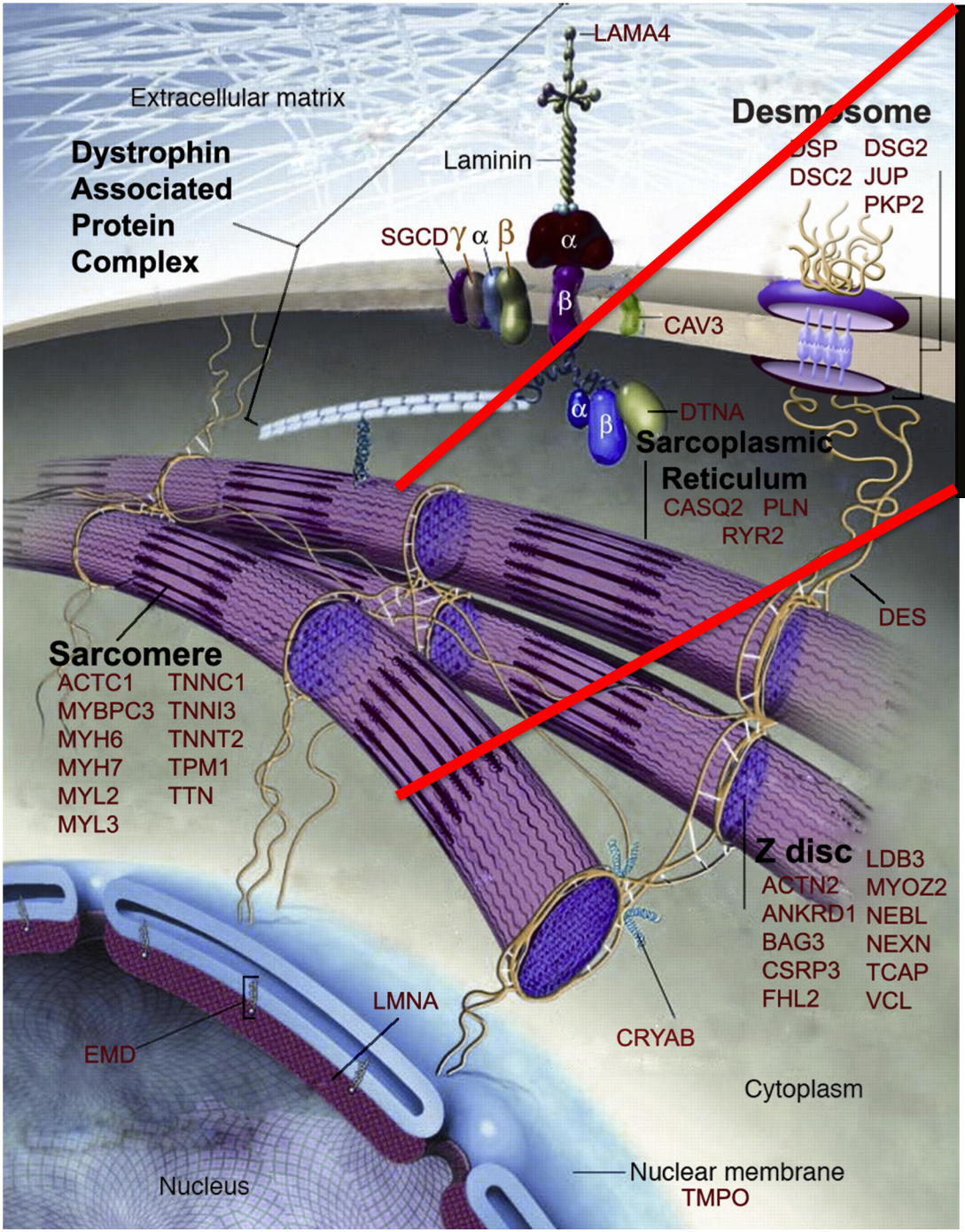
Genomic information is complex

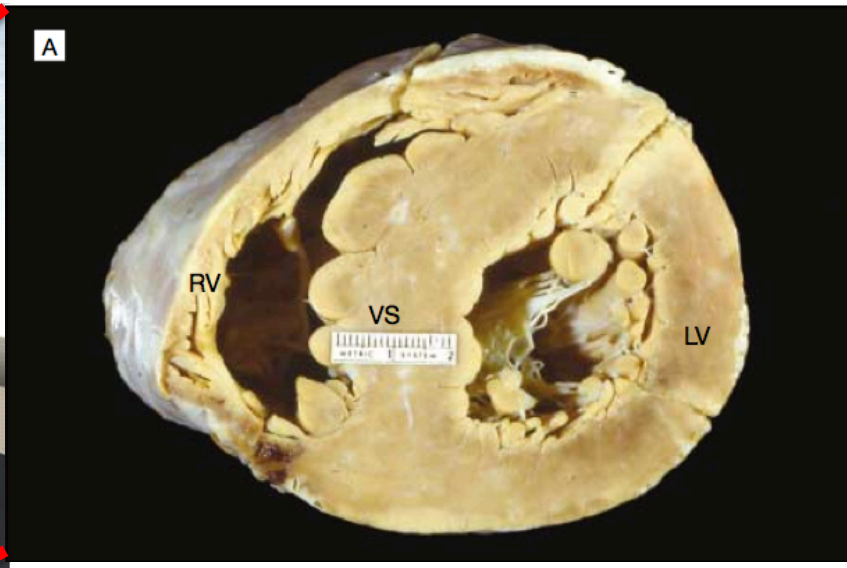
Isaac S. Kohane, MD, PhD

HARVARD MEDICAL SCHOOL
DEPARTMENT OF Biomedical Informatics

Key points

- **Under-appreciated durability and persistence of the fleeting present.**
- **Reminder that most essential first rule of clinical care is *Primum non nocere***
- ***Genetic reductionism is useful distraction from what really ails us.***
- **Most common diseases are mostly NOT genetic.**
- **Reminder: Family history is not result of HGP and is grossly underused.**





Hypertrophic Cardiomyopathy (HCM)

- Heart failure
- Arrhythmias
- Obstructed blood flow
- Infective endocarditis
- Sudden cardiac death

Prevalence 1:500

Autosomal Dominant

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Age	Ethnicity	Report Year	Originally Reported Status	Current Status	Indication for Test
46	Unavailable	2005	P	B	Clinical Diagnosis of HCM
75	Unavailable	2005	P	B	Family History and Clinical Symptoms of HCM
32	Black or African American	2005	P	B	Clinical Diagnosis of HCM
34	Black or African American	2005	U	B	Clinical Diagnosis and Family History of HCM
12	Black or African American	2006	U	B	Family History of HCM
40	Black or African American	2007			
45	Black or African American	2007			
16	Asian	2008			
59	Black or African American	2006			
15	Black or African American	2007			
16	Black or African American	2007			
22	Black or African American	2007			
48	Black or African American	2008	U	B	Clinical Diagnosis of HCM

Pro82Ser

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.

N ENGL J MED 375;7 NEJM.ORG AUGUST 18, 2016

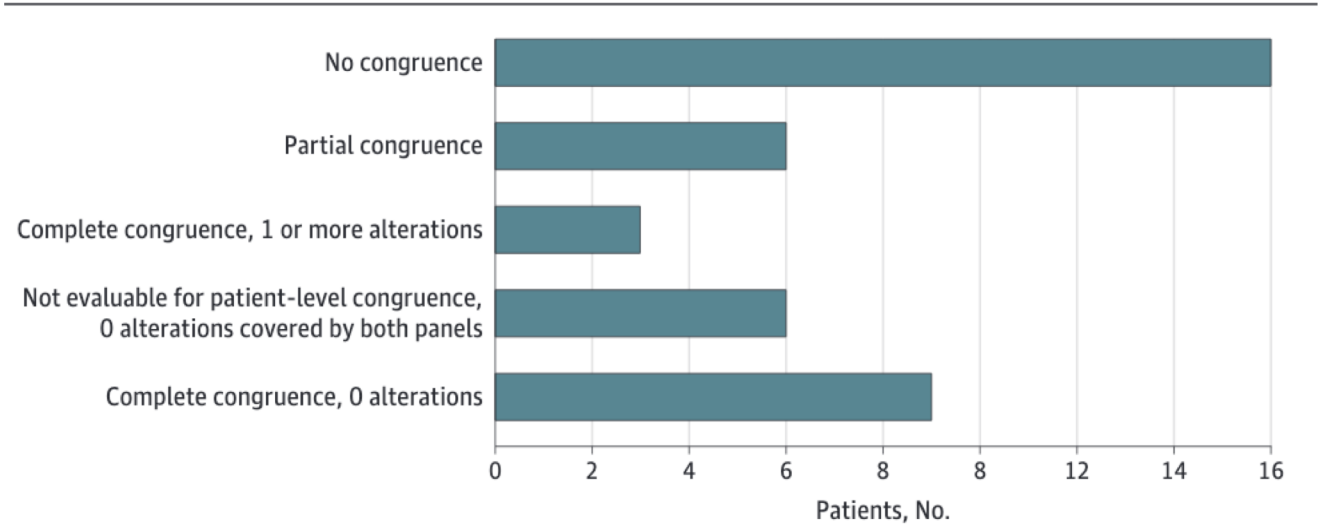
P = Pathogenic and Presumed Pathogenic
U = Pathogenicity Debated and Unknown Significance

Torga, Gonzalo, and Kenneth J. Pienta. 2018. “Patient-Paired Sample Congruence Between 2 Commercial Liquid Biopsy Tests.” *JAMA Oncology* 4 (6): 868–70.

40 patients

Guardant360 (Guardant Health, Inc) panel includes 73 genes with complete exon sequencing for 19 cancer genes,

PlasmaSELECT (Personal Genome Diagnostics, Inc) con- sists of a 64-gene panel



Family History is most important tool for diagnosis in medical genetics

RESULTS: **The family history is the most important tool for diagnosis and risk assessment in medical genetics, and promises to serve as a critical element in the use of predictive genetic testing in primary care. Traditional medical education about family history has often been unsophisticated and use of family history in adult primary care has been limited, compounded by multiple substantive barriers. Although there are numerous paper and computer-based aides for taking the family history, none currently meets all the needs of adult primary care.**

Rich, Eugene C., Wylie Burke, Caryl J. Heaton, Susanne Haga, Linda Pinsky, M. Priscilla Short, and Louise Acheson. 2004. "Reconsidering the Family History in Primary Care." *Journal of General Internal Medicine* 19 (3): 273–80. https://www.ncbi.nlm.nih.gov/pubmed/15009784.

NIH Conferences

National Institutes of Health State-of-the-Science Conference Statement: Family History and Improving Health

Alfred O. Berg, MD; Macaran A. Baird, MD, MS; Jeffrey R. Botkin, MD, MPH; Deborah A. Driscoll, MD; Paul A. Fishman, PhD; Peter D. Guarino, PhD, MPH; Robert A. Hiatt, MD, PhD; Gail P. Jarvik, MD, PhD; Sandra Millon-Underwood, PhD, RN; Thomas M. Morgan, MD; John J. Mulvihill, MD; Toni I. Pollin, PhD, MS; Selma R. Schimmel; Michael Edward Stefanek, PhD; William M. Vollmer, PhD; and Janet K. Williams, PhD, RN, PNP*

+ Author Affiliations

2009

National Institutes of Health (NIH) consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of 1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ); 2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session; 3) questions and statements from conference attendees during open discussion periods that are part of the public session; and 4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health or the U.S. government. The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

THE AMERICAN JOURNAL OF GASTROENTEROLOGY
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Published by Elsevier Inc.

Vol. 98, No. 6, 2003
ISSN 0002-9270/03/$30.00
doi:10.1016/S0002-9270(03)00256-9

Colorectal Cancer Screening and Familial Risk: A Survey of Internal Medicine Residents' Knowledge and Practice Patterns

Adam F. Barrison, M.D., Christopher Smith, M.D., Jaime Oviedo, M.D., Timothy Heeren, Ph.D., and Paul C. Schroy, III, M.D., M.P.H.

Department of Medicine, Section of Gastroenterology, Boston Medical Center; Department of Medicine, Beth Israel Deaconess Medical Center; and Department of Biostatistics, Boston University School of Public

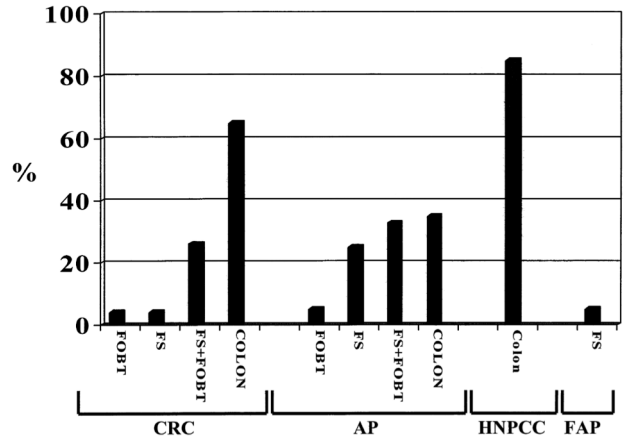


Figure 2. Proportion of residents selecting appropriate screening strategy for patients at familial risk of colorectal cancer based on American Cancer Society (5) and GI Consortium guidelines (3). CRC = colorectal cancer; AP = adenomatous polyps; FOBT = fecal occult blood testing; FS = flexible sigmoidoscopy; COLON = colonoscopy.

© American College of Medical Genetics and Genomics

ARTICLE | Genetics inMedicine

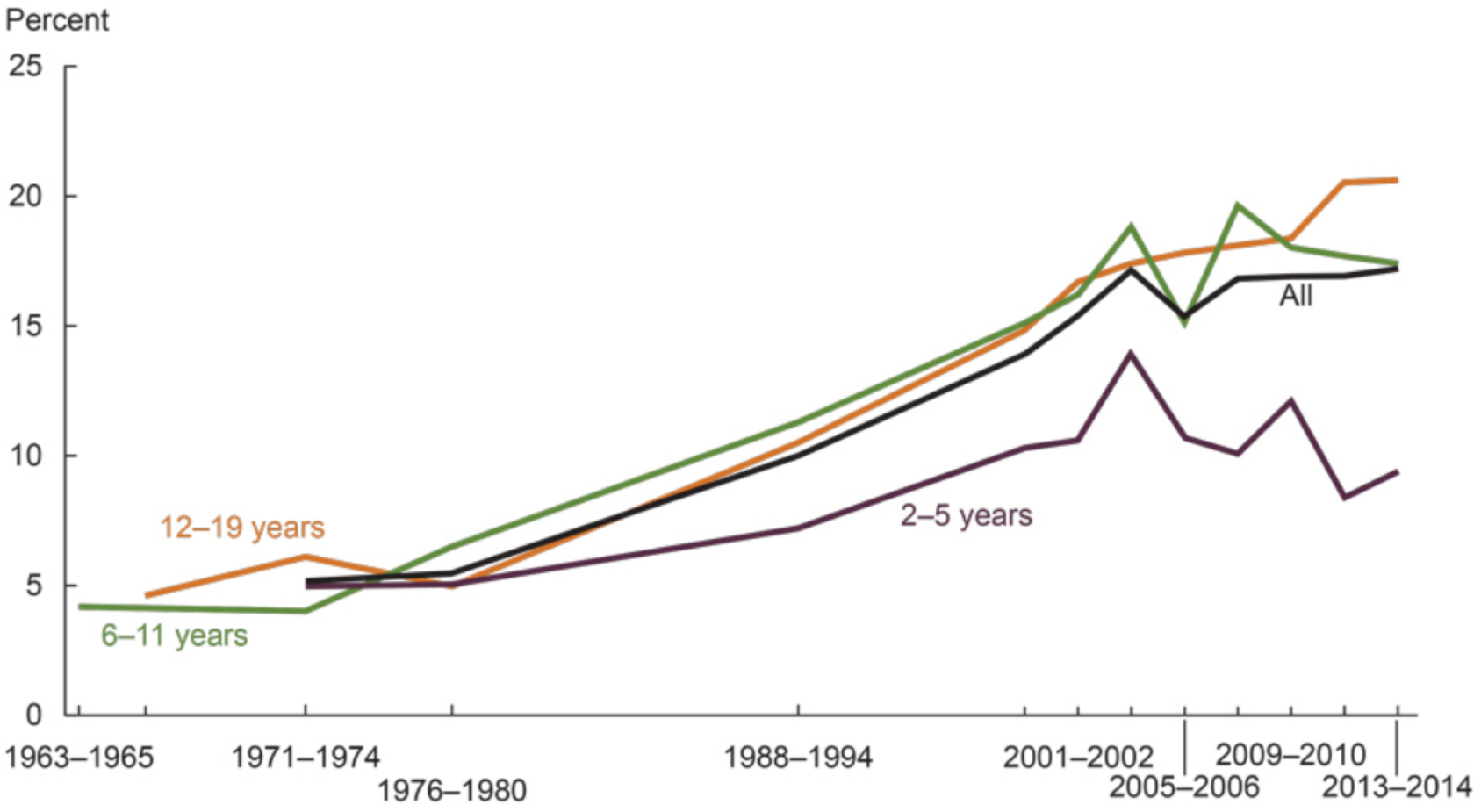
Implementation, adoption, and utility of family health history risk assessment in diverse care settings: evaluating implementation processes and impact with an implementation framework

R. Ryanne Wu, MD, MHS[1,2], Rachel A. Myers, PhD[1], Nina Sperber, PhD[1,3,4], Corrine I Voils, PhD[5,6], Joan Neuner, MD, MPH[7,8], Catherine A. McCarty, PhD, MPH[9], Irina V. Haller, PhD, MS[10], Melissa Harry, PhD, MSW[10], Kimberly G Fulda, DrPH[11], Deanna Cross, PhD[12], David Dimmock, MD[13], Teji Rakhra-Burris[1], Adam H. Buchanan, MS, MPH[14], Geoffrey S Ginsburg, MD, PhD[1] and Lori A Orlando, MD, MHS[1]

GENETICS in MEDICINE | Volume 21 | Number 2 | February 2019

HARVARD MEDICAL SCHOOL | DEPARTMENT OF Biomedical Informatics

Trends in obesity among children and adolescents aged 2–19 yea by age: United States, 1963–1965 through 2013–2014



NOTES: Obesity is defined as body mass index (BMI) greater than or equal to the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: NCHS, National Health Examination Surveys II (ages 6–11) and III (ages 12–17); and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014.

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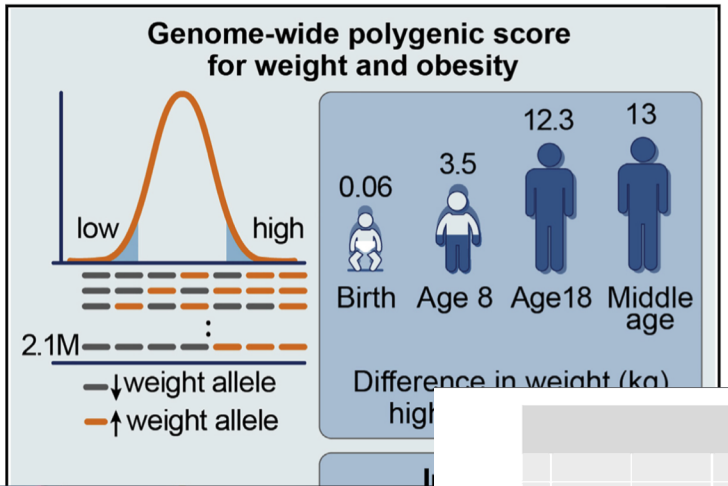
DEPARTMENT OF Biomedical Informatics

Cell

Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood

Graphical Abstract



Authors

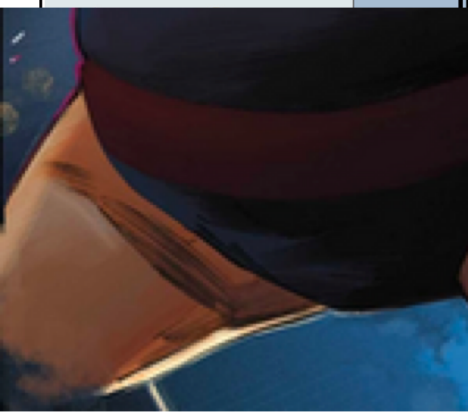
Amit V. Khera, Mark Chaffin, Kaitlin H. Wade, ..., Nicholas J. Timpson, Lee M. Kaplan, Sekar Kathiresan

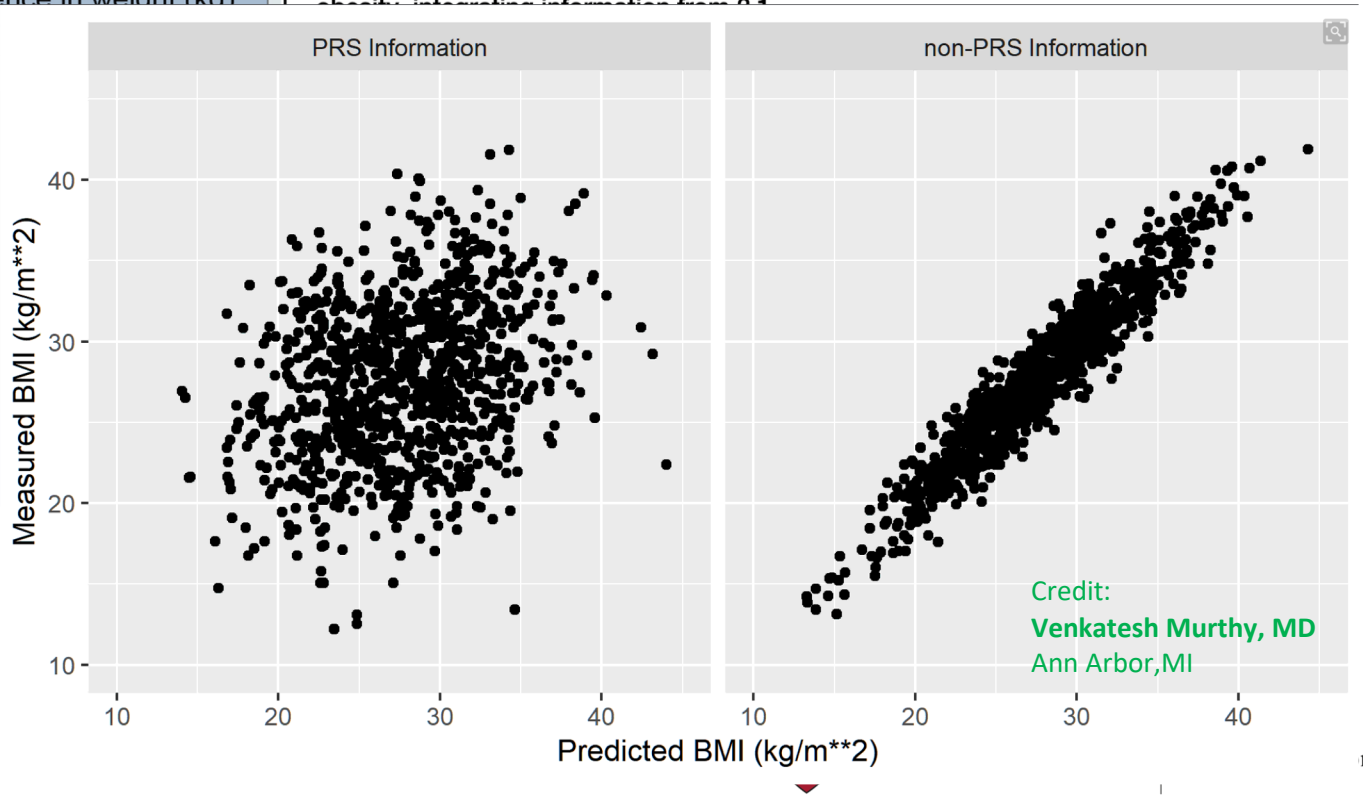
Correspondence

avkhera@mgh.harvard.edu (A.V.K.), skathiresan1@mgh.harvard.edu (S.K.)

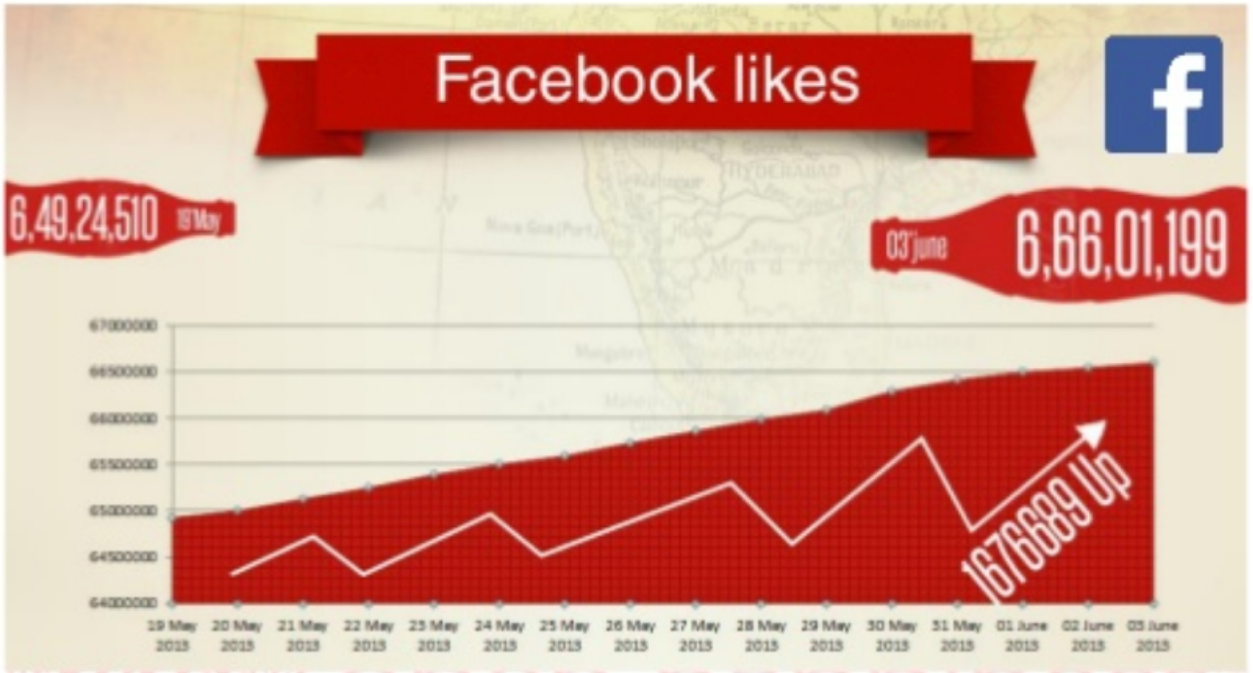
In Brief

A genome-wide polygenic score quantifies inherited susceptibility to

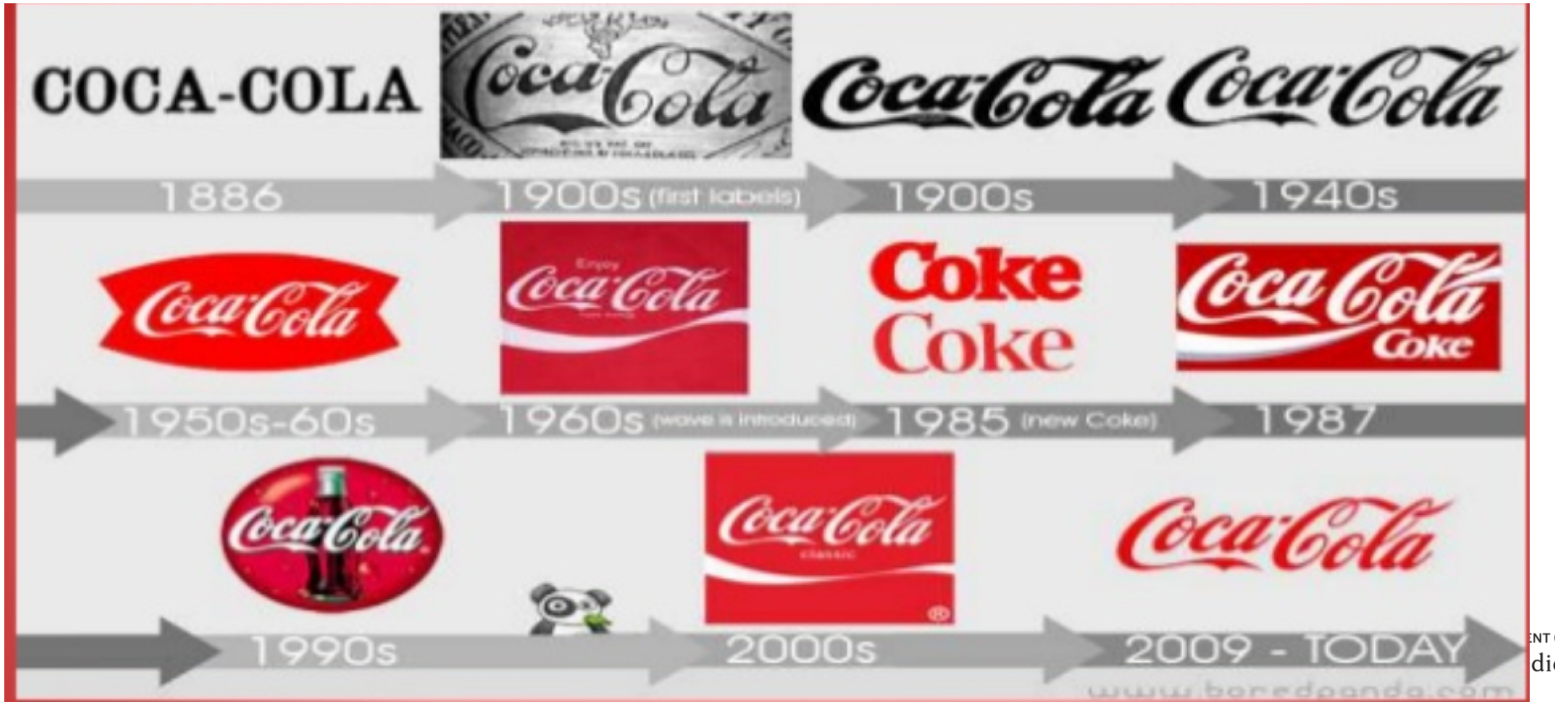




rmatics



(Social Samosa, 2013)

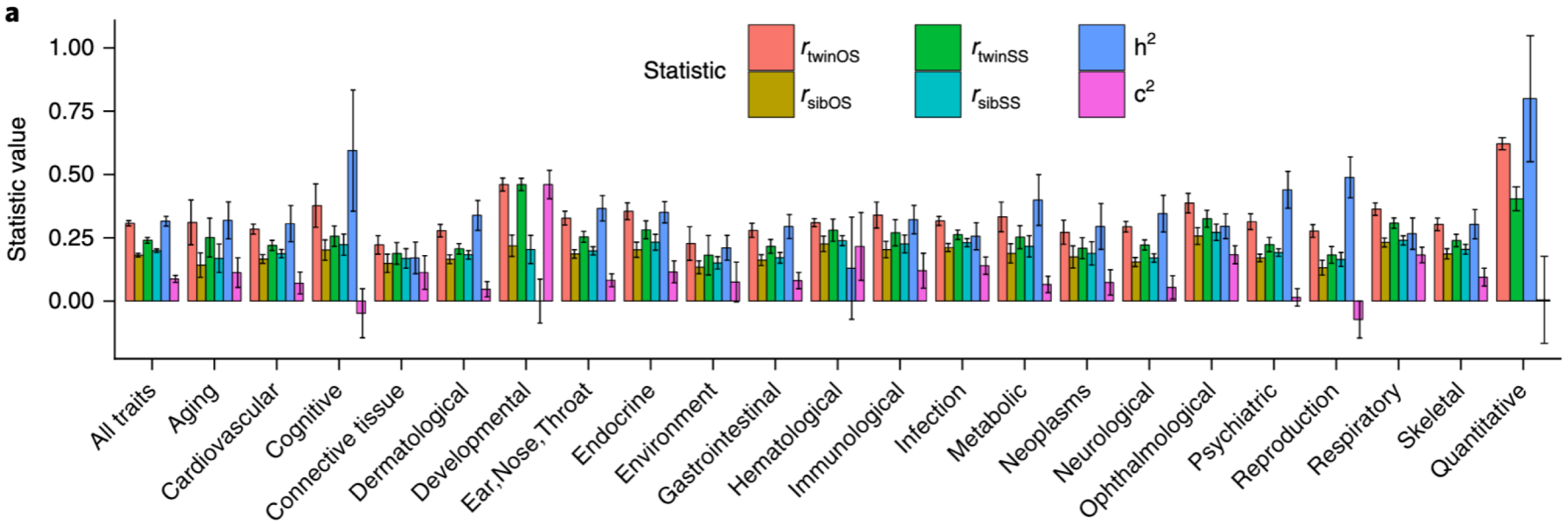


nature genetics

ANALYSIS

https://doi.org/10.1038/s41588-018-0313-7

Repurposing large health insurance claims data to estimate genetic and environmental contributions in 560 phenotypes



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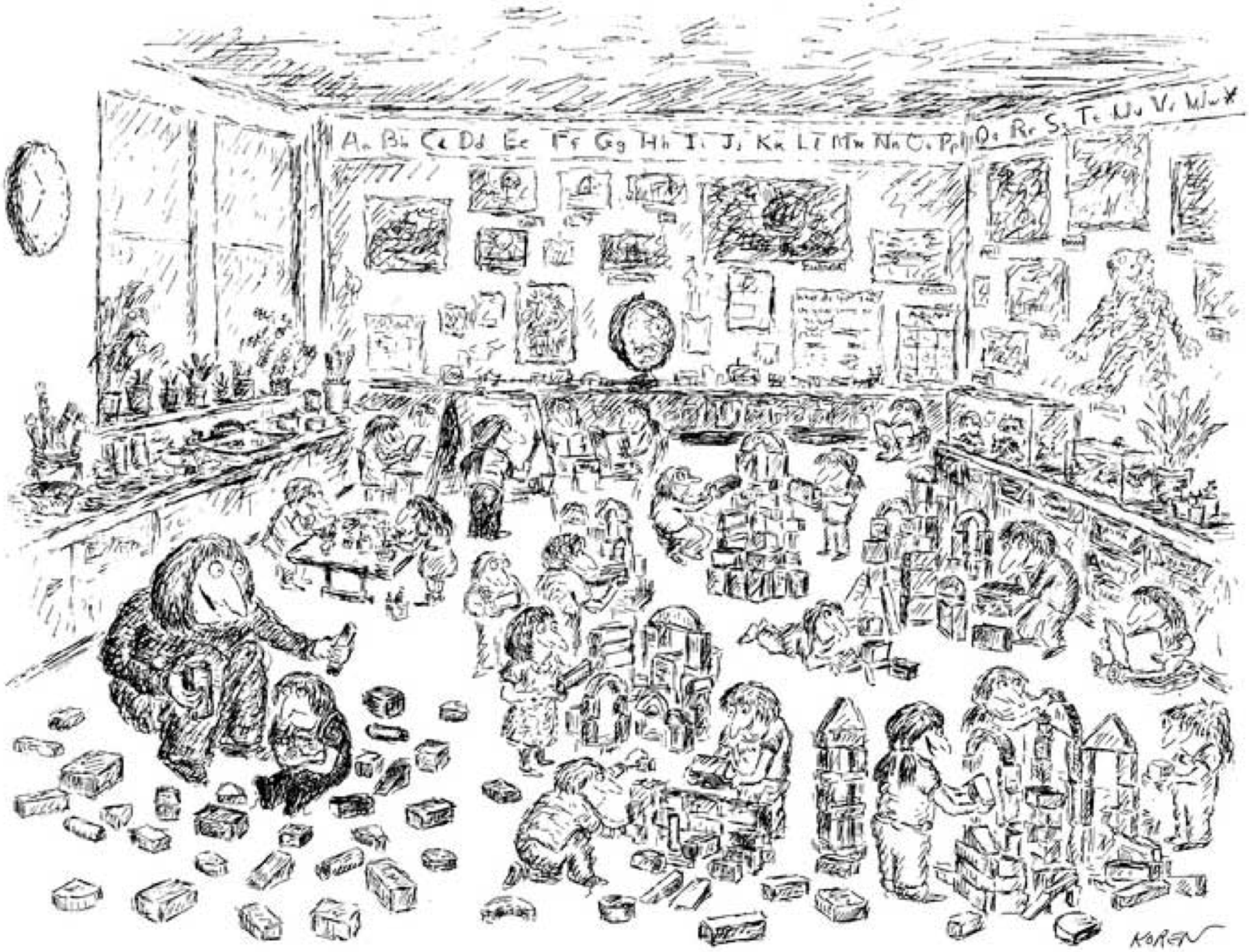
What to do?

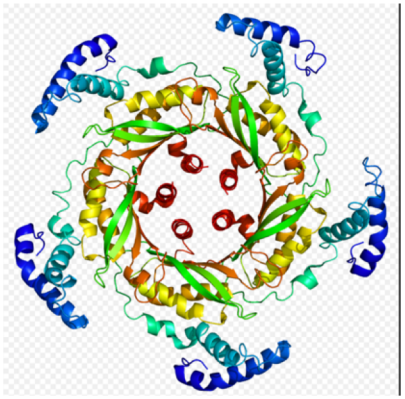
- Continue and scale up pan-ethnic germline sequencing linked to longitudinal health trajectories.
- Consumer Reports™ equivalent for genomics
- Scale-up environmental assessment.
- Multi-pronged Social-engineering for public health, cigarette style for modifiable risk.
- Fix medical education and automated work-flow around genetics and family history



"Timothy, success is nothing to fear."

CartoonStock.com

Worsening dystonia
(not walking, not speaking)



GTP cyclohydrolase I deficiency

Undiagnosed Disease Network

L-Dopa
Folinic Acid
5-hydroytryptophan

Walking, talking!

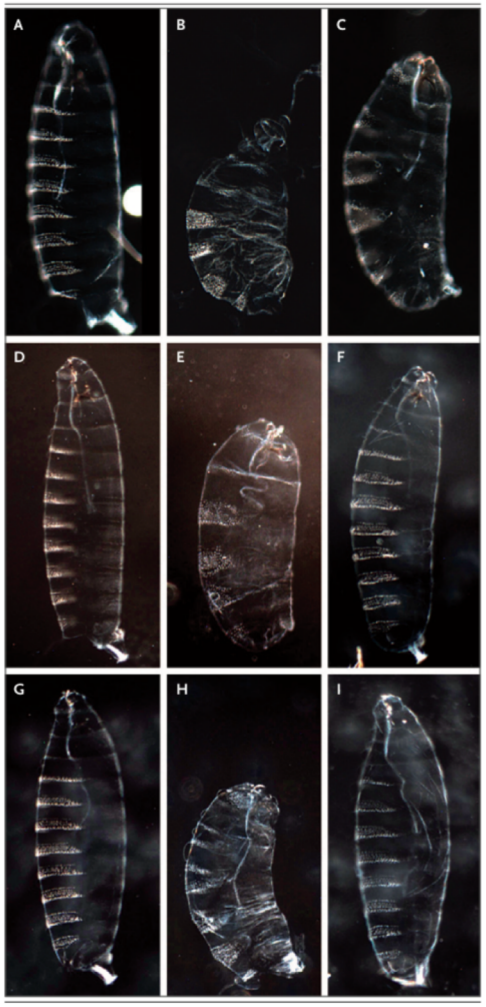
The NEW ENGLAND JOURNAL of MEDICINE

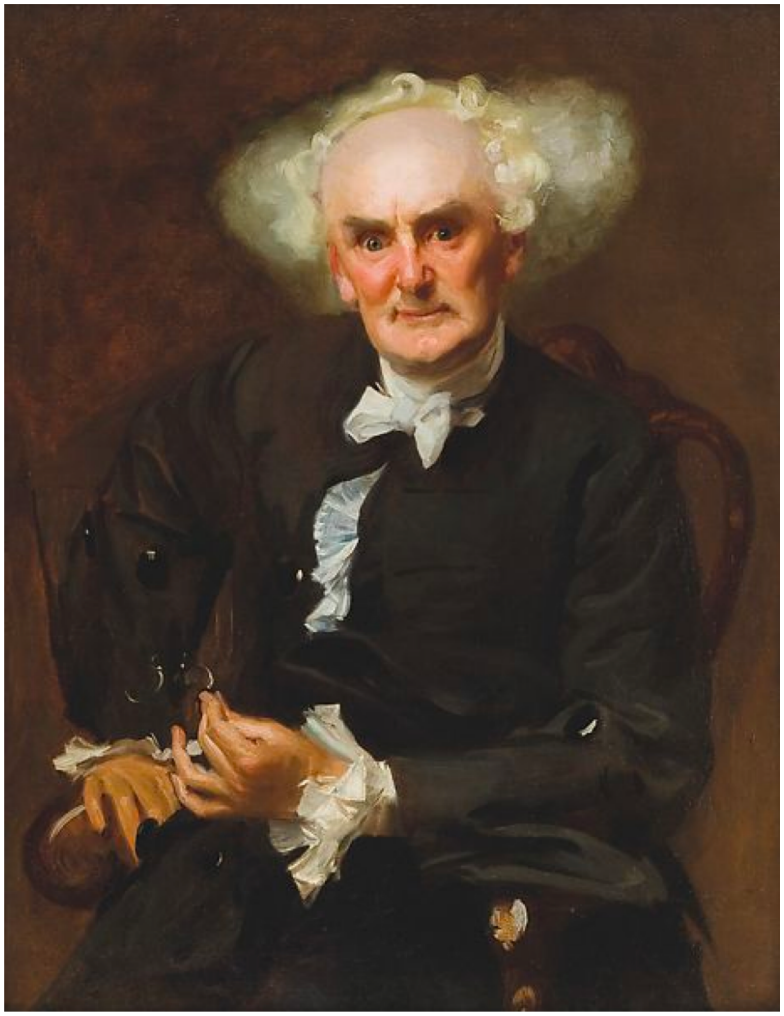
ORIGINAL ARTICLE

Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease

RESULTS

A total of 1519 patients (53% female) were referred to the UDN, of whom 601 (40%) were accepted for evaluation. Of the accepted patients, 192 (32%) had previously undergone exome sequencing. Symptoms were neurologic in 40% of the applicants, musculoskeletal in 10%, immunologic in 7%, gastrointestinal in 7%, and rheumatologic in 6%. Of the 382 patients who had a complete evaluation, 132 received a diagnosis, yielding a rate of diagnosis of 35%. A total of 15 diagnoses (11%) were made by clinical review alone, and 98 (74%) were made by exome or genome sequencing. Of the diagnoses, 21% led to recommendations regarding changes in therapy, 37% led to changes in diagnostic testing, and 36% led to variant-specific genetic counseling. We defined 31 new syndromes.





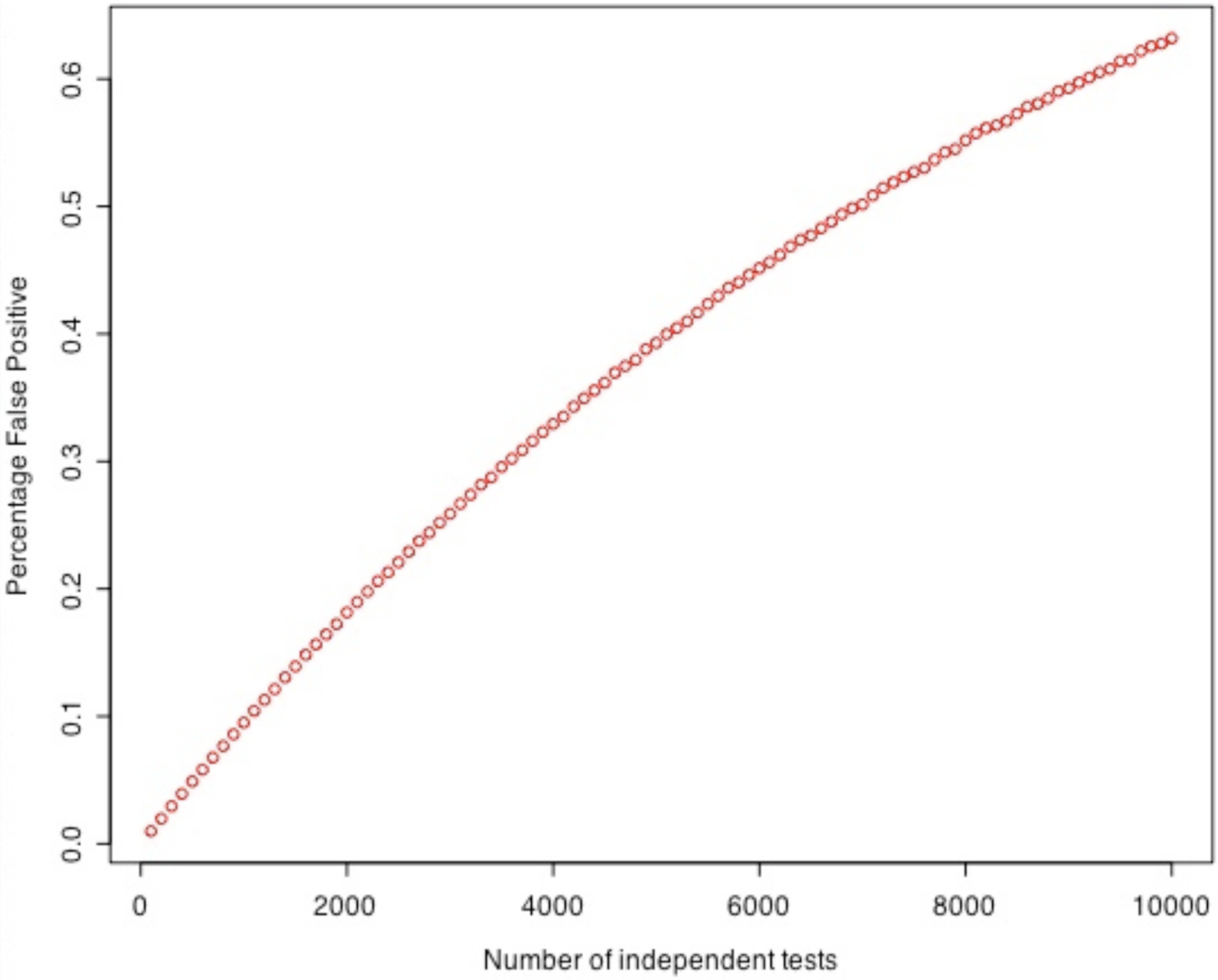
The Incidentalome
A Threat to Genomic Medicine

Isaac S. Kohane, MD, PhD
Daniel R. Masys, MD
Russ B. Altman, MD, PhD

GENOMIC MEDICINE IS POISED TO OFFER A BROAD ARray of new genome-scale screening tests. However, these tests may lead to a phenomenon in which multiple abnormal genomic findings are discovered, analogous to the "incidentalomas" that are often discovered in radiological studies. If practitioners pursue these unexpected genomic findings without thought,

There is a rich literature in radiology on the "incidentaloma," which is a finding (most commonly a mass) found on computed tomography or magnetic resonance imaging studies ordered for symptoms or concerns totally unrelated to the gland in which the mass is found. The workup of an incidentaloma is complicated by concerns that it may be associated with malignant disease and, at least initially, the lack of good data on the prevalence of malignant disease in the general population. Incidentalomas occur because imaging modes do not only report on the areas of direct clinical concern but, incidentally, report on all organs in the field of view.[1]

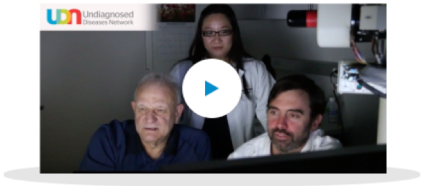
Dangers of Large N and small *p(D)*


Percentage False Positive
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
2000
4000
6000
8000
10000
Number of independent tests

Diseases Network

About Us | How to Apply | Sites | Participants | Research | News | Contact Us | En Español | Search

About The Undiagnosed Diseases Network



Every year hundreds of men, women and children face uncertainty when healthcare providers are unable to discover the cause for their symptoms.

The Undiagnosed Diseases Network (UDN) is a research study backed by the National Institutes of Health Common Fund that seeks to provide answers for patients and families affected by these mysterious conditions.

READ MORE

3392	491	1311	1106	308
Applications Received	Applications Under Review	Participants Accepted	Participants Evaluated	Participants Diagnosed

MORE FACTS & FIGURES

RUBES ™

By Leigh Rubin

DEPARTMENT OF
Biomedical Informatics

A question that has withstood the test of time:

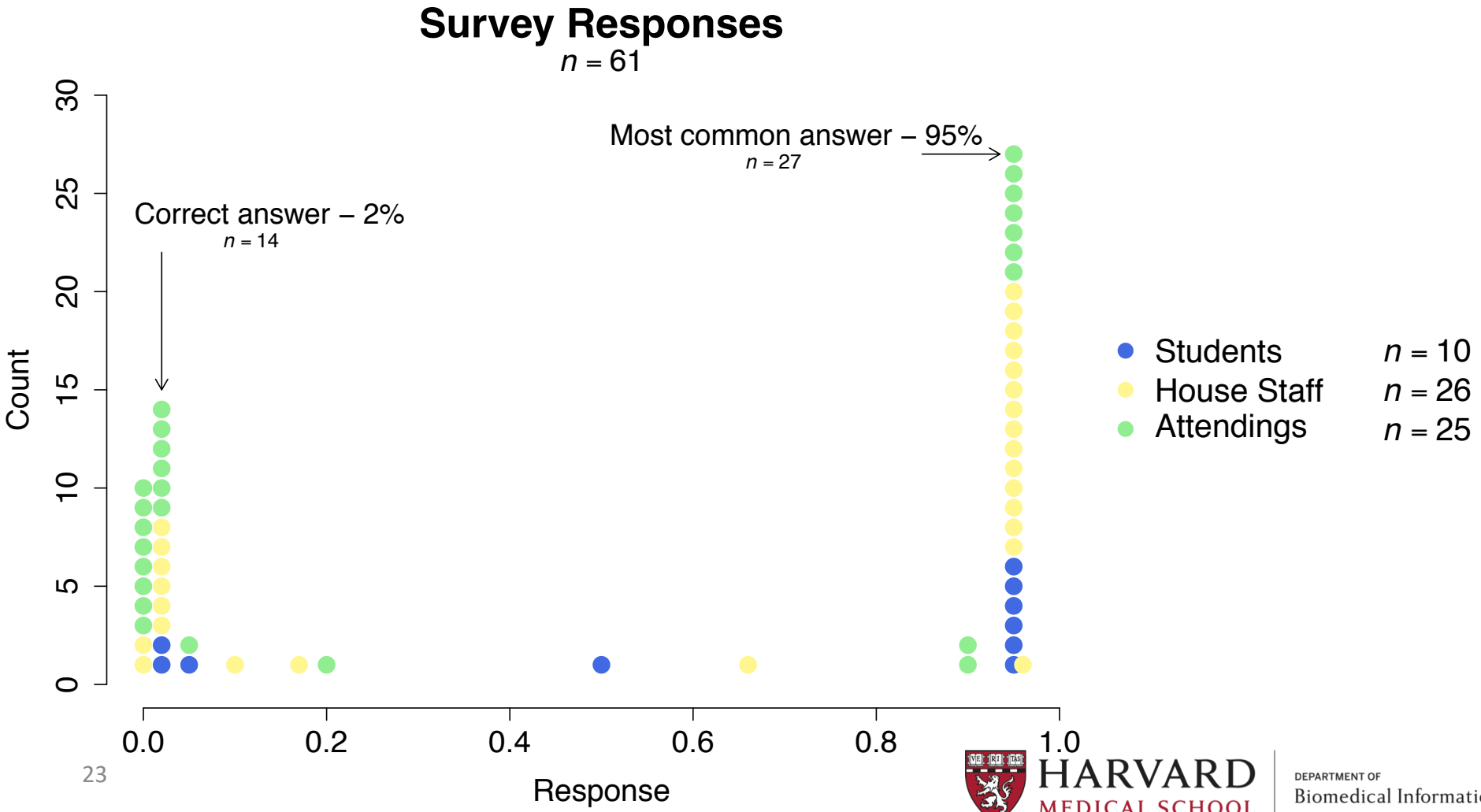
If a test to detect a disease whose prevalence is 1/1000 has a false positive rate of 5%, what is the chance that a person found to have a positive result actually has the disease, assuming you know nothing about the person's

symptoms or signs?

RESEARCH LETTER

Medicine's Uncomfortable Relationship With Math: Calculating Positive Predictive Value

JAMA Internal Medicine Published online April 21, 2014



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DEPARTMENT OF Biomedical Informatics

Authoritative interpretation?

Clin Genet 2003: 64: 355–360
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CLINICAL GENETICS
ISSN 0009-9163

Short Report

Use of cancer susceptibility testing among primary care physicians

Vol. 12, 295–303, April 2003 Cancer Epidemiology, Biomarkers & Prevention 295

Sifri R, Myers R, Hyslop T, Turner B, Cocroft J, Rothermel
and Schlackman N. Use of cancer susceptibility testing amo
care physicians.
Clin Genet 2003: 64: 355–360. © Blackwell Munksgaard, 20

Physician Use of Genetic Testing for Cancer Susceptibility: Results of a National Survey

American Journal of Medical Genetics 120A:63–71 (2003)

US Physicians' Attitudes Toward Genetic Testing for Cancer Susceptibility

A.N. Freedman,[1]* L. Wideroff,[1] L. Olson,[2] W. Davis,[1] C. Klabunde,[1] K.P. Srinath,[2] B.B. Reeve,[1] R.T. Croyle,[1] and R. Ballard-Barbash[1]
[1]*National Cancer Institute, Division of Cancer Control and Population Sciences, Bethesda, Maryland*
[2]*Abt Associates, Chicago, Illinois*

Introduction

Genetic testing for inherited germ-line mutations associated with increased cancer risk is an emerging technology in medical practice (1–3). CSTs[2] such as those that detect mutations in the *BRCA1* and *BRCA2* genes associated with familial breast and ovarian cancer (4–6) or in the *MLH1* and *MSH* genes associated with hereditary nonpolyposis colon cancer (7, 8) have been used primarily within research settings. However, increasing

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Valsartan for Attenuating Disease Evolution In Early Sarcomeric HCM (VANISH)

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2013 by *New England Research Institutes*

Sponsor:
New England Research Institutes

Collaborator:
National Heart, Lung, and Blood Institute (NHLBI)

Information provided by (Responsible Party):
New England Research Institutes

ClinicalTrials.gov Identifier:
NCT01912534

First received: June 5, 2013
Last updated: October 5, 2015
Last verified: July 2013
History of Changes

Group 1 (Overt HCM Cohort)

1. LV wall thickness ≥12 mm and ≤25 mm or z score ≥3 and ≤18 as determined by rapid assessment by the echocardiographic core laboratory
2. NYHA functional class I or II; no perceived or only slight limitations in physical activities
3. No resting or provokable LV obstruction (peak gradient ≤ 30 mmHg) on clinically-obtained Exercise Tolerance Test (ETT)-echo within the past 24 months or transthoracic echo with Valsalva maneuver within the past 12 months
4. Age 8-45 years
5. Able to attend follow-up appointments, complete all study assessments, and provide written informed consent

Group 2 (Preclinical HCM Cohort (G+/LVH-))

1. LV Wall Thickness <12 mm and z score <3 , as determined by rapid assessment by the echocardiographic core laboratory
2. Age 10-25 years
3. E' z score ≤ -1.5 OR ECG abnormalities other than NSSTW changes (Q waves, T wave inversion, repolarization changes) OR LV wall thickness z-score 1.5-2.9 combined with LV thickness to dimension ratio ≥0.19 (as determined by rapid assessment by the echocardiographic core laboratory)
4. Able to attend follow-up appointments, complete all study assessments, and provide written informed consent

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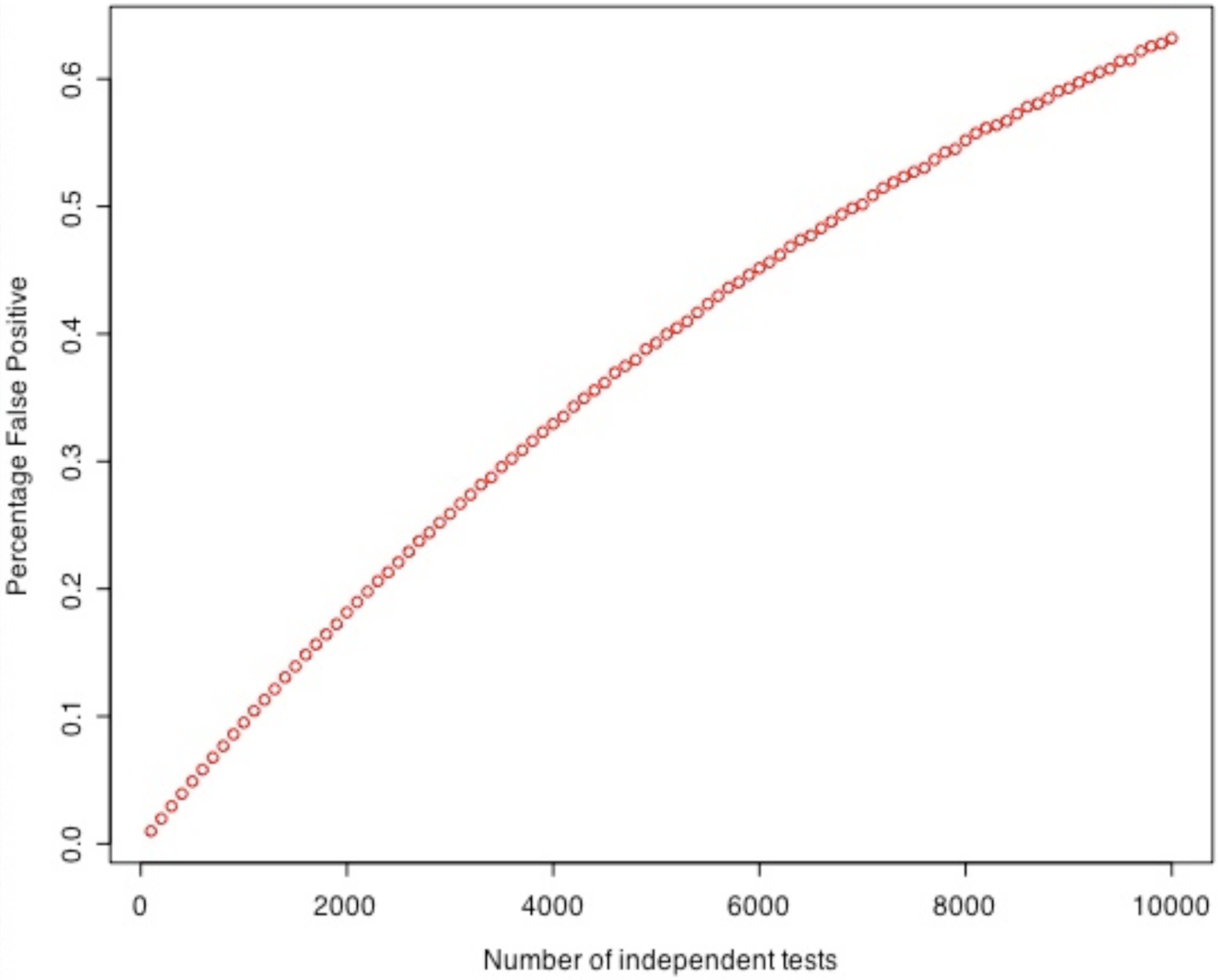
Dangers of Large N and small *p(D)*


Percentage False Positive
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
2000
4000
6000
8000
10000
Number of independent tests

Genetic Background

Mouse strain differences determine severity of iron accumulation in *Hfe* knockout model of hereditary hemochromatosis

Robert E. Fleming*, Christopher C. Holden†, Shunji Tomatsu†, Abdul Waheed†, Elizabeth M. Brunt‡, Robert S. Britto
Bruce R. Bacon§, Derry C. Roopenian‖, and William S. Sly†

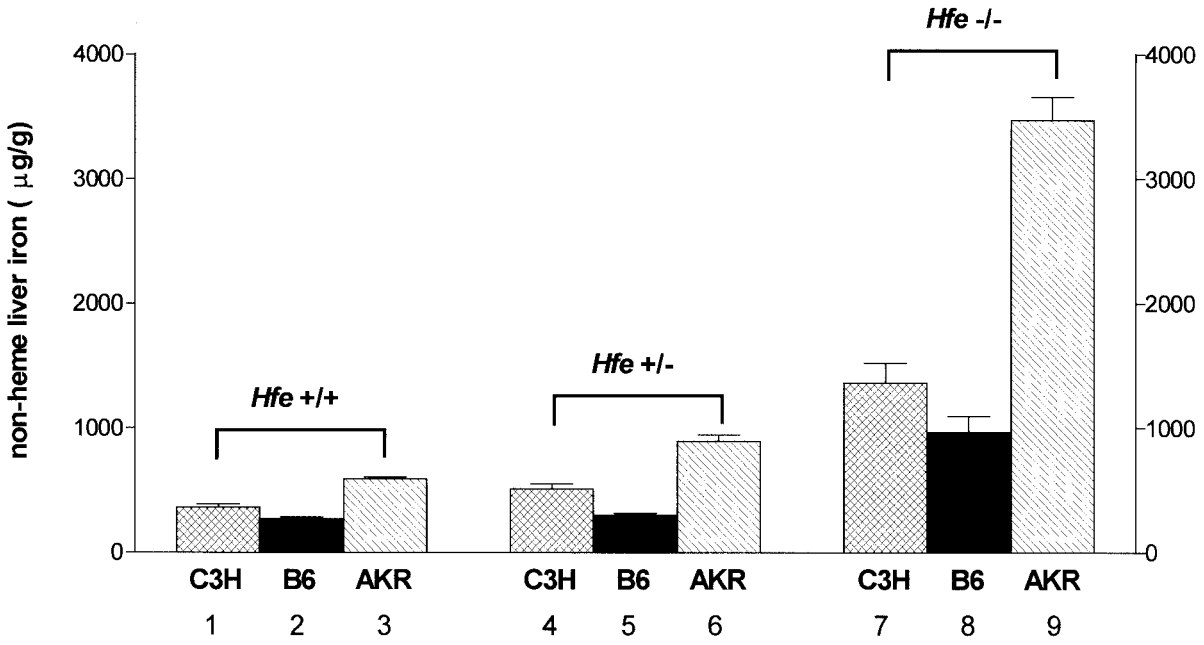


Fig. 2. Effect of strain differences and *Hfe* genotype on hepatic iron concentration. Hepatic nonheme iron concentrations were measured in wild-type (*Hfe* +/+), heterozygote knockout (*Hfe* +/−), and knockout (*Hfe* −/−) mice from three inbred mouse strains: C3H (hatched bars), C57BL/6 (B6, solid bars), and AKR (slashed bars). Data are presented as the mean ± SEM. Differences across strains within each genotype and across genotypes within each strain were determined separately by a one-way ANOVA. $P < 0.05$ across strains within genotype: bars 1 vs. 2, bars 1 vs. 3, bars 2 vs. 3, bars 4 vs. 5, bars 4 vs. 6, bars 5 vs. 6, bars 7 vs. 8, bars 7 vs. 9, and bars 8 vs. 9. $P < 0.05$ across genotypes within strain: bars 1 vs. 7, bars 2 vs. 8, bars 3 vs. 6, bars 3 vs. 9, bars 4 vs. 7, bars 5 vs. 8, bars 6 vs. 9.

Environment

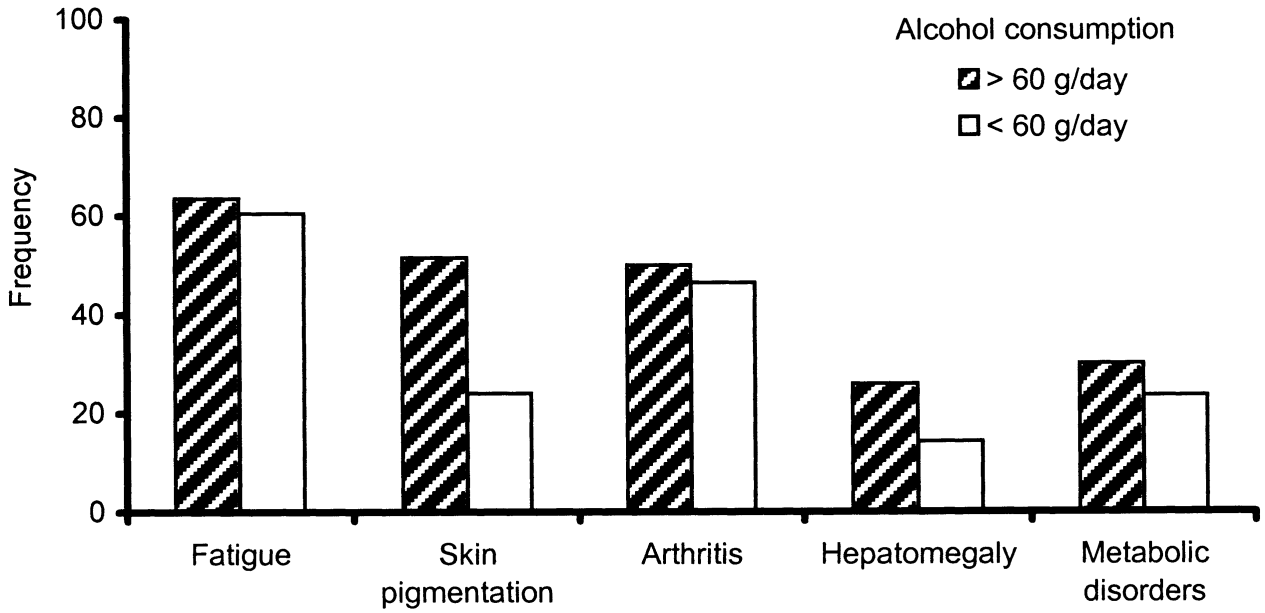


FIGURE 2. Frequency of the most common clinical signs of hereditary hemochromatosis, according to alcohol consumption (≥60 or <60 g per day), observed in 378 *C282Y*-homozygous patients in western Brittany (France), 1977–2002.

Am J Epidemiol 2003;158:129–134

Daniel G. MacArthur,[1,2*] Suganthi Balasubramanian,[3,4] Adam Frankish,[1] Ni Huang,[1]

A Systematic Survey of Loss-of-Function Variants in Human Protein-Coding Genes

[1]Wellcome Trust Sanger Institute,

www.sciencemag.org SCIENCE VOL 335 17 FEBRUARY 2012

- **Aim**: Validate LoF variants reported in published human genome sequences (thought to be 200-800/genome)

- **Results**: With high confidence, ~100 LoF alleles/genome with ~20 loci fully inactivated!

Surviving inherited diseases

Genetic superheroes

A study finds rare individuals resistant to inherited fatal diseases

Apr 16th 2016 | From the print edition

Timekeeper

Tweet

SUPERHEROES with powers that come from mutations in their genomes are, like the X-Men, a staple of comic books and movies. Now an extensive study of the genetics of more than 500,000 people has revealed a different kind of mutant superhero: a small number of individuals who seem to be perfectly healthy despite carrying in their DNA a mutation linked to a severe childhood disorder.

The 13 adults identified were found to have faulty genes associated with one of eight different inherited conditions. These included cystic fibrosis, a disease that interferes with breathing, and atelosteogenesis, which affects bone and limb development. People with the eight different genetic faults can die at birth or shortly after.

The heroism of homeostasis

Undiagnosed Diseases Network

UDN Data Process Overview

If accepted

Data Mgt. Step #1: Patient Application & initial response

UDN CC

UDN Gateway

Public summaries

UDN Data Warehouse

Metrics outcomes

UDN Record Archive and Electronic Trial Mgt.

STANFORD HOSPITAL & CLINICS | UCLA Health System | BAYLOR Health Care System | Vanderbilt University Medical Center | U | Harvard | National Institutes of Health

Data Mgt. Step #2: referral and data transfer to a UDN clinical center

Data Mgt. Step #4: post visit reporting and review

Digital files, workflow, admin reports, phenotype, genotype

STANFORD HOSPITAL & CLINICS | UCLA Health System | BAYLOR Health Care System | Vanderbilt University Medical Center | U | Harvard | National Institutes of Health

Data Mgt. Step #3: inpatient evaluation

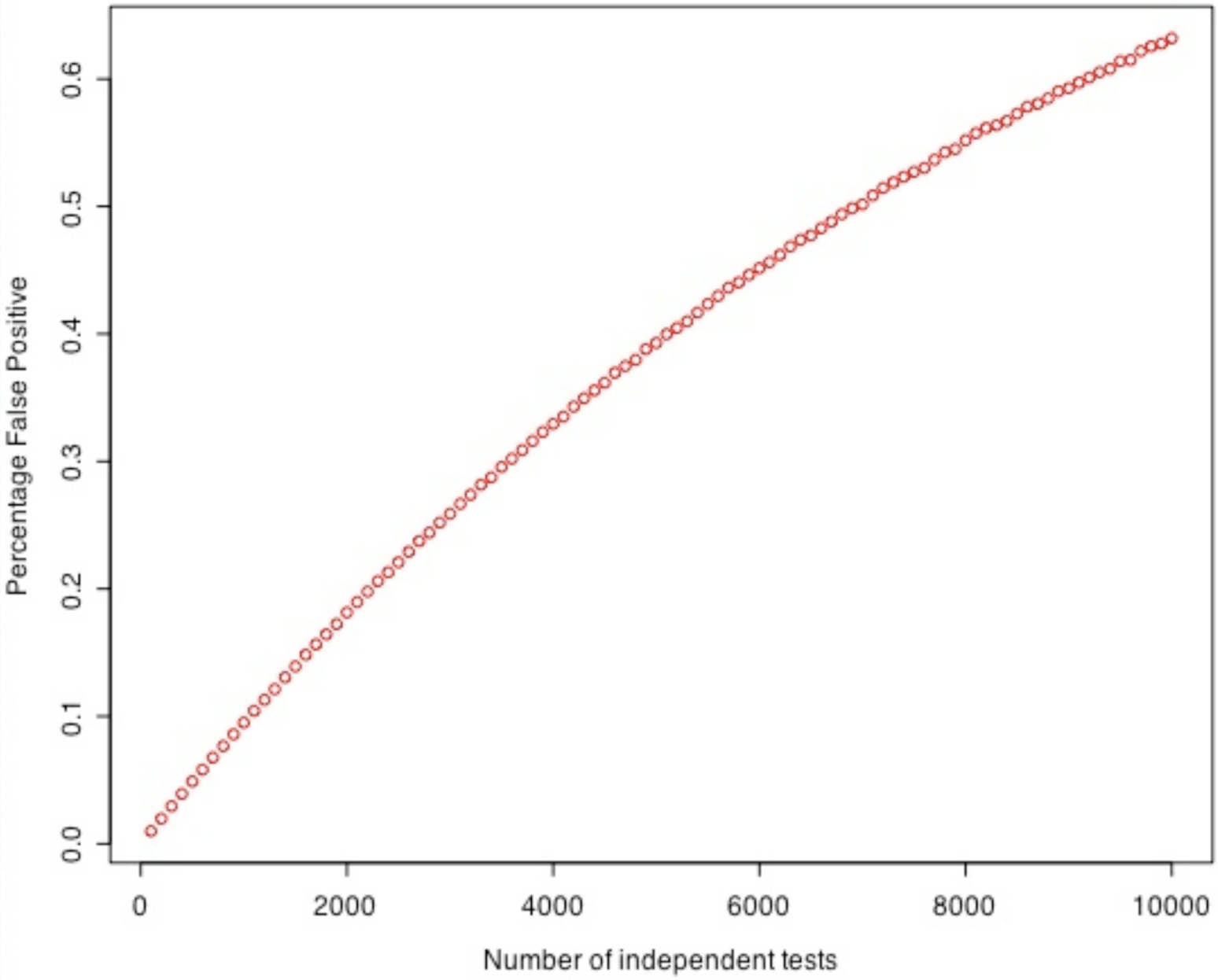
The Incidentalome
A Threat to Genomic Medicine

Isaac S. Kohane, MD, PhD
Daniel R. Masys, MD
Russ B. Altman, MD, PhD

GENOMIC MEDICINE IS POISED TO OFFER A BROAD ARray of new genome-scale screening tests. However, these tests may lead to a phenomenon in which multiple abnormal genomic findings are discovered, analogous to the "incidentalomas" that are often discovered in radiological studies. If practitioners pursue these unexpected genomic findings without thought,

There is a rich literature in radiology on the "incidentaloma," which is a finding (most commonly a mass) found on computed tomography or magnetic resonance imaging studies ordered for symptoms or concerns totally unrelated to the gland in which the mass is found. The workup of an incidentaloma is complicated by concerns that it may be associated with malignant disease and, at least initially, the lack of good data on the prevalence of malignant disease in the general population. Incidentalomas occur because imaging modes do not only report on the areas of direct clinical concern but, incidentally, report on all organs in the field of view.[1]

Dangers of Large N and small *p(D)*


Percentage False Positive
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
2000
4000
6000
8000
10000
Number of independent tests

Penetrance of 845G→A (C282Y) *HFE* hereditary haemochromatosis mutation in the USA

Ernest Beutler, Vincent J Felitti, James A Koziol, Ngoc J Ho, Terri Gelbart

Background There has been much interest in screening populations for disease-associated mutations. A favoured candidate has been the *HFE* gene, mutations of which are the most common cause of haemochromatosis in the European population. About five people in 1000 are homozygotes for the 845G→A mutation, but little is known of how many have mutation-caused clinical manifestations.

Methods We screened 41 038 individuals attending a health appraisal clinic in the USA for the 845G→A and 187C→G *HFE* mutations, and analysed laboratory data and data on signs and symptoms of haemochromatosis as elicited by questionnaire.

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Table 3. Genetic Testing for FAP

	General Population	Affected First Degree Relative	Affected First Degree Relative With Identified Mutation*
Risk for FAP in tested individual	1/8000	1/2	1/2
Test sensitivity, %	95	95	99.9
Test specificity, %	99.9	99.9	99.9
Positive predictive value, %	10.61	99.89	99.99
Negative predictive value, %	0.00006	4.77	0.10

Genetic Background

Mouse strain differences determine severity of iron accumulation in *Hfe* knockout model of hereditary hemochromatosis

Robert E. Fleming*, Christopher C. Holden†, Shunji Tomatsu†, Abdul Waheed†, Elizabeth M. Brunt‡, Robert S. Britto
Bruce R. Bacon§, Derry C. Roopenian‖, and William S. Sly†

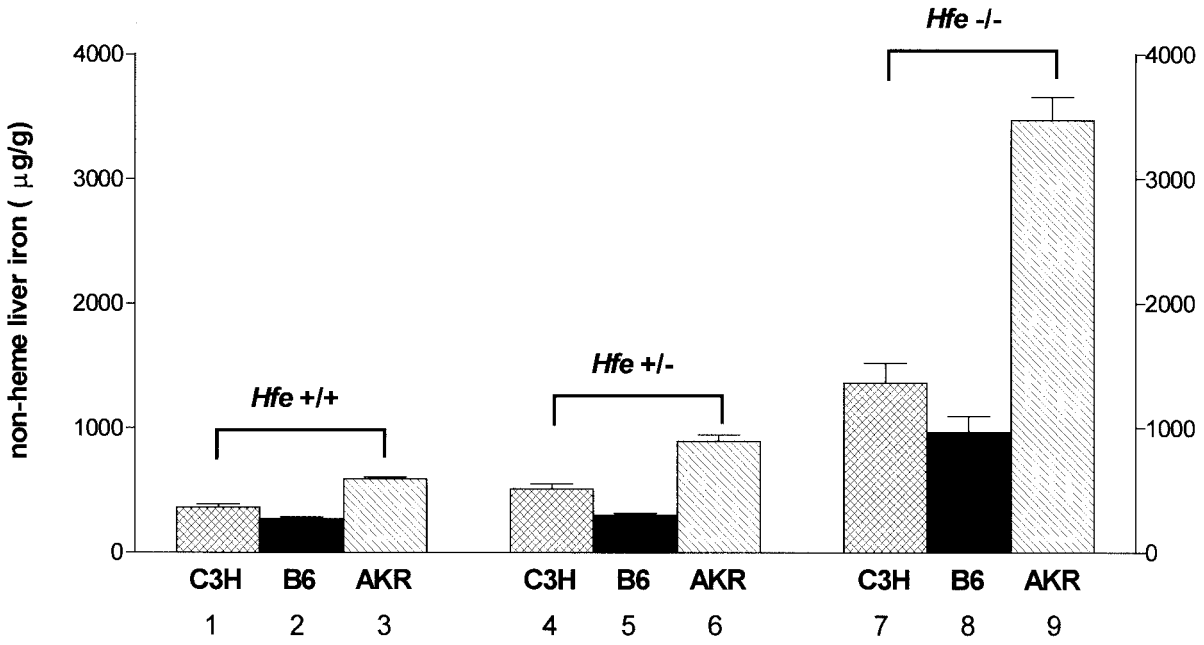

Fig. 2. Effect of strain differences and *Hfe* genotype on hepatic iron concentration. Hepatic nonheme iron concentrations were measured in wild-type (*Hfe* +/+), heterozygote knockout (*Hfe* +/−), and knockout (*Hfe* −/−) mice from three inbred mouse strains: C3H (hatched bars), C57BL/6 (B6, solid bars), and AKR (slashed bars). Data are presented as the mean ± SEM. Differences across strains within each genotype and across genotypes within each strain were determined separately by a one-way ANOVA. $P < 0.05$ across strains within genotype: bars 1 vs. 2, bars 1 vs. 3, bars 2 vs. 3, bars 4 vs. 5, bars 4 vs. 6, bars 5 vs. 6, bars 7 vs. 8, bars 7 vs. 9, and bars 8 vs. 9. $P < 0.05$ across genotypes within strain: bars 1 vs. 7, bars 2 vs. 8, bars 3 vs. 6, bars 3 vs. 9, bars 4 vs. 7, bars 5 vs. 8, bars 6 vs. 9.

Daniel G. MacArthur,[1,2*] Suganthi Balasubramanian,[3,4] Adam Frankish,[1] Ni Huang,[1]

A Systematic Survey of Loss-of-Function Variants in Human Protein-Coding Genes

[1]Wellcome Trust Sanger Institute,

www.sciencemag.org SCIENCE VOL 335 17 FEBRUARY 2012

- **Aim**: Validate LoF variants reported in published human genome sequences (thought to be 200-800/genome)

- **Results**: With high confidence, ~100 LoF alleles/genome with ~20 loci fully inactivated!

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