Using Genomic Variants to Guide Treatment

Workshop on Sequencing in
Cohort Studies and Large Sample Collections
NHGRI Bethesda MD
June 29th 2012

Mike Murray, MD
Clinical Chief, Genetics Division
Brigham and Women's Hospital
Harvard Medical School

Disclosure of Financial Relationships

Michael F. Murray, MD

Genzyme Corporation
Educational and Research Grants

Generation Health
Advisory Board

Coriell Personalized Medicine Project
Advisory Board

Using Genomic Variants to Guide Treatment

ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

N ENGL J MED 354;12 WWW.NEJM.ORG MARCH 23, 2006

Using Genomic Variants to Guide Treatment

- PCSK9
- APOL1
- FBN1, TGFBR1 and 2
- Pharmacogenomics

Reason for Workshop

- …intended to get everyone on board with why we're really doing all this sequencing in complex diseases-- to reduce disease and help patients.

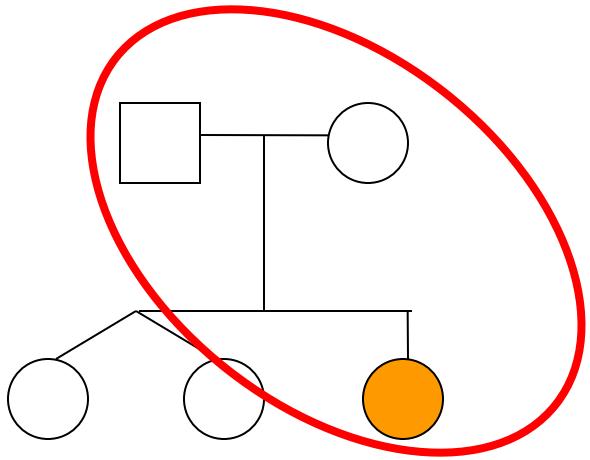
The Primary Outputs of Workshop

- The key questions that can be addressed by genome sequencing
- The criteria for selecting samples to sequence that address each question.

Clinical Genotype Phenotype Correlation

36 year old patient

Known Autosomal Dominant Disease



Samples Sent for WGS

Division of Genetics

- Services
- Clinical Genetics
- Department of Medicine

Genome Services

Adult Genetics Clinic | **Personal Genomic Consultation Service**

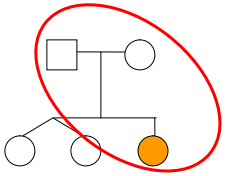
Brigham and Women's Hospital Clinical Genetics together with Partners HealthCare Center for Personalized Genetic Medicine are collaborating on a pilot project that will offer Whole Genome Sequencing (WGS) to patients as a clinical service. This pilot project seeks to identify patients for WGS who have the greatest likelihood of receiving significant short-term benefit from this testing Specifically, these are patients for whom WGS may provide a genomic diagnosis that has implications for clinical management. We believe that to understand the clinical significance of WGS variants we will need to utilize sophisticated bioinformatics as well as engage teams of clinicians with disease-specific and genetic expertise. The goals of this pilot project are to confirm the diagnostic utility of WGS and to establish the pathway for the clinical management of WGS data at BWH and Partners.

We invite all clinicians to propose patients who they think may benefit from this diagnostic procedure. The referral form with case information can be emailed to Dr. Michael Murray, Clinical Chief, Genetics Division, mmurray@partners.org. For a PDF of the referral form, click here.

http://www.brighamandwomens.org/Departments_and_Services/medicine/services/genetics/services/genome_svs.aspx

36 year old patient

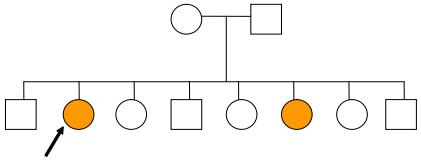
Known Autosomal Dominant Disease



Trio Consented and Samples Sent for WGS

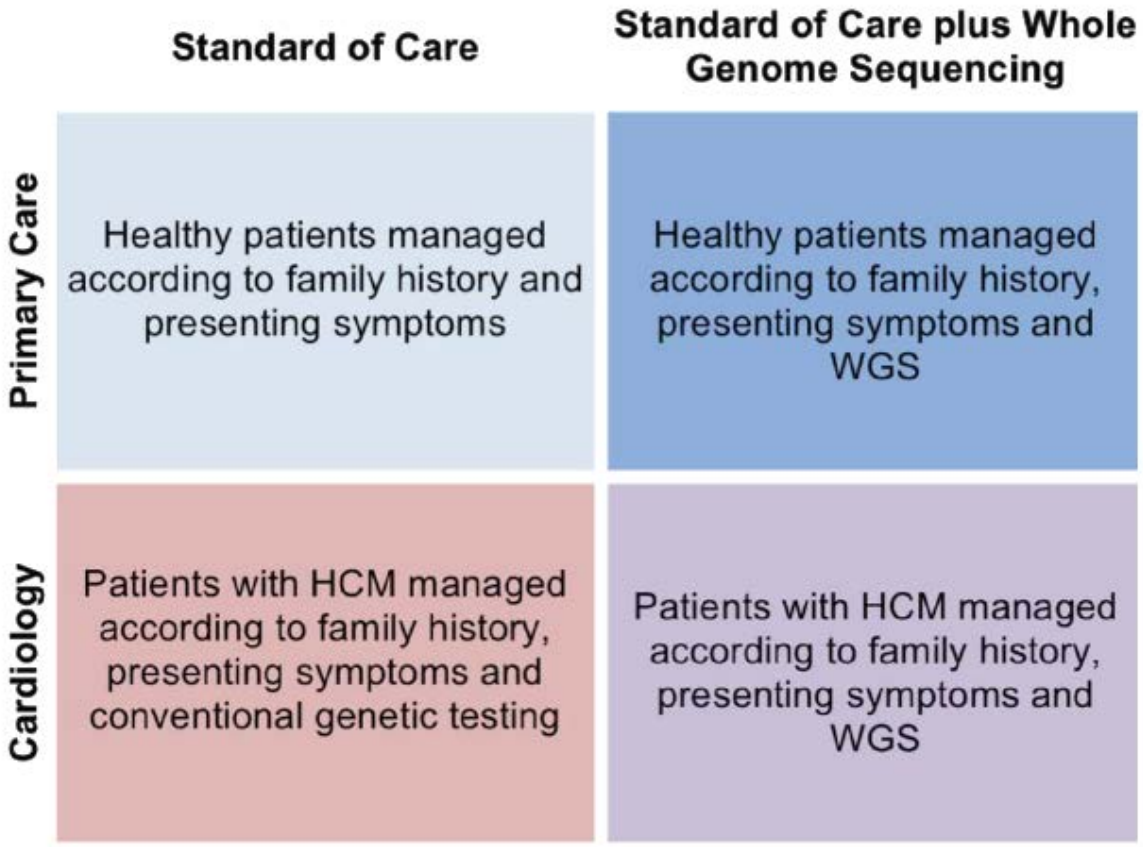
Sisters with skeletal anomalies and T-cell lymphoma

Skeletal change and lympoma



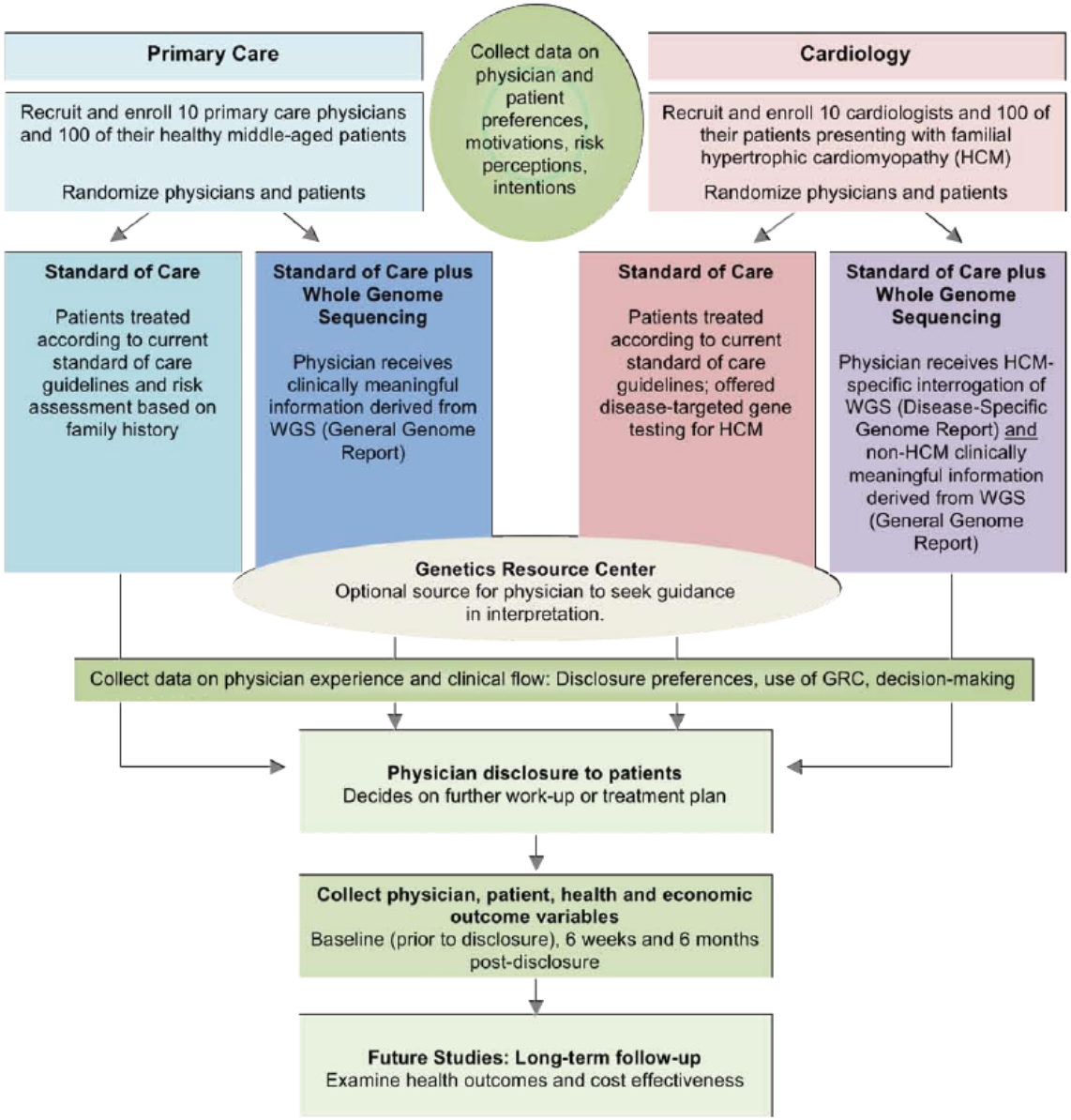
Pedigree Analysis = Autosomal Recessive

Integration of Whole Genome Sequencing into Clinical Medicine



N=200

Integration of Whole Genome Sequencing into Clinical Medicine

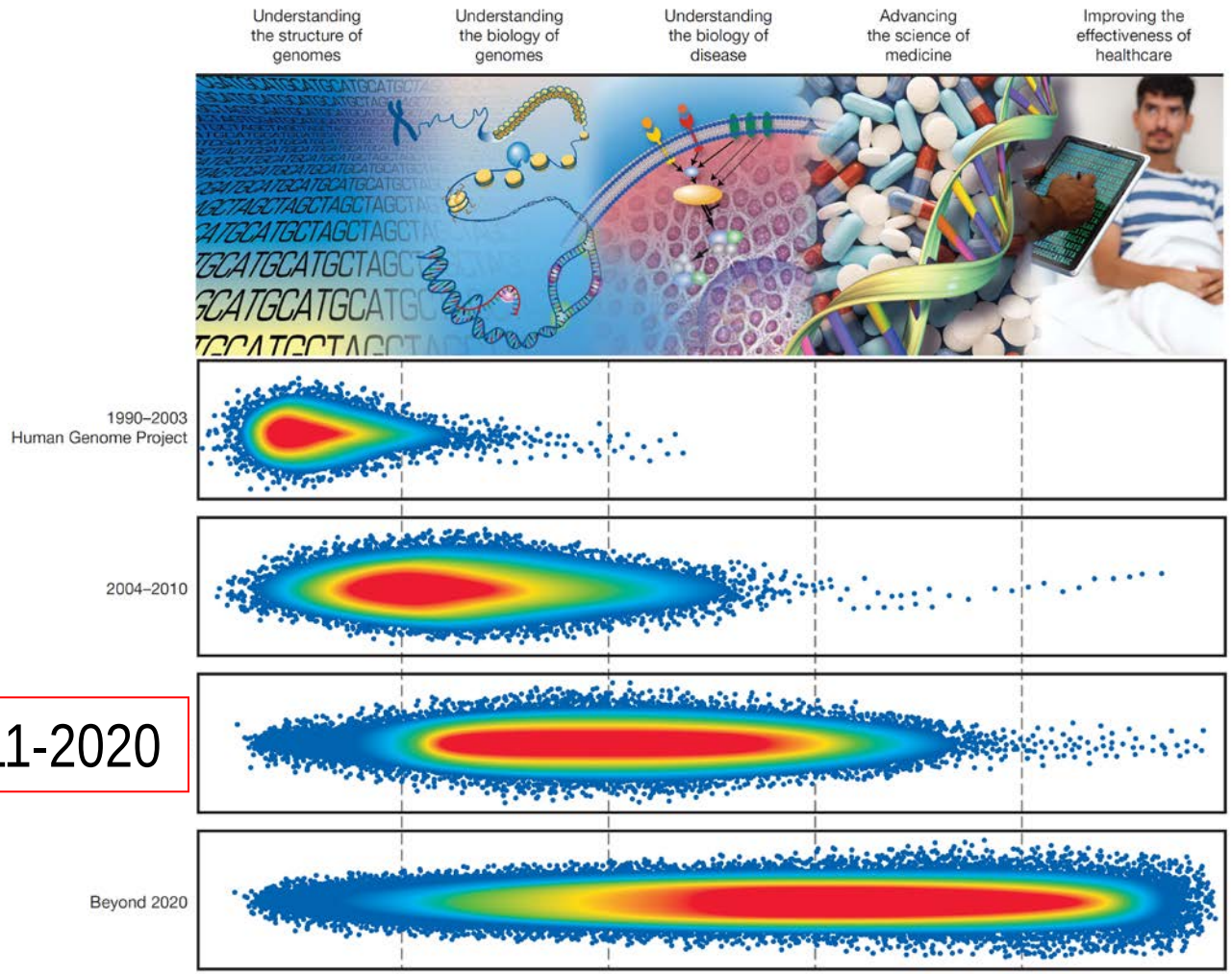


N=200

Deep Phenotyping and Unreported Genotype Phenotype Correlations

Create a low threshold mechanism for reporting cases that directly annotate the genome.

Align the motivations so that clinicians report associations.

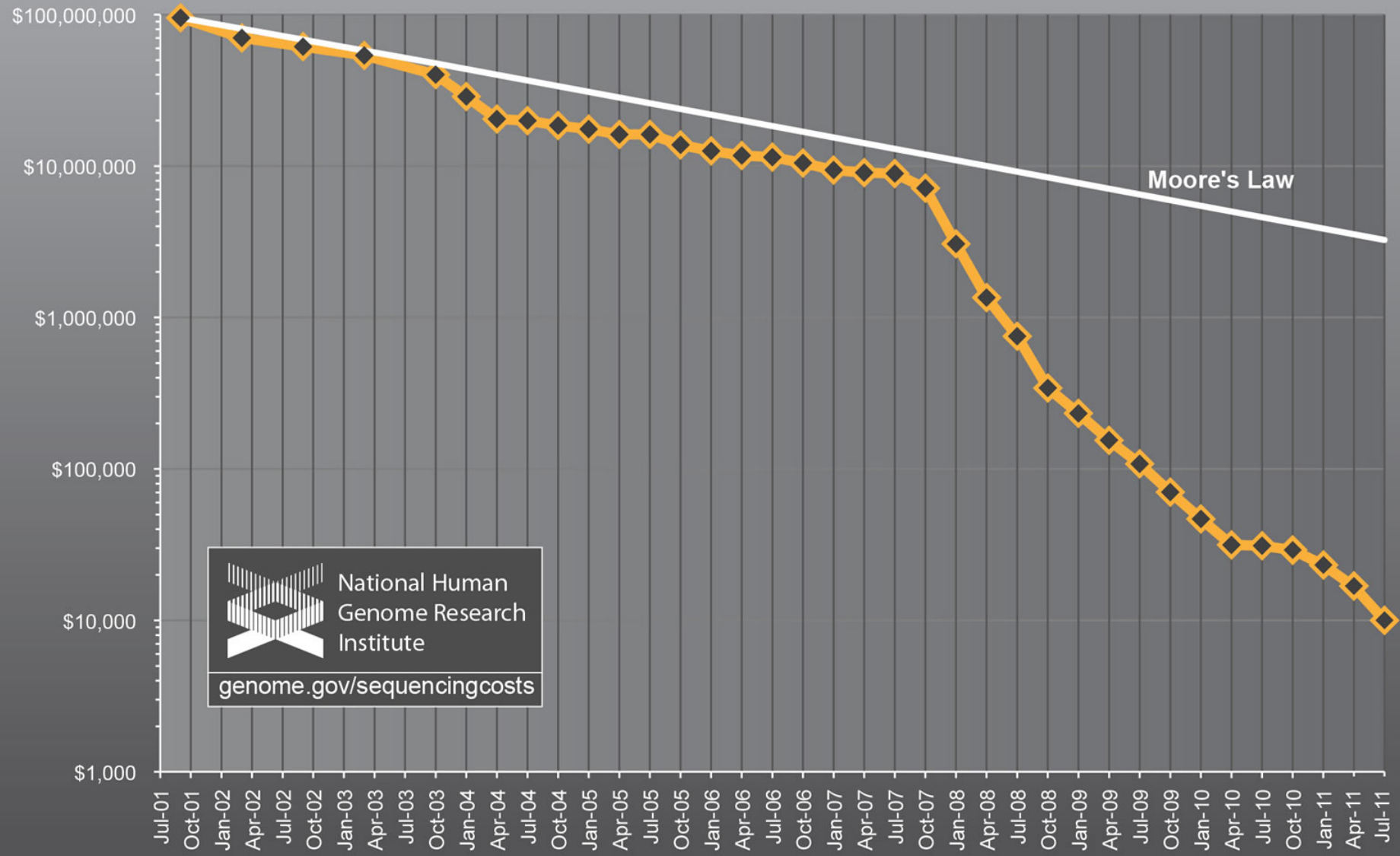


2011-2020

Figure 2 | Schematic representation of accomplishments across five domains of genomics research. The progression from base pairs to bedside is depicted in five sequential, overlapping domains (indicated along the top). Genomic accomplishments across the domains are portrayed by hypothetical, highly schematized density plots (each blue dot reflecting a single research accomplishment, with green, yellow and red areas reflecting sequentially higher densities of accomplishments). Separate plots are shown for four time intervals: the HGP; the period covered by the 2003 NHGRI vision for the future of genomics research[17]; the period described here (2011–2020); and the open-ended future beyond 2020.

We are not in control of the pace of Genomic Medicine's incorporation into clinical medicine

Cost per Genome



http://www.genome.gov/sequencingcosts

How much DNA Sequence does $10 get you?

- 1985 $10 1 base
- 1991 $10 10 bases
- 2001 $10 2,000 bases

http://www.dartmouth.edu/~cbbc/courses/bio4/bio4-1997/16-HumanGenome.html

TIME's Best Invention of 2008

Invention of the Year

TIME

1. The Retail DNA Test

By Anita Hamilton

ARTICLE TOOLS

Print

Email

Sphere

AddThis

RSS

Yahoo! Buzz

Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin,

For the First Time, DNA Sequencing Technology Saves A Child's Life | Popular Science - Mozilla Firefox

File Edit View History Bookmarks Tools Help

NCBI Reference Sequence (RefSeq) | BWH Biomedical Research Institute - Ind... | (tumor suppressor) AND "Homo sapiens"[... | PS For the First Time, DNA Sequencing Tech...

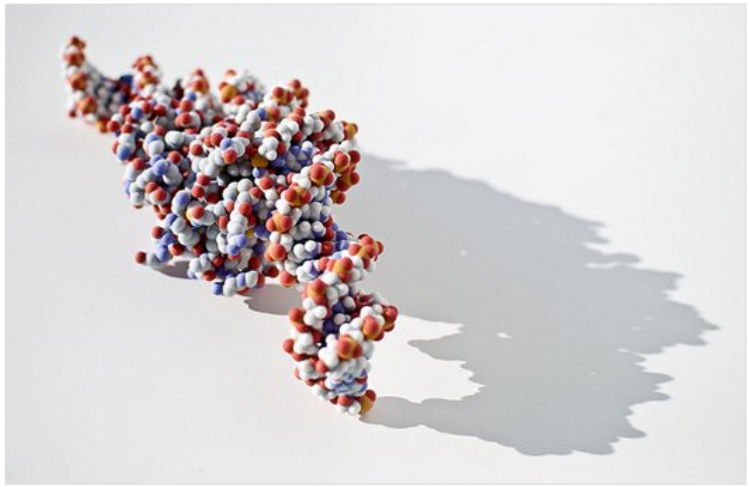
www.popsci.com/science/article/2011-01/dna-sequencing-appears-have-saved-its-first-child

genome saves life

Like 156 +1 1 Tweet 81 4,502 reddit

For the First Time, DNA Sequencing Technology Saves A Child's Life

By Clay Dillow Posted 01.06.2011 at 2:08 pm 3 Comments



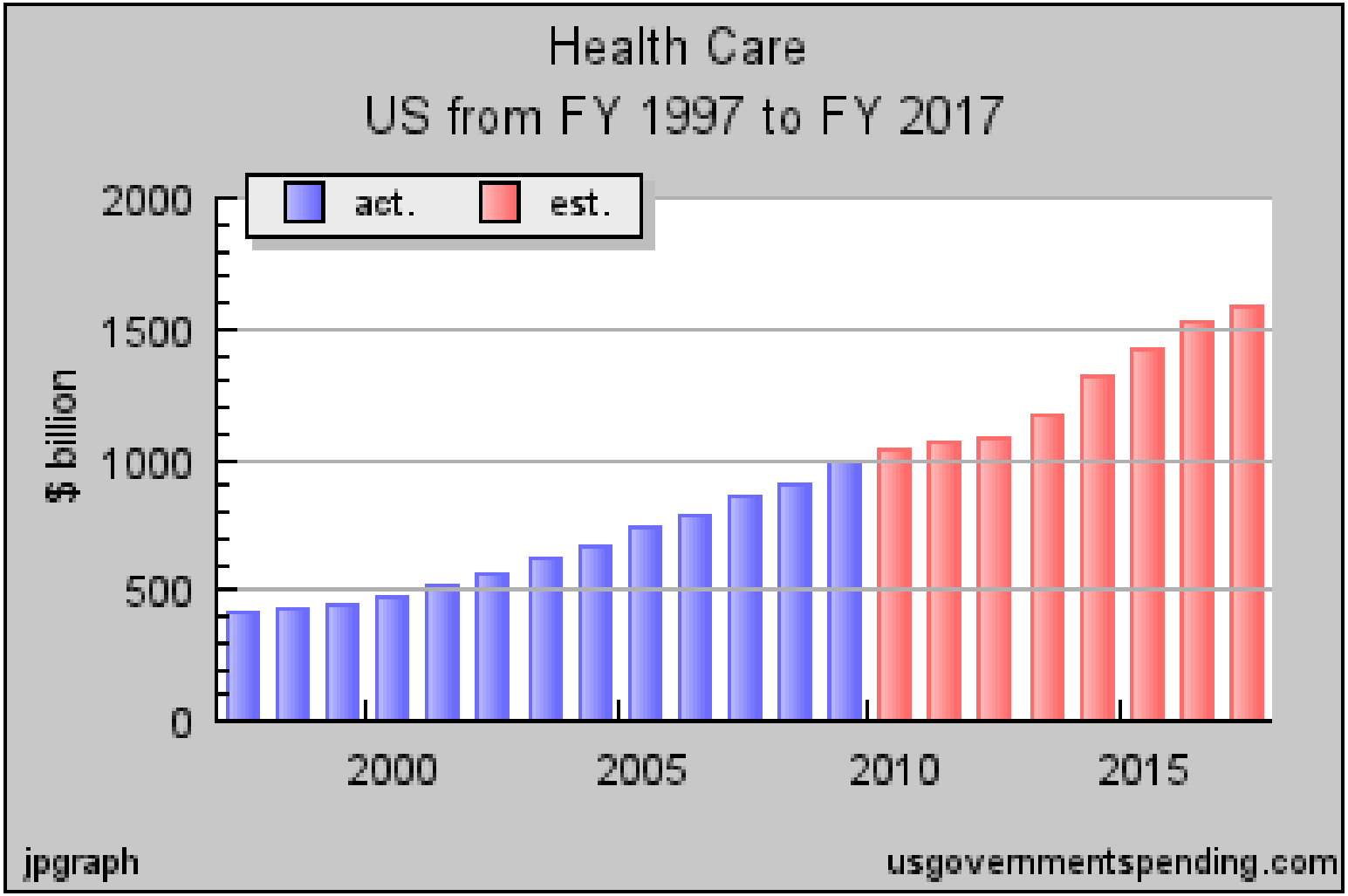
A 3-D Model of a DNA Binding Protein Attaching to DNA *widdowquinn via Flickr*

Proponents of genetic medicine say DNA sequencing is the future of medicine and that soon every truly sick person will have his or her genome sequenced. Critics cite privacy concerns and note that genetic mutations and variations don't necessarily lead to medical outcomes. Whatever the position, it's hard to argue that this isn't good news: the first child – plagued by undiagnosable illness – has been saved by DNA sequencing.

start | For the Firs... | 3 Microsof... | 7 Internet... | 2 Microsof... | Microsoft Po... | H:\BWH Ad... | 12:35 PM

Threats to Genomic Medicine

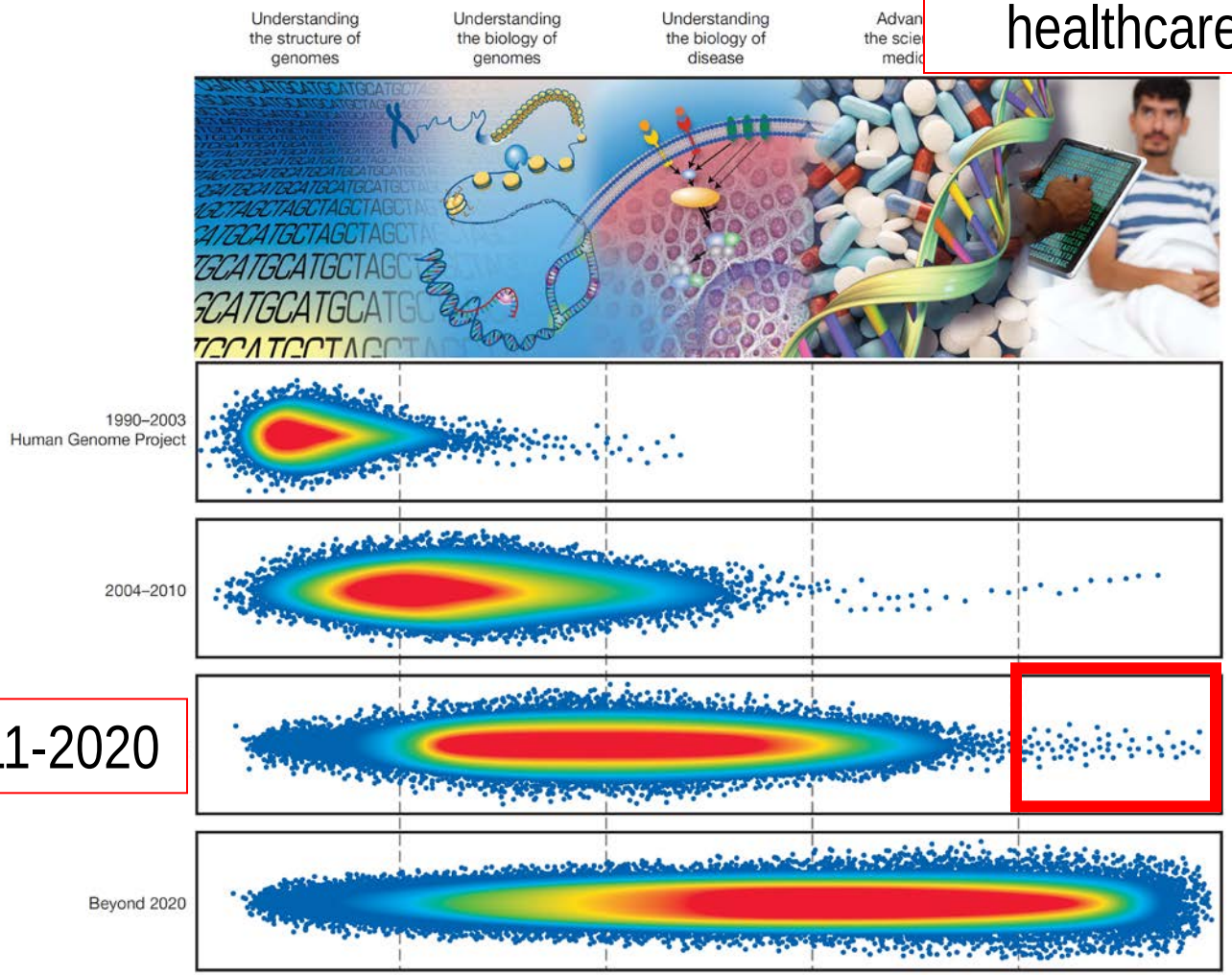
- Primarily Economic
- Possibly political


Health Care
US from FY 1997 to FY 2017
act.
est.
$ billion
2000
1500
1000
500
0
2000
2005
2010
2015
jpgraph
usgovernmentspending.com

Acting on False Positives

- CFTR
  - I148T
- BRCA
  - Surgical intervention
- Others?

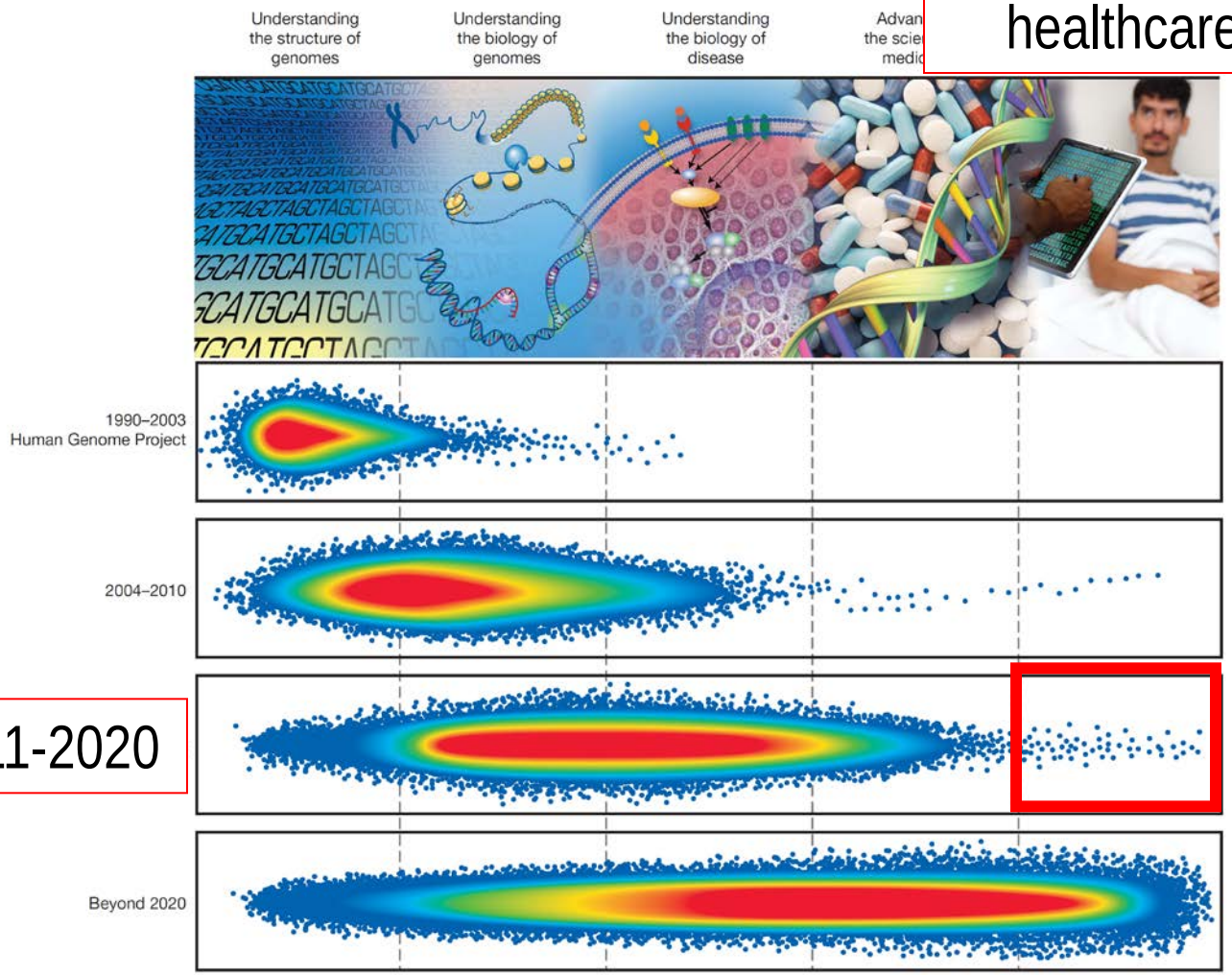
Improving the effectiveness of healthcare



2011-2020

Figure 2 | Schematic representation of accomplishments across five domains of genomics research. The progression from base pairs to bedside is depicted in five sequential, overlapping domains (indicated along the top). Genomic accomplishments across the domains are portrayed by hypothetical, highly schematized density plots (each blue dot reflecting a single research accomplishment, with green, yellow and red areas reflecting sequentially higher densities of accomplishments). Separate plots are shown for four time intervals: the HGP; the period covered by the 2003 NHGRI vision for the future of genomics research[17]; the period described here (2011–2020); and the open-ended future beyond 2020.

Improving the effectiveness of healthcare



2011-2020

Figure 2 | Schematic representation of accomplishments across five domains of genomics research. The progression from base pairs to bedside is depicted in five sequential, overlapping domains (indicated along the top). Genomic accomplishments across the domains are portrayed by hypothetical, highly schematized density plots (each blue dot reflecting a single research accomplishment, with green, yellow and red areas reflecting sequentially higher densities of accomplishments). Separate plots are shown for four time intervals: the HGP; the period covered by the 2003 NHGRI vision for the future of genomics research[17]; the period described here (2011–2020); and the open-ended future beyond 2020.

Priorities in Choosing Targets for which Genomic Medicine can/should Guide Treatment?

- Things we are really bad at taking care of in clinic care arena.
- Things that drive significant healthcare spending.
- Things where moderate impact could lead to significant improvements in health.
- Things that effect a lot of people.
- Obviously, things with a strong genomic basis.

Picking Targets for which Genomic Medicine can/should Guide Treatment

- Smoking Cessation

A Large Cohort needs a Grand Vision

- We will understand the genomic basis of _____ and we anticipate that this understanding will contribute to the development of significant therapies to control _____ by the end of this decade.

Obesity Trends* Among U.S. Adults

BRFSS, 1990, 2000, 2010

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)

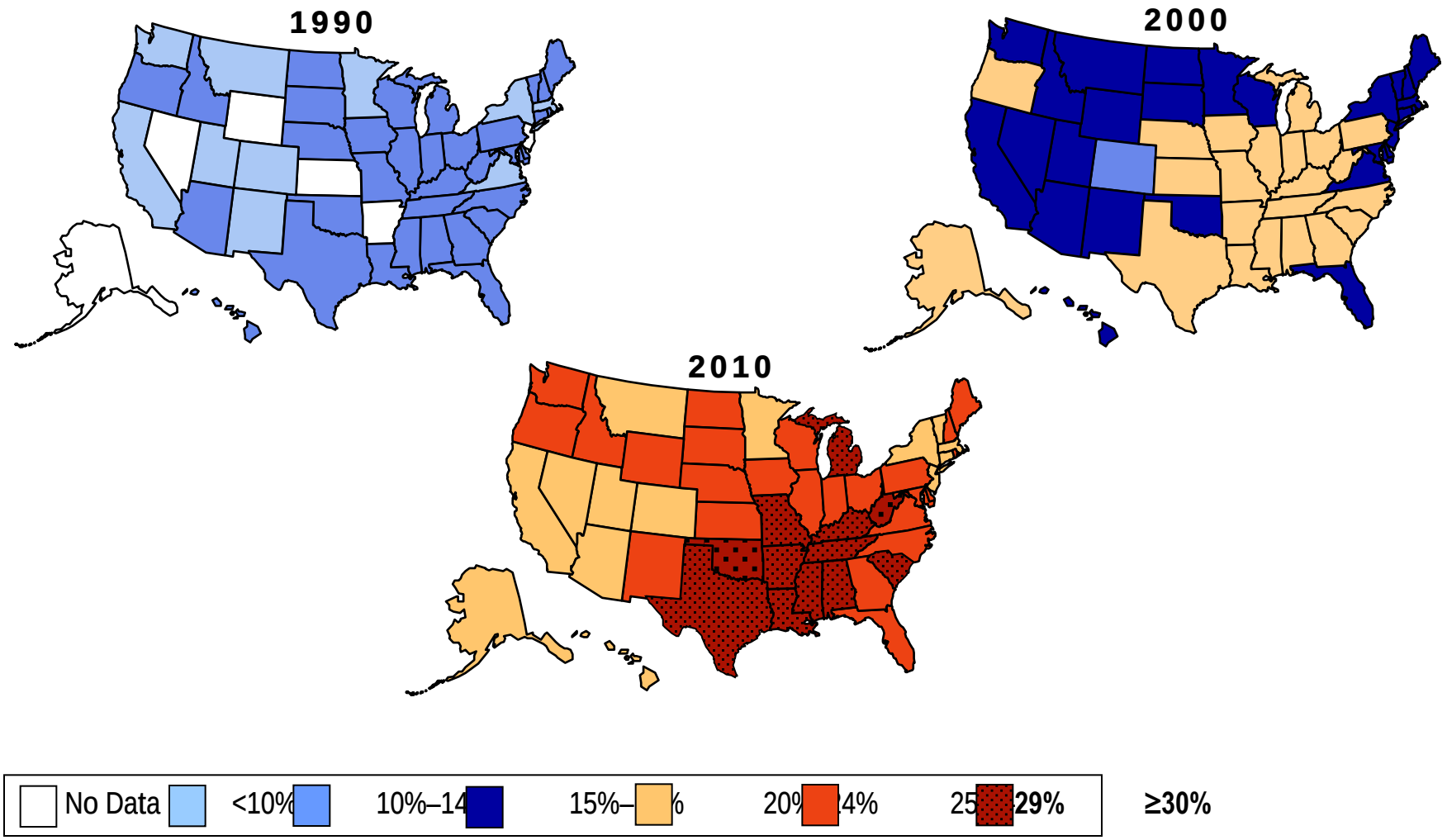


Figure 1. Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2009–2010

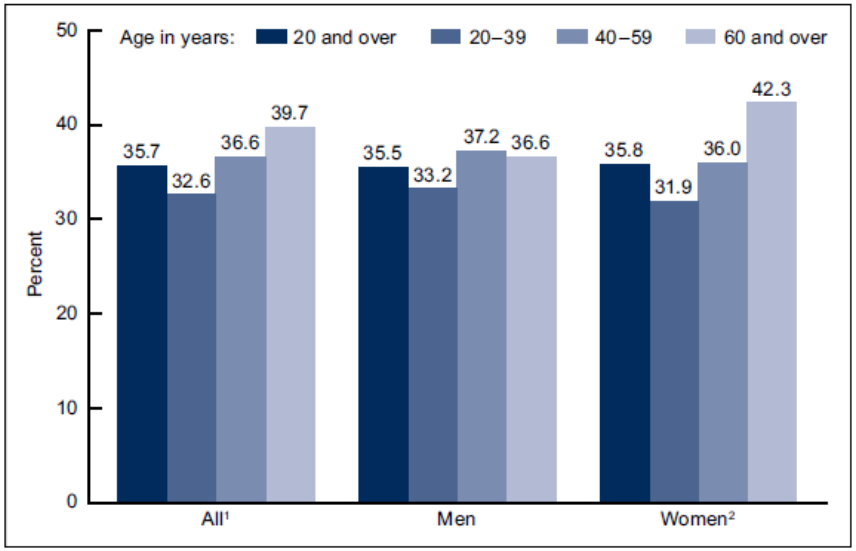
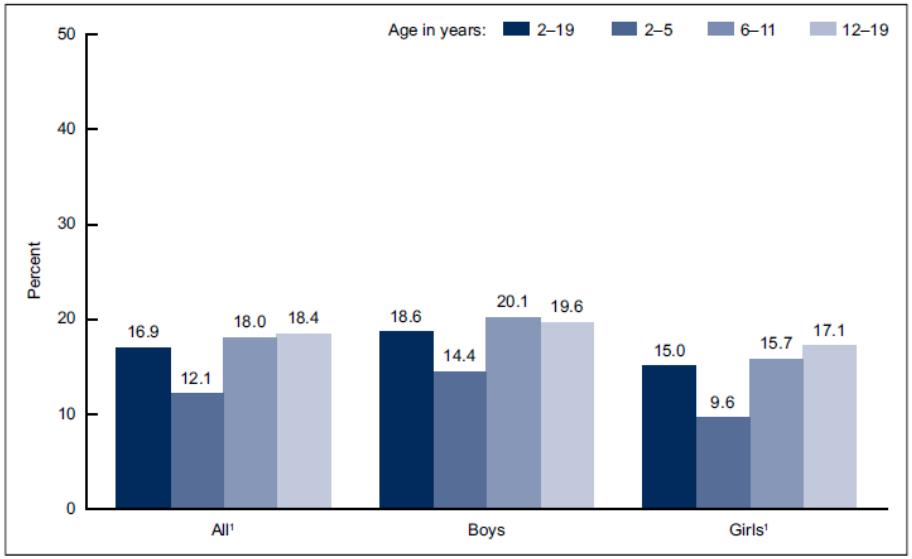


Figure 2. Prevalence of obesity among children and adolescents aged 2–19, by sex and age: United States, 2009–2010



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

World Health Organization

Worldwide obesity has more than doubled since 1980.

In 2008, more than 1.4 billion adults, 20 and older, were overweight.

Of these over 200 million men and nearly 300 million women were obese.

65% of the world's population live in countries where overweight and obesity kills more people than underweight.

More than 40 million children under the age of five were overweight in 2010.
Obesity is preventable.

http://www.who.int/topics/obesity/en/

A Large Cohort needs a Grand Vision

- We will understand the genomic basis of human obesity and we anticipate that this understanding will contribute to the development of significant therapies to control obesity by the end of this decade.