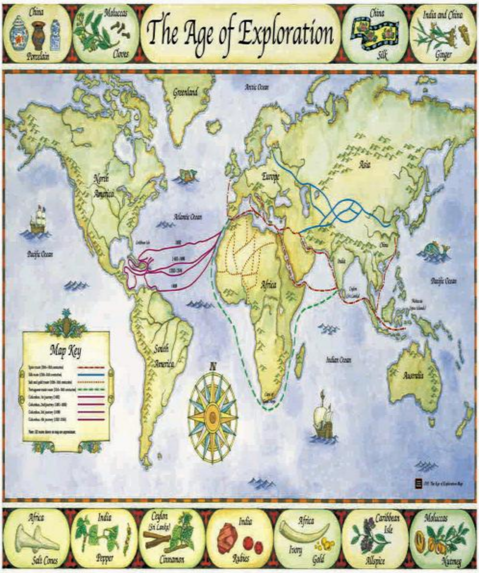
Genomics, Population Health, and Technology

What's Genomics Good For?



Institute of Medicine
Workshop:
Assessing the
Economics of Genomic
Medicine

Washington DC
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UNC Chapel Hill

Analyzing a Human DNA Sequence

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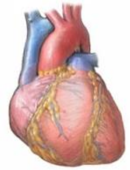
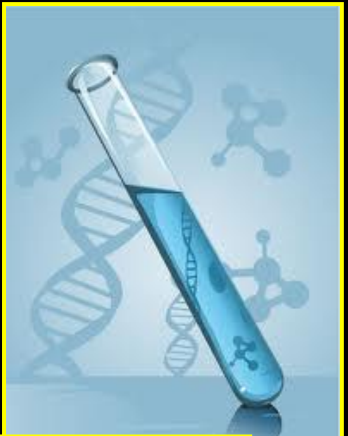
- ~1/1,000,000th of the Human Genome
- Interspersed with genes
- Polymorphisms
  - Much of it meaningless
  - Some influencing traits
  - or medically important characteristics

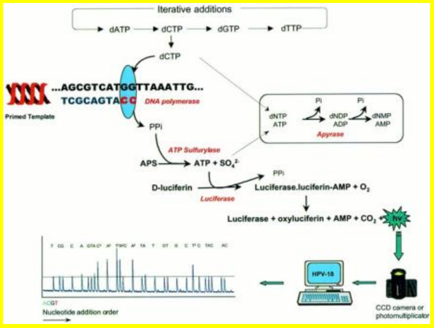


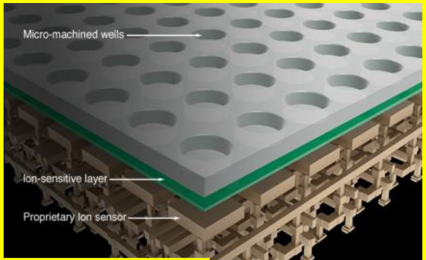
- Occasional rare mutations that greatly influence health

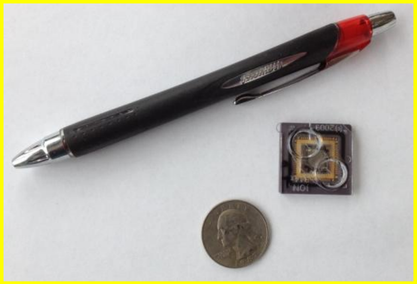
DNA Sequence Analysis by Miniaturization & Multi-Tasking

- A variety of chemical and physical strategies exist
- 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





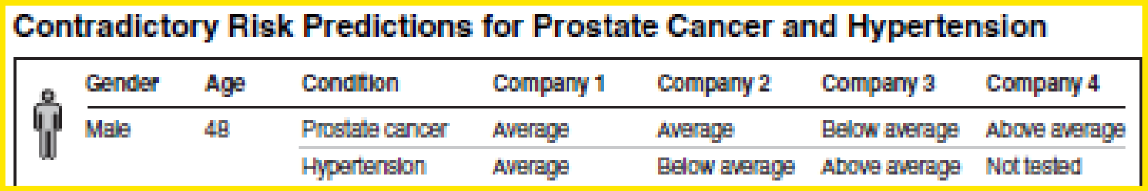




Risk SNPs *vs.* Determinative Mutations

High frequency/low penetrance variants vs. low frequency high penetrance mutations

- Most genetic variants (e.g. GWAS-identified risk SNPs) are common but are modestly probabilistic (low penetrance)
  - We don’t even know how to aggregate such SNPs to predict overall risk
  - Low penetrance means little utility in most settings
- Rarely, individuals harbor mutations that are far more determinative
  - *Dramatically* increasing risk of such disorders
  - Sometimes making the blunt tools at our disposal useful for prevention in highly selected situations
    - e.g. risk reducing mastectomy, annual colonoscopy, etc.

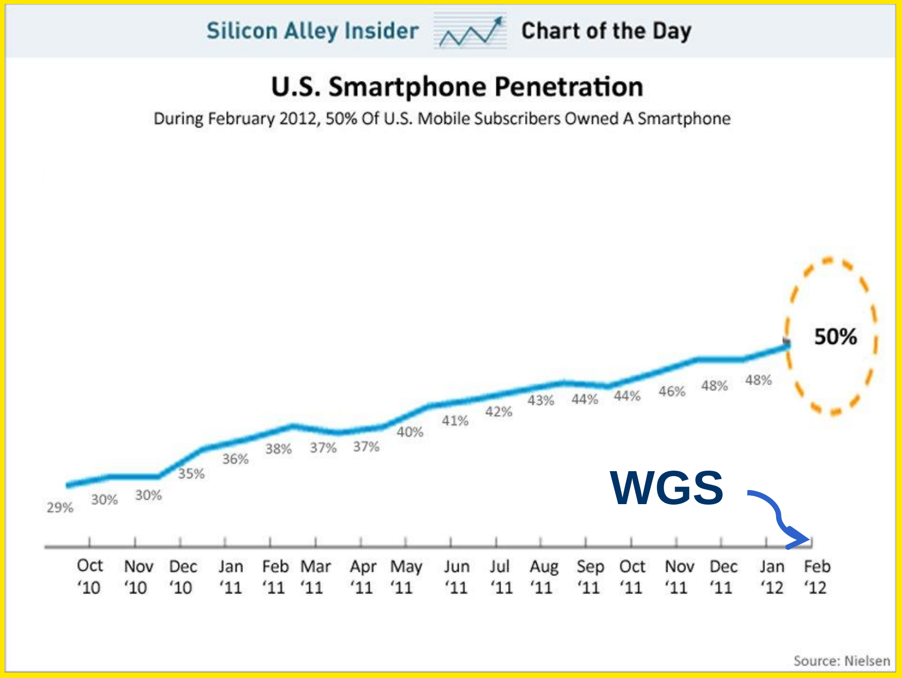


Contradictory Risk Predictions for Prostate Cancer and Hypertension

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

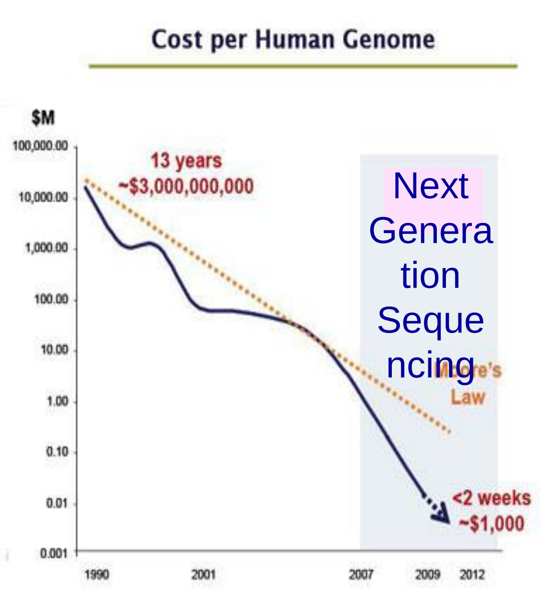
Accelerating Technology, Plummeting Cost & Penetration to the Individual

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



Source: Nielsen

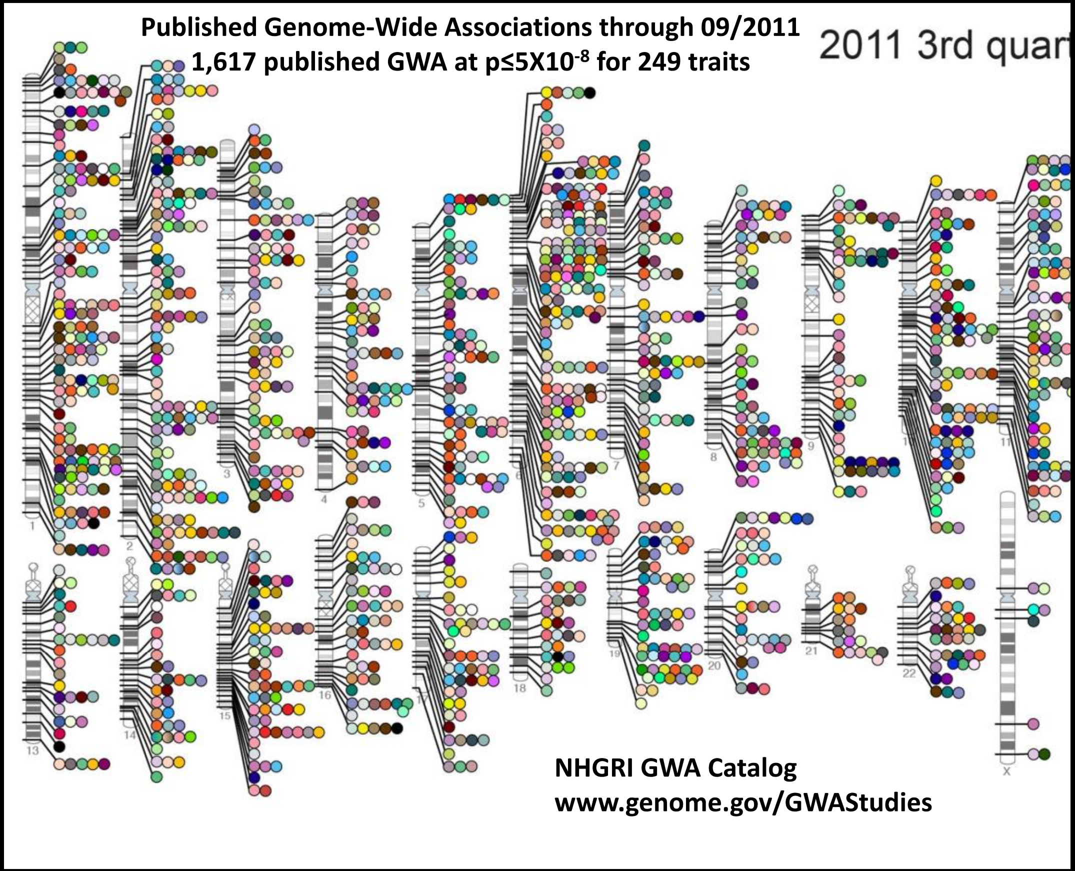
WGS



Next Generation Sequencing

Genomics' Long Term Promise

- An avalanche of Genome Wide Association Studies (GWAS) in common diseases
- WGS is now a practical reality
- Will shed light on the genetic underpinnings of every disease imaginable



Published Genome-Wide Associations through 09/2011
1,617 published GWA at p≤5X10^{-8} for 249 traits

NHGRI GWA Catalog
www.genome.gov/GWAStudies

Ultimately transforming Medical Science

Medical Science ≠ Medical Practice

- Medical Science is the indispensible foundation of Medical Practice
- But is far more complex than the underlying science
  - More variables
- Theory alone is insufficient to guide practice
- Time-line for translation is long
  - And is not guaranteed by scientific understanding
    - See sickle cell disease
- It's far more expensive
- The stakes are much higher in Medical Practice
  - Because the power to harm is real and potent

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
- Strict bed rest for back pain
- Coronary stents do not prolong life
- Excessively strict glucose control in diabetes
- Routine use of PSA screening has arguably caused more harm than good

Near to Midterm 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

Genomic Diagnositics 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 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 represents a new diagnostic tool which will soon transform the diagnosis of disorders whose etiology is primarily genetic

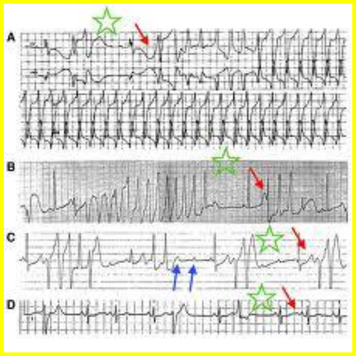
©Cartoonbank.com

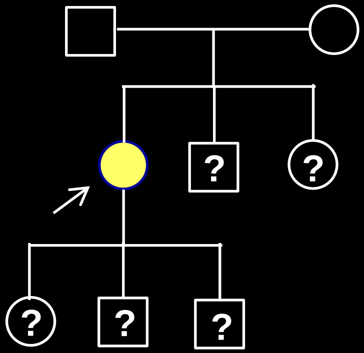
“We think it has something to do with your genome.”

Sick People

Massively Parallel 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
  - Treatable
  - Dozens of genes implicated
- Application of MPS to detect mutation
  - In this case, a panel of multiple genes
- Guiding patient’s treatment and prevention of death in family members

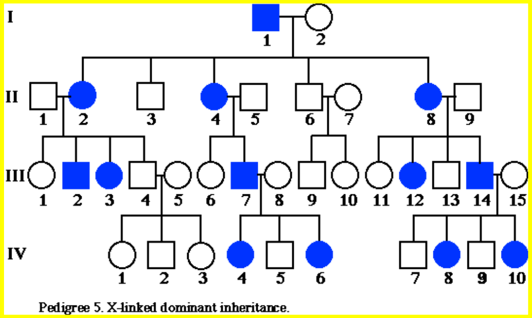




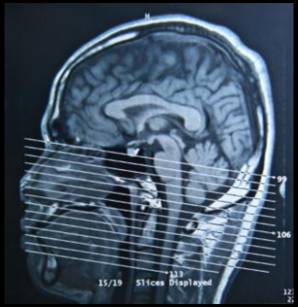
Targeting the Right Patients

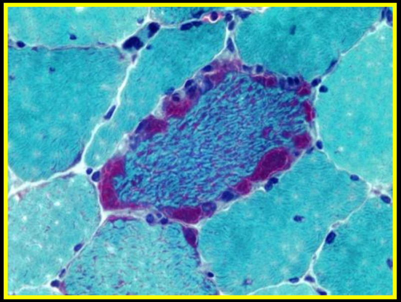
- Those with genetically heterogeneous disorders
- Those with enigmatic conditions & clues suggesting a *primary* genetic etiology
    - Children
        - Multiple malformations
    - Familial phenotypes
    - Disorders suggesting mitochondrial etiology
    - Progressive neurological disorders
    - Unusual presentations (e.g. cancer at young age)
  - WGS/WES vs. panels (real or virtual)
  - Unique opportunities in Cancer

Will benefit a subset of patients



Pedigree 5. X-linked dominant inheritance.

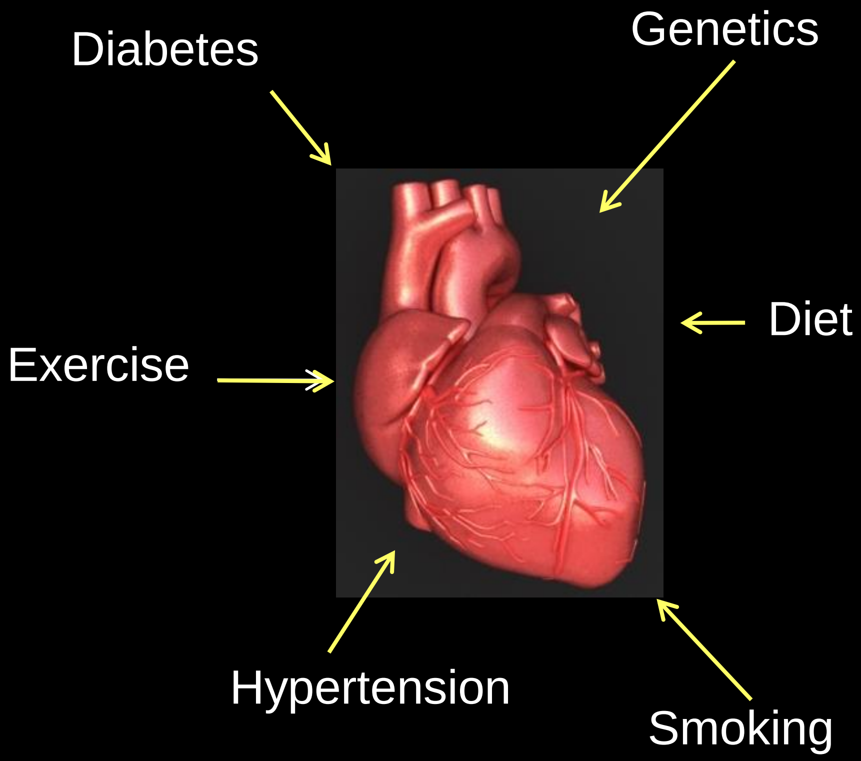




The Wrong Nail

Application of MPS in those with common diseases

- Common diseases have many etiologic factors
  - The genetic component is typically small
  - Placing an inherent ceiling on the utility of germline genetic information in these disorders



Diabetes

Genetics

Exercise

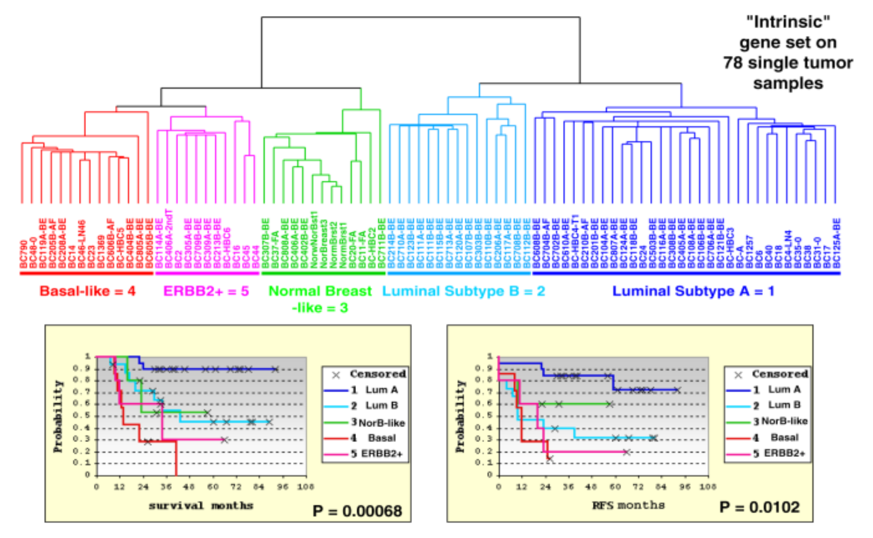
Diet

Hypertension

Smoking

Somatic Genomic Analysis in Cancer Offers Unique Opportunities

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



Healthy People

- How can genomics improve the health of those who are not yet sick?
- More difficult than applications in the sick, since healthy people have less to gain and more to lose
  - Assessing risk of common diseases
    - And doing something about it
  - Pre-emptive delineation of select PGx variants
  - As an adjunct to newborn screening
  - Finding those relatively unusual individuals who are at high risk of preventable disease
  - Enabling a variety of reproductive decisions

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

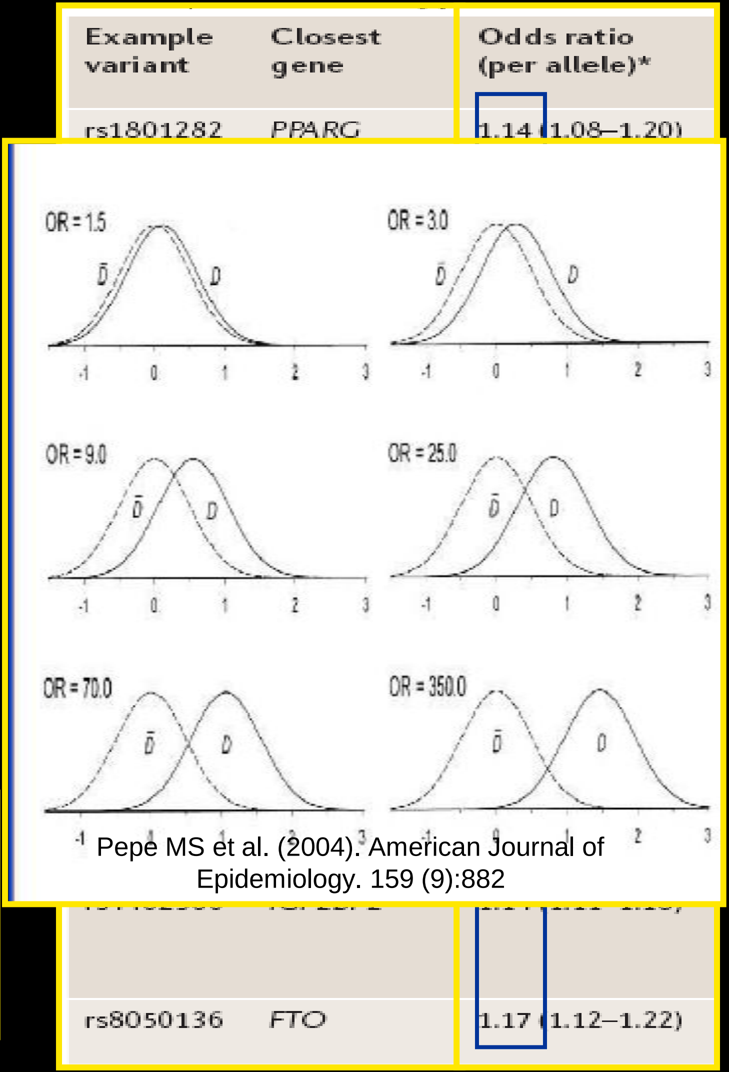
We now have the ability to analyze the individual's genome deeply and define statistically significant variation

However, our tools in medicine are blunt…

And Predictive Power is Feeble

The Problem of Relative Risk

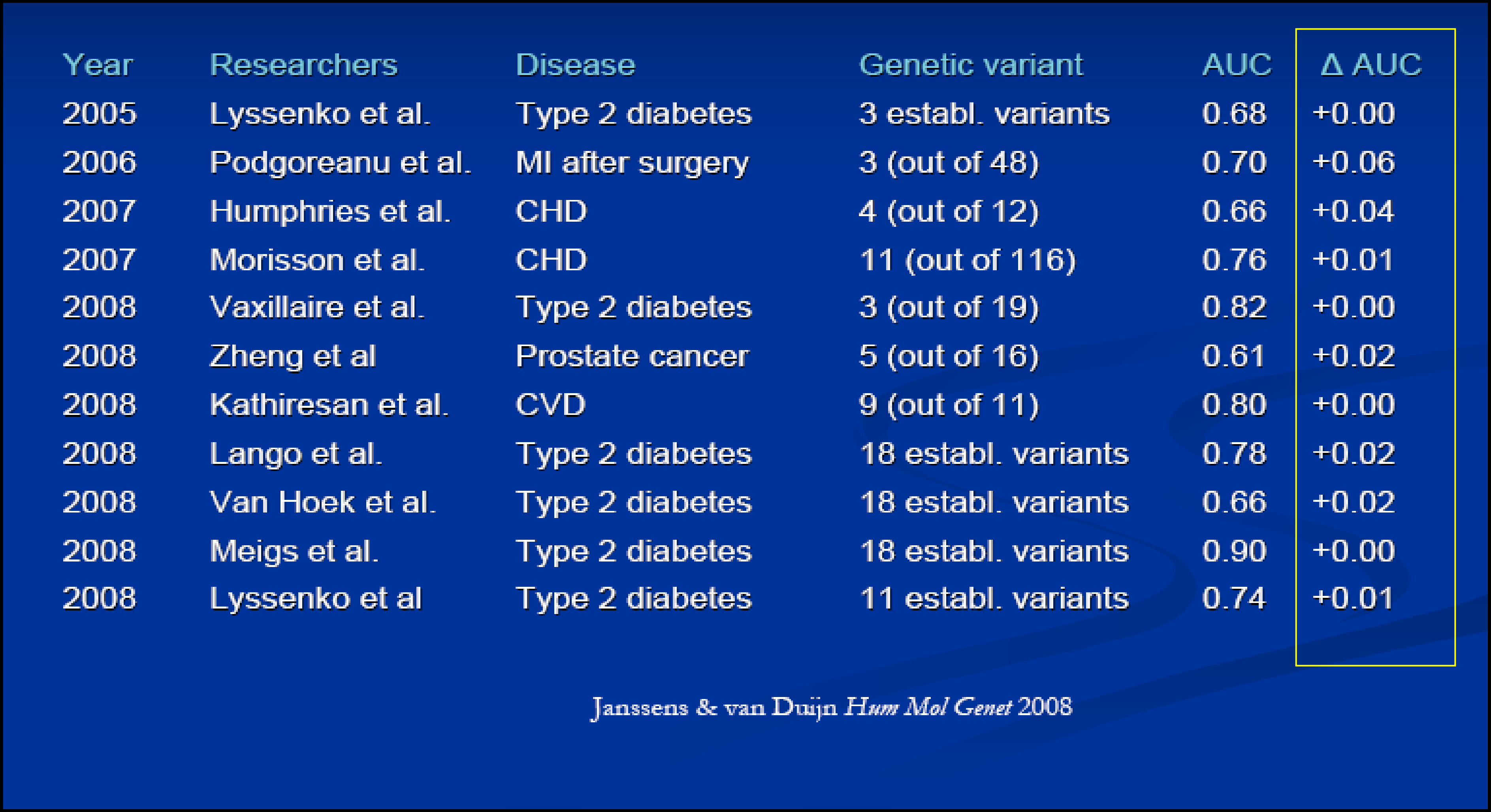
- Numerous risk alleles identified
  - The vast majority of RR ~1-2
    - What do I ***do*** with such information?
  - From a clinical standpoint the information is so lacking in robustness that it is of no clinical utility
    - At either the individual or population level
- Few data to suggest that 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	*PPARG*	1.14 (1.08–1.20)
rs8050136	*FTO*	1.17 (1.12–1.22)

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

Little Added Value for Combinations of Variants



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 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
    - We are all at high risk for these maladies - regardless of our relative risk
    - Many at “decreased risk” for heart dise will still die of heart disease

- For uncommon diseases what does it mean?
    - Risk of developing Crohn’s Disease = ~5/1,000

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

Public Health Genomics

Targeting the 1%

- We now have the capacity to identify those relatively unusual individuals 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 now only identify such people after they and numerous family members develop cancer
- MPS allows population screening for such disorders
- ~1% (~3 million) of population carries mutations that predispose to lethal but preventable disease
  - e.g. certain cancers, certain specific cardiovascular disorders

Pharmacogenomics for Healthy People

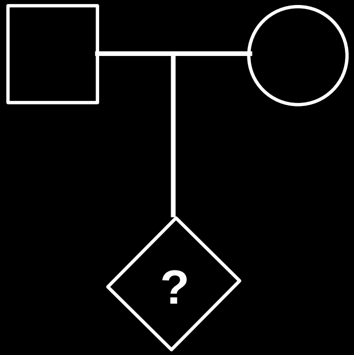
- Some rationale to the idea of “preemptive” identification of relevant PGx variants in the healthy population
- However it may apply to a minority of drugs
  - Few loci have demonstrated value in improving outcomes or reducing cost
    - HLA-B & abacavir
    - ?VKOR, ?CYP2C19, CYP2D6…
    - Hardly requiring a genomic approach
  - Targeted POC genotyping may be preferable
    - PGx info is needed only when *and if* a given drug is ever prescribed
    - Realizing the benefits of preemptive genomic PGx will require a well integrated, seamless EMR
    - Would/should clinicians trust a 10 year old WGS result?
      - Your WGS from 2012 is likely vastly inferior to your WGS of 2014
      - Prior to blood Trx cross match is always done regardless of what’s in the EMR

New Born Screening

- Will not replace metabolically based approaches since metabolic markers:
  - Are far more reflective of phenotype
  - Have much greater specificity
    - e.g., it is far easier to interpret a high phenylalanine than a genetic VUS
    - Potential metabolic FPs can be readily adjudicated
- MPS holds promise as an *adjunct* to traditional NBS
  - Helping to further define ambiguous biochemical results
  - Detection of the subset of treatable diseases for which no good metabolic markers exist
    - Examples might include deafness, storage disorders, neonatal diabetes, etc.

Pre-conceptual carrier screening

- Offering PCCS is currently recommended for a few specific disorders
  - Based solely upon cost and mutation prevalence
    - Not upon what couples would like to really know
    - We recommend CF or Tay Sachs screening simply because they are affordable, not because they are any worse than, e.g., Batten's Disease
- MPS eliminates this arbitrariness
  - Such screening is already offered commercially
  - Potentially profound and welcome impact on family planning
  - Highly actionable information to some
  - Morally problematic for others
    - Making formulation of policy variable and difficult for this application



My Take on the Genomics Scorecard

☑ Powerful diagnostic tool for patients with primary genetic disorders

☒ Broad preemptive PGx application

☑ Improved treatment of cancer through genomic somatic analysis

☒ Prevention of common diseases through genomic risk assessment

☑ Prevention of rare diseases through selective genomic discovery of highly penetrant mutations

☑ Utility in newborn screening

☑ Preconceptual screening to inform reproductive choice

A Few Challenges to Effectively Harnessing MPS

- 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
    - Do we really want/need to keep them all?
    - Your 2014 WGS is likely to be much better than your 2012 WGS – and cheaper
    - "Evolution is cleverer than you are"
- Surprises

Incidental Information & the Other 1%

A Potentially Important Negative Externality

- Most of our genomes are boring
- But it is an unpredictable – and not necessarily friendly - place
- Upon WGS we discover many things we weren't looking for …Surprise!
  - About 1% of us may be s useful ways
  - But some of us will discover we possess a dramatic risk of lethal, untreatable, late onset conditions
- Some wish to know such information; many do not

Next Generation Sequencing is Just Another (Highly Complex) Medical Test

- Claims are often made that “soon everyone will have their whole genome sequenced”
  - Typically predicated upon high perceived utility and low cost
  - Even if “free”, perceived low cost is an illusion
    - The misapplication of medical tests is very expensive
      - Morbidity/mortality to individuals (e.g. PSA screening)
      - Expense to society

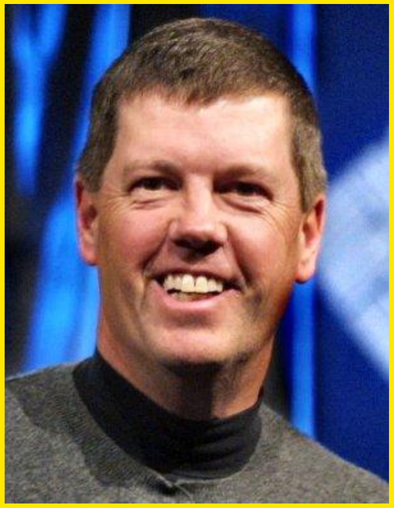
- I suspect it will be applied as are other medical tests:
  - When and if the situation warrants
  - With genomic analysis targeted in a panel-specific manner in most non-diagnostic settings
  - With WGS/WES useful in some diagnostic settings and in research
    - There’s no point in burdening the system with a flood of extraneous information which we have no idea of how to use or even interpret
    - Targeting could be actual or virtual
- We need (and are generating) data on its uses

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
  - 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 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