Patient zero

and the new world of genomic medicine

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STANFORD CENTER FOR INHERITED CARDIOVASCULAR DISEASE

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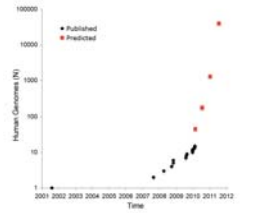
The question

- 10 years since draft HGP
- 2 years since the "Year of the GWAS"
- Very little impact on clinical medicine
- But, sequencing is getting cheaper
- The number of genomes is set to rise
- What does a consultation look like in 5 years?

Year	Cost estimate	Technology
2001	$300,000,000	Sanger (ABI)
2001	$100,000,000	Sanger (ABI)
2007	$10,000,000	Sanger (ABI)
2008	$2,000,000	Roche (454)
2008	$1,000,000	[illegible]
2008	$500,000	Illumina
2008	$250,000	Illumina
2009	$48,000	Helicos
2010	$15,000	Complete



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The idea

What if everybody's genome was available in their medical record?

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LETTERS

nature biotechnology

Single-molecule sequencing of an individual human genome

Dmitry Pushkarev[1,2], Norma F Neff[1,2] & Stephen R Quake[1]

USA TODAY

Technology » Science & Space

U.S. professor sequences own genome in weeks

SAN FRANCISCO (AP) — It might not be long until there is a gene scanner in every doctor's office, as DNA sequencing becomes faster and cheaper.

A Stanford University professor reported Monday that he has sequenced his entire genome in a few weeks for under $50,000 using a single machine.

Six years ago, hundreds of researchers at the Human Genome Project completed the same task for $300 million. It took 13 years.

"It's continuing down the path to making it so every Tom, Dick and Harry are going to have their genomes sequenced," said Eddy Rubin, director of the U.S. Department of Energy Joint Genome Institute, who was not involved in the study.

The breakneck pace of technological progress in the field of DNA sequencing has raised hopes that affordable gene scans will be available to all patients soon.

Researchers hope cheap gene sequencing will lead to highly customized disease prevention, diagnosis and treatment tailored to an individual's genetic code.

Only a handful of human genomes have been sequenced so far. Typically those scans have used several machines working side-by-side to read the four chemicals that make up a "letter" in the DNA sequence.

"We've shown it can be done with one machine and just three people, with just one operating the machine," said Stanford bioengineering professor Stephen Quake, whose results were published in the journal *Nature Biotechnology* on Monday.

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Patient zero

- 40 year old male in good health presents to his doctor with his whole genome
- No symptoms
- Exercises regularly
- Takes no medication
- Family history of aortic aneurysm
- Family history of sudden death

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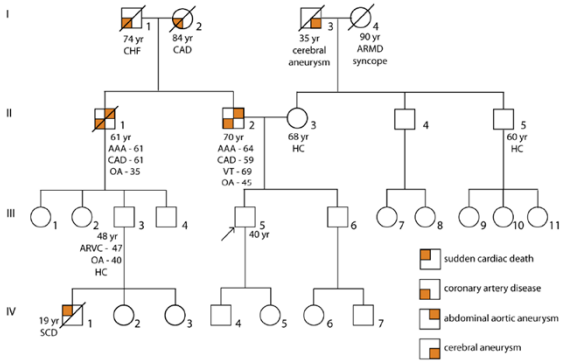

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Clinical examination

- Normal appearing male
- Comfortable at rest
- HS 1,2+0
- No murmurs, rubs or gallops
- Chest clear, abdomen nad
- Musculoskeletal, neuropsych examinations grossly normal
- Afebrile
- HR 60pm, BP 128/80

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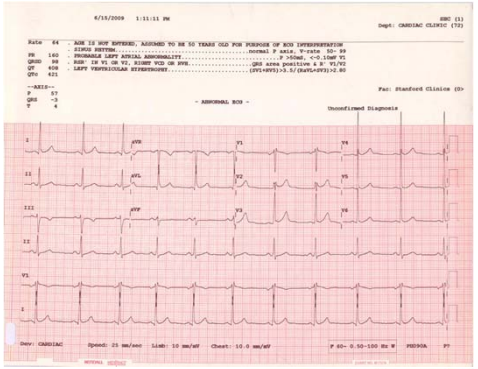
Electrocardiogram



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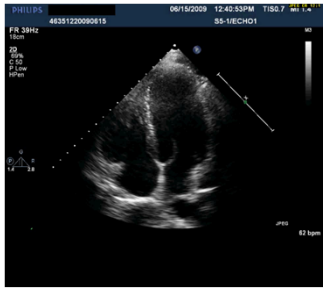
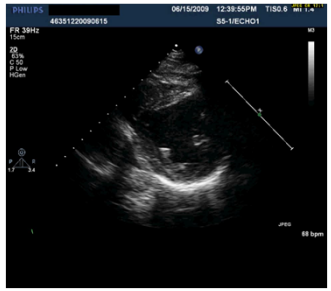
Echocardiography





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Exercise test

Test Date	09/04/2009			
Name (First Last)			MRN	11581501
Referring MD	Exam Ashley		Diagnosis	Health care maintenance
Age (years)	40		Weight (lbs): 190	Height (in): 71
Exercise mode	Bike		Protocol	Ramp (Actual exercise time: 16 mins 9 secs)
	Rest	Max		
Heart rate (bpm)	76	191	% pred HR	106
VO_2 (ml/kg/min)	3.5	49.6	% pred VO_2/max	145
Systolic blood pressure (mmHg)	100	192		
O_2 saturation (%)	99	99		
Respiratory exchange ratio	0.93	1.13	RER > 1.05 indicates adequate exercise challenge	
Perceived exertion	--	17	Scale of 6 - 20 (13 - somewhat hard, 15 - hard, 17 - very hard)	
Ve/VCO2 slope	26		< 30 normal > 34 is an adverse prognostic marker in the heart failure population	
Ventilatory threshold (%)	42		Anaerobic Threshold - generally > 40% of VO_{2max} is normal	
Heart rate recovery at 1 minute (bpm)	41		< 12 beat drop at 1 minute is abnormal (general, classically-referred population) < 6 beat drop at 1 minute is abnormal (heart failure)	
External work equivalent	450Watts			
Breathing reserve			< 30% suggests possible pulmonary limitation to exercise	
ECG findings	Rhythm: Sinus Arrhythmias? None A 1.5 mm upsloping ST depression was seen in one region			
Notes	Some artifact noted during exercise. 1.5mm upsloping ST depression noted in leads V4-V6, resolved immediately in recovery Estimated cardiac output available separately			

Musculature not to scale

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Lab tests panel

WBC	4.9		Total bili	0.5
Hb	15.7		AST	25
Platelets	147		ALT	33
Na	143		ALP	93
K	4.0		Alb	4.2
BUN	20			
Cr	1.2		Cholesterol	218
eGFR			LDL	156
Ca	9.4		HDL	48
Fasting glucose	93		TG	68
			hsCRP	<0.2
			Lp(a)	114

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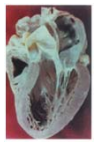
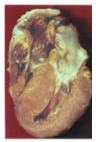
Parsing 6,000,000,000 data points

When one base pair change can turn this



into this



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The Teams

Assembly / Error

Rare and Mendelian variants

Common variants

PGx variants

Ethics

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Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Lancet 2010; 375: 1525–35

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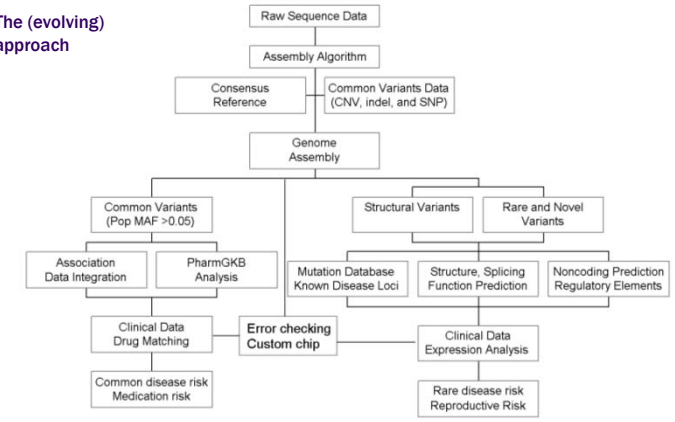
The (evolving) approach



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Rare, novel and Mendelian variants

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Rare/novel algorithm

- What does it mean for a variant to be associated with disease?
  - Cosegregation in a large kindred?
  - Early stop in key gene
    - in one proband? in several individuals?
  - Splice site mutation?
  - Novel mutation?
  - Not seen in ?how many ?controls
    - What's a control?

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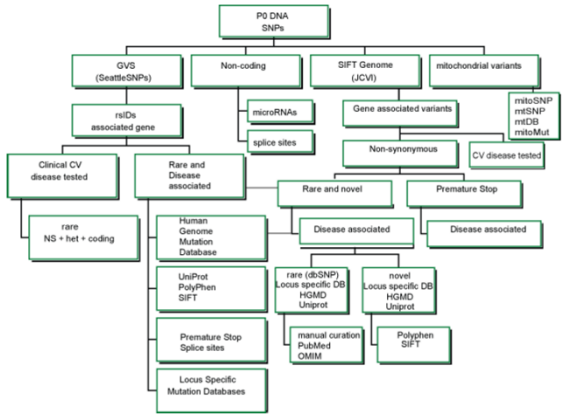

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Rare variant databases

- Human Genome Mutation database
  - Public/professional
- Human Variome project
- Human genome variation database
- Private databases

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ABCA4	ATP-binding cassette transporter retina	Retina International
ABCC6	Multidrug resistance-associated protein 6	Retina International
ABCC8	Sulfonylurea receptor	Hôpital Necker-Enfants Malades (Paris), France
ABCD1	X-linked adrenoleukodystrophy	Academic Medical Center, Amsterdam, Holland and Kennedy Krieger Institute, Baltimore MD, USA
ABO	Blood group antigen mutation database	Albert Einstein College of Medicine, New York, USA
ACHE	Blood group antigen mutation database	Albert Einstein College of Medicine, New York, USA
ACTC	FHC mutation database	Australian National Genomic Information Service
ACTC	Sarcomere gene mutations	Harvard University, USA
ACVRL1	Hereditary hemorrhagic telangiectasia mutation database	Heriot-Watt University, Edinburgh, UK
ADA	Adenosine deaminase deficiency	University of Tampere, Finland
ADRB3	Beta-3 adrenergic receptor	Tel-Aviv University, Israel
ADSL	ADSL mutation database	University of Louvain Medical School, Belgium
AIPL1	Aryl hydrocarbon receptor interacting protein-like 1	Retina International
ALB	Albumin database	Mary Imogene Bassett Hospital Research Institute, New York, USA
ALDH1B1	Aldehyde dehydrogenase	University of Colorado Health Sciences Centre, USA
ALDH2	Aldehyde dehydrogenase	University of Colorado Health Sciences Centre, USA
ALDH3A1, ALDH3A2	Aldehyde dehydrogenase	University of Colorado Health Sciences Centre, USA
ALDH4	Aldehyde dehydrogenase	University of Colorado Health Sciences Centre, USA
ALDH9	Aldehyde dehydrogenase	University of Colorado Health Sciences Centre, USA
ALDOB	Hereditary fructose intolerance	Boston University, USA
ALG6	Congenital disorders of glycosylation	Leuven University, Belgium
ALPL	ALPL mutation database	University of Versailles-Saint Quentin en Yvelines, France
AMELX	Amelogenesis imperfecta	University of North Carolina, USA
AP3B1	Albinism database	University of Minnesota, USA
APC	Adenomatous polyposis coli note - currently unavailable	Mayo Clinic, USA
APC	Adenomatous polyposis coli	Institut Curie (Paris), France
APC	Adenomatous polyposis coli	Tel-Aviv University, Israel
APP	Alzheimer disease	Antwerp University, Belgium
AQP1	Blood group antigen mutation database	Albert Einstein College of Medicine, New York, USA
AQP2	Diabetes insipidus	McGill University (Quebec), Canada
AR	Androgen receptor	McGill University (Quebec), Canada
AT3	Antithrombin mutation database	Imperial College School of Medicine, London, UK
ATM	Ataxia-telangiectasia	Virginia Mason Research Center (Seattle), USA
ATP7B	Wilson disease	University of Alberta, Canada
ATP7B	Wilson disease	Tel-Aviv University, Israel
AVP	Diabetes insipidus	McGill University (Quebec), Canada
AVPR2	Diabetes insipidus	McGill University (Quebec), Canada

Private mutation databases

http://www.hgmd.cf.ac.uk/docs/oth_mut.html
Accessed 3/11/2010

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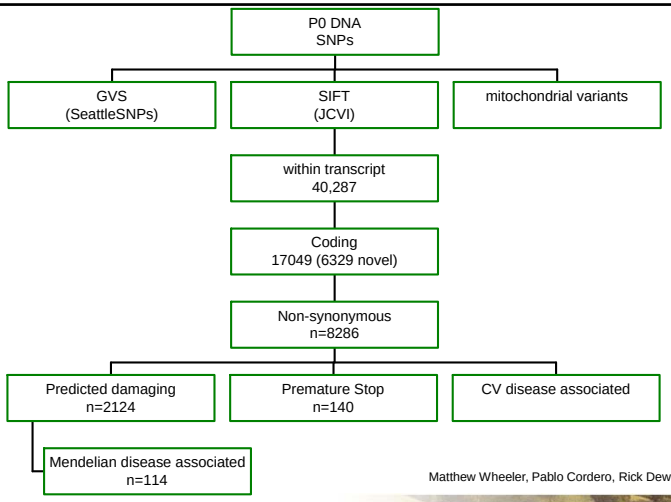

Matthew Wheeler, Pablo Cordero, Rick Dewey

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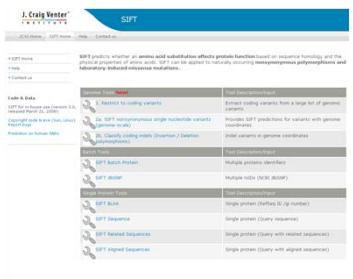
Algorithms for entirely novel variants



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Polygenic disease – what we have now

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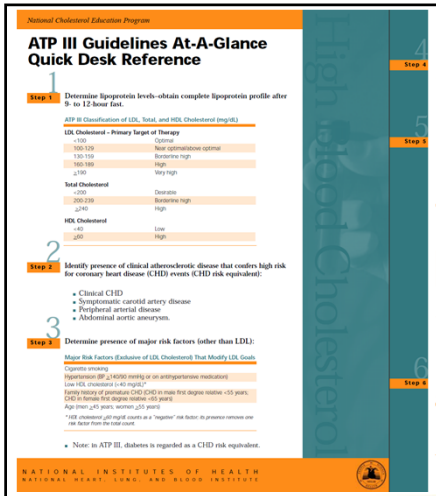

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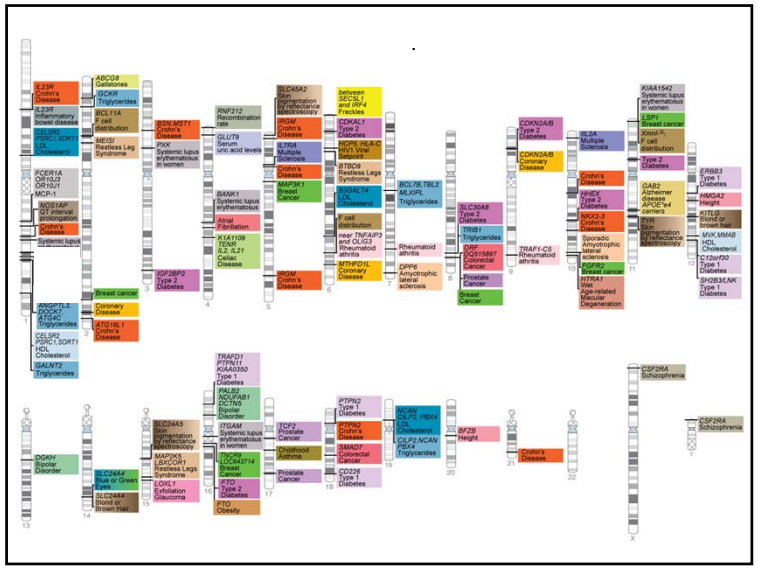
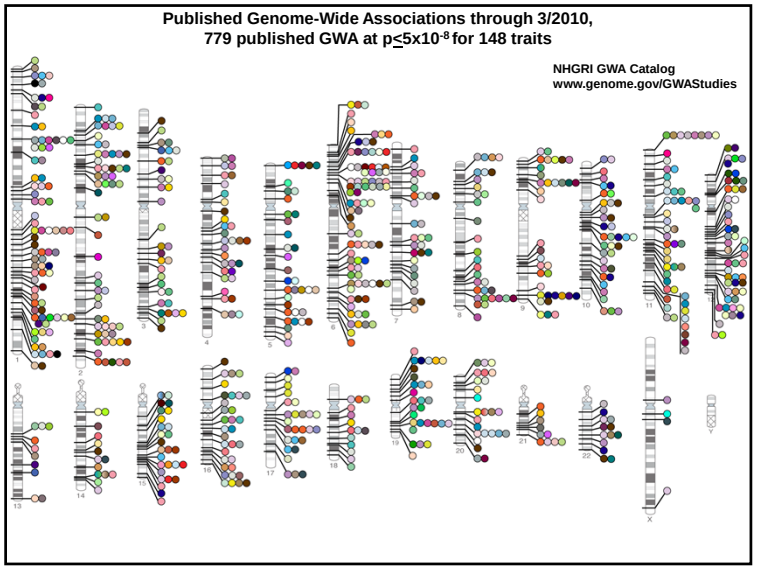
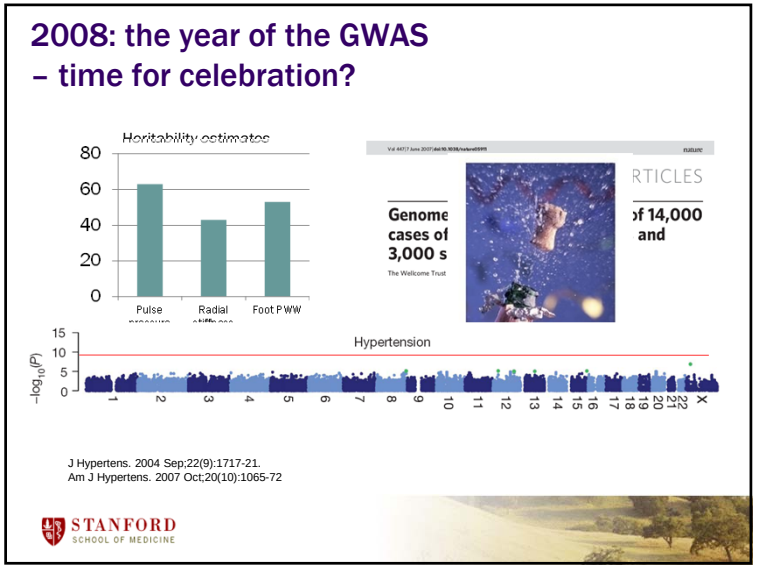



Published Genome-Wide Associations through 3/2010,
779 published GWA at p≤5x10-8 for 148 traits
NHGRI GWA Catalog
www.genome.gov/GWAStudies


Acute lymphoblastic leukemia
Adhesion molecules
Adiponectin levels
Age-related macular degeneration
AIDS progression
Alcohol dependence
Alzheimer disease
Amyotrophic lateral sclerosis
Angiotensin-converting enzyme activity
Ankylosing spondylitis
Arterial stiffness
Asthma
Atherosclerosis in HIV
Atrial fibrillation
Attention deficit hyperactivity disorder
Autism
Basal cell cancer
Bipolar disorder
Bilirubin
Bladder cancer
Blond or brown hair
Blood pressure
Blue or green eyes
BMI, waist circumference
Bone density
Breast cancer
C-reactive protein
Cardiac structure/function
Carnitine levels
Carotenoid/tocopherol levels
Celiac disease
Chronic lymphocytic leukemia
Cleft lip/palate
Cognitive function
Colorectal cancer
Coronary disease
Creutzfeldt-Jakob disease
Crohn's disease
Cutaneous nevi
Dermatitis
Drug-induced liver injury
Eosinophil count
Eosinophilic esophagitis
Erythrocyte parameters
Esophageal cancer
Essential tremor
Exfoliation glaucoma
F cell distribution
Fibrinogen levels
Folate pathway vitamins
Freckles and burning
Gallstones
Glioma
Glycemic traits
Hair color
Hair morphology
HDL cholesterol
Heart rate
Height
Hemostasis parameters
Hepatitis
Hirschsprung's disease
HIV-1 control
Homocysteine levels
Idiopathic pulmonary fibrosis
IgE levels
Inflammatory bowel disease
Intracranial aneurysm
Iris color
Iron status markers
Ischemic stroke
Juvenile idiopathic arthritis
Kidney stones
LDL cholesterol
Leprosy
Leptin receptor levels
Liver enzymes
LP (a) levels
Lung cancer
Major mood disorders
Malaria
Male pattern baldness
Matrix metalloproteinase levels
MCP-1
Melanoma
Menarche & menopause
Multiple sclerosis
Myeloproliferative neoplasms
Narcolepsy
Nasopharyngeal cancer
Neuroblastoma
Nicotine dependence
Obesity
Open personality
Osteoarthritis
Osteoporosis
Otosclerosis
Other metabolic traits
Ovarian cancer
Pain
Pancreatic cancer
Panic disorder
Parkinson's disease
Periodontitis
Peripheral arterial disease
Phosphatidylcholine levels
Platelet count
Primary biliary cirrhosis
PR interval
Prostate cancer
Protein levels
Psoriasis
Pulmonary funct. COPD
QRS interval
QT interval
Quantitative traits
Recombination rate
Red vs.non-red hair
Renal function
Response to antipsychotic therapy
Response to hepatitis C treatment
Response to statin therapy
Restless legs syndrome
Rheumatoid arthritis
Schizophrenia
Serum metabolites
Skin pigmentation
Speech perception
Sphingolipid levels
Statin-induced myopathy
Stroke
Systemic lupus erythematosus
Telomere length
Testicular germ cell tumor
Thyroid cancer
Tooth development
Total cholesterol
Triglycerides
Type 1 diabetes
Type 2 diabetes
Ulcerative colitis
Urate
Venous thromboembolism
Vitamin B12 levels
Warfarin dose
Weight
White cell count
YKL-40 levels


2008: the year of the GWAS
– time for celebration?
Heritability estimates
80
60
40
20
0
Pulse
Radial
Foot PWW
RTICLES
Genome
cases of
3,000 s
The Wellcome Trust
of 14,000
and
Hypertension
15
10
5
0
−log10(p)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
J Hypertens. 2004 Sep;22(9):1717-21.
Am J Hypertens. 2007 Oct;20(10):1065-72
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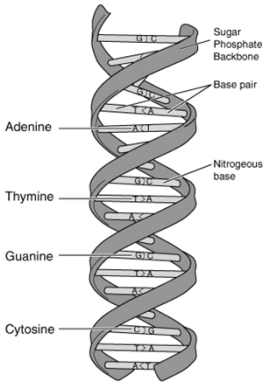
Missing heritability

- Rare variants
- Structural variants
- Epigenetic phenomena
- Over-zealous bounding of FWER
- G-G interaction
- G-E interaction
- G-G-E interaction



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Can we apply this to individual genomes?

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One approach


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events

Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Dragi Anevski, Ph.D., Candace Guiducci, B.S., Noël P. Burtt, B.S., Charlotta Roos, M.Sc., Joel N. Hirschhorn, M.D., Ph.D., Göran Berglund, M.D., Ph.D., Bo Hedblad, M.D., Ph.D., Leif Groop, M.D., Ph.D., David M. Altshuler, M.D., Ph.D., Christopher Newton-Cheh, M.D., M.P.H., and Marju Orho-Melander, Ph.D.

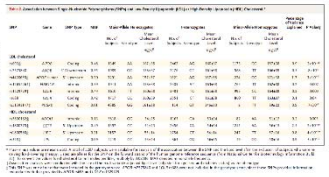
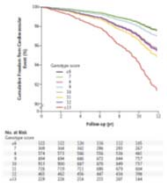


Table 3. Lipid Levels and Crude Incidence Rates of Cardiovascular Disease, According to Genotype Score.*

Variable	Genotype Score†								P for Trend
	≤6 (N=122)	7 (N=309)	8 (N=574)	9 (N=894)	10 (N=913)	11 (N=726)	12 (N=465)	≥13 (N=229)	
LDL cholesterol (mg/dl)	152±41	152±37	158±38	159±38	163±37	165±38	168±41	171±36	2×10^{-16}
HDL cholesterol (mg/dl)	60±16	57±14	56±14	55±14	53±14	53±14	51±13	51±13	3×10^{-14}
Crude incidence rate per 1000 person-years	3.1	2.7	5.1	3.9	5.3	6.8	5.7	11.0	

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.
† The genotype score represents the number of unfavorable alleles (the allele associated with higher LDL cholesterol or lower HDL cholesterol) at each of nine SNPs. These nine SNPs were *APOB* rs693, *APOE* cluster rs4420638, *HMGCR* rs12654264, *LDLR* rs1529729, *PCSK9* rs11591147, *ABCA1* rs3890182, *CETP* rs1800775, *LIPC* rs1800588, and *LPL* rs328.



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Challenges in applying results of GWAS to individual genomes

- Theoretical
  - Not enough variance explained
- Practical
  - Most NCBI databases are catalogs
  - Although sharing and making data publicly available (despite ethical concerns) remains routine, journals have not traditionally insisted on sufficient data for genome interpretation (standard is 'reproduce the expt' but even that often not met)
  - Even the GWAS catalogs do not contain sufficient data
    - Genotype frequencies
    - Strand direction variable, rarely reported
    - Chromosomal position changes with each genome build

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Existing SNP databases are limited in resource and content

- NHGRI GWAS Catalog
  - 2,387 SNPs → 321 diseases, curated from 509 PubMed
  - Odds Ratio, but no genotypes
- NHLBI GWAS Catalog
  - 52,546 SNPs → 87 diseases, curated from 119 PubMed
  - p_value, no OR

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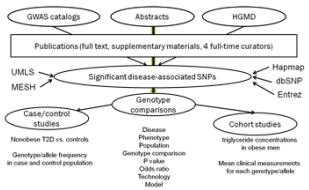
Stanford genetic variation database



Field name	Description
Broad Phenotype	The general disease or phenotypic condition under study
Narrow Phenotype	Detailed description of the studied phenotype
Is_it_disease	Diseases or phenotypic trait?
MESH heading	MESH heading of the studied disease
UMLS CUI	Manually curated UMLS CUI for the disease
dbSNP ID	Identifier used in dbSNP build 130, or rsID
Significance	Whether the association was reported as significant in the literature
Study ID	An internal identifier to distinguish multiple studies in one literature
P-value	P-value of the association
Model	The genetic model used to calculate the p-value, such as additive, multiplicative, recessive, or dominant
Odds Ratio	The odds ratio, relative risk, or hazards ratio of disease association between two comparing genotypes or alleles
95% CI	95% confidence interval of the odds ratio
Comparison	Two genotypes or alleles used to calculate the odds ratio
Total sample size	Sum of patients in the case and control groups or the cohort size
Cases/Affected	Description of the patients in the case group
Controls/Unaffected	Description of the patients in the control group
Cohort	Description of the patients in the cohort
Gender	The gender of the studied patients
Population	The ethic group of the studied patients
Major/minor alleles	The major/minor alleles of the SNP
Strand direction	The strand direction was determined by comparing the major/minor alleles in the literature with the major/minor alleles in a similar population in the Hapmap project
Risk allele	The allele susceptible to diseases
Single SNP/haplotype	Was the association studied for single SNP or haplotype?
Interaction	Was the association studied for gene-environmental interaction?
GWAS	GWAS or candidate gene/SNP study
PubMed	PubMed ID of the publication
Method	Genotyping technology, such as Taqman or Affymetrix 6.0
Comment	Comments from curators
Status	Review status of the entry

Rong Chen,
Atul Butte

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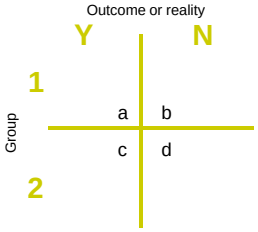
Ways to apply this for genomic medicine



b= type 1 error
c= type 2 error

Parameter	expression
Sensitivity	a/a+c
Specificity	d/d+b
Prevalence	a+b+c+d
NPV	d/d+c
PPV	a/a+b
OR	(a/b) / (c/d)
OR	ad/cb
RR	(a/a+b) / (c/c+d)
LR+	sen/1-spec
LR-	1-sen/spec

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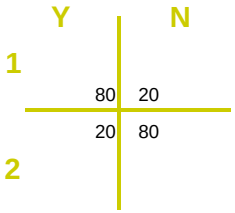
Odds are....the effect will appear exaggerated

- Two groups (n=100), two conditions
- First group Y=80, N=20
- Second group Y=20, N=80
- First group is 4x more likely to be Y
- However, OR=(80/20)/(20/80) = 16
- This can be even more extreme
  - eg (90/10)/(10/90), OR=81!
- Remember that for GWAS, most OR are in the range 1.3-1.6
- 60/40 vs 50/50 = 1.5



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The Likelihood is . . . you will at least account for group-wise frequency characteristics

- The LR is easily overlaid on the pre-probability to provide a post-test probability
- This helps with the "relative risk" problem

Parameter	Expression
Pre test probability	Prevalence
Pre test odds	Prev/1-prev
Post test odds	Pre-test odds x LR
Post test probability	Post test odds / post test odds +1

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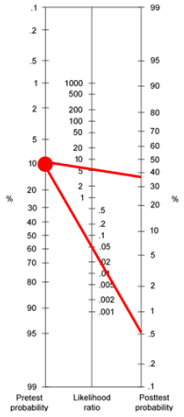

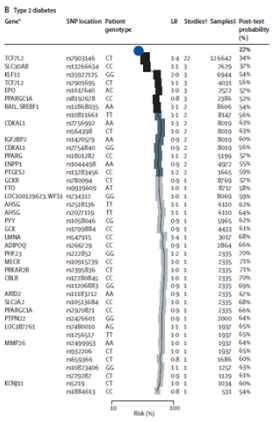

Fagan TJ. Nomogram for Bayes theorem. *N Engl J Med*. 1975 31;293(5): 257.

Alex Morgan, Atul Butte

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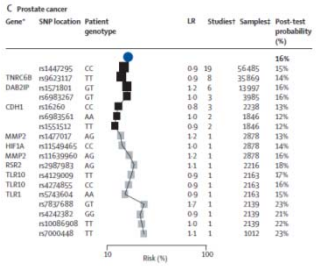
Riskogram methods and figure

- Pre test prob from various sources
  - Prevalence usually (matched to age, sex, ethnicity if possible)
  - Lifetime risk occasionally
- Mean LR when multiple studies for same SNP
  - Weighted mean (square root of sample size)
- Only one SNP per haplotype block (largest LR)
- Pre test odds multiplied by LRs cumulatively
  - Presented in decreasing order of studies, then sample size



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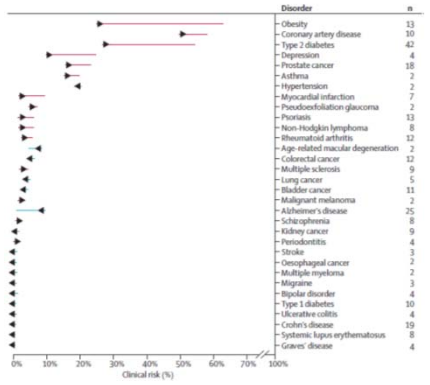
Report card



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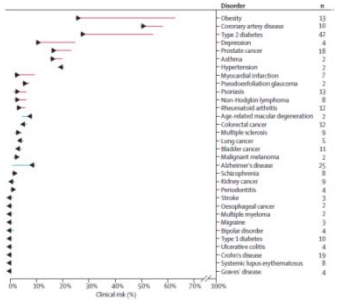
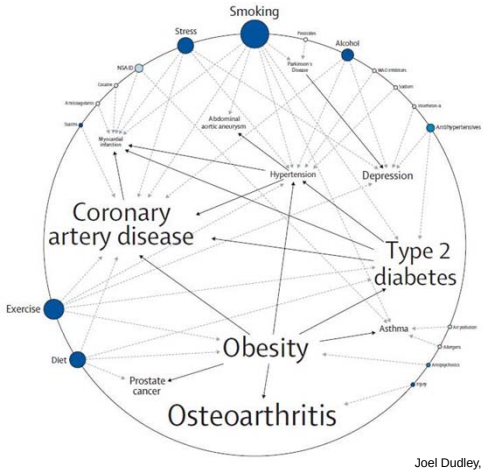
Challenges

- Calls were made vs human reference sequence
  - Risk alleles in human reference sequence
- Winner's curse
  - Literature bias towards positive results
- Negative studies need to be included in algorithm
- Data for LR only available for 40% papers



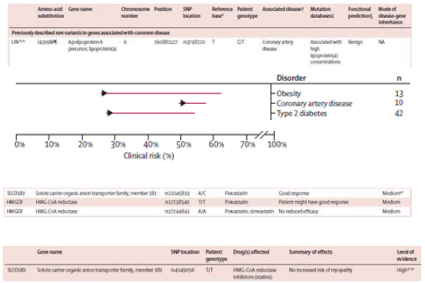
Gene environment interaction



Joel Dudley, Atul Butte

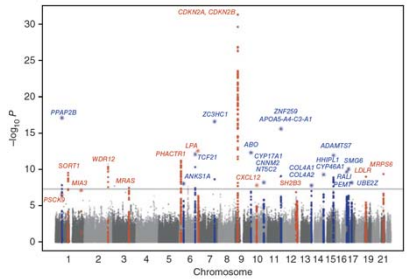
What of "patient" zero?

- SQ feedback
  - PGx information welcome
  - Approach to personal and family screening
- Medical advice
  - Personal and family screening
  - CAD risk
    - ATP3+LPA+LR+PGx +clinical judgement
    - Rx statin



nature genetics

Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease



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FAMILY ZERO

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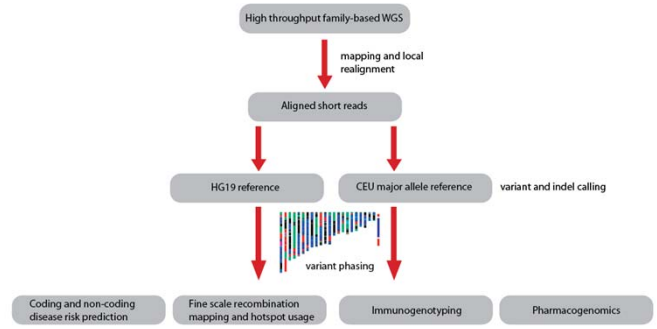

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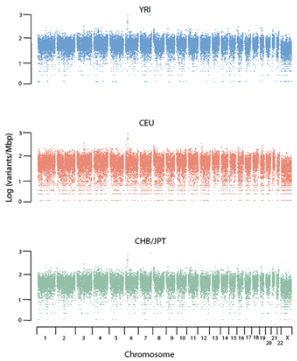

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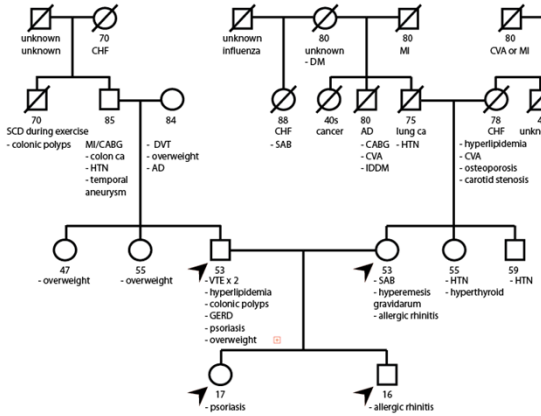

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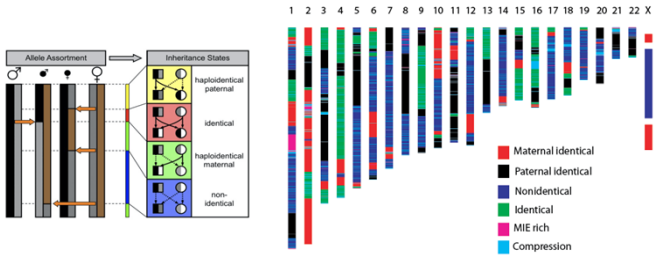
Inheritance state analysis



Rick Dewey

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	All variants		All rare/novel		Rare/novel and OMIM-disease associated gene	
Variant type	HG19 reference (n = 4302405)	CEU reference (n = 3733299)	HG19 reference (n = 351555)	CEU reference (n = 354074)	HG19 reference	CEU reference
Coding-missense	9468	7982	1276	1276	203	200
Coding-nonsense	52	50	13	13	1	1
Coding-synonyn	11663	9928	1061	1059	186	186
Intronic	1303341	1128283	116276	115397	19544	19766
Splice-5'	156	147	16	16	0	0
Splice-3'	98	96	9	9	1	1
UTR-5'	40142	37794	3637	3619	510	516
UTR-3'	61826	59396	5989	5953	848	857
miRNA target	0	0	0	0	0	0
Pri-miRNA	2	2	1	1	0	0
Mature miRNA	0	0	0	0	0	0
Coding indels	1519	1476	432	412	73	71
Coding frameshift indels	440	418	273	253	29	27

Abbreviations: CEU reference, variant calls against CEU major allele reference; HG19 reference, variant calls against NCBI reference sequence 37.1; miRNA, micro RNA; Pri-miRNA, primary microRNA transcript; OMIM, Online Mendelian Inheritance in Man database; UTR, un-translated region.

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SNP Location	Drug(s)	Drug(s) More Likely to Work	Drug(s) Less Likely to Work	Drug(s) More Likely to Cause Side Effect	Drug(s) Less Likely to Cause Side Effect	Drug Dose(s) Above Average	Drug Dose(s) Below Average	Drug Dose(s) Average	No PGx Action/ Phenotype Unknown	Confidence Level
rs9934438	warfarin	·	·	·	·	·	·	■○■○	·	High
rs1954787	citalopram	■○○	■	·	·	·	·	·	·	High
rs776746	cyclosporine	·	·	·	·	·	■○■○	·	·	High
rs1800460	thiopurines	·	·	·	·	·	·	·	·	High
rs2108622	warfarin	·	·	·	·	·	■○■○	·	·	Medium
rs4680	morphine	·	·	·	·	■○■○	·	·	·	Medium
rs5443	statins	■○	■○	·	·	·	·	·	·	Medium
rs4253778	beta blocking agents	○	■○■	·	·	·	·	·	·	Medium
rs622342	metformin	○■	■○	·	·	·	·	·	·	Medium
rs7569963	citalopram	·	·	■	■	·	·	·	○○	Medium
rs8012552	ACE inhibitors	·	·	·	■○■○	·	·	·	·	Low
rs11209716	ACE inhibitors	·	·	·	■■○	·	·	·	○	Low
Key: Father, Mother, Brother, Sister =	■○■○									

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Chromosome	Gene	rsid	Affected family members	Disease	Inheritance	Onset-earliest	Onset-median	Severity	Actionability	Lifetime risk	Variant pathogenicity
12	*VWF*	rs61750615		Von Willebrand disease	Incomplete dominant	1	1	5	5	variable	7
10	*HABP2*	rs7080536		Carotid stenosis, thrombophilia	AD	4	4	1	5	variable	7
19	*SLC7A9*	rs79389353		Cysteinuria – kidney stones	AR	1	1	3	5	7	7
1	*F5*	rs6025		Thrombophilia	Incomplete dominant	4	4	4	5	2	7
1	*MTHFR*	rs1801133		Hyperhomocystein-emia	AR	1	1	1	6	2	7

Key:
- Daughter heterozygous for maternal risk allele
- Daughter heterozygous for paternal risk allele
- Son heterozygous for maternal risk allele
- Son heterozygous for paternal risk allele
- Mother heterozygous
- Father heterozygous

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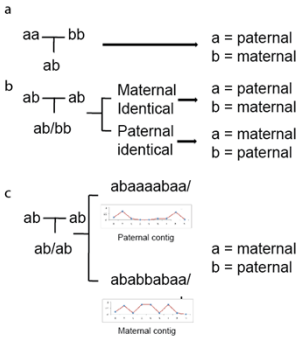
Phasing



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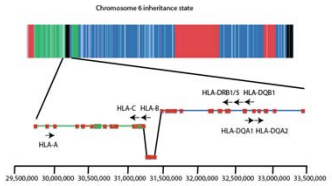

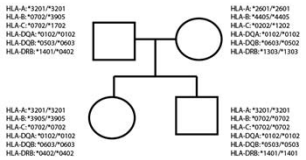

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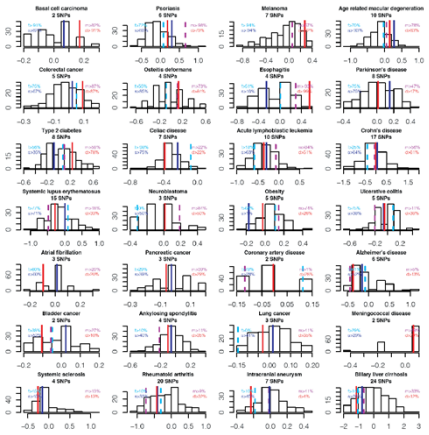

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Conclusion

- In the future, we will not be limited by the availability of genetic information
- For medicine to become "personalized" we will need to learn how to parse this data

Acknowledgements

Patient Zero

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