of care
  - Tamoxifen and CYP 2D6
  - Warfarin and CYP 2C9
  - Clopidogrel CYP 2C19
- Will not be applicable to all drugs
  - Alternatives
  - Robust positive predictive value

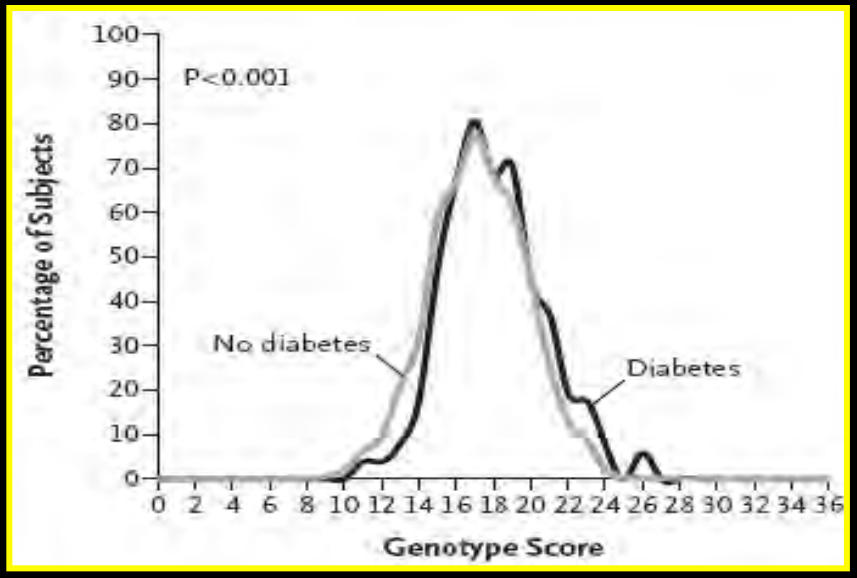
Type 2 Diabetes

Table 1. Established type 2 diabetes susceptibility loci

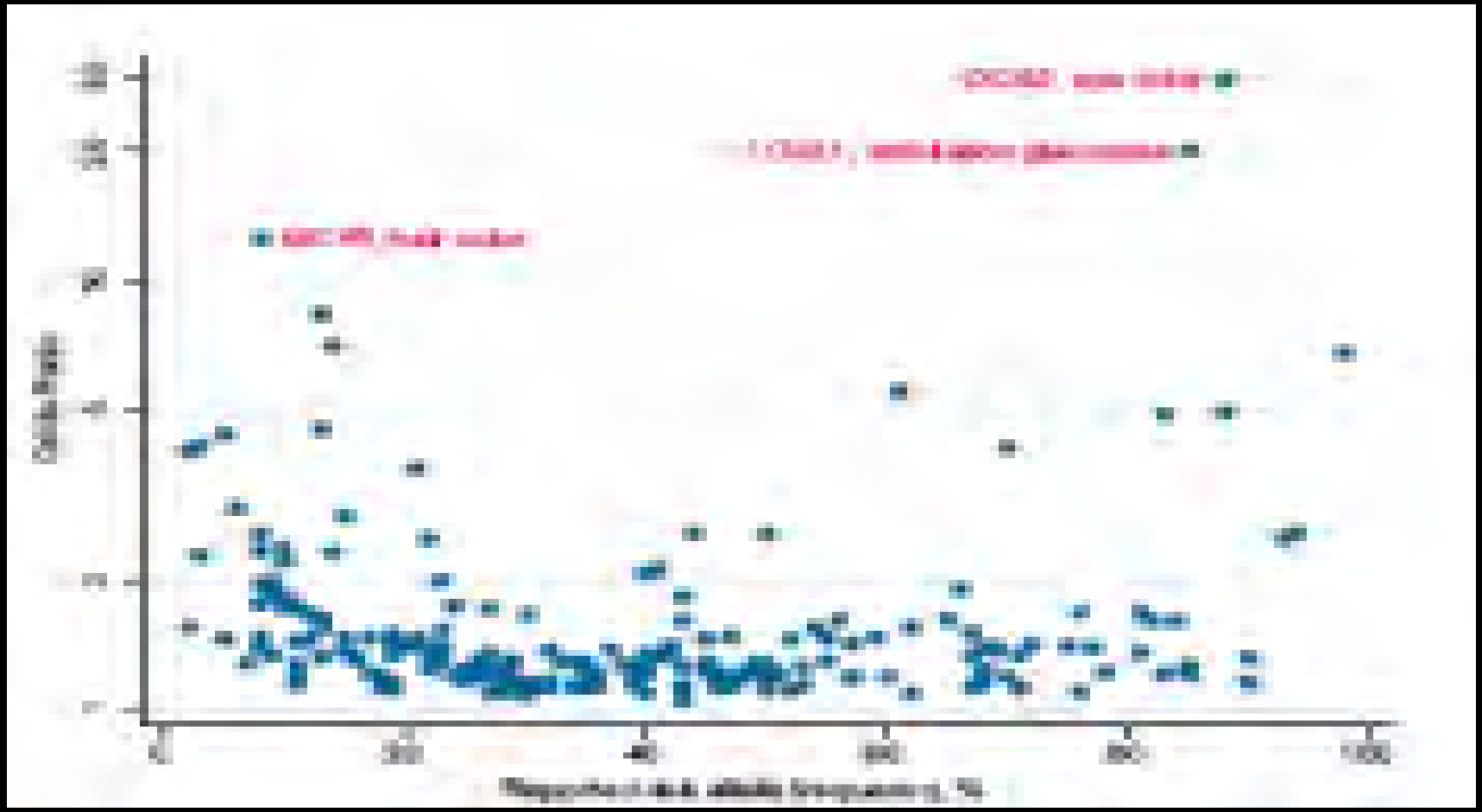
Index SNP	Chromosome	Position	Region/gene	Identification	λ_s*
rs10010131	4	6343816	*WFS1*	Candidate gene	1.034
rs1801282	3	12360125	*PPARG*	Candidate gene	1.005
rs757210	17	33170628	*HNF1B (TCF2)*	Candidate gene	1.002
rs5219	11	17366148	*KCNJ11*	Candidate gene	1.005
rs7901695	10	114744078	*TCF7L2*	Linkage peak fine-mapping	1.022
rs10811661	9	22124094	*CDKN2A/B*	GWA	1.003
rs10946398	6	20769011	*CDKAL1*	GWA	1.002
rs13266634	8	118253964	*SLC30A8*	GWA	1.003
rs4402960	3	186994381	*IGF2BP2*	GWA	1.002
rs5015480	10	94455539	*HHEX/IDE*	GWA	1.002
rs8050136	16	52373776	*FTO*†	GWA	1.009
rs2237892	11	2796327	*KCNQ1*	GWA	1.031
rs10830963	11	92348358	*MTNR1B*‡	GWA	1.001
rs10923931	1	120319482	*NOTCH2*	GWA meta-analysis	1.001
rs12779790	10	12368016	*CDC123/CAMK1D*	GWA meta-analysis	1.002
rs4607103	3	64686944	*ADAMTS9*	GWA meta-analysis	1.002
rs7578597	2	43586327	*THADA*	GWA meta-analysis	1.002
rs7961581	12	69949369	*TSPAN8/LGR5*	GWA meta-analysis	1.001
rs864745	7	28147081	*JAZF1*	GWA meta-analysis	1.001

*The sibling recurrence risk ratio calculated in European populations, with the exception of the KCNQ1 locus, which was based on East Asian populations.
†The primary association for this locus is with body mass index.
‡The primary association for this locus is with fasting glucose levels.
GWA—genome-wide association; SNP—single nucleotide polymorphism.

McCarthy et al. Current Diabetes Reports 2009, 9:164–171



Genotype Adds Little to Conventional Risk Estimation



Aggregate Risk Scores

deCODE genetics
Delivering on the promise of the new genetics

Table 1: Individual genotype results and their associated risks

Locus	SNP	Genotype	Risk	Pop. freq.	Cases/ controls	References
PPARG	rs1801282	CC	1.03	0.81	14586 / 17968	11
CDKN2A	rs10811661	CC	0.74	0.03	14586 / 17968	8-10
CDKAL1	rs7756992	AG	1.09	0.38	3836 / 12562	7-10
TCF7L2	rs7903146	CC	0.82	0.52	14586 / 17968	4,5,6
	Combined genetic risk		0.67			

- One purveyor of such testing (deCODE Genetics) offers the calculation of a risk score using one's genotype at 4 loci
  - ~40% of population have increased relative risk (RR >1)
  - 8% have RR 1.5-2.2
  - ~3% have RR 1.8-2.2
- Cost is $370
- Calculation of aggregate risks assumes no interactions
- But the real problem is the clinically meaningless nature of such information

"revealing your genetic predisposition for important health conditions and empowering you with knowledge to help you take control of your health future

"

Calculate genetic risk – Empower prevention

your genes are a road-map to better health"

Genomics for the Masses

Boutique Genotyping

- Several companies are now offering “boutique” genotyping
- Most genotyping may soon be performed outside of the traditional medical setting
- “Buying is more American than thinking”

Comparison With Others

- Family members
- Friends
- “Famous Scientists like Craig Venter”!!
- “We envision a new type of community where people will come together around specific genotypes and these artificial barriers of country and race will start to break down”- Anne Wojcicki, co-founder of 23andMe

Robust Genetic Analysis

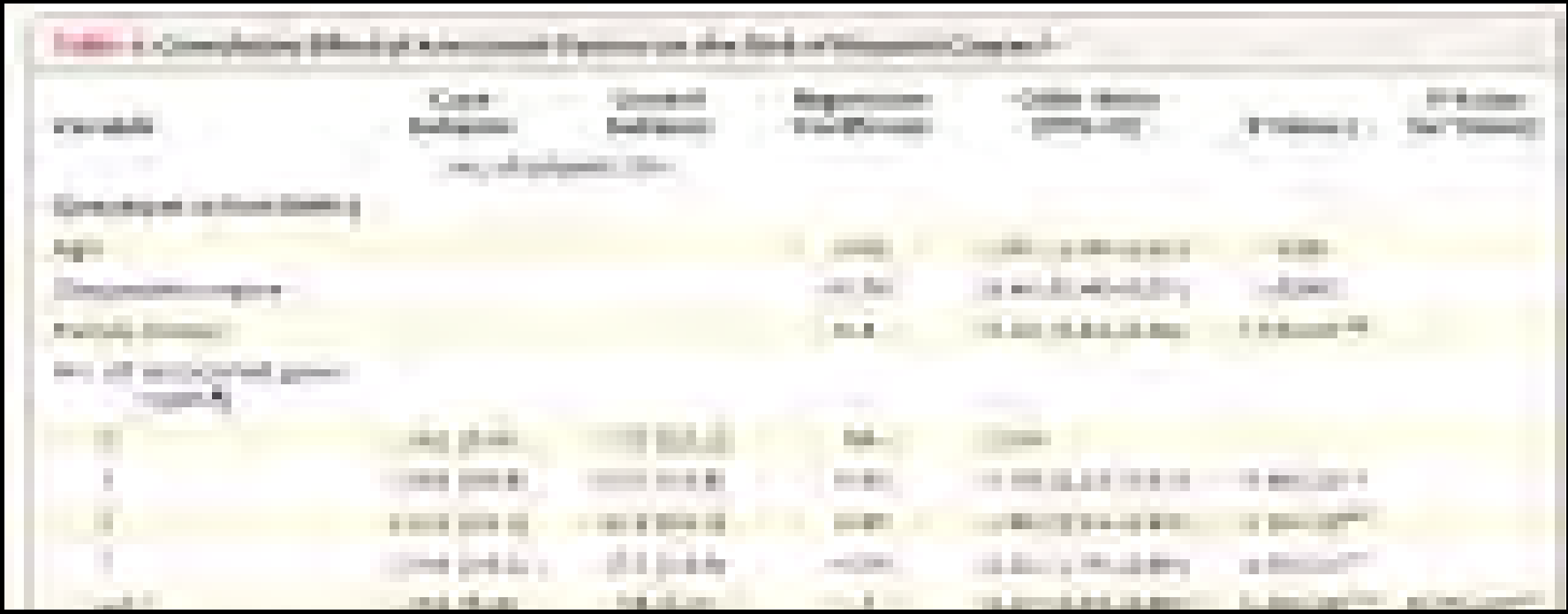
- We now have the ability to analyze the genome and define individual variation
  - At the heart of the concept of "personalized medicine"
- Massively parallel genotyping now is widely available
  - Delineation of the individual's genome at ~1 million sites
  - for << $500…and dropping

The Coming Deluge

- The $1,000 genome is coming
- We will be awash with new highly complex genetic information
- Whole genome analysis is the first test in the history of medicine which will yield positive results in everyone tested
  - We are all mutants
  - We'll all have myriad false positive and false negative tests
- There are serious medical challenges in its interpretation
  - Patients
  - Public
  - Medical practitioners
- And social challenges
  - "Privacy is dead. Get over it"

Why Can't We Combine Risks?

- A small subset of the population will have higher RR due to having inherited many risk alleles



Applying Genetic Risk Information to the Individual

deCODE genetics
Delivering on the promise of the new genetics

23andMe

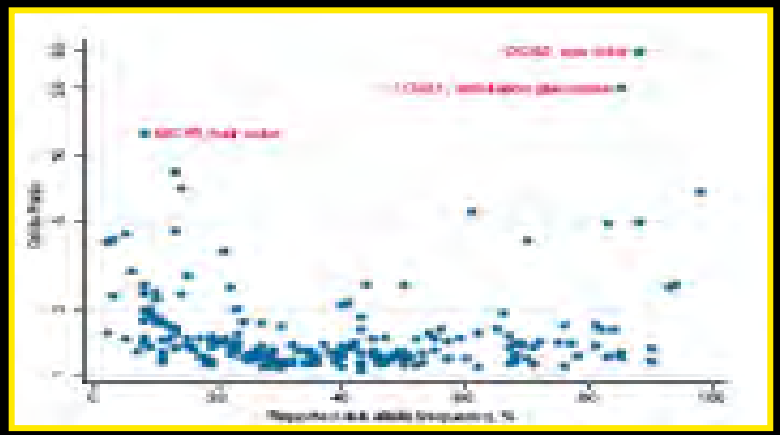
- Numerous companies are now offering "boutique" genotyping
  - Most include estimates of T2DM risk
- Heavily covered by the media
- Most genotyping may soon be performed outside of the traditional medical setting
- Is such information useful towards the goal of improving health?
- "Buying is more American than thinking"

Navigenics

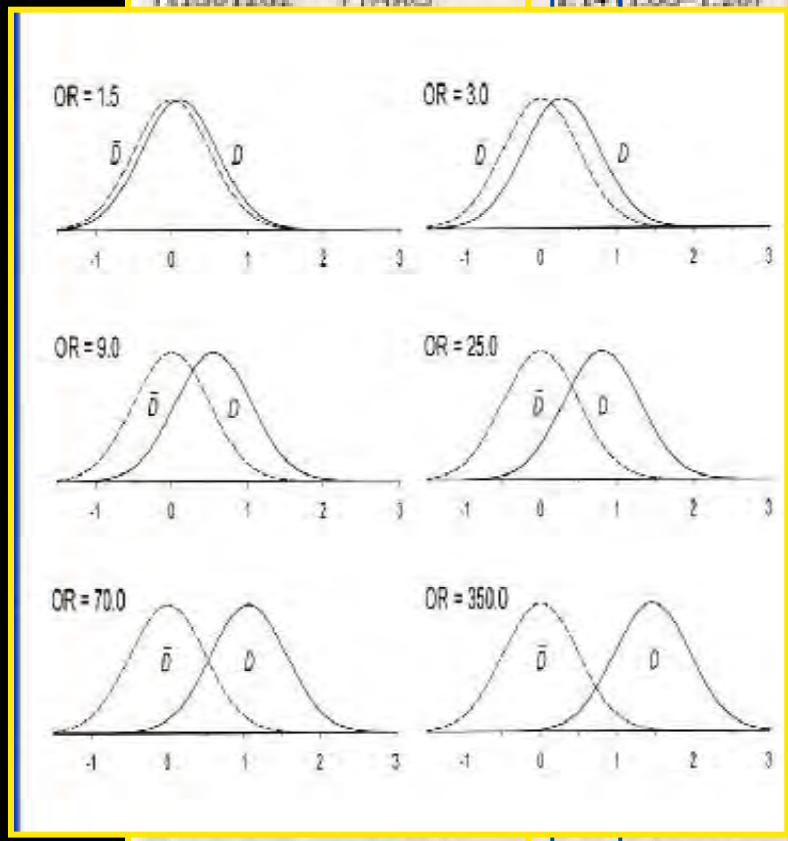
The Problem of Relative Risk

The Example of Type 2 Diabetes

- Numerous risk alleles have been identified
  - The vast majority of RR defined by GWAS are between 1-2
    - What do I ***do*** with such information?
  - From a clinical standpoint the information is so lacking in robustness that it is of questionable utility



Example variant	Closest gene	Odds ratio (per allele)*
rs1801282	*PPARG*	1.14 (1.08–1.20)
rs8050136	*FTO*	1.17 (1.12–1.22)



Frayling T; Nature Reviews 8:657.2007

What ***Else*** Can We Do With Such Information?

- Make money!!!
  - After all, this is the USA
- Several companies are now offering "boutique" genotyping
- Their success threatens to prove Andy Warhol's adage that "buying is more American than thinking"

23andMe

deCODE ME

Navigenics

Controlling the Genetic Genie

- Genetic Discrimination
  - There is no federal legislative protection…yet
- Gene Patenting
  - Most of our genes have patent claims on them
  - BRCA1/2 are under restrictive patents
- Privacy Issues
  - "Privacy is dead. Get over it."
  - What happens when 23andMe is subpoenaed?
  - Problems compounded by the acceleration of Information Technology and the World Wide Web
  - Corporate, government and public genetic databases are being formed all over the world
- Who will control this information?
  - Do you want to know ?
  - Do you want others to know?
    - Your insurance / managed care plan
    - Your employer
    - Your family
    - Dick Cheney
    - Your neighbor who surfs the web

23andme / DeCode Genetics

- Heavily covered by the media
  - NY Times, Newsweek, etc.
- Offer genotyping at ~500,000 – 1,000,000 loci
- Individual sends a saliva or mouth brush sample
- And a credit card number
- Genotyping of SNPs associated to provide information about:

Ancestry

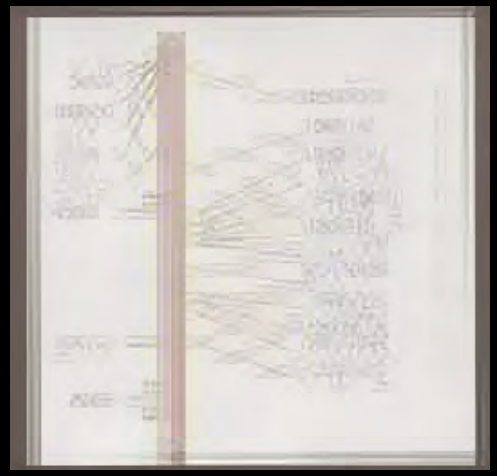
- My ancestors are from Europe
- ***Who'd have thought?!!***

Haplogroup R1b (M343)

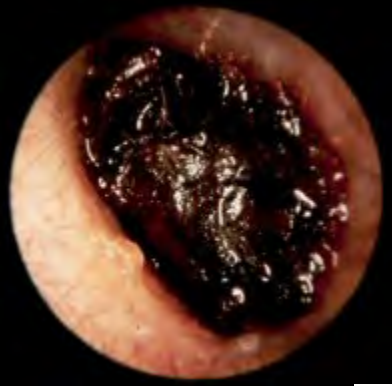
The designations for all twelve loci examined for this purpose are listed here, along with the Short Tandem Repeats (STRs) outcome for each.

393	19	391	439	389-1	389-2	388	390	426	385a	385b	392
13	14	11	11	13	16	12	23	12	11	11	13

July 21, 2005



Traits



- Earwax type
- Alcohol Flush Reaction
- Bitter Taste Perception
  - E.g. Brussels Sprouts

- Eye color
  - DeCode's narrator:
    - "My likelihood of having brown eyes is 67% and of having brown hair is 92%; ***and I do have brown eyes and brown hair!"***
- Behavioral traits
  - Aggression, novelty seeking, propensity for depression, etc.

Comparison With Others

- Family members
- Friends
- “Famous Scientists like Craig Venter”!!
  - DeCode’s narrator shares 2-3% of his genome with Craig
  - Forthcoming Facebook invitation to Craig to be his gene-friend
- “We envision a new type of community where people will come together around specific genotypes and these artificial barriers of country and race will start to break down”- Anne Wojcicki, co-founder of 23andMe

Disease Risk

- Breast Cancer
- Prostate Cancer
- Alzheimer Disease
- Crohn's Disease
- Risk of cardiovascular disease
- Multiple Sclerosis
- Diabetes
- Restless Legs Syndrome
- Venous Thromboembolism

- *For the vast majority of such risk assessments, the increased risk of one developing the disease is modest*
  - *On the order of 1-2 fold risk over baseline*
- *In few such conditions are there specific effective interventions to diminish the risk*

What Will We Find Out?

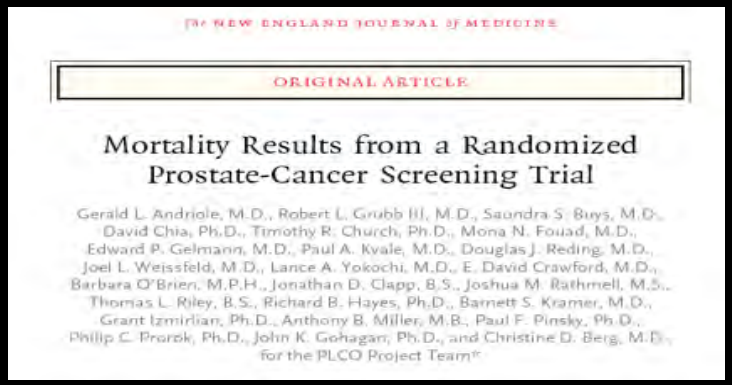
- Things that are useful to know
  - At least for now a distinct minority of what will emerge from such analyses
- Things that we already know
  - e.g. your are at risk for heart disease and you should exercise and eat right
- Things we don't want to know
  - I'm at increased risk for Alzheimer Disease
- Things that are fun to know
  - Ancestry
  - Whether you'll like Brussels sprouts (but also see above)
  - How many polymorphisms you share with Craig Ventor*
- Things we *think* we know but don't
  - All the spurious associations that will be "found" and later not confirmed

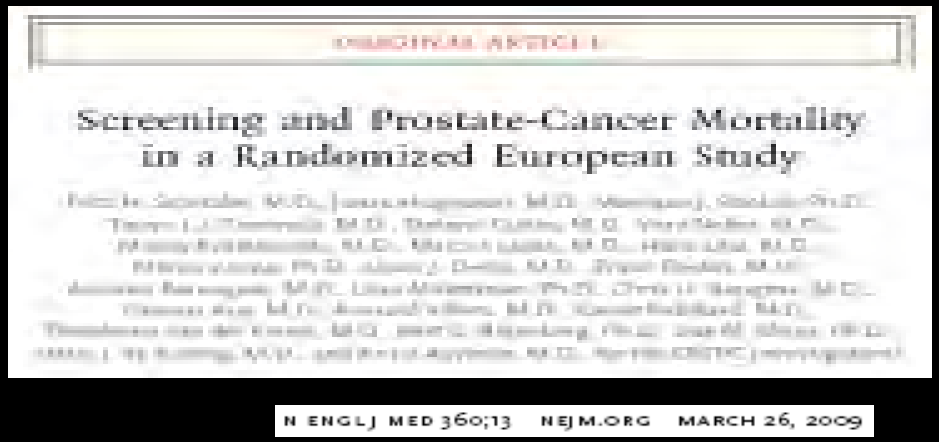
*Depends on your idea of fun

The Problem of Relative Risk
Prostate Cancer

- The proportion of the population who have inherited numerous risk alleles will be progressively smaller as more loci are added
- We still don't know what do with such information for that small subset of men at significantly increased risk
- Increased surveillance through modalities like PSA have recently proven to be questionable
  - Whether PSA screening reduces mortality is an open question
  - Cost in terms of excess morbidity is high
    - One study has shown a reduced mortality with PSA screening
      - » 48 men are diagnosed with cancer *and go through treatment* with its attendant morbidities for each one who had life extension

Screening PSA





- 76,693 men randomized to PSA screening vs. usual care
- 7 years of follow up
  - Cancer
    - 2,820 cancers in screening group
    - 2,344 cancers in control group
  - Death
    - 50 deaths in screening group
    - 44 deaths in control group
    - No significant difference

- 182,000 men randomized
  - 8.2% in screened group
  - 4.8% in control group
  - Death
    - 20% reduction in screened group
  - 1,410 men need to be screened to prevent one death
  - 48 additional cases of prostate cancer need to be treated to prevent one death
    - 48 men are diagnosed with cancer *and go through treatment* for each one who may have had life extension
    - The psychological burden of a cancer diagnosis is not trivial
  - Treatment is not trivial
    - Incontinence
    - Erectile dysfunction
    - Morbidity from treatment

Our typical screening options are not good

N ENGL J MED 360;13 NEJM.ORG MARCH 26, 2009

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

- 182,000 men randomized to PSA screening or not
- Cancer
  - 8.2% in screened group
  - 4.8% in control group
- Death
  - 20% reduction in screened group
  - 1,410 men need to be screened to prevent one death
  - 48 additional cases of prostate cancer need to be treated to prevent one death
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    - The psychological burden of a cancer diagnosis is not trivial
  - Treatment is not trivial
    - Incontinence
    - Erectile dysfunction
    - Morbidity from treatment

The Problem of Relative Risk
Prostate Cancer

- GWAS have illuminated multiple loci involved in prostate cancer risk
- High levels of statistical significance
- But tiny relative risks
- Again…what do we do with such information?

Table 2. Association of SNPs at Five Chromosomal Regions with Prostate Cancer.*

SNP	Chromosomal Region	Position†	Alternative Alleles	Allelic Tests				
				Associated Allele§	Frequency		Odds Ratio (95% CI)¶	P Value
					case subjects	control subjects		
rs4430796	17q12	33,172,153	T, C	T	0.61	0.56	1.24 (1.14–1.36)	6.0×10^{-7}
rs7501939	17q12	33,175,269	G, A	G	0.66	0.62	1.22 (1.12–1.33)	9.0×10^{-6}
rs3760511	17q12	33,180,426	A, C	C	0.41	0.38	1.17 (1.07–1.27)	5.0×10^{-4}
rs1859962	17q24.3	66,620,348	G, T	G	0.54	0.50	1.17 (1.08–1.28)	2.1×10^{-4}
rs7214479	17q24.3	66,702,544	C, T	T	0.50	0.48	1.08 (0.99–1.18)	0.07
rs6501455	17q24.3	66,713,406	A, G	A	0.56	0.54	1.09 (1.00–1.19)	0.05
rs983085	17q24.3	66,723,656	A, G	A	0.57	0.55	1.07 (0.98–1.16)	0.13
rs6983561	8q24 (region 2)	128,176,062	A, C	C	0.06	0.03	1.65 (1.33–2.05)	4.2×10^{-6}
rs16901979	8q24 (region 2)	128,194,098	C, A	A	0.06	0.03	1.65 (1.33–2.05)	4.3×10^{-6}
rs6983267	8q24 (region 3)	128,482,487	G, T	G	0.56	0.51	1.22 (1.12–1.33)	3.9×10^{-6}
rs7000448	8q24 (region 3)	128,510,352	C, T	T	0.43	0.40	1.15 (1.06–1.25)	1.4×10^{-3}
rs1447295	8q24 (region 1)	128,554,220	C, A	A	0.17	0.14	1.21 (1.07–1.36)	1.6×10^{-3}
rs4242382	8q24 (region 1)	128,586,755	G, A	A	0.16	0.14	1.24 (1.10–1.39)	5.3×10^{-4}
rs7017300	8q24 (region 1)	128,594,450	A, C	C	0.20	0.18	1.15 (1.03–1.28)	0.01
rs10090154	8q24 (region 1)	128,601,319	C, T	T	0.16	0.13	1.26 (1.11–1.42)	2.0×10^{-4}
rs7837688	8q24 (region 1)	128,608,542	G, T	T	0.15	0.13	1.17 (1.04–1.13)	9.6×10^{-3}

Zheng et al. N Engl J Med 2008;358

Lessons from EBM As Applied to the PSA Test

- Outcomes are not always intuitive
- The magnitude of an effect is important
  - We *might* be able to prevent some deaths…is it worth it?
    - In terms of morbidity
    - time/resources
    - Anxiety and quality of life
- Because something is "non-invasive" doesn't mean it lacks risk
- More information is not always better
  - We have to be able to be confident that such knowledge leads to desired outcomes
- Answering these questions is difficult, expensive and time consuming

- Our options for screening and for intervention are limited

Clinical Applications of Emerging Genetic Knowledge for the Individual

- Many T2DM risk loci have been identifited
- Genotyping to define T2DM risk is being marketed directly to individuals
  - deCODE, 23andMe, Navigenics
- Can we use such information to predict the individual's risk of DM and ultimately improve health?

Aggregate Risk Scores

Table 1: Individual genotype results and their associated risks

Locus	SNP	Genotype	Risk	Pop. freq.	Cases/ controls	References
PPARG	rs1801282	CC	1.03	0.81	14586 / 17968	11
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	Combined genetic risk		0.67			

- One purveyor of such testing (deCODE Genetics) offers the calculation of a risk score using one's genotype at 4 loci
  - ~40% of population have increased relative risk (RR >1)
  - 8% have RR 1.5-2.2
  - ~3% have RR 1.8-2.2
- Cost is $370
- Calculation of aggregate risks assumes no interactions
- But the real problem is the clinically meaningless nature of such information

The Need for Clinical Outcome Data

- The history of medicine is riddled with the corpses of good ideas that didn't pan out
  - EC/IC bypass to prevent stroke
  - HRT to prevent every possible bad outcome of female aging
  - PSA?
- Good ideas are not enough to guide medical care
  - We have the power to harm
  - Even through "non-invasive" testing
    - Such information has the potential to put our patients on a trajectory that leads to dangerous and harmful interventions
- We need to insist on data to prove that our good ideas actually result in improved outcomes
- We have to be leery of shortcuts and attractive theories

What Will We Find Out?

- Things that are useful to know
  - At least for now a distinct minority of what will emerge from such analyses
- Things that we already know
  - e.g. your are at risk for heart disease and you should exercise and eat right
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  - How many polymorphisms you share with Craig Ventor*
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  - All the spurious associations that will be "found" and later not confirmed

*Depends on your idea of fun

Benefits & Risks of Recreational Genotyping

- Spur technological development and the integration of genetics into medicine
- Eventually allow truly “personalized medicine”
- Perversion of medical genetics rendering it akin to cosmetic surgery
- Further fostering of unfounded extreme degree of genetic determinism
- Promoting nonsensical ideas about race
- Promoting a new form of discrimination and stigmatization; “allelism”
- Satisfaction of our deep drive to know ourselves
  - Such offerings tap into a profound aspect of human nature and the special status which we accord to our genome

Dilemmas for the Law & Society

Correlations for identical twins reared apart (N = 40-50 pairs)

Trait	Correlation
Fingerprints	0.97
Height	0.86
Weight	0.73
Systolic blood pressure	0.64

(Bouchard et al., 1990, *Science* 250: 223-50)

Predictive Genetic Testing (PGT)

- PGT represents a new class of testing in medicine
- Consists of testing for mutations/ polymorphisms that predispose an individual to a specific disease
- The time-line is long (decades)
- predictive power varies from low to very high
- Many factors affect the clinical utility of PGT

PGT vs. Conventional Medical Testing

- Genetic tests affect other individuals who have not chosen to undergo testing
  - Duty to warn vs. Doctor-Patient confidentiality
- "Conventional" medical tests inform us about the pt's present condition, while genetic tests "inform" us about a possible future condition
  - adding a new dimension of uncertainty
- Our genome cannot be changed in a meaningful way
  - *Should it* be changed if it were even possible?
- Genetic testing touches upon concerns related to the underlying essence of a person's uniqueness
  - "DNA R US"
  - Issues related to personality and characteristics

An Example of Predictive Genetic Testing

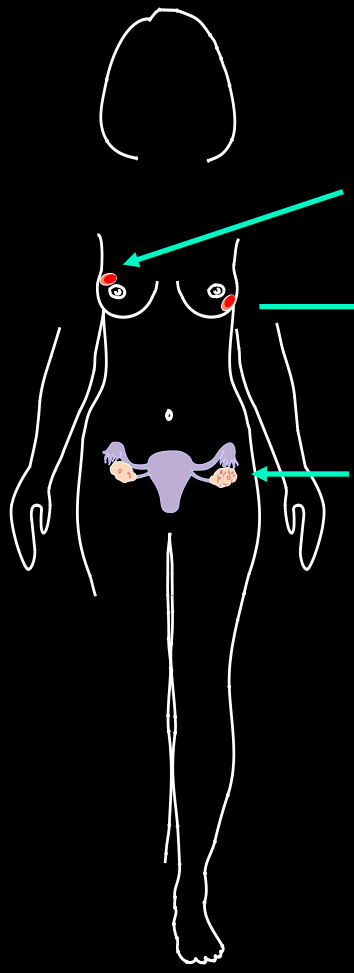
BRCA1 and BRCA2

- Breast cancer is the most common cancer in women
- 200,000 new diagnoses each year of breast cancer in the US
  - 45,000 deaths
- 30,000 new cases of ovarian cancer
  - 15,000 deaths
- 5-10% of these cases are because a woman carries a mutation in either the BRCA1 or BRCA2 gene
  - BRCA1 and BRCA2 are genes that normally regulate cell growth

Molecular Aspects of BRCA 1

- Located on chromosome 17
- Spans 81 kb of genomic DNA
- 5,592 nucleotides
- 24 exons
- Involved in DNA repair/recombination
  - Implications for treatment of br cancer?
- Involved in development

Cancer Risks for a woman who carries a mutation in BRCA1



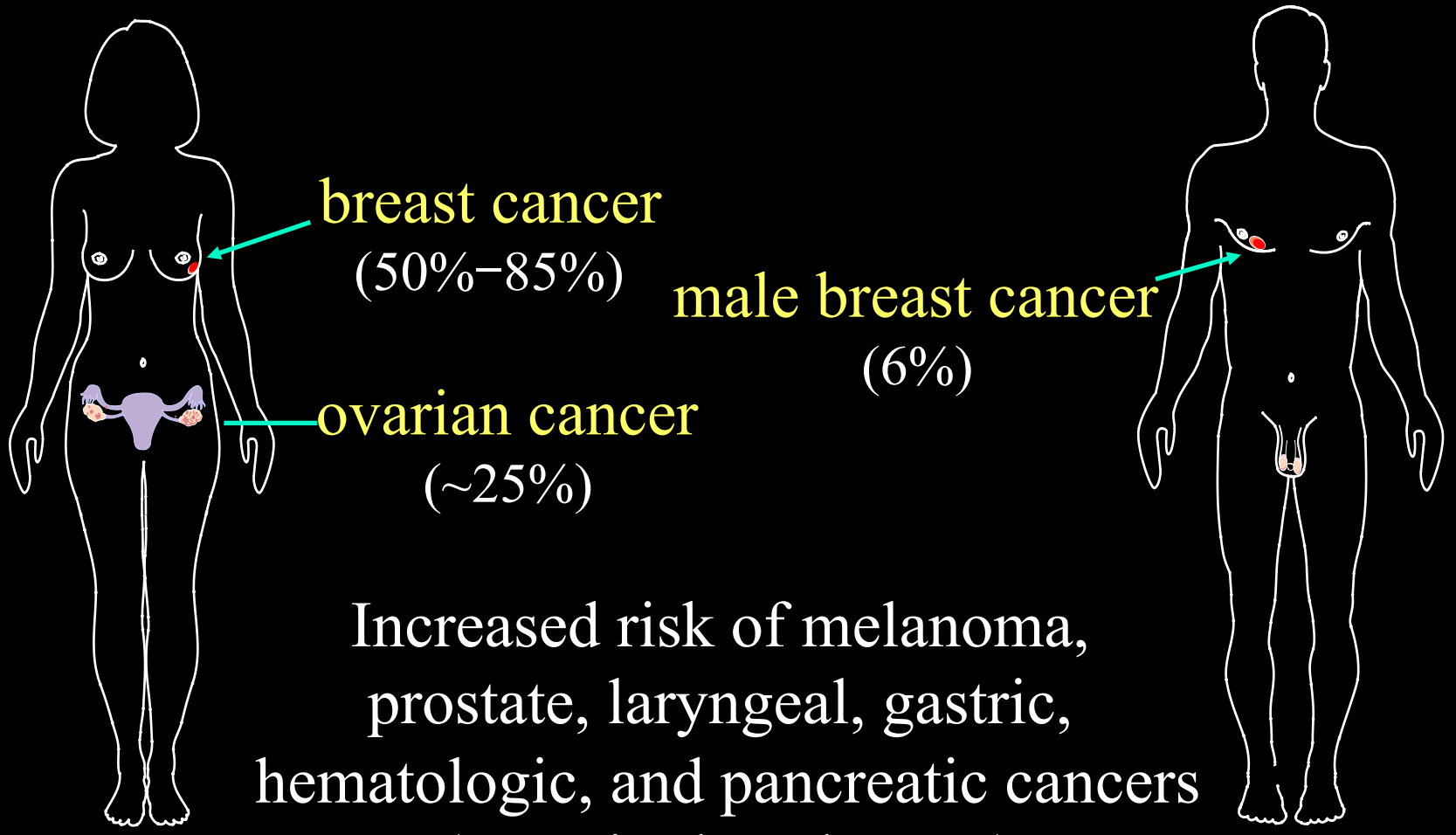
Life time risk of breast cancer ~50-85%

10 year risk of a second breast cancer ~30-70%

Life time risk of ovarian cancer ~50%

Probable increased risk of other cancers (eg, prostate, gastric)

BRCA2-Associated Cancers: Lifetime Risk

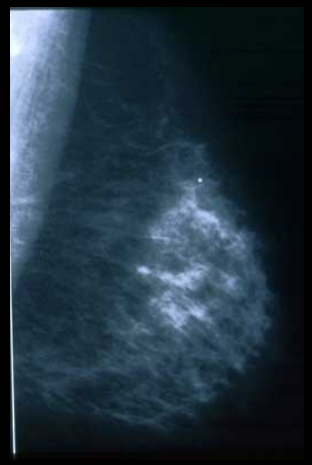


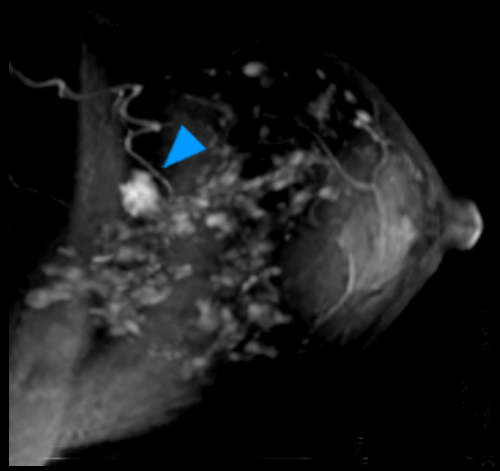
Increased risk of melanoma, prostate, laryngeal, gastric, hematologic, and pancreatic cancers (magnitude unknown)

ASCO

High-Risk Patients / High-Stakes Decisions

- Surveillance
  - Mammography
  - MRI
  - Ovarian
- Pharmacologic risk reduction
- Risk-reducing surgery
  - Bilateral mastectomy
  - Bilateral oopherectomy



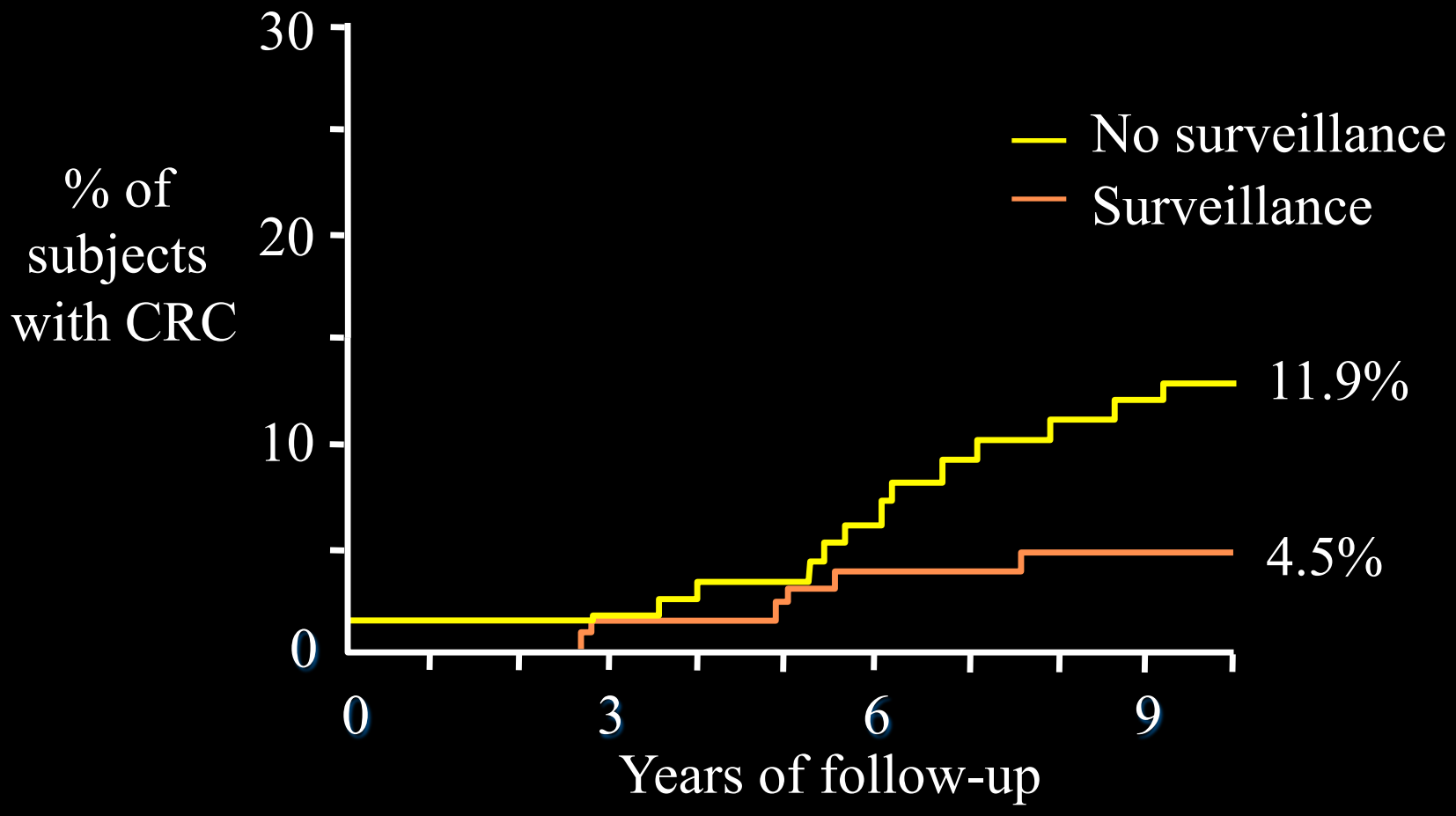


BRCA1/2 analysis can inform these decisions but is complex in its interpretation

Genetics & Colorectal Carcinoma

- HNPCC or “Lynch” syndrome
  - Accounts for 5-10% of “sporadic” colon cancer
  - Results from mutations in any one of several DNA-editing enzymes (mismatch repair genes)
    - MSH2
    - MLH1
    - MSH6
- Tumors in HNPCC individuals (& ~ 15% of sporadic CRCs show MSI (Microsatellite Instability)
  - The presence or absence of MSI may have therapeutic implications

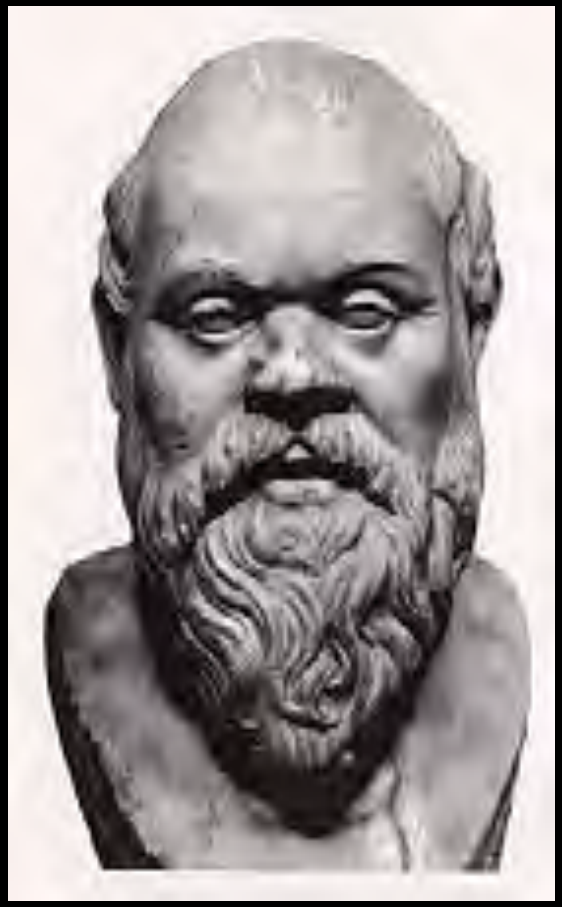
Surveillance Reduces Risk of Colorectal Cancer in HNPCC



Jarvinen HJ et al. *Gastro* 108:1405, 1995

ASCO

Colorectal cancer screening

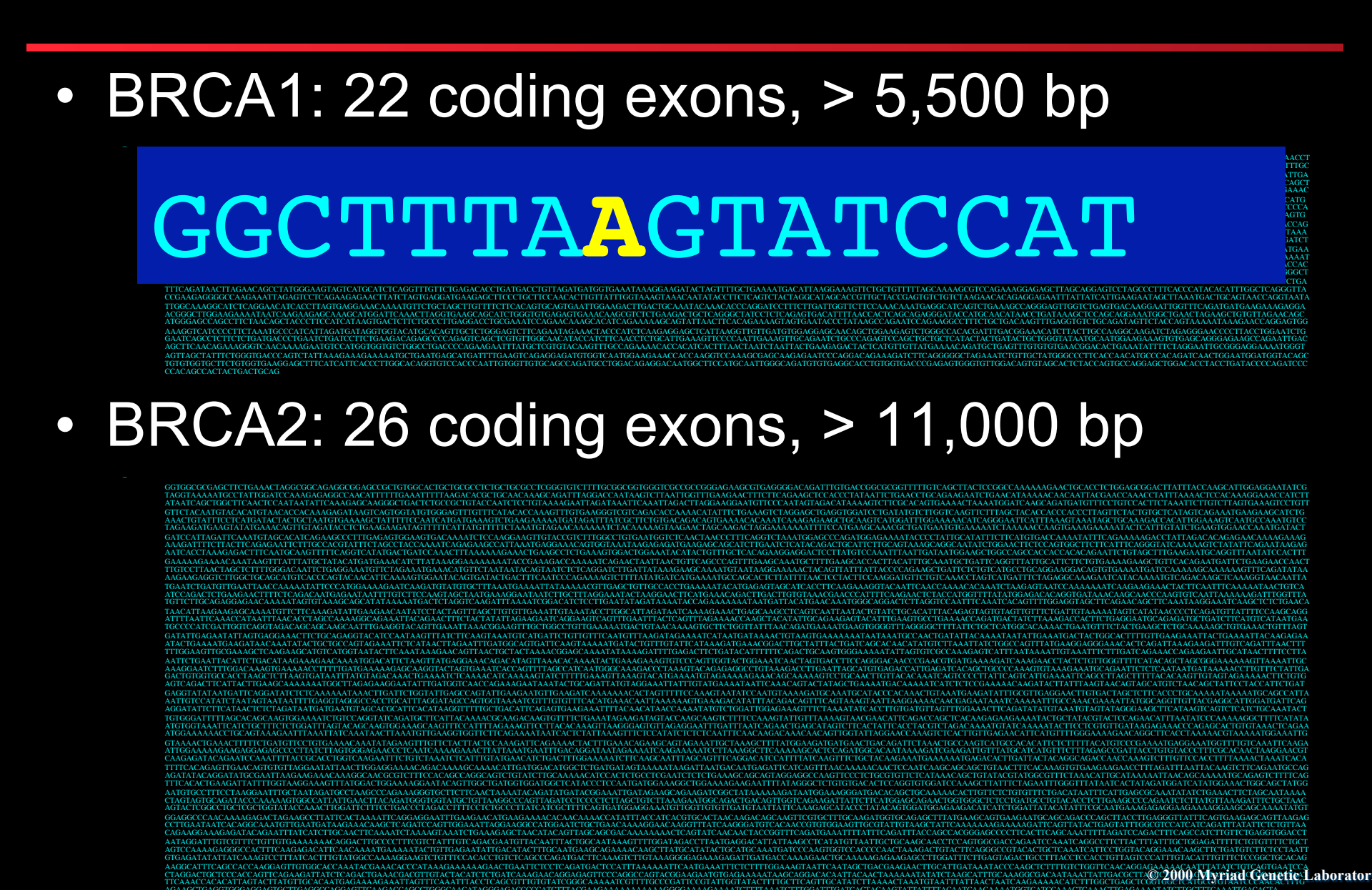


"The life which is unexamined is not worth living."

Socrates

Finding Mutations is Difficult

- BRCA1: 22 coding exons, > 5,500 bp



- BRCA2: 26 coding exons, > 11,000 bp

© 2000 Myriad Genetic Laborator

Interpreting Results

- What does a "negative" test mean?
  - Does this mean there is no mutation in the patient / family?
  - Or did we just fail to find it (a false negative)?
  - Sophisticated statistical analysis is necessary to determine residual risk
- What does a positive test mean?
  - Highly specific but…
    - Not everyone with a mutation will get cancer
    - And for those who will we can't predict when
    - Options for surveillance and for prevention are highly imperfect
    - …And expensive
- What does an indeterminate test mean?

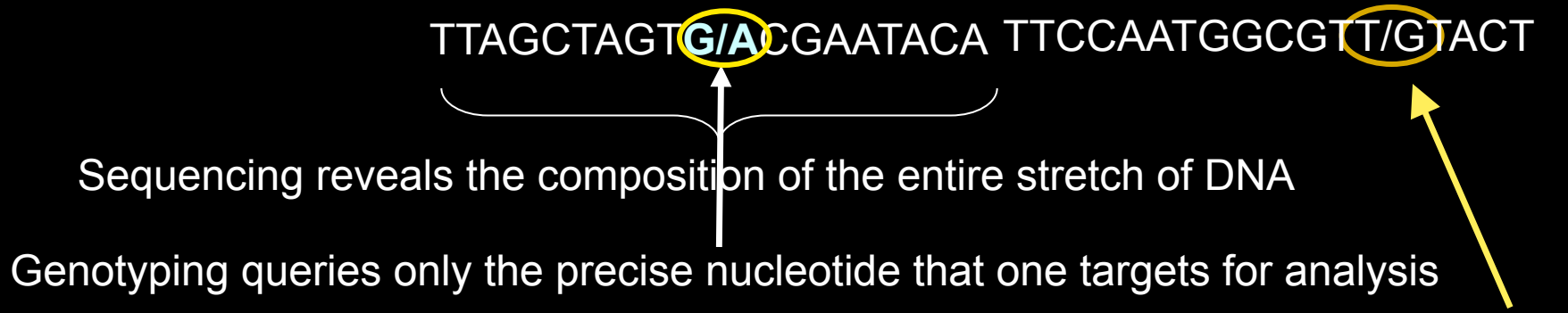
Accelerating Technology

- In 1997 it took a day to genotype a single SNP
  - Cost was ~$100
- Now in a matter of hours one can genotype an individual at >500,000 sites
  - At a cost of rougly $1,000
- Enabled by “chip” and “bead” technology
    - Reduction in cost of >500 fold

- The Cost of Sequencing is Declining Rapidly
- The $1,000 genome
- Flood of information will be a problem

Genomic Analysis
Genotyping

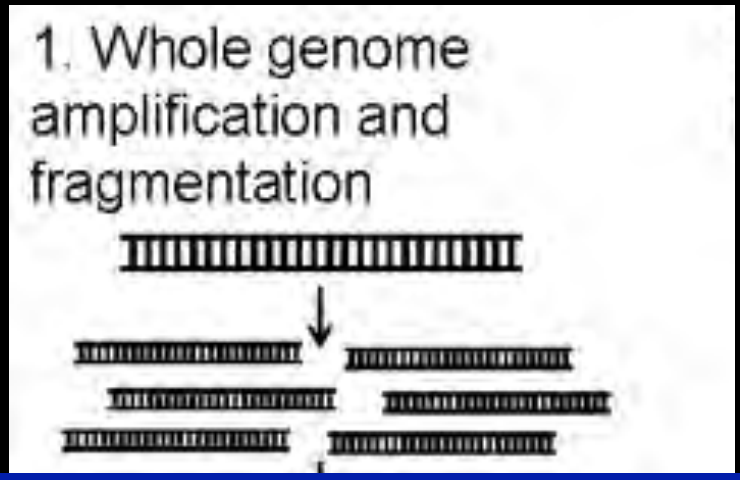
- Very different from sequencing
- The determination at specific individual sites (loci) of what version (allele) of a gene is present



Due to the haplotype structure of the human genome, querying ~1 million carefully selected sites provides information about much of the genome

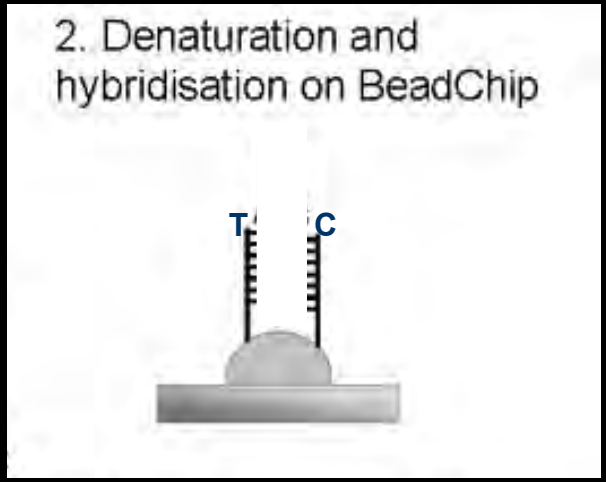
Illumina Infinium Assay

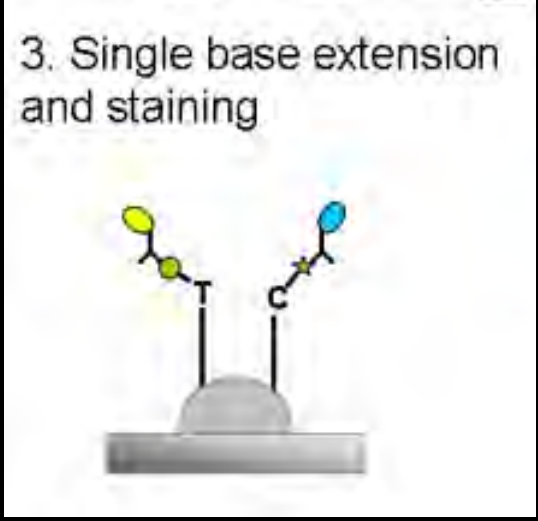
- Whole-genome amplification of DNA sample to increase the amount of DNA ~ 1000-fold
- Random fragmentation of DNA



Illumina Infinium Assay

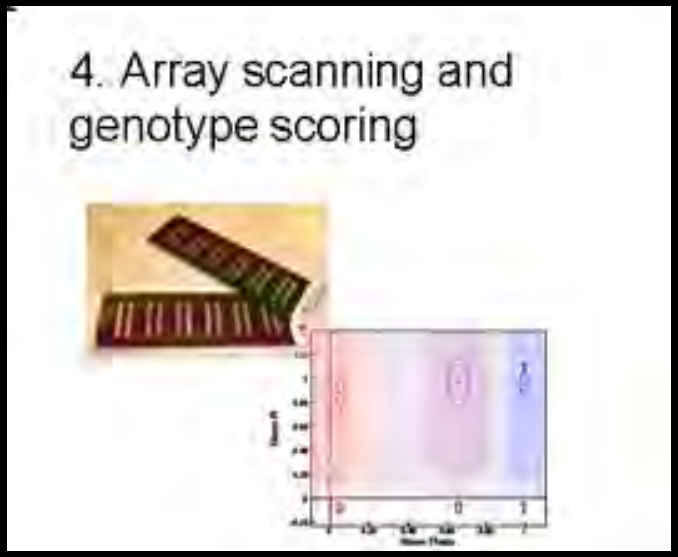
- Fragmented DNA is incubated with a “bead array” consisting of immobilized SNP-specific primers
- Fragments hybridize adjacent to corresponding SNPs
- Extended with hapten-labelled nucleotides if there is a match





Illumina Infinium Assay

- The incorporated hapten-modified nucleotides are detected by adding fluorescently labeled antibodies in several steps to amplify the signals
- Data analysis is performed using scatter plots



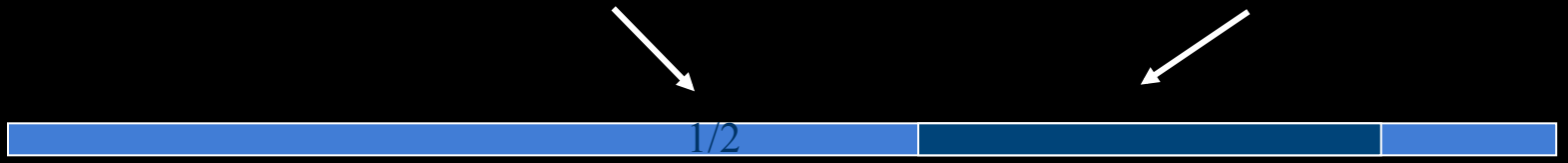
So, What Do We *Do* With It?

- Genome-Wide Association Studies
  - Provide the ability to search the genome for genetic factors that predispose to common diseases
  - Significant because of the general difficulty in identifying such factors by other means

Haplotype Analysis For Identification of Genetic Predisposition to Disease

A marker which defines haplotype 1 or 2

A nearby polymorphic gene which influences disease predisposition



If, in a large sample of individuals with disease, a statistical excess have haplotype 1, this is evidence that haplotype 1 contains a version (allele) of a nearby gene that can predispose to that disease

THE NEW ENGLAND
JOURNAL of MEDICINE

doi:10.1038/nature05887

ARTICLES

Genome-wide association study identifies novel breast cancer susceptibility loci

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Breast cancer exhibits familial aggregation, consistent with variation in genetic susceptibility to the disease. Known susceptibility genes account for less than 25% of the familial risk of breast cancer, and the residual genetic variance is likely to be due to variants conferring more moderate risks. To identify further susceptibility alleles, we conducted a two-stage genome-wide association study in 4,398 breast cancer cases and 4,316 controls, followed by a third stage in which 30 single nucleotide polymorphisms (SNPs) were tested for confirmation in 21,860 cases and 22,578 controls from 22 studies. We used 227,876 SNPs that were estimated to correlate with 77% of known common SNPs in Europeans at $r^2 > 0.5$. SNPs in five novel independent loci exhibited strong and consistent evidence of association with breast cancer ($P < 10^{-7}$). Four of these contain plausible causative genes (*FGFR2*, *TNRC9*, *MAP3K1* and *LSP1*). At the second stage, 1,792 SNPs were significant at the $P < 0.05$ level compared with an estimated 1,343 that would be expected by chance, indicating that many additional common susceptibility alleles may be identifiable by this approach.

Breast Cancer Risk Loci

- 1st stage:
  - 4,398 breast cancer cases / 4,316 controls
- 2nd stage:
  - 21,860 cases / 22,578 controls from 22 studies
- 227,876 SNPs evaluated in each subject
- Five novel independent loci exhibited strong and consistent evidence of association with breast cancer
- Four contain plausible causative genes (FGFR2, TNRC9, MAP3K1 and LSP1)

Correction for Multiple Tests

- P value of 0.05 assumes 1/20 false associations
- Current WGA studies test >500,000 loci per experiment
- For the equivalent significance of p=.05 when doing many tests, one needs to correct (the use of Bonferroni correction)
  - 0.05/500,000 = 1×10^{-7}
  - And this is just the edge of significance

Inherent Weakness of Whole Genome Strategies

- The immense size of the human genome
  - Lots of tests need to be done and pure chance will result in some that look significant
- Isolation of genes so-identified is difficult b/o large # of genes in a haplotype
- Each gene is likely to contribute little to the disease, so confirmation of a gene's influence is epidemiological
  - Relative risk conferred by "risk" allele is typically <2
- Different populations will have different allele distributions, different haplotype structures, different environmental exposures, etc.
  - Thus, such results may not be widely generalizable to other populations
- An identified polymorphism will be neither necessary nor sufficient for acquisition of the disease in question

Genetics & Epidemiology are Fusing

- 1926 cases with CAD / 2938 controls
- 9 loci associated with CAD
- Strongest association was a SNP at 9p21.3
  - Rs1333049; P = 1.80×10^{-14}
- CAD risk increased by 36% per copy of the C allele
  - Approximately 22% of the study participants homozygous for this allele
  - ~50% with one copy of the risk allele

Potential Benefits

- Provide knowledge of individual genetic predisposition
  - individualized screening
    - mammography schedule, PSA, HbA1c, etc.
  - Presymptomatic therapies
    - e.g. chemoprevention for cancer
- Pharmacogenomics
- Medicine as a public health endeavor
- Fundamental understanding of etiology
- Novel drug targets

What *Else* Can We Do With It?

- Make money!!!
  - After all, this is the USA
- Several companies are now offering "boutique" genotyping
- "Buying is more American than thinking"

23andMe

deCODE ME

Genetic Testing is Potentially Harmful

23andme / DeCode Genetics

- Heavily covered by the media
  - NY Times, Newsweek, etc.
- Offer genotyping at ~500,000 – 1,000,000 loci
- Individual sends a saliva or mouth brush sample
- And $1,000 by credit card
- Genotyping of SNPs associated to provide information about:

Ancestry

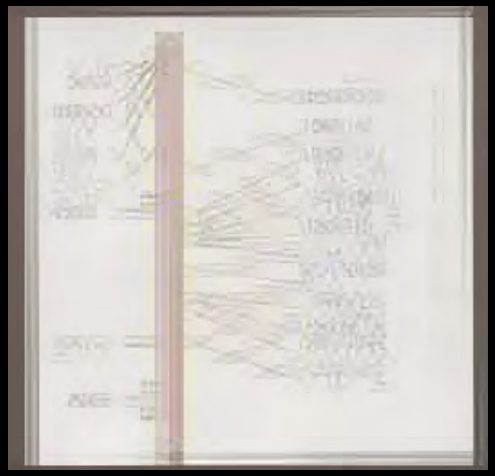
- My ancestors are from Europe
- ***Who'd have thought?!!***

Haplogroup R1b (M343)

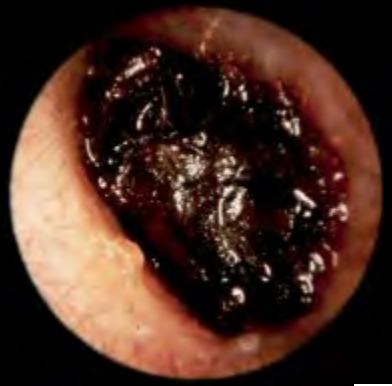
The designations for all twelve loci examined for this purpose are listed here, along with the Short Tandem Repeats (STRs) outcome for each.

393	19	391	439	389-1	389-2	388	390	426	385a	385b	392
13	14	11	11	13	16	12	23	12	11	11	13

July 21, 2005



Traits



- Earwax type
- Alcohol Flush Reaction
- Bitter Taste Perception
  - E.g. Brussels Sprouts

- Eye color
  - DeCode's narrator:
    - "My likelihood of having brown eyes is 67% and of having brown hair is 92%; ***and I do have brown eyes and brown hair!"***
- Behavioral traits
  - Aggression, novelty seeking, propensity for depression, etc.

Comparison With Others

- Family members
- Friends
- “Famous Scientists like Craig Venter”!!
  - DeCode’s narrator shares 2-3% of his genome with Craig
  - Forthcoming Facebook invitation to Craig to be his gene-friend
- “We envision a new type of community where people will come together around specific genotypes and these artificial barriers of country and race will start to break down”- Anne Wojcicki, co-founder of 23andMe

Disease Risk

- Breast Cancer
- Prostate Cancer
- Alzheimer Disease
- Crohn's Disease
- Risk of cardiovascular disease
- Multiple Sclerosis
- Diabetes
- Restless Legs Syndrome
- Venous Thromboembolism

- *For the vast majority of such risk assessments, the increased risk of one developing the disease is modest*
  - *On the order of 1-2 fold risk over baseline*
- *In few such conditions are there specific effective interventions to diminish the risk*

What Will We Find Out?

- Things that are useful to know
  - At least for now a distinct minority of what will emerge from such analyses
- Things that we already know
  - e.g. your are at risk for heart disease and you should exercise and eat right
- Things we don't want to know
  - I'm at increased risk for Alzheimer Disease
- Things that are fun to know
  - Ancestry
  - Whether you'll like Brussels sprouts (but also see above)
  - How many polymorphisms you share with Craig Ventor*
- Things we *think* we know but don't
  - All the spurious associations that will be "found" and later not confirmed

*Depends on your idea of fun

Benefits & Risks of Recreational Genotyping

- "Knowledge is Power"
  - Is it always?
  - What about knowledge about those things over which we have no control?
- Identification of risks which can be modified
  - Utility is highly dependent upon the magnitude of risk
    - 1.4 RR for prostate cancer vs. 85% lifetime risk of breast cancer
  - Will such knowledge actually lead to adoption of "healthier lifestyle"?
    - We already know that smoking is bad for us
  - Identification of lower risk leading to bad decisions
    - I have a reduced risk of lung cancer; why stop smoking?

Benefits & Risks of Recreational Genotyping

- Spur technological development and the integration of genetics into medicine
- Eventually allow truly “personalized medicine”
- Perversion of medical genetics rendering it akin to cosmetic surgery
- Further fostering of unfounded extreme degree of genetic determinism
- Promoting nonsensical ideas about race
- Promoting a new form of discrimination and stigmatization; “allelism”
- Satisfaction of our deep drive to know ourselves
  - Such offerings tap into a profound aspect of human nature and the special status which we accord to our genome

DNA “Я” US

Dilemmas for the Law & Society

Correlations for identical twins reared apart (N = 40-50 pairs)

Trait	Correlation
Fingerprints	0.97
Height	0.86
Weight	0.73
Systolic blood pressure	0.64

(Bouchard et al., 1990, *Science* 250: 223-50)

Controlling the Genetic Genie

- Genetic Discrimination
  - There is no federal legislative protection…yet
- Gene Patenting
  - Most of our genes have patent claims on them
  - BRCA1/2 are under restrictive patents
- Privacy Issues
  - "Privacy is dead. Get over it."
  - What happens when 23andMe is subpoenaed?
  - Problems compounded by the acceleration of Information Technology and the World Wide Web
  - Corporate, government and public genetic databases are being formed all over the world
- Who will control this information?
  - Do you want to know ?
  - Do you want others to know?
    - Your insurance / managed care plan
    - Your employer
    - Your family
    - Dick Cheney
    - Your neighbor who surfs the web

Pharmacogenomics

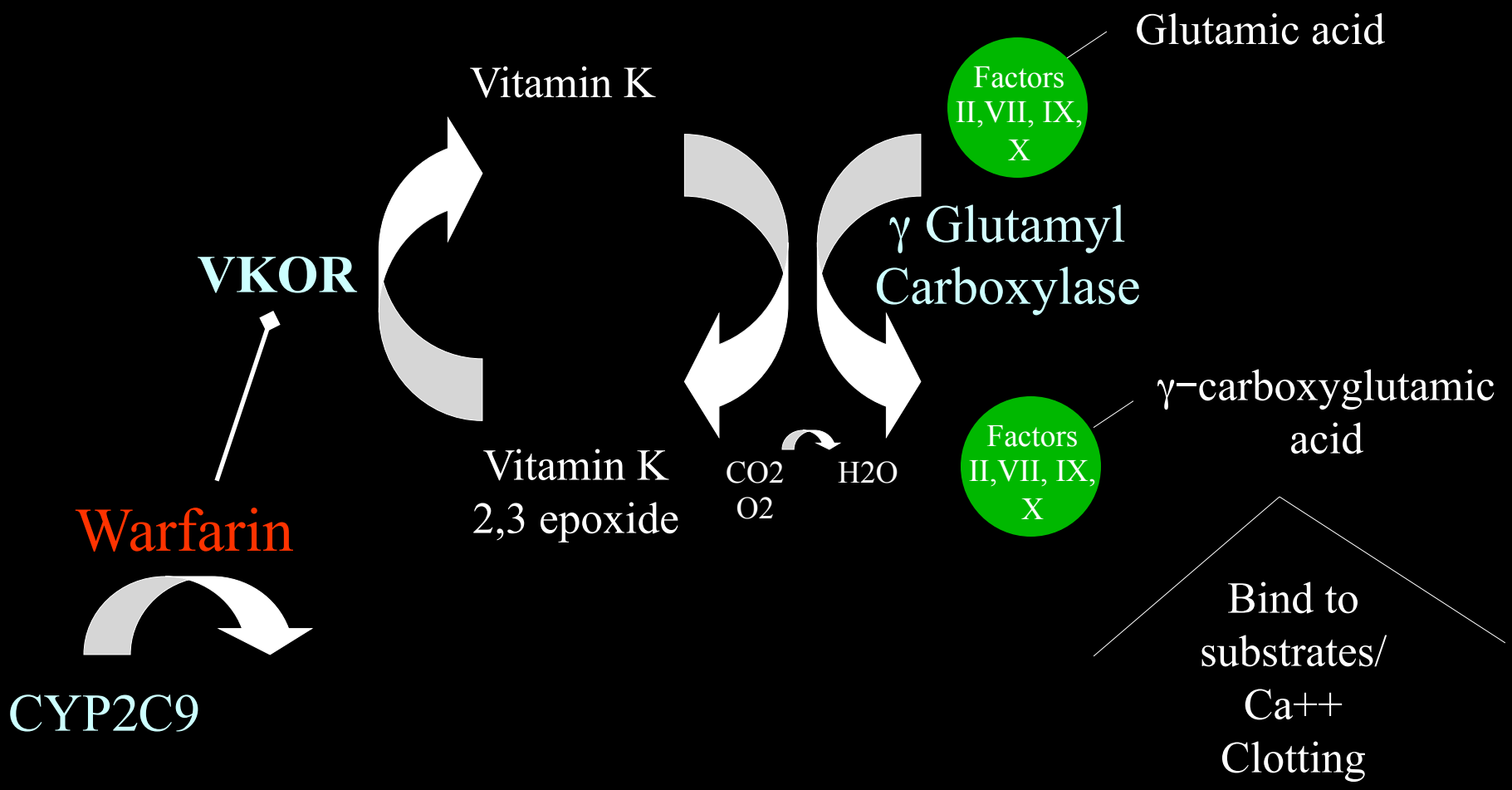
- The use of genetic analysis to predict the individual's response to a drug
  - The right drug
  - The right dose
  - Avoidance of adverse effects

Pharmacogenomics

- The Perfect drug for PGx intervention…
  - Commonly prescribed
  - Prescribed for serious indications
  - Narrow therapeutic window
  - Great hazard if outside of therapeutic window
  - Significant variability in individual response to standard dosages
  - No good alternative

Warfarin (Coumadin)

Vitamin K dependent clotting factors



VKOR SNP association results (Caucasians)

VKOR gene SNPs	N	Avg Weekly Dose	INR
1173 C>T			
CC	32	47.7	2.44
CT	40	34.7	2.61
TT	24	27.0	2.66
P-value		0.0000095	0.083
1542 G>C			
GG	33	46.8	2.45
GC	41	34.6	2.61
CC	22	27.2	2.66
P-value		0.0000027	0.098
2255 T>C			
TT	22	27.3	2.63
TC	43	34.7	2.62
CC	31	47.3	2.45
P-value		0.0000021	0.12

Clinical Significance

- VKOR genotype is a robust indicator of warfarin sensitivity
  - Weekly dose is virtually doubled with inheritance of “sensitive” genotype
- The responsible SNPs are common
- SNP genotyping is easy and cheap
- May ultimately offer clinical guidance for a drug with a very narrow therapeutic window
  - Especially when combined with P450 genotype and demographics

Human Variation

- We differ by a single nucleotide every ~500-1000 bases
  - SNPs (Single Nucleotide Polymorphisms)
    - Further variation due to CNV

How Much Human Variation?

A Matter of Perspective

- In relative terms we're all the same (~99.9% identical)
- However, in absolute terms we're very different
- 1/1,000 differences translate to >3,000,000 differences between any two unrelated individuals
- Some of these differences are medically relevant
  - Influencing disease predisposition
  - Response to drugs
- Or of interest in other non-medical ways
  - Ancestry
  - Behavioral traits
  - Innate curiosity about our genes

DNA "Я" US

Where is the Genome's "Dark Matter"?

- Conventional* interpretation of epidemiological and twin studies support substantial genetic component for many diseases
  - Breast Cancer 27%
  - Prostate 42%
  - Pancreatic 36%
  - Bladder 31%
- But GWAS consistently fail to identify most of the genetic component
- *Perhaps our interpretation is wrong
- Perhaps there are many more low-penetrance risk alleles
  - Undiscovered b/o very low RR

When Rare Becomes Common…

- Rare high-penetrance alleles
  - Which will be seen upon large scale WGS of many individuals

Either way, documenting the validity of such alleles and applying them in practice will be very challenging