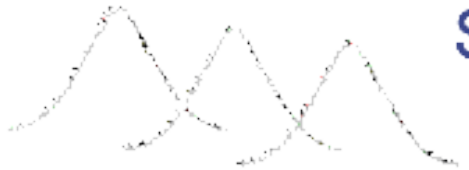


Summer Institute
in Statistical Genetics

2016

Introduction to Genetics and Genomics

5b. Personalized Genomics

ggibson.gt@gmail.com

http://www.cig.gatech.edu

Firsst genome sequencing success story

Diagnosed at age 5 with dopa-responsive dystonia

Worsening respiratory and neuromuscular disease not responsive to dopamine precursor therapy

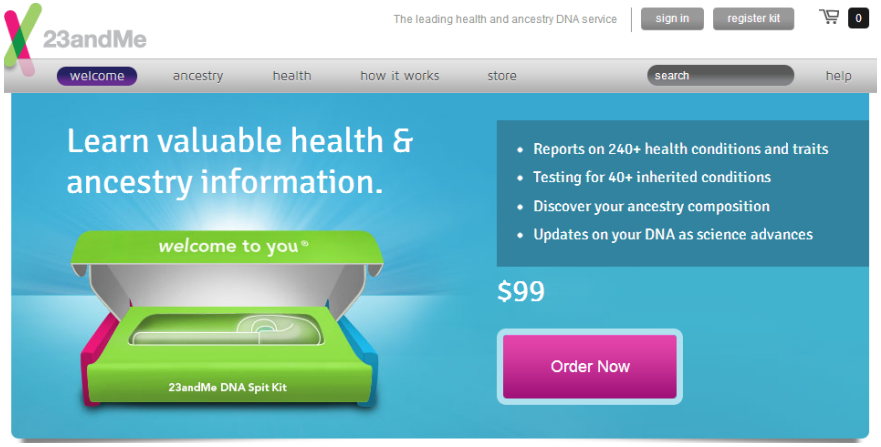
WGS shows mutation in SPR "sepiapterin reductase" gene

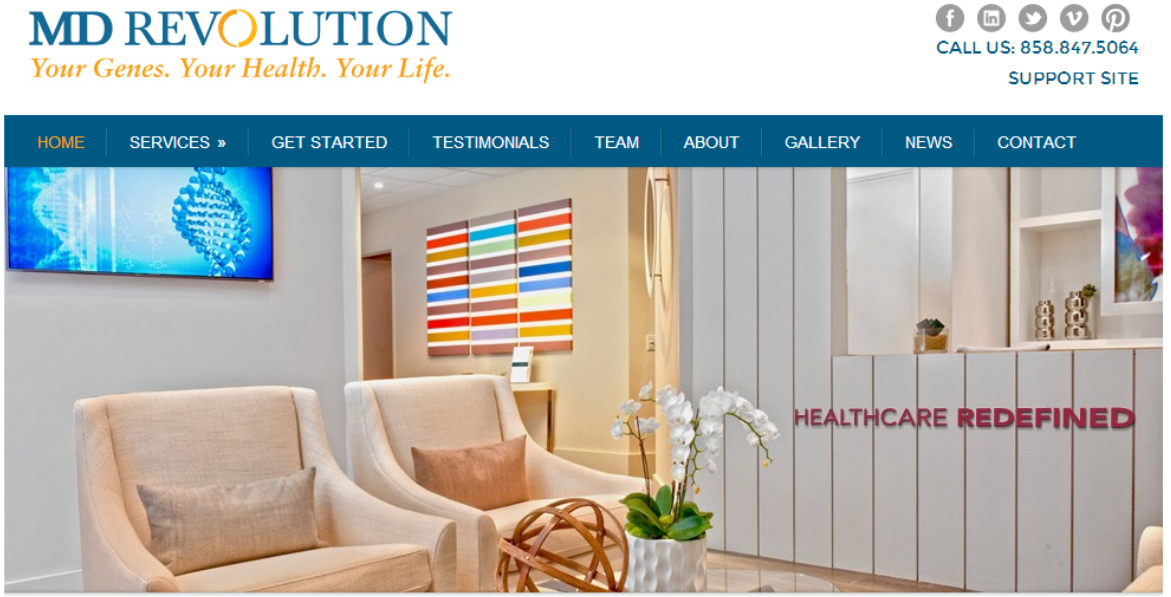
5-HT serotonin precusor supplementation had immediate impact

The Beery twins

Bainbridge, M. N. *et al.* (2011) *Sci. Transl. Med.* **3,** 87re3

Some Personal Genomics Companies





Some Public Initiatives

Personal Genome Project

Home | Project Overview | Participation Overview | PGP Community | Blog

Volunteers from the general public working together with researchers to advance personal genomics.

We believe individuals from the general public have a vital role to play in making personal genomes useful. We are recruiting volunteers who are willing to share their genome sequence and many types of personal information with the research community and the general public, so that together we will be better able to advance our understanding of genetic and environmental contributions to human traits. Learn more about how to participate in the Personal Genome Project.

Project Overview. The PGP hopes to make personal genome sequencing more affordable, accessible, and useful for humankind. Learn more about our mission.

Want to participate? We aim to enroll 100,000 informed participants from the general public. Learn more about participation in the PGP and how you can get involved.

Meet our volunteers. Participants may volunteer to publicly share their DNA sequence and other personal information for research and education. Meet the "PGP-1K".

patientslikeme

Username or Email | Password | Sign in

Remember me | I forgot

Live better, together!™

making healthcare better for everyone through sharing, support, and research

learn about living with & treating your condition

connect with others who share your experiences

track your history & progress for access anywhere

HHS.gov/Open

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Home | Data Sets | >Initiatives | Records & Reports | Executive Orders | Stay Connected | HHS Leadership

Home > Initiatives > mHealth Initiative

mHealth Initiative

In recent years, the expansion of mobile health (mHealth) technologies, including health text messaging, mobile phone apps, remote monitoring and portable sensors, have changed the way healthcare is being delivered in the U.S. and globally. The potential to provide citizens with an unprecedented level of access to health resources can help HHS achieve its goal of a healthier and more secure nation.

HHS had been actively involved in mHealth activities over the past 5 years and there are a number of ongoing mHealth efforts throughout the Department. In light of these activities, as well as, HHS's desire to strategically encourage and/or develop future health text messaging and mobile health programs, HHS formed Text4Health Task Force to provide recommendations to the Secretary. In addition to providing recommendations and guiding principles, the Task Force was charged with identifying both ongoing initiatives and proposals for feasible new projects which would deliver health information and resources to users' fingertips via their mobile phones. Read the recommendations

HHS has launched several mHealth initiatives that have been guided by the HHS Text4Health Task Force:

The National Cancer Institute (NCI) at the National Institutes of Health has launched the SmokeFreeTXT program, a mobile smoking cessation service designed for teens and young adults across the United States. The service is an extension of the core smoking cessation website,www.smokefree.gov, which consistently reaches between 70,000 – 100,000 visits on a monthly basis. Teens and young adults who wish to stop smoking can enroll in this program by going to the link: http://smokefree.gov/smokefreetxt/default.aspx.

The Health Resources and Services Administration (HRSA) has launched TXT4Tots, a public text messaging library which provides evidence-based information on nutrition and physical activity targeted to parents, providers, and caregivers of children ages 1 – 5 years. Content for the messages was derived from HRSA and the American Academy of Pediatrics' Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents. The library is available for use at www.hrsa.gov/healthit/mhelath.html.

HHS Office of Minority Health has launched a collaborative effort in partnership with American Association of Diabetes Educators (AADE), AT&T, and Baylor University to investigate the use of smart phones' secure video streaming by demonstrating live clinician/community health worker directed diabetes self-management education courses (see: http://minorityhealth.hhs.gov/templates/content.aspx?ID=9109&lvl=1&lvlID=10). These courses, accompanied by text prompts/reminders, will be offered in healthcare provider shortage areas.

genomes unzipped

public personal genomics

Home | About | Project | Members | Resources | Data/Code | Browser | Subscribe | Contact | Search

Project

The goal of the Genomes Unzipped project is to provide genetic testing consumers with independent and informed analysis of developments in the field of genetics and the genetic testing industry. To better illustrate the uses and limitations of genetic information we have chosen to take an unusual approach: **sharing our own genetic data publicly.**

Who are we?

Members of Genomes Unzipped include active researchers in various fields of genetics, as well as specialists in the legal and public health issues surrounding new genomic technologies. Many of us have also been extensively involved in public communication about genetics.

You can see full profiles of group members here.

What are we doing?

Members of the group have had their DNA tested with a variety of products. **We have released all of these genetic data openly to the public**, both as raw data and in a custom genome browser. As the project proceeds we plan to obtain more genetic tests – up to and including whole genome sequencing – and to continue to release these data to the world.

About

Genomes Unzipped is a group blog providing expert, independent commentary on the personal genomics industry.

About The Project

About The Contributors

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Recent Posts

ACMG guidelines on IFs – responding to the response…

Identification of genomic regions shared between distant relatives

Why predicting the phenotypic effect of mutations is hard

No choice for you

Henrietta Lacks's genome sequence has been publicly available for years

Precision Medicine and Predictive Health

Precision Medicine is molecular pathology based on a patient's genome sequence. It is about finding the mutation or perturbed genetic pathway that is largely responsible for a congenital birth defect, or for a specific cancer.

Predictive Health is about using your own clinical and genomic profile to make better decisions about wellness in an effort to prevent the onset of chronic disease.

Personalized genomic medicine encompasses both, and essentially captures the idea that each person's individual genome sequence will eventually be part of their own medical care.

Types of Predictive Health Information

1. Clinical, Survey, and Anthropomorphic Data

2. Family History

3. Genotypes and Genome Sequence
   - Common variants
   - Rare mutations

4. Gene Expression Profile

5. Metabolome Profile

6. Microbiome Profile

Types of things you might like to know about

1. Your Ancestry

2. Things that are just plain interesting
   - eye and hair color, handedness, unusual features

3. Things that you might be able to act on
   - BRCA, warfarin resistance, metabolic deficiencies

4. (Scary) things that you cannot do anything about
   - Predispositions to late onset disease

5. Things you might want to know about before having kids
   - Mendelian disease carrier status

6. Things you might consider selecting for (or against) in the future
   - Intelligence, athletic ability, good looks
   - OR against depression, complex disease risk

Types of Genetic Test

Table 1 | **Factors considered in selecting a genetic test**

Test	Description	Example	Embryo or blastocyst (pre-implantation genetic diagnosis)	Fetus (prenatal testing)	Child	Adult
Newborn screening	Targeted tests for recessive genetic disorders	Phenylketonuria, cystic fibrosis, sickle-cell anaemia	Not applicable	Not applicable	Tests provided at birth vary by country and state or region	Not applicable
Diagnostic testing	Confirmatory test or differential diagnosis testing for a symptomatic individual	Skeletal dysplasias, thalassaemias, craniosynostoses	Specimen type and limited available amount for sampling may restrict platform selection (for example, WES or WGS versus SNP or STR typing)		Where treatment is desired, turnaround time may restrict platform selection	
			Turnaround time necessary may restrict platform selection			
Carrier testing	Targeted testing for asymptomatic individuals potentially carrying one or more recessive mutation	Cystic fibrosis, thalassaemias, Tay–Sachs disease	Applied typically for rare disease but applicable for other familial mutations		Carrier testing of minors is considered in the context of individual paediatric cases[164,165]	According to standard of care
Predictive testing	Tests for variants causing or associated with diseases or disorders with a hereditary component, usually with adult-onset symptoms	Most cancers, cardiovascular disease, diabetes	Some have discouraged genetic testing of asymptomatic minors for adult-onset conditions			According to standard of care
Pre-symptomatic testing	Tests for variants causing or associated with diseases or disorders known to be inherited in the family, often with adult-onset symptoms	Huntington's disease, haemo-chromatosis, Alzheimer's disease	Some have discouraged genetic testing of asymptomatic minors for adult-onset conditions[152,153]			According to standard of care
			Interpretation of VUSs will depend on presenting phenotypes in the family			
Pharmaco-genetics	Targeted tests for variants associated with pharmaceutical dosage choice or adverse reactions	DNA tests for abacavir, warfarin, carbamazepine	Application not currently conducted but theoretically feasible	Application not currently conducted, but conceivably applicable for screening treatment approaches *in utero*	Pharmacogenetic testing is considered in context of individual paediatric cases[166]	According to standard of care

Katsanis and Katsanis (2013) *Nat Rev Genet.* 14: 415-426

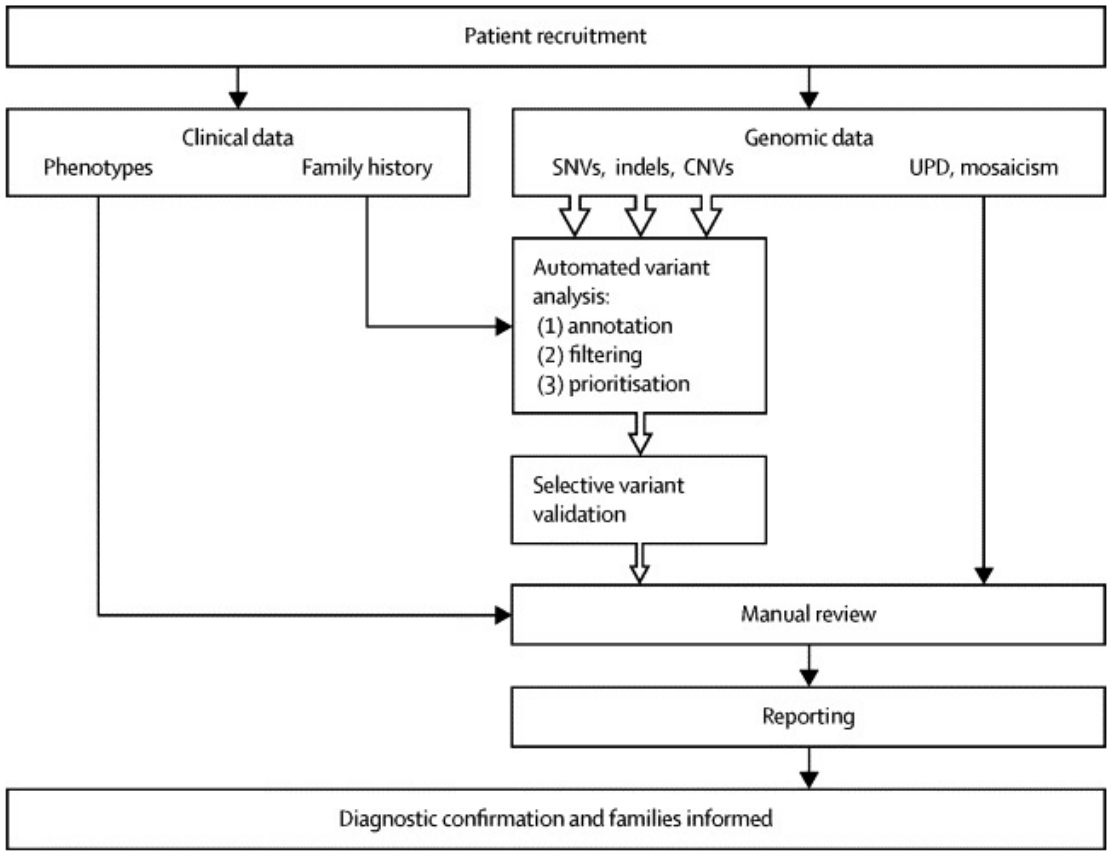
Variation in 12 genomes

Table 1. Summary of genetic variations in genome sequences of twelve individuals.

Subject ID	Eth, sex	Total Variants (>q20)			Coding variants (based on Gencode v7)								Homozygous nsSNPs (based on dbSNP build 137)			
					SNPs				Indels			SVs				
		SNPs	Indels	SVs	S	MS	NS	Splice Overlap	Indels FS	Indels NFS	Overlap	SVs Overlap	#Known nsSNPs	#Unique genes	*#de novo* nsSNPs	#Unique genes
1	Afr, F	4513763	733596	4251	14793	14039	72	98	381	342	137	37	88	77	2	2
2	Afr, F	4472988	754399	4545	14500	13712	66	106	393	335	147	55	71	63	3	3
3	Afr, F	4287739	722922	4447	13755	13166	84	79	374	301	120	43	77	71	3	2
4	Afr, F	4443799	746111	4368	14488	13874	73	104	366	338	142	40	58	56	1	1
5	Cau, F	3734820	645032	3977	11929	11745	62	90	343	307	123	43	57	40	2	2
6	Cau, F	3691337	633475	4114	11757	11457	56	90	317	280	106	49	52	45	none	none
7	Cau, F	3691270	632544	4033	11912	11488	65	71	279	304	116	37	50	44	4	4
8	Cau, F	3722234	641792	4197	11887	11434	64	76	303	299	125	41	55	42	none	none
9	Cau, M	3647944	590064	3828	11619	11255	54	76	311	281	95	38	60	50	2	2
10	Cau, M	3643046	597363	4011	11814	11480	61	85	289	287	109	31	82	65	2	2
11	Cau, M	3650690	602744	3916	11560	11285	60	80	342	280	112	32	72	65	5	5
12	Cau, M	3701558	639005	4739	11842	11708	60	81	334	290	118	37	75	64	5	5
													#Total = 797	#Unique = 575	#Total = 29	#Unique = 25

Patel, Sivadas et al (2013) *Genome Med*. **5**: 58.

The UK Deciphering Developmental Disorders (DDD) Study



The DDD Consortium scanned for CNV and sequenced the exomes of 1133 previously undiagnosed children with developmental disorders, and identified 400 rare, potentially pathogenic variants. Filtering on the biological parents' exomes, they estimate a diagnostic yield of 27%.

Wright et al (2015) *Lancet* **385**: 1305-1314.

StatSeq: Genomic Analysis in the PICU in 24 hours

Results of five large, retrospective case studies of the diagnostic rate of genome or exome sequencing in children with suspected genetic diseases, particularly neurodevelopmental disabilities

Reference	Number of subjects	Disease	Age in years (mean or median)	Diagnosis rate	De novo mutation	Management changed by diagnosis
[9]	100	NDD	7	47 %	51 %	49 %
[10]	78	NDD	9	41 %	56 %	100 %
[11]	1756	Any	6	27 %	49 %	Not examined
[12]	520	Any	<18	26 %	50 %	Not examined
[13]	1133	NDD	6	27 %	62 %	Not examined

Stephen Kingsmore, formerly of Children's Mercy Hospital in Kansas City, now at Rady Children's in San Diego, is pioneering efforts to sequence the genomes of very sick newborns within 24 hours. In a pilot of 35 kids, 20 were 'diagnosed', 4 of these were able to have positive interventions, and 6 were given immediate palliative care.

Kingsmore et al (2015) *Genome Med*. **7**: 82.

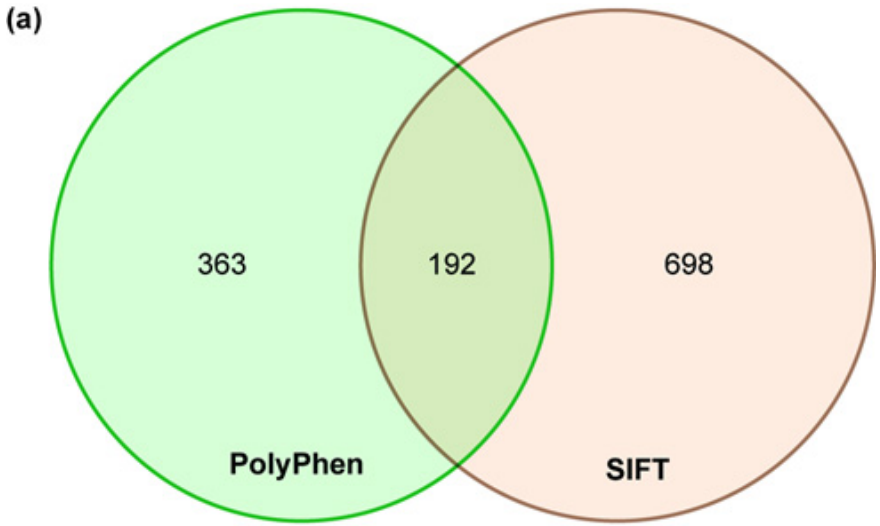
Resilience and Rare Pathogenic Variants

Chen et al (2016) *Nature Biotech* **34**: 531-538 surveyed the exomes of 590,000 people and discovered 13 cases where a healthy adult is homozygous for an unambiguously pathogenic rare mutation. 3 of them were in the CFTR They conclude that for rare pathogenic alleles with a MAF < 0.1%, penetrance is typically about 90%.

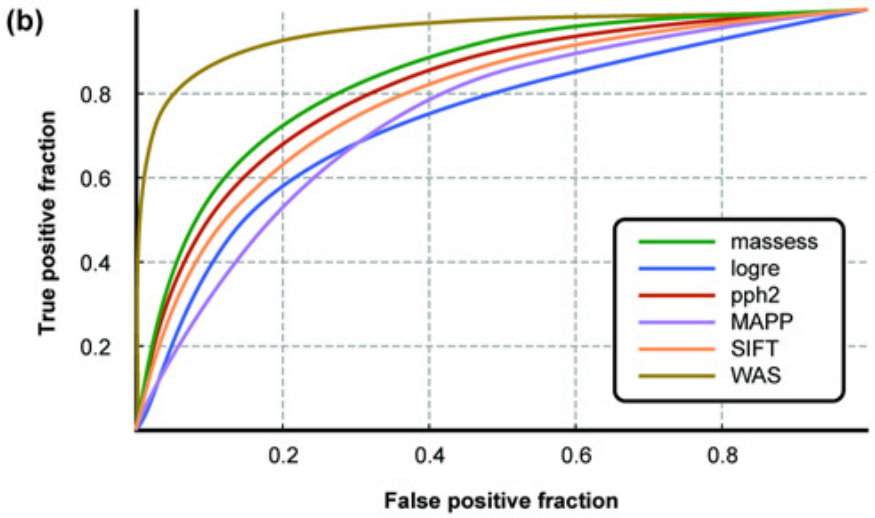
Narisamhan et al (2016) *Science* **352**: 474-477 surveyed the exomes of 3,222 Britons of Pakistani heritage with high consanguinity, and found that one third of them are homozygous for a loss of function allele embedded in an autozygous stretch. These cases were 13% less prevalent than expected, implying lethality, and that we each carry 1.6 lethal-equivalent mutations. But also that our genomes are full of rare mutations that look pathogenic but are not.

Zanoni et al (2016) *Science* **351**: 1166-1171 surveyed the exomes of 328 people in the upper 5% of HDL, found one case homozygous for a knock-out scavenger receptor, and argued that it may be causing mild heart disease. This study to me highlights the extreme difficulties we face predicting disease from genome sequences.

Predicting Pathogenicity



Predictions on the Venter Genome for 7,534 non-synonymous SNPS



WAS is a consensus deleterious score (Condel) averaging the others

Katsanis and Katsanis (2013) *Nat Rev Genet*. 14: 415-426

Levels of Evidence

1. Previously ascribed clinical function
2. Bioinformatic prediction from protein structure or attributes
3. Evolutionary conservation
4. Experimental validation (animal models, cellular manipulation, in vitro studies)

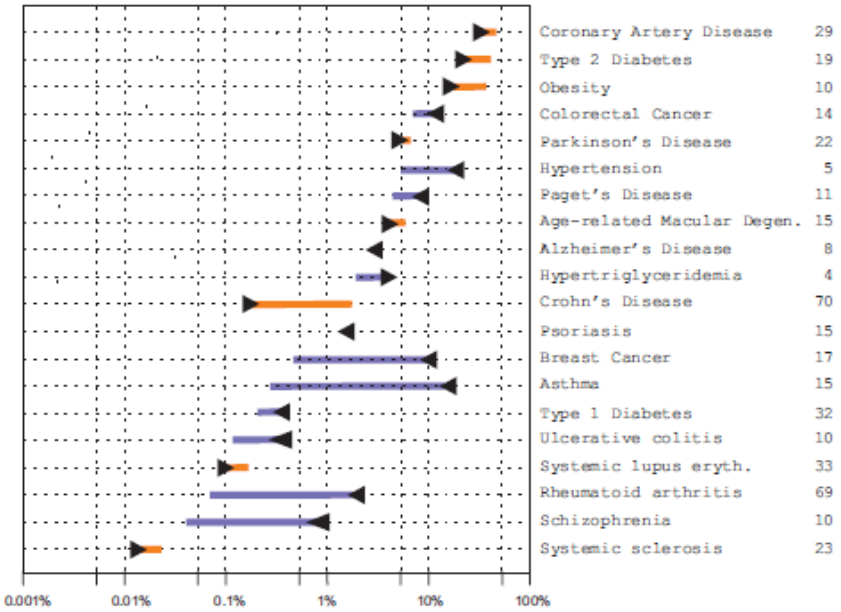
5. BUT, it is easy to get trapped in a genetically deterministic worldview:
   - even Mendelian variants have incomplete penetrance
   - expressivity is modified by genetics and environment
   - deleterious to the protein is not necessarily deleterious to the organism

6. We do not have parallel methods for evaluating function of regulatory variants

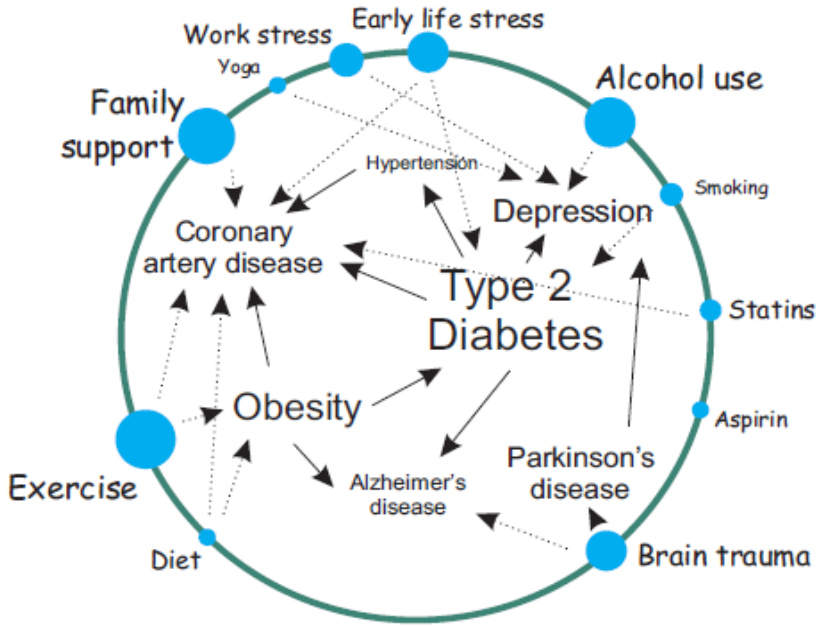
Bottom line: N = 1 genetics is in its infancy

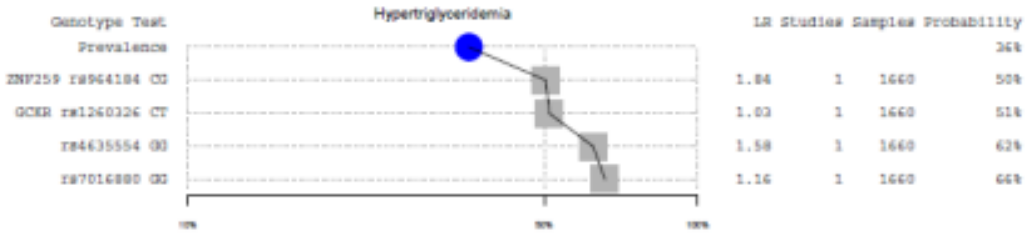
Common Variant Risk-o-Grams

A.



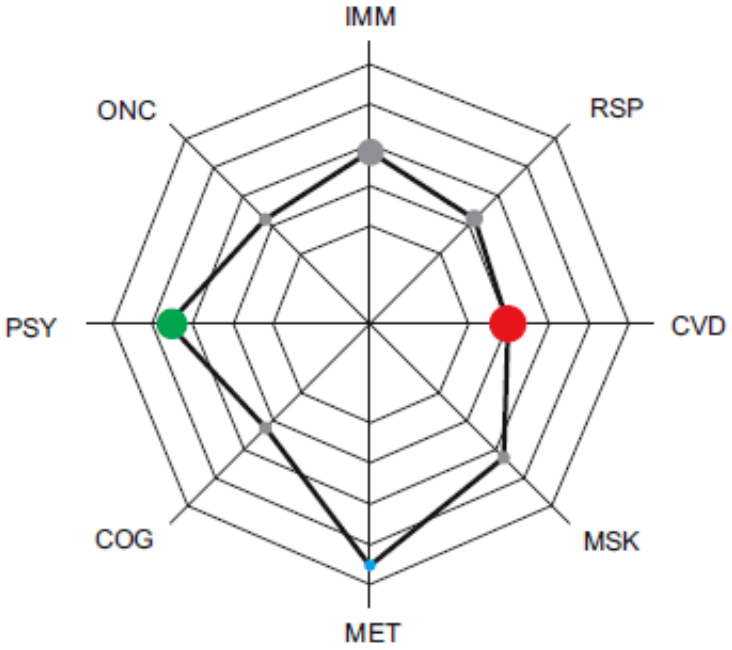
B.

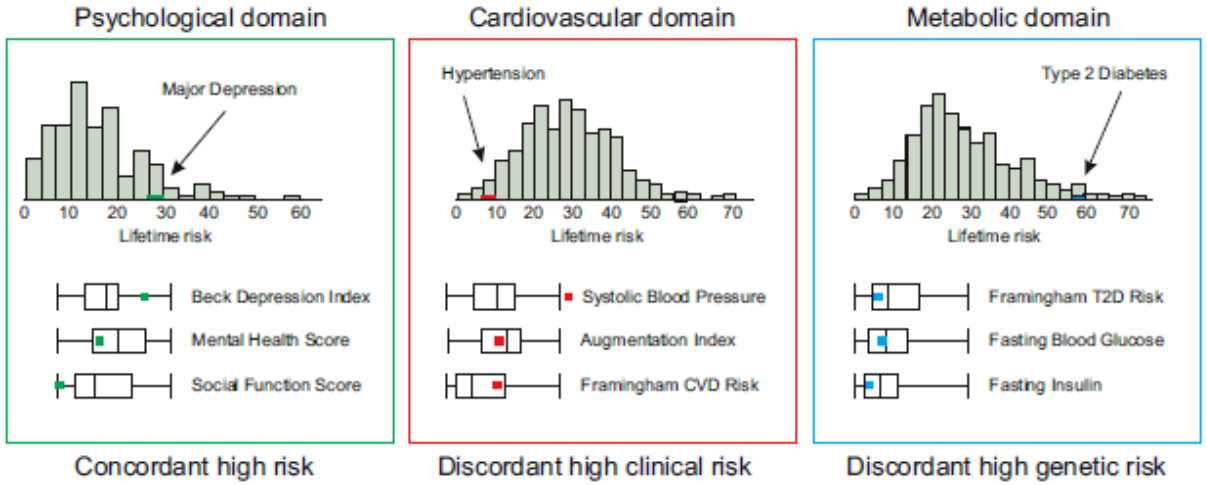




Ashley et al (2010) *Lancet* 375: 1525-1535

A Sample Predictive Health Profile





Homozygous Variants of Interest

rs28940292	MFN2	Thought to cause Charcot-Marie-Tooth disease
rs2266780	FMO3	Cause of mild trimethylaminurea (Fish-Odor Syndrome)
rs2871156	MYH6	Associated with familial hypertrophic cardiomyopathy
rs7412	APOE2	On protective allele for Alzheimer's Disease, but may promote weight gain

Heterozygous Carrier Status

rs113991360	CFTR $_{\Delta}$F508 known causal variant for cystic fibrosis
15q12 CNV	Duplication in UBE3A ubiquitin ligase associated with autism

Patel, Sivadas et al (2013) *Genome Medicine* 5: 58

Prediction and Stratification

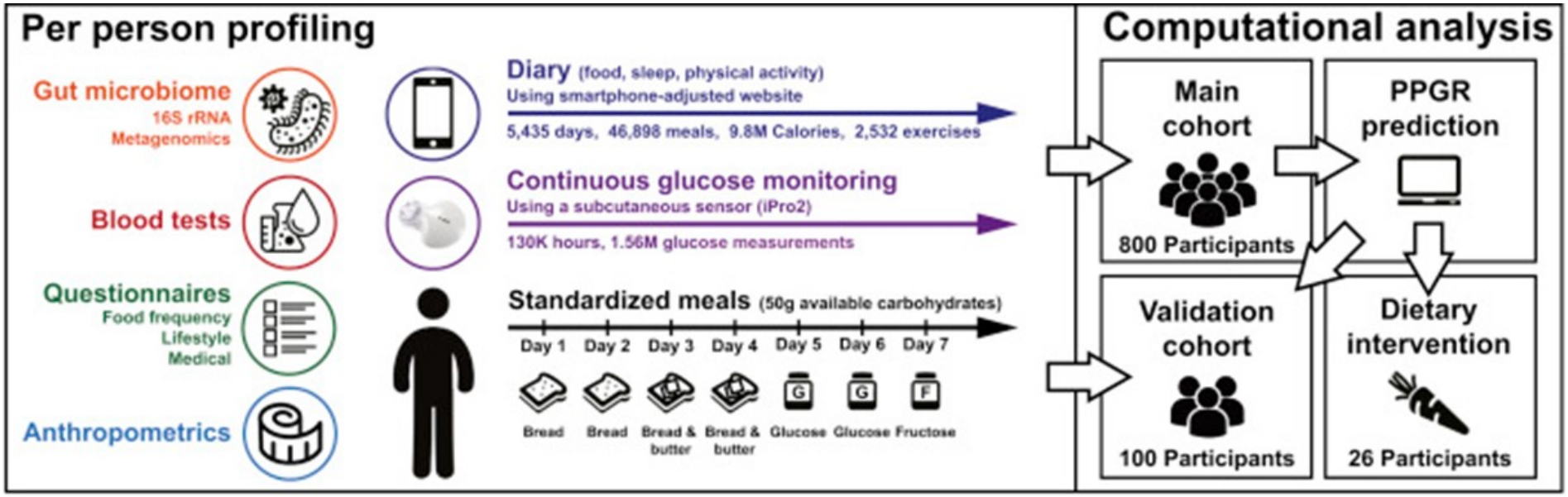
For complex traits, the upper limit of the correlation between an as yet unobserved phenotype and a genetic predictor is h, the square root of the heritability (h2).

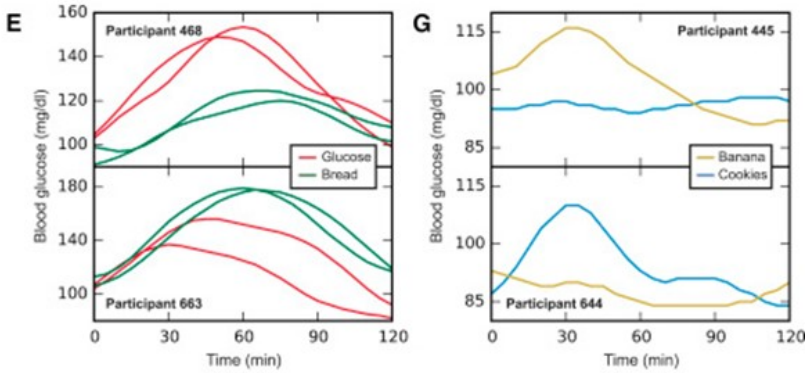
Imagine if we had a perfect genetic predictor for height (e.g. all causal variants known without error) then the prediction error for any individual would be 7*√(1-0.8) = 3.1cm, assuming that h^2=0.8 and that the standard deviation for height is 7cm. So we would predict someone's height with a 95% confidence interval of about +/-6cm. The top and bottom 10% of any sample are generally 1.6 standard deviation units above or below the average. For height that translates to 1.6*7*√(0.8) = 10cm, so individuals at the genetic tails will tend to be 20cm apart. That's about the same as we get from knowing the parents.

However, the point is not to predict so much as to classify. Personalized medicine is about targeting therapy: who is most likely to need the drug; or perhaps more importantly, who is unlikely to benefit from it and hence can be spared the expense and the common deleterious side-effects.

Some suspect, though, that genetic prediction may also be used to guide pre-implantation diagnosis: given a choice among 10 embryos, how many parents would choose the one with a probable IQ 10 points higher than the mean?

Microbiome-directed personalized nutrition





How can pre-diabetics control their blood glucose given that we each respond differently to different diets? In part, by monitoring our micriobiome, which in combination with other tests, is remarkably predictive.

Zeevi et al (2015) *Cell* **163**: 1079-1094