





Top 10 Genomic Markers & What to Do With Them (and use of AI for Wellness and Prevention)

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Chief Innovation Officer and Founder
Pathway Genomics

Age Management AMMG Medicine Group

24th Clinical Applications for Age Management Medicine
April 26-29, 2018



Medical DATA ISSUE

BIG DATA AND
'OMICS IN MEDICINE

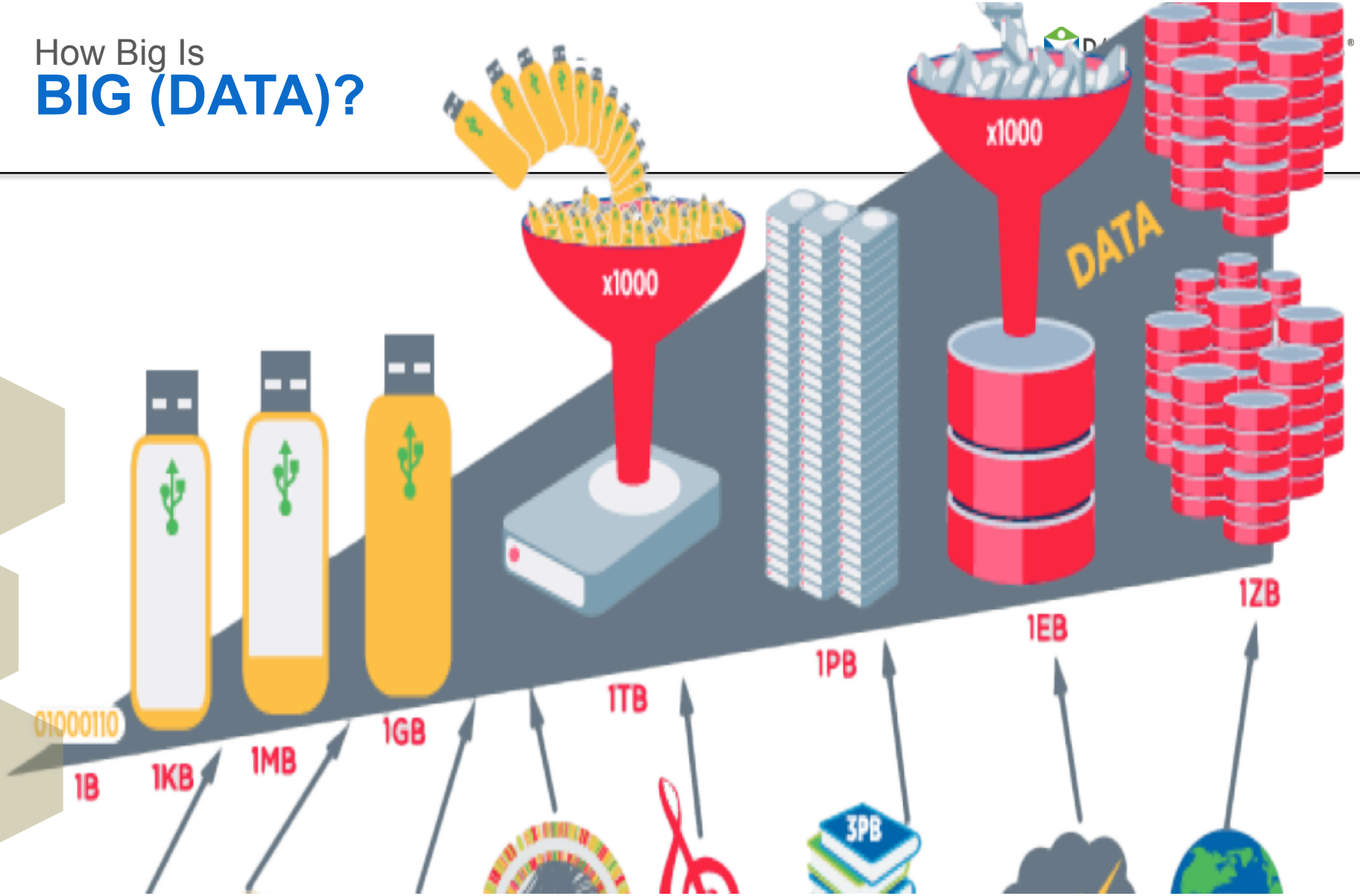
90% of all the world's data was created in the last 2 years

Medical information **doubles every 3 years,** and by 2020 will **double every 73 days.**

Source: Gartner 2013, IBM 2014

How Big Is

BIG (DATA)?



500 Gigabytes! = **Whole genome sequence**

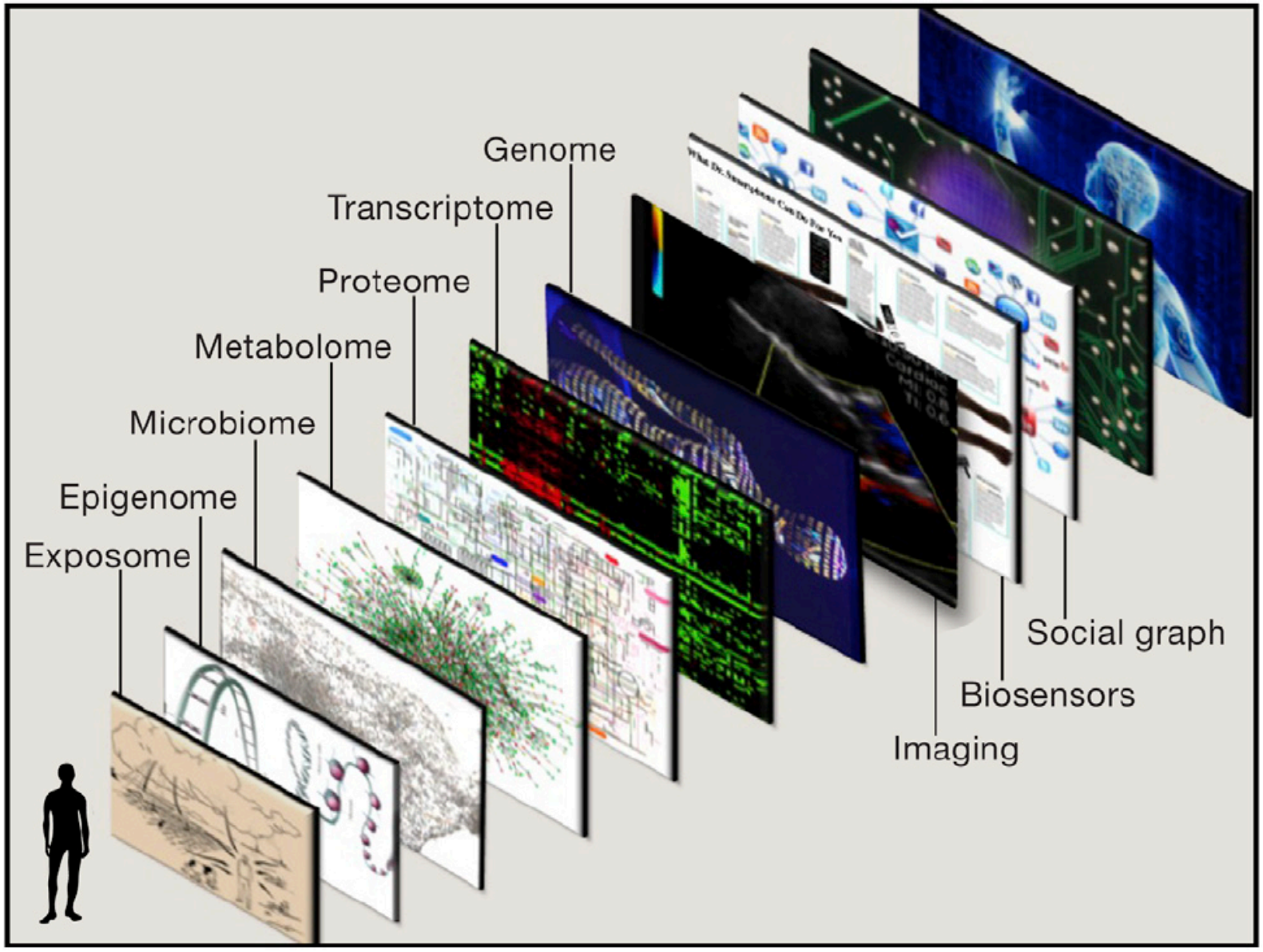
All the word's recorded music as of 2011

Library of congress digital holdings as of 2012

Weather modeling anticipated to produce first single-discipline exabyte dataset

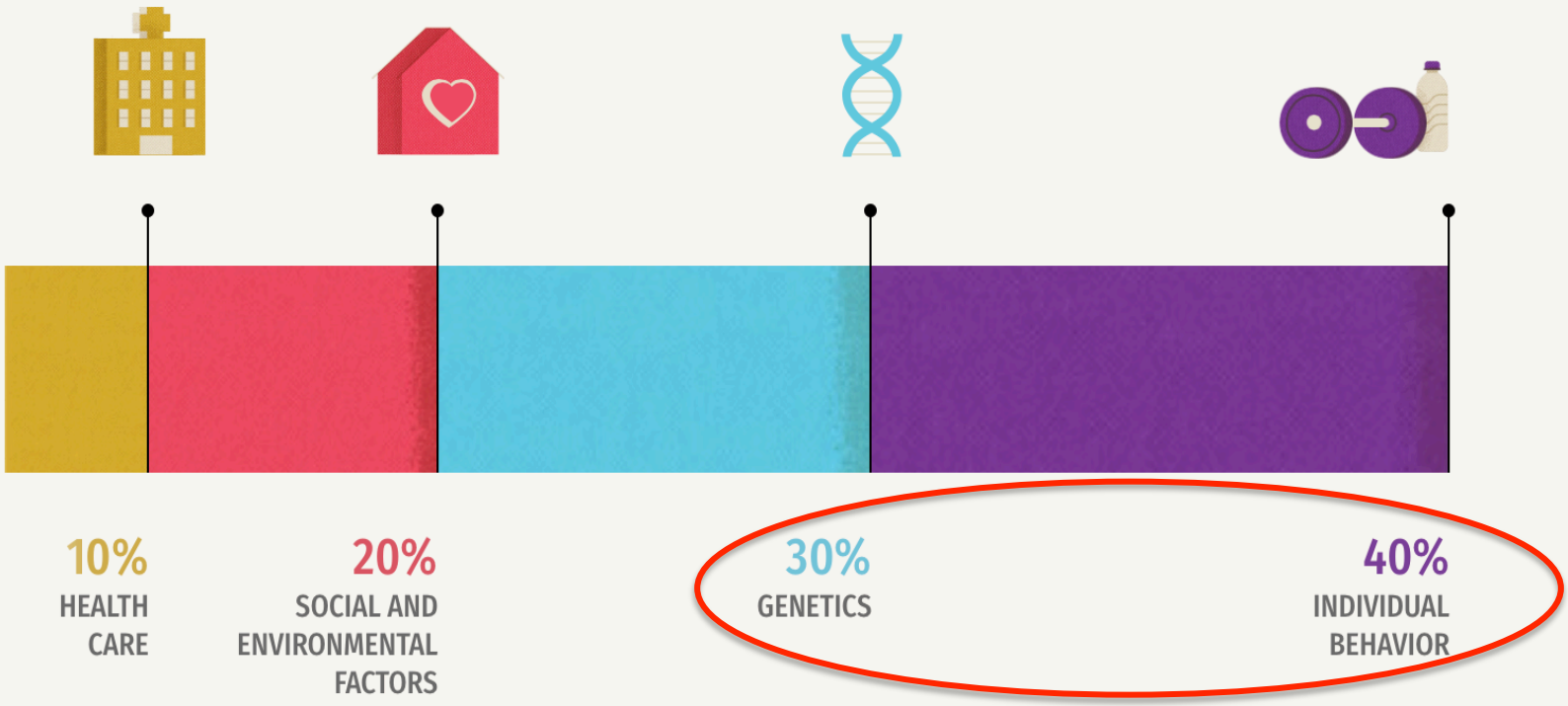
In 2010 the world produced 1.27b

Healthcare is a data and systems problem…..



aetna®

What Really Determines Health Outcomes?



Source: AETNA 2017

CONTRIBUTIONS TO LONGEVITY



- Genetics : 25%
- Lifestyle: 75%



Hjelmborg JB, Iachine I, Skytthe A, et al. Genetic influence on human lifespan and longevity. *Human Genetics*. 2006;119(3):312–321

Tan Q, Zhao JH, Kruse T, Christensen K. Power Estimation for Gene-Longevity Association Analysis Using Concordant Twins. *Genetics Research International*. 2014;2014

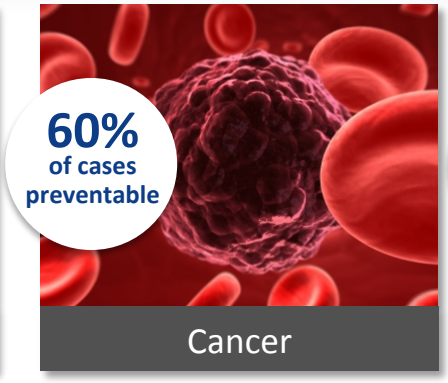
Employer Healthcare Costs Out of Control

87.5% of all health-care claims costs are due to an individual's lifestyle.

-- Source: Indiana University-Purdue University, Fort Wayne (IPFW) Study, 2006

74% OF ALL COSTS ARE CONFINED TO FOUR CHRONIC CONDITIONS:









Over $120 Billion in annual costs (hospital stay, morbidity, mortality) due to drug compliance, correct dosing, adverse effects of wrong medication, correct tailored medication, account for >100,000 deaths in U.S. per year. $3T Healthcare budget.

DNA not Completely Deterministic

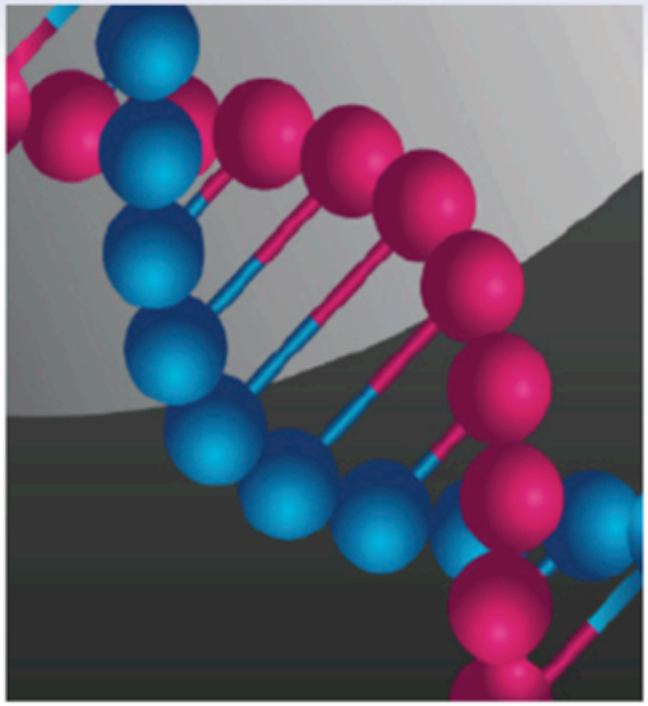






Why Is There Phenotypic Variation?

Old Thinking
The Genome is constant



New Understanding
SNPs, and genetic flexibility



The Human
GENOME AND MEDICAL DATA



22,000 GENES

6 BILLION
DNA LETTERS

$1,000
COST TO SEQUENCE

49
CHROMOSOMES



70%
OF PATIENT'S PERMANENT HEALTH RECORD IS MADE UP OF CLINICAL LABORATORY **TEST DATA**

Still at 1% level of human genome understanding

Human Variation

- 99.9% nucleotide bases are exactly the same in all humans
- 0.1% is responsible for phenotypic variation
- Approximately a million locations where single-base DNA differences (SNPs) occur in humans and has an “affect”

For example: AGGCCTA to AGGCTTA

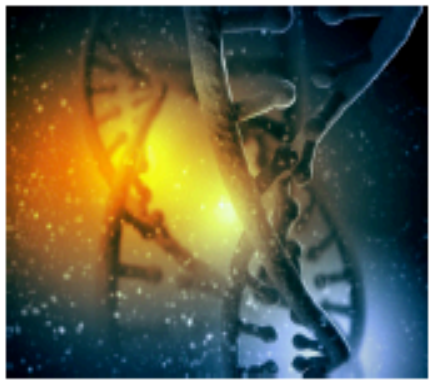
- Can affect disease and response to:
  - Pathogens
  - Medicine
  - Exercise
  - Nutrition



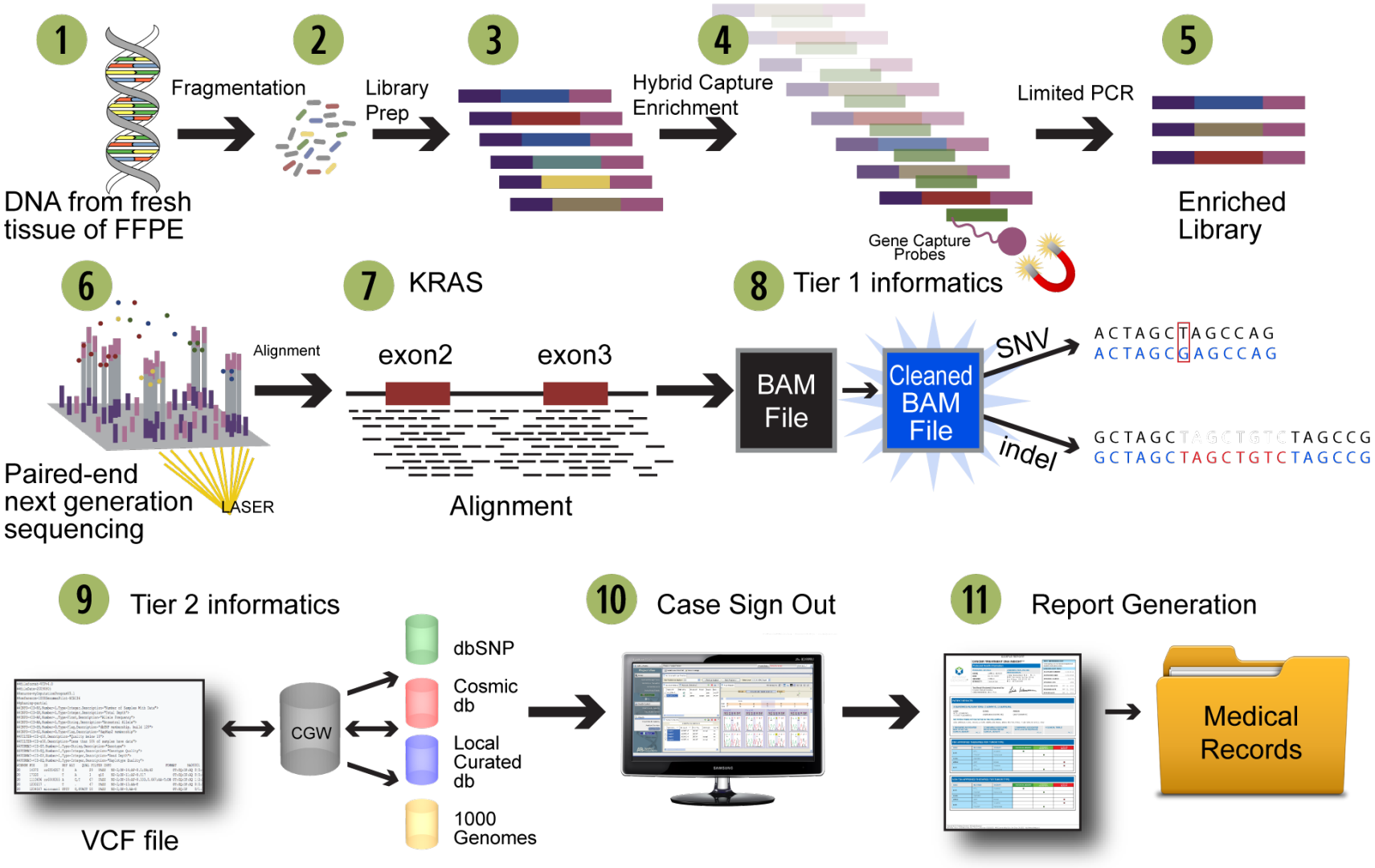
Human Genomic FEATURES

- About **40 million common polymorphic sites** in the genome of Homo sapiens
- An individual carries **3-4 million common variant** alleles
- An individual carries 200,000-500,000 rare variants
- Copy number variants of repeat sequences are common and cover about 10% of the human genome
- Less than 21,000 protein-coding genes
- About 1000 miRNAs, 9000 other small RNAs and 10,000 long RNAs are transcribed
- About 1800 transcription factors binding at about 8% of the genome: an average of about 12 per protein-coding gene





Workflow of DNA Report Generation



Genetic Testing 2017

"The world genomics market is expected to exceed $7.5 billion by 2017, and $25 billion by 2020."

– Nature Magazine

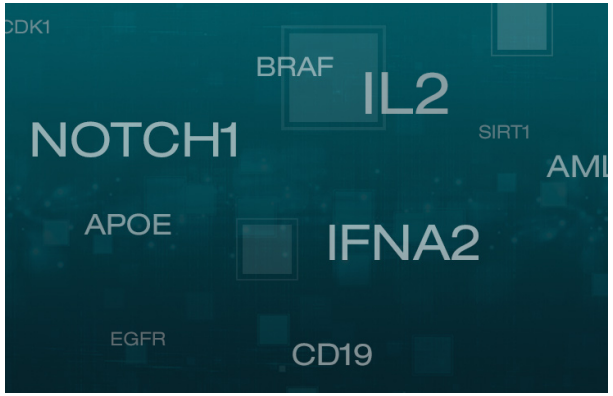
The global genomics industry is forecast to record in excess of 18% yearly growth for the ten-year period ending 2017, according to research from many Industry Experts.



Where Genetics is Going

Diagnosis vs Prevention

- Mendellian
- Carrier
- H-Dominate

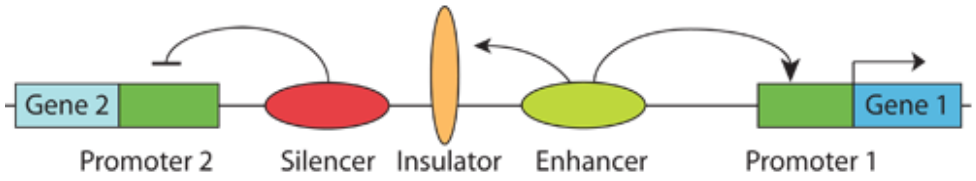


Less genes/traits

Risk

Action!

- Chronic conditions - behaviors
- Personalized therapy
- Pharmacogenetics



-Many more genes/trait

-Regulatory Elements

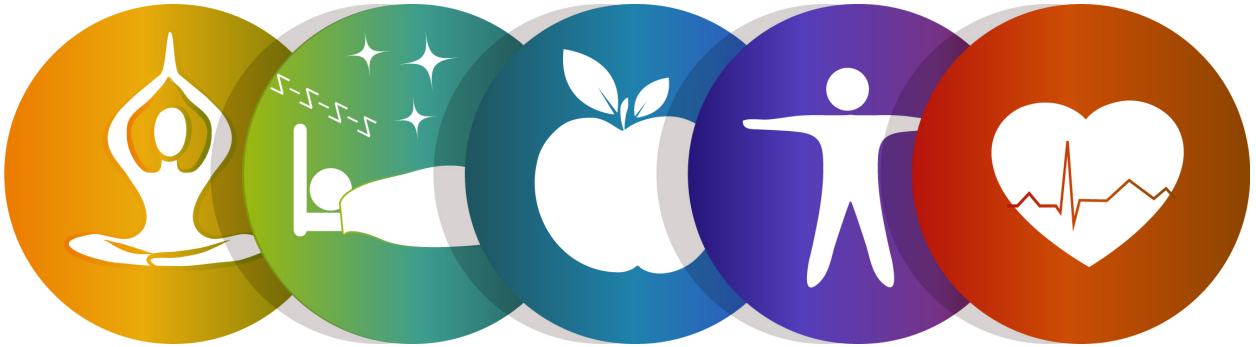
-Clinical info

Recommendations by Genetics

- Drug
- Nutrition
- Exercise
- Behavior Modification
- Recessive Pre-natal
- Predisposition

Wellness vs Treatment





10 Common Conditions with Genes

Obesity	FTO, MC4R (GRS)
Heart disease	(GRS) 67 genes
T2D	TCF7L (GRS)
Cancer	BRCA, MYC, many
Mental Health	Lrk, SLN
Nutrition/Metabolism	PPARg, FTO, many
Drug Metabolism	Cyp2C9
Skin (psoriasis, acne)	CARD14, TNF, IL (GRS)
Hereditary/carrier	CF, many
Longevity	Foxo, Klotho, Sirts

SNPedia

NCBI

dbSNP
Short Genetic Variations

NIH U.S. National Library of Medicine

Genetics Home Reference
Your Guide to Understanding Genetic Conditions

Metabolism Genetics

Condition	Gene	Marker(s)
Adiponectin	ADIPOQ	rs17366568
Blood sugar	MTNR1B, ADRA2A, CRY2, ADCY5, SLC2A2, FADS1, PROX1, GCK, G6PC2, GLIS3, GCKR, MADD, C2CD4B, DGKB-TMEM195, SLC30A8, TCF7L2	rs10830963, rs10885122, rs11605924, rs11708067, rs11920090, rs174550, rs340874, rs4607517, rs560887, rs7034200, rs780094, rs7944584, rs11071657, rs2191349, rs13266634 rs7903146
HDL Cholesterol-Exercise	PPARD	rs2076167
Insulin resistance-exercise	LIPC	rs1800588
LDL Cholesterol	ABCG8, TIMD4-HAVCR1, MAFB, HNF1A, CELSR2, APOB, LDLR, HMGCR, NCAN, PCSK9, APOE-APOC1-APOC4-APOC2, LDLR	rs6544713, rs1501908, rs6102059, rs2650000, rs12740374, rs515135, rs6511720, rs3846663, rs10401969, rs11206510, rs4420638, rs1985096, rs2738446, rs4953023
Metabolism	LEPR	rs1805094
MUFA	ADIPOQ, PPARG	rs17300539, rs1801282
PUFA	PPARG	rs1801282
Obesity	FTO, MC4R	rs9939609, rs17782313
Triglycerides	ANGPTL3, ZNF259, APOB, FADS1-FADS2-FADS3, GCKR, LPL, MLXIPL, NCAN, PLTP, TRIB1, XKR6-AMAC1L2	rs10889353, rs964184, rs7557067, rs174547, rs1260326, rs12678919, rs714052, rs17216525, rs7679, rs2954029, rs7819412, rs894210

Actionable Genetics

Tell me what to do!



(please)

Tell Me What to do! – *MD version*

The role of the clinician in the multi-omics era: are you ready?

Clara D. M. van Karnebeek[1,2,3] · Saskia B. Wortmann[4,5,6] · Maja Tarailo-Graovac[2,7,8,9] · Mirjam Langeveld[10] · Carlos R. Ferreira[11] · Jiddeke M. van de Kamp[12] · Carla E. Hollak[10] · Wyeth W. Wasserman[2,7] · Hans R. Waterham[13] · Ron A. Wevers[14] · Tobias B. Haack[15] · Ronald J.A. Wanders[13] · Kym M. Boycott[16]

Received: 1 October 2017 / Revised: 10 December 2017 / Accepted: 12 December 2017
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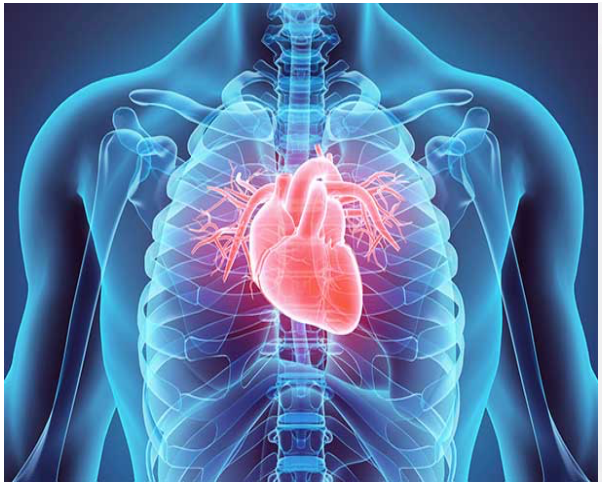
*43% of PCPs in survey anticipated ordering genetic or genomic tests within the next 6 months, while roughly 60% to 75% of ob/gyn specialists, surgeons, pediatricians and psychiatrists said they would**

Review article

Implementing genome-driven personalized cardiology in clinical practice

Ares Pasipoularides ✉

⊞ Show more





Source: Sanders, 2018

Causal Factors of Overweight and Obesity



Lifestyle Choices

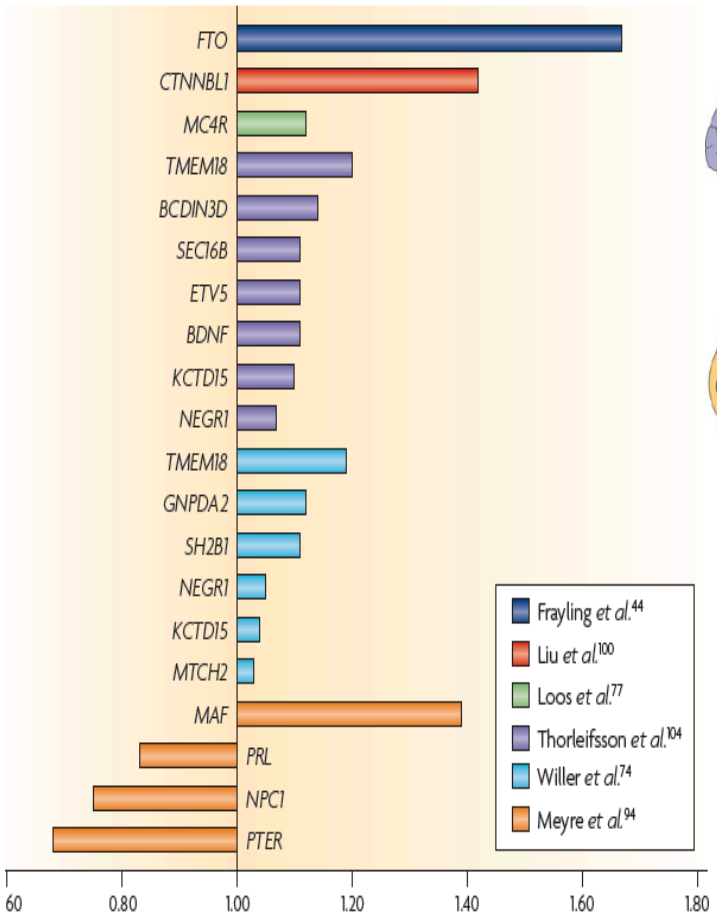
- Overeating or eating nutrient poor foods
- Abnormal eating patterns
- Lack of exercise, excessive sedentary time, and sedentary

Genetics and Weight Management

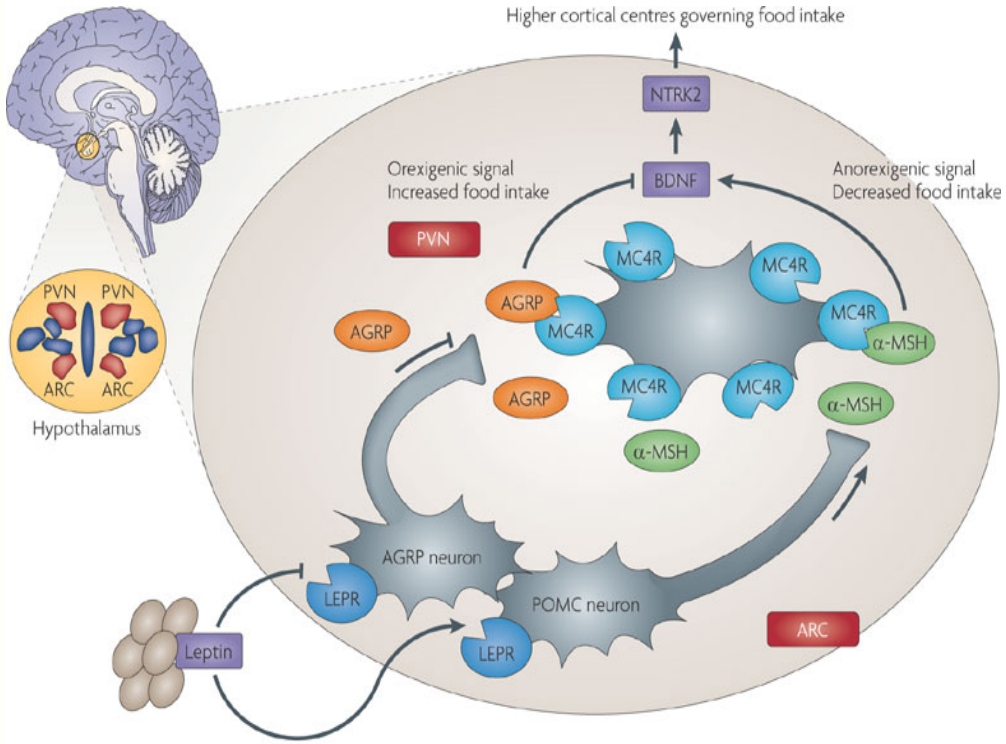
- Variable genetic predisposition (40-70%)
- Genetic predisposition made worse by poor nutrition
- Genetic predisposition made worse by lack of physical activity

Source: Bouchard 2011 (Pennington), Qi 2012 (Harvard)

Obesity and genetics



iqure 2 | **Odds ratios for genes associated with obesity in genome-wide studies.**



Source: Nature 2012

Gene-based PN targeted to APOE was more effective in reducing SFA intake than standard dietary advice

August 10, 2016 as doi: 10.3945/ajcn.116.135012

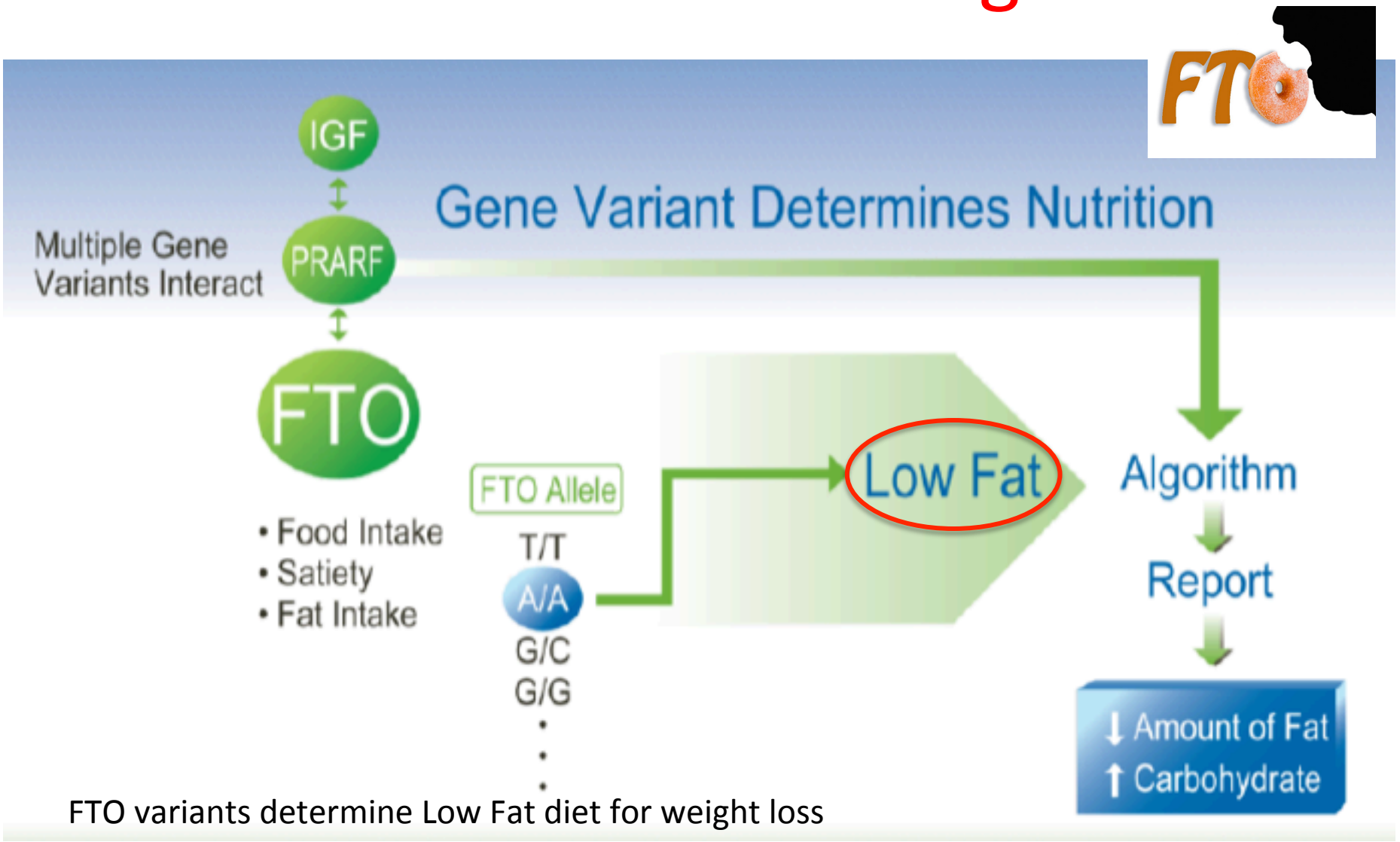
The effect of the apolipoprotein E genotype on response to personalized dietary advice intervention: findings from the Food4Me randomized controlled trial[1]

Rosalind Fallaize,[2] Carlos Celis-Morales,[3] Anna L Macready,[2] Cyril FM Marsaux,[4] Hannah Forster,[5] Clare O'Donovan,[5]

food4me.org



Actionable Genetics – FTO gene



FTO variants determine Low Fat diet for weight loss

Sources: Li, 2016; Sanders 2016

Actionable Genetics – FGF21 gene

450,000 cohort
GWAS



A Common Allele in FGF21 Associated with Sugar Intake Is Associated with Body Shape, Lower Total Body-Fat Percentage, and Higher Blood Pressure

Timothy M. Frayling[10], Robin N. Beaumont, Samuel E. Jones, Hanieh Yaghootkar, Marcus A. Tuke, Katherine S. Ruth, Francesco Casanova, Ben West, Jonathan Locke, Seth Sharp, Yingjie Ji, William Thompson, Jamie Harrison, Amy S. Etheridge, Paul J. Gallins, Dereje Jima, Fred Wright, Yihui Zhou, Federico Innocenti, Cecilia M. Lindgren, Niels Grarup, Anna Murray, Rachel M. Freathy, Michael N. Weedon, Jessica Tyrrell, Andrew R. Wood

Multi-SNP Algorithm (!)

1. If [{(Risk ≥ High* for LDL) or (Risk ≥ High* for Triglycerides)} and {(Risk < High* for HDL) and (Risk < High* for Blood Sugar)}], then “Low Fat”

2. If [{(Risk ≥ High* for HDL) or (Risk ≥ High* for Blood Sugar)} and {(Risk < High* for LDL) and (Risk < High* for Triglycerides)}], then “Low Carb”

3. If [{(Risk ≥ High* for LDL) or (Risk ≥ High* for Triglycerides)} and {(Risk ≥ High* for HDL) or (Risk ≥ High* for Blood Sugar)}], then “Balanced diet”

4. If {LOW disease risk*} and {(FTO rs9939609 = AA) or (APOA2 rs5082 = CC) or (LIPC rs1800588 = TT)}, then “Low Fat”

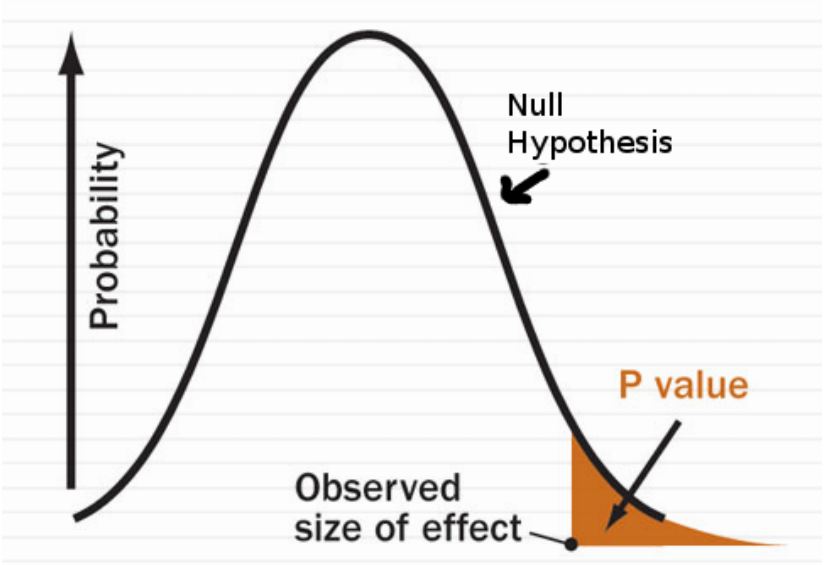
5. If {LOW disease risk*} and {(KCTD10 rs10850219 = GG) and (MMAB rs2241201 = CC)}, then “Low Carb”

6. If {LOW disease risk*} and {(Response to Monounsaturated Fats = Increased Benefit)}, then “Mediterranean diet”

7. If {none of the above}, then “Balanced diet”

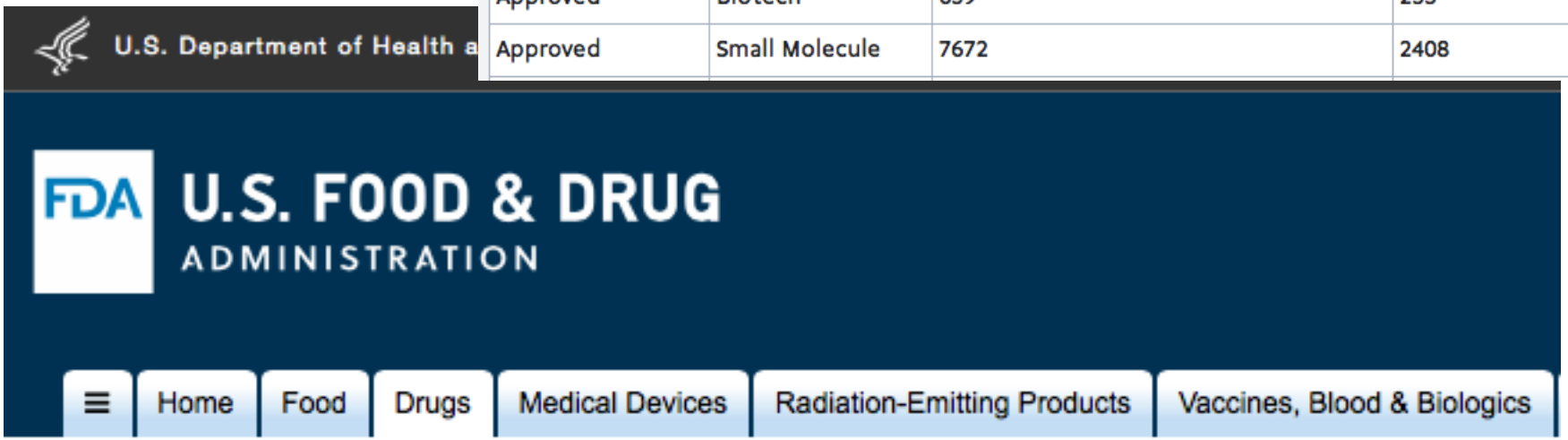
Algorithm Constraints (Curation)

Ethnicity
Phenotype in same direction
Large population study
More than one study
P-Value
Effect size
SNP Weights



Pharmacogenetics

DRUG GROUP	DRUG TYPE	Nº DRUG-TARGET ASSOCIATIONS	Nº UNIQUE TARGETS
Approved	Biotech	639	253
Approved	Small Molecule	7672	2408



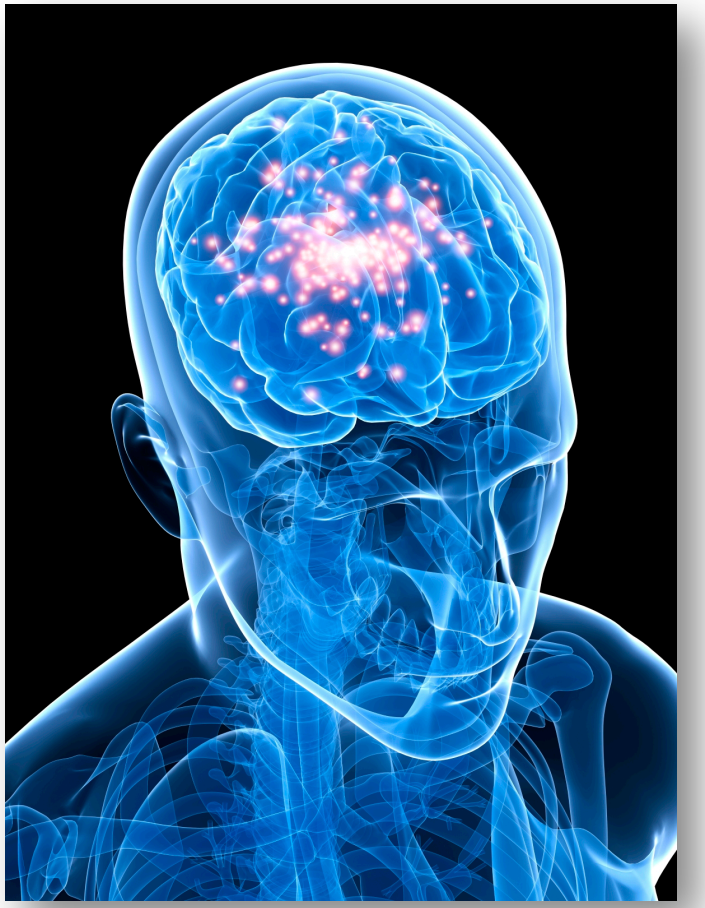
Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions
Clozapine	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Codeine	Anesthesiology	CYP2D6	Boxed Warning, Warnings and Precautions, Use in Specific Populations, Patient Counseling Information

FDA-Approved Drugs Requiring Genetic Test Label

Drug	Genetic Marker	Application
Imipramine	CYP2D6	Psychiatry
Indacaterol	UGT1A1	Pulmonary
Irinotecan	UGT1A1	Oncology
Lansoprazole	CYP2C19	Gastroenterology
Maraviroc	CCR5	Antiviral
Metoprolol	CYP2D6	Analgesic
Modafinil	CYP2D6	Psychiatry
Nefazodone	CYP2D6	Psychiatry
Nilotinib (2)	UGT1A1	Oncology
Nortriptyline	CYP2D6	Psychiatry
Omeprazole	CYP2C19	Gastroenterology
Panitumumab (2)	KRAS	Oncology
Pantoprazole	CYP2C19	Gastroenterology
Paroxetine	CYP2D6	Psychiatry
Perphenazine	CYP2D6	Psychiatry
Phenytoin	HLA-B*1502	Neurology
Pimozide	CYP2D6	Psychiatry
Prasugrel	CYP2C19	Cardiovascular

Drug	Genetic Marker	Application
Propafenone	CYP2D6	Cardiovascular
Propranolol	CYP2D6	Cardiovascular
Protriptyline	CYP2D6	Psychiatry
Quinidine	CYP2D6	Cardiovascular
Rabeprazole	CYP2C19	Gastroenterology
Risperidone	CYP2D6	Psychiatry
Tamoxifen (2)	Factor V Leiden (FV)	Oncology
Terbinafine	CYP2D6	Antifungal
Tetrabenazine	CYP2D6	Neurology
Thioridazine	CYP2D6	Psychiatry
Ticagrelor	CYP2C19	Cardiovascular
Tolterodine	CYP2D6	Reproductive
Tramadol and Acetaminophen	CYP2D6	Analgesic
Trimipramine	CYP2D6	Psychiatry
Vemurafenib	BRAF	Oncology
Venlafaxine	CYP2D6	Psychiatry
Voriconazole	CYP2C19	Antifungal

Parkinson Genes and Variants



Parkinson's Disease
Volume 2017 (2017), Article ID 4318416, 11 pages
https://doi.org/10.1155/2017/4318416

Source: Silva, 2017

SNCA (REP1 repeat polymorphism)
LRRK2 (number of exonic variants)
BST1
Park16
GAK
HLA
MAPT

↓↑ 25%

Alpha-synuclein protein misfolding is a major proposed theme

Alcohol
Caffeine
Smoking

↓ RISK!

T2D Genetics

Review

Nutrigenetics and Nutrigenomics Insights into Diabetes Etiopathogenesis

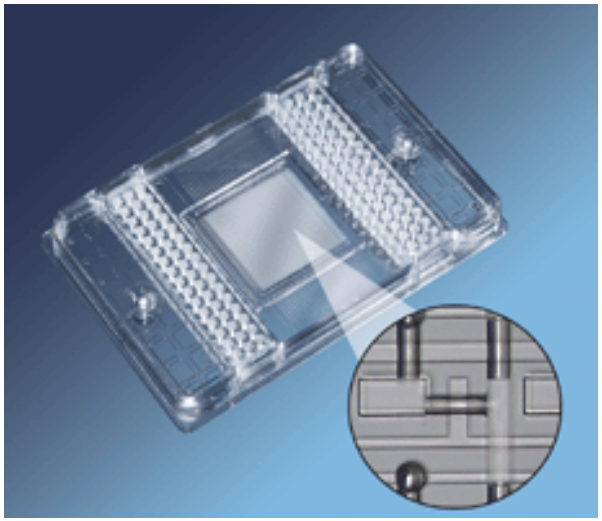
Genoveva Berná [1,2], María Jesús Oliveras-López [1], Enrique Jurado-Ruiz [1,2], Juan Tejedo [2,3], Francisco Bedoya [2,3], Bernat Soria [1,2] and Franz Martín [1,2,*]

[1] Department of Stem Cells, Andalusian Center of Molecular Biology and Regenerative Medicine, University Pablo Olavide (CABIMER-UPO), Seville 41091, Spain;

Many involved with lipid regulation

Direct gene target for Sulphonylurea's

ADAM30	CACNA1D	CDKAL1	GAS1	HMGA2	WWOX
SLC44A3	PPARG	C6orf57	CAMK1D	TMEM19	SGSM2
SNX7	SYN2	TP53INP1	CDC123	LGR5	SRR
PROX1	ZPLD1	GCK	VPS26A	TSPAN8	HNF1B
CR2	PLS1	CPVL	KIF11	IGF1	LPIN2
PCNXL2	SLC2A2	JAZF1	HHEK	HNF1A	PAPL
BCL11A	PEX5L	DGKB	ADRA2A	TRIAP1	PEPD
THADA	IGF2BP2	ACHE	TCF7L2	SPRY2	GIPR
GCKR	ST6GAL1	GCC1	TCERG1L	C14orf70	HNF4A
ITGB2	PPP2R2C	PAX4	CRY2	ATP10A	HUNK
RBM43	WFS1	KLF14	MADD	C2CD4A	PCBP3
RND3	MAEA	ZMAT4	KCNJ11	C2CD4B	SEZ6L
ITGB6	ZBED3	KCNU1	GALNTL4	VPS13C	DUSP9
RBMS1	AP3B1	CSMD1	LOC72903	LARP6	
GRB14	CETN3	SLC30A8	KCNQ1	HMG20A	
G6PC2	LOC72901	CDKN2A	ARAP1	ZFAND6	



WELLNESS PROGRAM – METABOLIC RISK

ROI !



FTO – Satiety, CHO metabolism, energy balance
MC4R – Increased appetite, food intake
DRD2 – higher BMI, reward center

Aetna

TABLE 3. Clinical Outcomes

Clinical Measure	Control ($N=945$)*	Invited (Groups 1 and 2 Combined) ($N=1890$)*	P
Waist (inches)	−0.48 ($n=653$)	−0.77 ($n=1311$)	0.06
Triglycerides (mg/dL)	−2.56 ($n=737$)	−8.12 ($n=1477$)	**0.05**
HDL (mg/dL)	1.44 ($n=722$)	1.63 ($n=1475$)	0.60
Glucose (mg/dL)	−0.10 ($n=723$)	2.11 ($n=1499$)	0.08
BP systolic (mm Hg)	−1.48 ($n=650$)	−0.97 ($n=1306$)	0.47
BP diastolic (mm Hg)	−1.47 ($n=650$)	−0.86 ($n=1306$)	0.22
	Control ($N=945$)	**Participants (Groups 1 and 2 combined) ($N=264$)**	**P**
Waist (inches)	−0.48 ($n=653$)	−1.06 ($n=222$)	**0.02**
Triglycerides (mg/dL)	−2.64 ($n=737$)	−18.47 ($n=235$)	**<0.01**
HDL (mg/dL)	1.44 ($n=722$)	2.81 ($n=235$)	**0.02**
Glucose level (mg/dL)	−0.10 ($n=723$)	−0.91 ($n=234$)	0.68
BP systolic (mm Hg)	−1.48 ($n=650$)	−1.44 ($n=221$)	0.97
BP diastolic (mm Hg)	−1.47 ($n=650$)	−1.33 ($n=221$)	0.86

This table outlines the 1-year change from baseline for both control and intervention groups for the five Met S factors. In addition, the table breaks out invited or the intent-to-treat population (top half of the table) from those subjects who actively participated in the entire study (bottom half of the table). Values that are highlighted in bold were found to be significant.

ROI: Average Healthcare costs were reduced by $122/month per participant

Total savings >$660,000/year

J Occup Environ Med. 2015 Oct 15.
Reducing Metabolic Syndrome Risk Using a Personalized Wellness Program.
Steinberg G1, Scott A, Honcz J, Spettell C, Pradhan S.

Pathway genotyped over 300 Biggest Loser TV show contestants

Over 97% at high or above average genetic markers/risk for Obesity. Many more than in general population....



"Classic" Obesity Genes		Risk Genotype	Biggest Losers Freq.	General Population
→ FTO	Fat Mass & Obesity	A/A	33%	16%
→ DRD2	Brain Derived Factors	C/C	56%	17%
→ MC4R	Obesity & BMI	C/C	22%	3%
→ GAD2	Neurotransmitter, Appetite Stimulating	A/A	78%	64%

News > WebMD Health News

Are Patients Ready for Direct-to-Consumer Genetic Testing?

Matt Smith

March 29, 2018

Added to Email Alerts

WebMD

Of Course……it's the HCP's that are the issue!



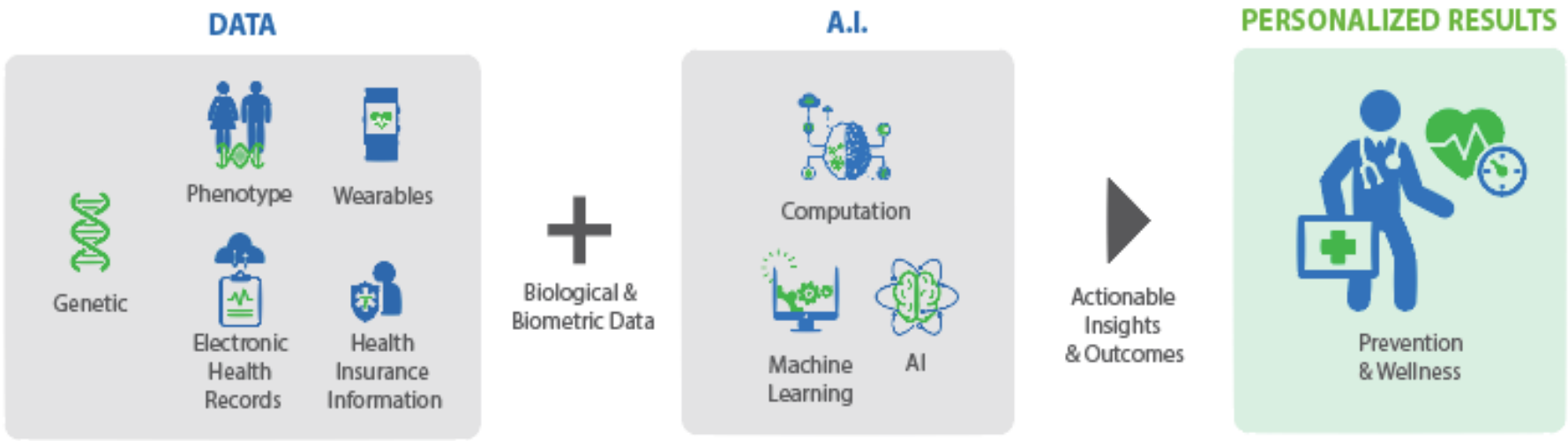


PROBLEM SPACE IN HEALTHCARE



UNDERSTANDING &
RELATING MANY DATA SETS

Creating
PERSONALIZED RESULTS





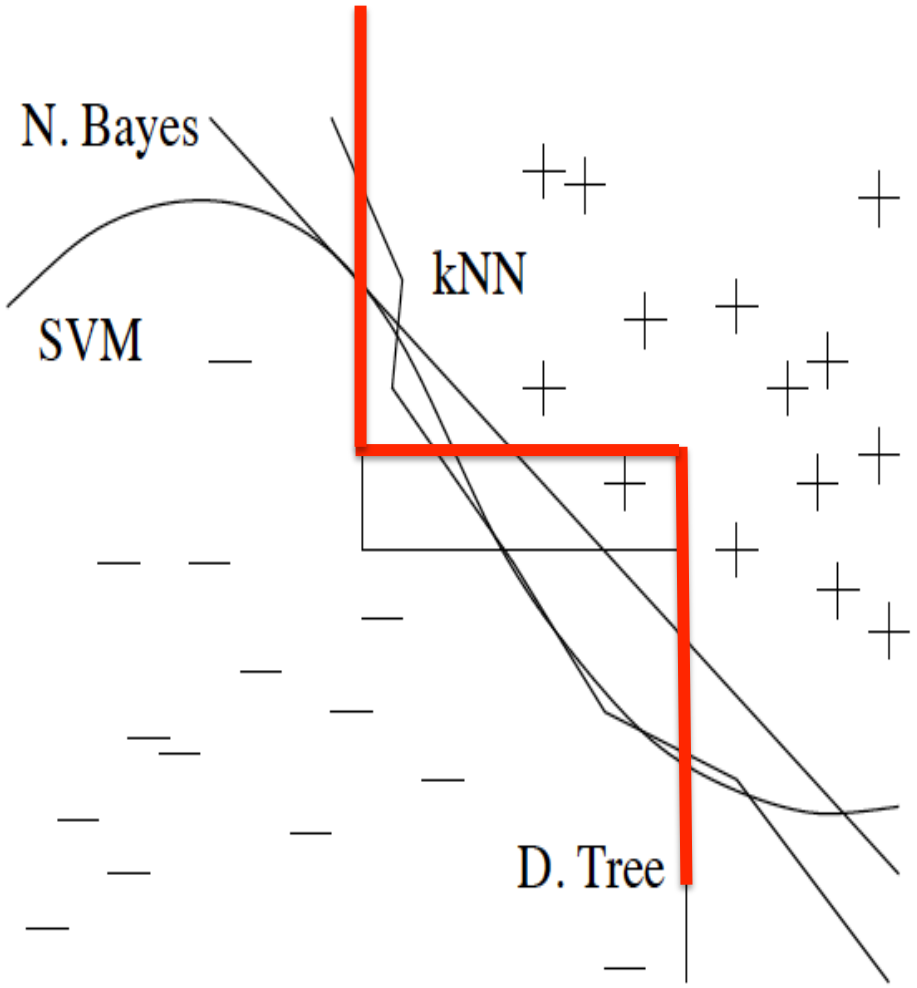


Decision Tree Algorithm and Hyperplane

"9 lines of code"

Algorithm 1 LearnDT(*TrainSet*)

if all examples in *TrainSet* have the same class y_* **then**
  return MakeLeaf(y_*)
if no feature x_j has InfoGain(x_j,y) > 0 **then**
  $y_* \leftarrow$ Most frequent class in *TrainSet*
  return MakeLeaf(y_*)
$x_* \leftarrow \text{argmax}_{x_j}$ InfoGain(x_j,y)
$TS_0 \leftarrow$ Examples in *TrainSet* with $x_* = 0$
$TS_1 \leftarrow$ Examples in *TrainSet* with $x_* = 1$
return MakeNode(x_*, LearnDT(TS_0), LearnDT(TS_1))



Learning from big data

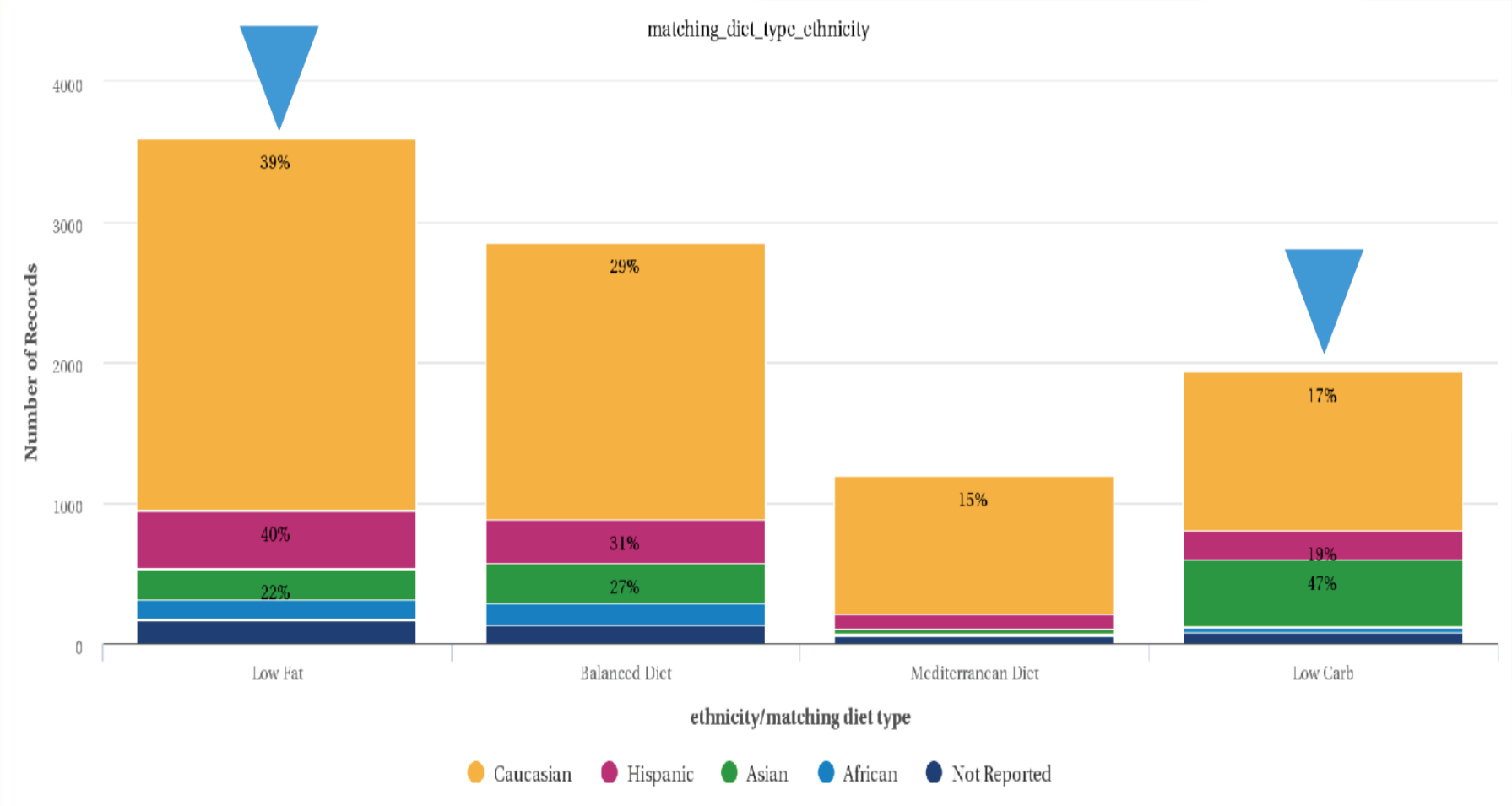
K-means clustering
15,000 clinical database
85 genes/sample

Large feature set:
Genetics + Clinical Data



Source: Hernreid, 2018

Dietary recommendations by Ethnicity



Atypical Eating Disinhibition Genotype

Lori E. Arguello, DNP, ANP-BC, Kasuen Mauldin, PhD , RD, and Deepika Goyal, PhD, FNP-BC

EMR + Genetics +AI

2018

Table 3. Comparison of Frequency of Genotypes Based on Body Mass Index (BMI)[a]

Eating Behavior and Genotype	BMI 25-29.9 (n = 116), % (n)	BMI ≥ 30 (n = 582), % (n)	Effect Size	*P* Value	Power
Eating disinhibition[b]					
Typical (less likely)	57.8 (67)	22.7 (132)	2.210	2.15×10^{-14}	1.0
Atypical (more likely)	42.2 (49)	77.3 (450)			
Food desire					
Typical	62.6 (72)	61.6 (358)	0.002	.842	0.05
Atypical (Increased)	37.4 (43)	38.4 (223)			
Hunger					
Typical	97.4 (113)	94.1 (545)	0.079	.150	0.55
Atypical (Increased)	2.6 (3)	5.9 (34)			
Satiety					
Typical	83.6 (97)	83.0 (483)	0.001	.868	0.05
Atypical (difficulty feeling full)	16.4 (19)	17.0 (99)			
Snacking					
Typical	85.2 (98)	87.6 (509)	0.019	.483	0.08
Atypical (increased)	14.8 (17)	12.4 (72)			
Sweet tooth					
Typical	75.9 (88)	75.4 (439)	0.0004	.921	0.05
Atypical (increased)	24.1 (28)	24.6 (143)			

[a] Percentages may not add up to exactly 100% because of rounding or exclusion of 1 inconclusive test result.
[b] $P < .001$.



Jackass Genomics – Did Donkeys Arise from an Inverted Chromosome?

Thank you!