DNA and Consumer Genetic Testing in Primary Care

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Disclosure

I have no financial interests or relationships to disclose.

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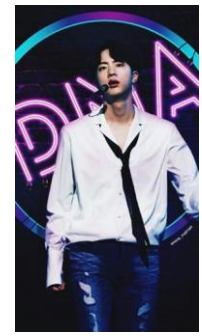
DNA AS A SECULAR ICON



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DNA IN PRIMARY CARE

A. The human genome

B. The human genome and medicine

C. The personal genome

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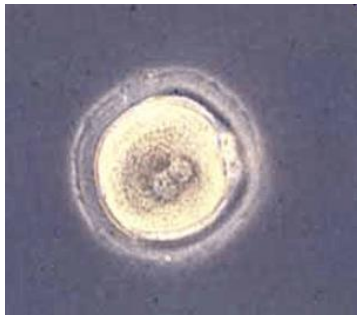
GENES DETERMINE PHENOTYPE



Determine

Genes: DNA in two cell nuclei fusing in the fertilized egg

***Phenotype*:** The characteristics of an individual

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GENES ARE NOT DESTINY

This is important to keep in mind

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THE INFORMATION CONTENT OF DNA IS ITS BASE SEQUENCE

DNA base sequence of the gene for human insulin

1
AGCCCTCCAGGACAGGCTGCATCAGAAGAGGCCATCAAGCAGATCACTGTCCTTCTGCCATGGC
CCTGTGGATGCGCCTCCTGCCCCTGCTGGCGCTGCTGGCCCTCTGGGGACCTGACCCAGCCGC
AGCCTTTGTGAACCAACACCTGTGCGGCTCACACCTGGTGGAAGCTCTCTACCTAGTGTGCGGG
GAACGAGGCTTCTTCTACACACCCAAGACCCGCCGGGAGGCAGAGGACCTGCAGGTGGGGCAG
GTGGAGCTGGGCGGGGGCCCTGGTGCAGGCAGCCTGCAGCCCTTGGCCCTGGAGGG
GTCCCTGCAG AGCGTGGCATTGTGGAACAATGCTGTACC
AGCATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAACTAGACGCAGCCCGCAGGCAGCCCCA
CACCCGCCGCCTCCTGACCGAGAGAGATGGAATAAAGCCCTTGAACCAGCAAAA 469

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DNA CAN BE CHANGED (MUTATED)

Normal DNA sequence: ATC**G**GTTAACT

Mutated DNA sequence: ATC**A**GTTAACT

Two ways to change DNA in *any* cell:

- ***Spontaneous***: it's just chemistry
- ***Induced***: the environment

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DNA TECHNOLOGIES

Late 1960s: Sequencing a bacterial virus (5386 b)

1 million years to complete human genome (~3,000,000,000 b)

Late 1980s: sequencing techniques improved

1,000's of years to complete human genome

1990s: Human genome project: still faster methods

13 years to complete human genome; $150M

2020s: New sequencing technologies

Less than 1 day and about $300

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VIRAL GENOME SEQUENCES

1918-19 flu pandemic: First case 4/18

- No virus isolated or sequenced at the time
- Virus isolated and sequenced from Inuit burial area: 2005
- **86 years** from disease to sequence

2002-3 SARS epidemic: First case: 12/02

- Virus isolated and genome sequenced 4/03
- **4 months** from disease to sequence

2019-present, SARS-COVID19 pandemic: First case 12/8/19

- Virus isolated and genome sequenced 1/5/20
- **28 days** from disease to sequence

Test for COVID19 RNA: 1/15/20; RNA based vaccine: 1/30/20

Variants: From immune serotyping to sequencing

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CLINICAL VIGNETTE: GENOME SURVEILLANCE

- 70-year-old man, London area, UK, 4/8/21
- Exposure in family to COVID-19
- Seen by primary care practitioner (NHS)
- Office / lab test for COVID19: positive
- Sequence RNA: Covid19 Genomics UK Consortium

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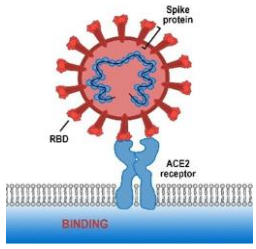
CLINICAL VIGNETTE: GENOME SURVEILLANCE

- Genome sequencing: done *within 1 hr:* 30,000 bases
- **Delta mutation** in gene encoding "spike" protein: better attachment receptor on airway cell surface **Mutation B.1.617.2**
- First identified in India, 12/20
- Rapid spread: by 5/20/21: 90% new infections UK; 7/21: 80 % USA



Result: Intensive treatment

Genome surveillance population
> 1 million cases sequenced

Increased death rate

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HUMAN GENOME SEQUENCES

As of 5/24, over **4 million** human genomes have been fully sequenced

Many more partial sequences: e.g., protein encoding *exomes*

Illumina HiSeq 4000: 6 billion DNA bases sequenced and analyzed / day

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THE HUMAN GENOME: A USER'S GUIDE

- 3.1 billion base pairs of DNA; draft sequence 2000; verified full sequence 2021
- About 1.5% encode specific proteins: 19,969 genes
- About 2% are RNA-encoding genes regulating the expression of protein-coding genes: 25,862 genes
- Over 99.9% is the same in all people: 3 million bases differ
- Most of the differences between people are at single base pairs or short repeats

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VARIATIONS IN THE HUMAN GENOME

TGCATTACGTAGGC

- **Single base changes** (**SNP**) 1 every few hundred bases

TGCATTGCGTAGGC

- *Uses: Identify groups; ancestry*
  Diagnosis of genetic variations, diseases

- **Short tandem repeats** (**STR**) repeat number
  - 1 every few thousand bases

TGCTCATCATCATCAGC

- *Uses: Identify individuals*

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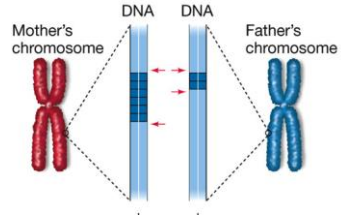
STR: IDENTIFYING INDIVIDUALS

TGCTCATCATCATCATCATCAGC

6 repeats

TGCTCATCAGC

2 repeats



Tandem repeats are stable and passed on to the next generation

There are numerous different tandem repeats

Taken together, the pattern of tandem repeats is unique for each individual:
a DNA barcode

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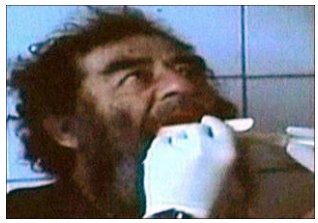
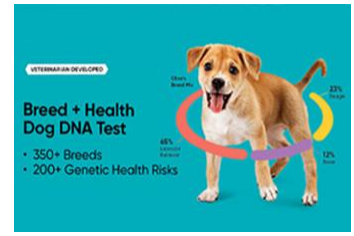
STR: IDENTIFYING INDIVIDUALS





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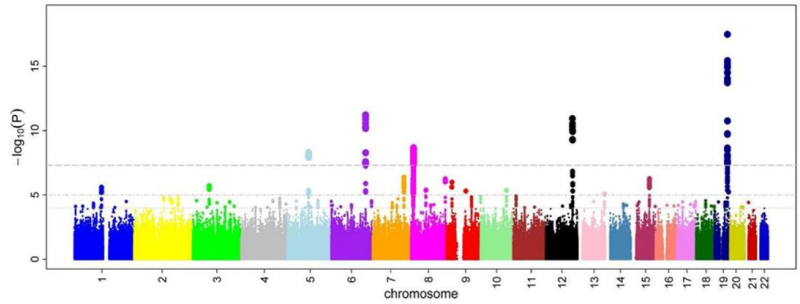
SNP: RELATING GENETIC VARIATION TO PHENOTYPE

Genome-wide association study:
e.g., microcirculation disorder
Look for variants that correlate with phenotype
Compare people **with** and **without** phenotype



SNPs on chromosomes 5,6,8,12,19 relate to disorder

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USES OF HUMAN DNA VARIATION

- ***Medicine***: Relate genetic variants to diseases for diagnosis and treatment
- ***Personal genome***: Know thyself

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DNA IN PRIMARY CARE

A. The human genome

B. The human genome and medicine

C. The personal genome

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CLINICAL VIGNETTE: PRENATAL GENETIC SCREENING

- 40-year-old pregnant woman
- 1% chance of trisomy 21 (Down syndrome)
- 0.5% chance of another chromosome abnormality
  X chromosomes, trisomies 13, 18

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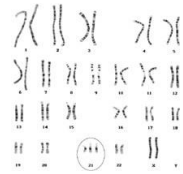
PRENATAL GENETIC SCREENING

Down syndrome (trisomy 21)



Screening: wk 11-13:

- *Serum*: HCG, PAPP-A (pregnancy associated plasma protein),
- *Ultrasound*: fetal nuchal translucency

85-90% detection rate, false positive 4%

Diagnosis*:* (invasive): wk 14-16

Chorionic villus sampling
Amniocentesis

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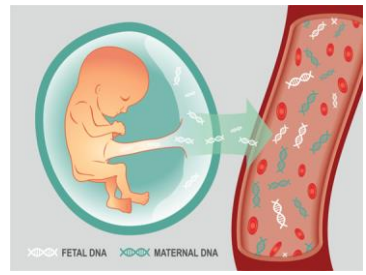
NONINVASIVE PRENATAL DNA TESTING

DNA in plasma from apoptotic cells:

- Maternal: adipocytes, blood cells
- Fetal: trophoblasts



20% of serum DNA is fetal

Screening: wk 8-12

99.99% detection rate, 0.05% false positives
for trisomies 13, 18, 21 X, XYY and X monosomy

Reduces need for follow-up invasive tests

Can detect fetal sex

Can detect many non-chromosomal conditions

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GENETIC TESTING

Newborn screening: detects disorders in newborns; immediate treatment possible; *done by biochem. or DNA*

Carrier testing: detects heterozygous condition at any age; risk of transmission to offspring; *done mostly by DNA*

Predictive testing: detects mutations that can affect risk of disease later in life; *done mostly by DNA*

Some tests are physician-ordered; other tests are patient-initiated

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GENETIC DISEASES: INBORN ERRORS

Hundreds of inborn errors, each determined by DNA mutation

Each inborn error is rare: 1/4000 to 1/100,000 newborns

Total is about 1/300 of all newborns; carrier is 1/6

Some are treatable: e.g., PKU (phenylketonuria)

Others are not treatable: e.g., Tay-Sachs disease

Many can be detected by genetic analysis: DNA

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CLINICAL VIGNETTE: FAMILIAL HYPERCHOLESTEROLEMIA

- 8-year-old boy: cholesterol 200 mg/dl (11.1 mmol/L)
- mother age 45 diagnosed with FH; treated with statins
- her mother also diagnosed with FH; died age 50 CHD
- FH is inherited as autosomal dominant: heterozygous
- 1/250 worldwide: *most common monogenic disorder*
- *Early diagnosis and intervention are key*

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CLINICAL VIGNETTE: FAMILIAL HYPERCHOLESTEROLEMIA

- *DNA analysis* by gene or genome seq parents and children
- Also analyze other relatives
- LDLR: LDL receptor (defective synth., transp.) 94% of FH
  APOB: apolipoprotein B (binds LDL and LDLR) 5% of FH
  PCSK9 proprotein convertase subtilisin kexin type 9:
  (degrades LDLR) 1% of FH
- *Intervention:* for pediatric patients with FH:
  - lifestyle; statins age 10; target cholesterol 160 mg/ dl

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DNA GENETIC TESTING: CHOOSING WISELY

American College of Medical Genetics and Genomics

Things Physicians and Patients Should Question

Don't order genetic sequencing before obtaining informed consent that includes the possibility of secondary findings

ACMG 2021

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DNA POPULATION GENETIC SCREENING

Hypothetical vignette:

2041: Male, age 18; eligible for, voting, military service and genetic screening

What if everyone was screened for three CDC "Tier 1" conditions:
Genetic syndromes with a significant impact of life expectancy that have effective therapies

Genetic variant	Increased risk	Treatment
BRCA1 and 2	Breast, ovarian cancer	Prophylactic mastectomy, oophorectomy
MLH, MSH, PMS (Lynch syndrome)	Colon cancer	Earlier screening, polypectomy
LDLR, APOB, (Familial hyperchol)	Heart attack, stroke	Statin therapy

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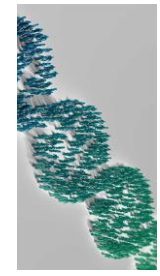
DNA POPULATION GENETIC SCREENING

Results: Model estimates for every 100,000 general population screened at age 30:

- 101 fewer cancer cases (breast, ovarian, colon)
- 15 fewer cardiovascular events (heart attack, stroke)
- 495 increased quality adjusted (good health) life years



Cost-benefit:

- Cost: $250 per test: $25 million and $9 million for treatments
  Total: $34 million

Cost / benefit ratio: $69,000 per quality-adjusted life year

Comparisons of cost-benefit: Hypertension screening: 27.5K; mammography screening: $35K; coronary bypass: $5K;
heart transplant: $65K

Guzauskas et al., 2023

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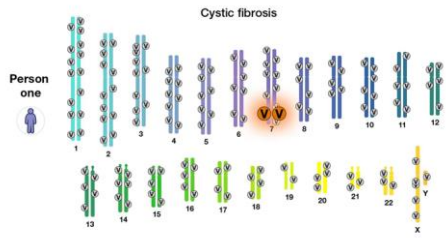
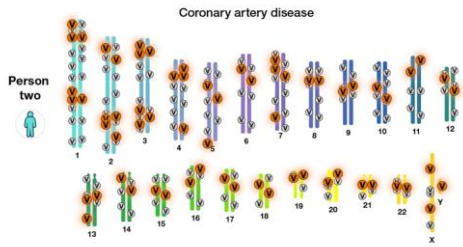
POLYGENIC RISK SCORE: DNA SNP



Single gene disease



Poly gene disease

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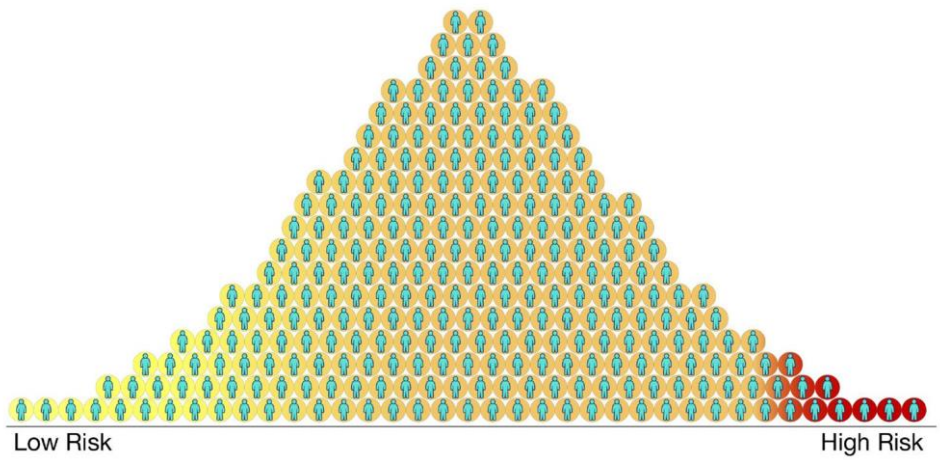
POLYGENIC RISK SCORE: DNA SNP

PRS can be used with other factors to make clinical decisions



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NEWBORN SCREENING

PRINCIPLES OF SCREENING

- Test has *low cost* (e.g., < $1?)
- Test can be *automated* for large population
- Treatment *beneficial* if begun early
- *High sensitivity* (low false negatives) and *high specificity* (low false positives)

Interventions based on DNA tests assume genetic determinism

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NEWBORN SCREENING

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

"Action sheets" for each disorder

Parents can opt out

1978: 1 disorder (hypothyroidism)

1988: 6 disorders

1998: 17 disorders

2008: 48 disorders

2018: 84 disorders

Core treatable : 30 disorders (incl. hearing and pulse oximetry)

2023: 4 million babies born and screened, 12,500 treatable disorders
40 million babies screened worldwide

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NEWBORN SCREENING

	Detection	*Frequency*	*Treatment*
Congenital hypothyroidism	Immunoassay	1/3,500	Thyroxine
Phenylketonuria	Chemical analysis	1/12,000	Diet
Sickle-cell disease	Chemical analysis and DNA (1 mutation)	1/2,500	Transfusion, drugs
Cystic fibrosis	Chemical analysis and/or DNA (25 mutations)	1/3,500	Antibiotics, nasal sprays, etc.

*Screening must be done on **day 2** onwards*

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NEWBORN GENOMIC DNA SEQUENCING

BABYSEQ

Ongoing study at Harvard, Broad Institute: 127 healthy newborns followed 5 y

Objective: Supplement newborn screening with more actionable information

Results so far (1/24):

MDR: Unanticipated monogenic disease risks

Gene	Condition
ANKRD11	KBG syndrome; *AD*
BTD	Biotinidase deficiency; *AR*
ELN	Supravalvular aortic stenosis; *AD*
GLMN	Glomuvenous malformations; *AD*
KCNQ4	Non-syndromic hearing loss; *AD*
SLC7A9	Cystinuria; *AR*
TTN (4)	Dilated cardiomyopathy; *AD*
BRCA2 (2)	Hereditary breast and ovarian cancer; *AD*
MSH2	Lynch syndrome; *AD*
MYBPC3	Hypertrophic cardiomyopathy; *AD*
VCL	Dilated cardiomyopathy; *AD*
CD46	Atypical hemolytic-uremic syndrome; *AD*
CYP21A	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency; *AR*
G6PD	Glucose-6-phosphate dehydrogenase deficiency; *XL*

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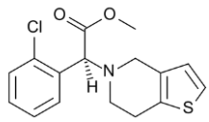
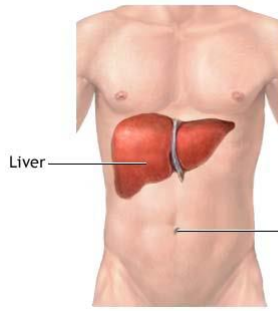
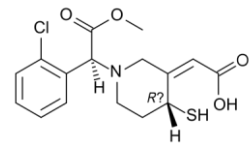
PREDICTIVE GENETIC TESTING: PHARMACOGENOMICS

Clopridogrel



This molecule enters the liver from the digestive system





This molecule leaves the liver and enters the blood system:
It may be the active form or inactive form

- *There are 57 CYP450 genes in the human genome*
- *Some CYP genes are "promiscuous" – many substrates*
- *Many mutations in the CYP450 genes encoding drug metabolism*

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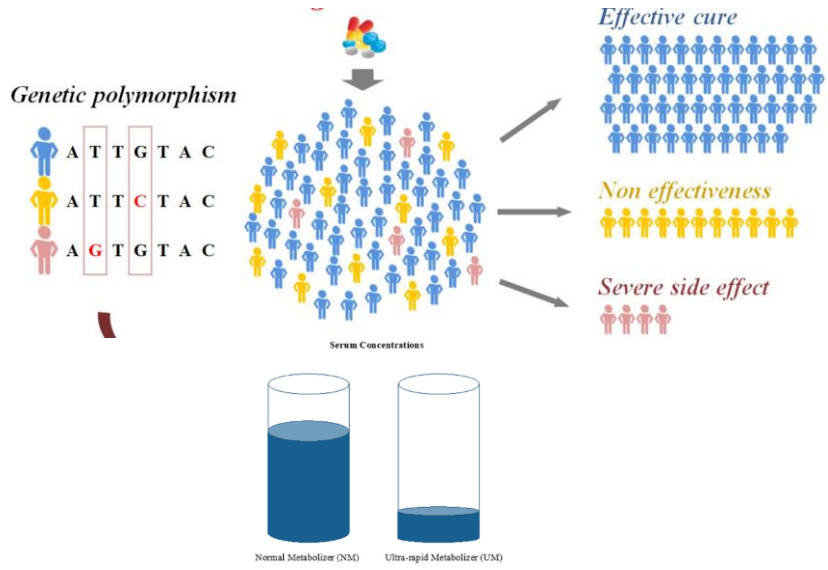
PREDICTIVE GENETIC TESTING: PHARMACOGENOMICS



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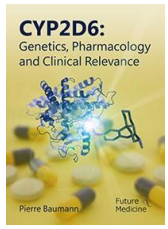
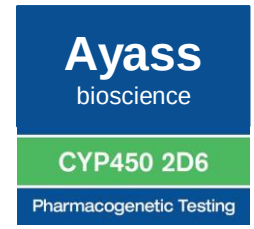
PREDICTIVE GENETIC TESTING: PHARMACOGENOMICS

Example: CYP2D6:



- Debrisoquine, metoprolol, sparteine, propranolol, encainide, codeine, dextromethorphan, clozapine, desipramine, haloperidol, amitriptyline, imipramine, tramadol
- Over 100 known genetic variants, 30 common: 2 normal, 1 increased, 5 decreased, 22 no activity
- DNA testing reveals *normal, increased or poor metabolizers*



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CLINICAL VIGNETTE: BACK PAIN

- 60-year-old man with chronic lower back pain
- Failed response to codeine

Pharmacogenomic testing:

Gene	*Genotype*	*Phenotype*	*Examples*
CYP2D6	3/4	Poor metabolizer	Tramadol. codeine
CYP2C9	1/1	Normal metabolizer	Ibuprofen, celecoxib

Result: Use ibuprofen

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PREDICTIVE GENETIC TESTING: PHARMACOGENOMICS

"Here's my sequence..."

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DNA IN PRIMARY CARE

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C. The personal genome

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THE PERSONAL GENOME

Genome-wide associations with phenotype: mostly SNP's

e.g., 23and Me: $200, XCode 13 million done

Total genome sequencing and scanning for mutations related to phenotype 4 million done

e.g., Nebula (commercial - $600); AllofUs (public, free); UK Biobank (free)

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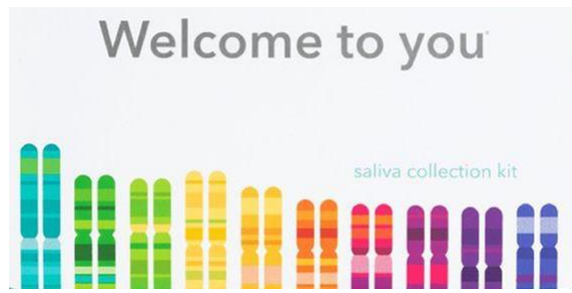
THE PERSONAL GENOME

Example



28 million people genotyped as of 1/22
(12 million by 23andMe; 16 million by Ancestry)

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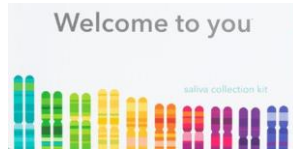
THE PERSONAL GENOME

Basis: *DNA changes associated with phenotypes*

- Association is statistical argument; genetic determinism
- Mostly SNPs
- DNA extracted from saliva: buccal epithelial cells and WBCs
- Well-written, authoritative web site



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THE PERSONAL GENOME: ANCESTRY

Sources of DNA variations associated with specific populations:

- HapMap: Groups of sequences in paternal (Y chromosomes) and maternal (mitochondria)
- Human Genome Diversity Project (Stanford)
- 1000 Genomes Project (International)
- Population data as defined by customers

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PERSONAL GENOME: ANCESTRY HAPMAP

DS

- Maternal Haplogroup N1b2 ›
- Paternal Haplogroup J-P58 ›

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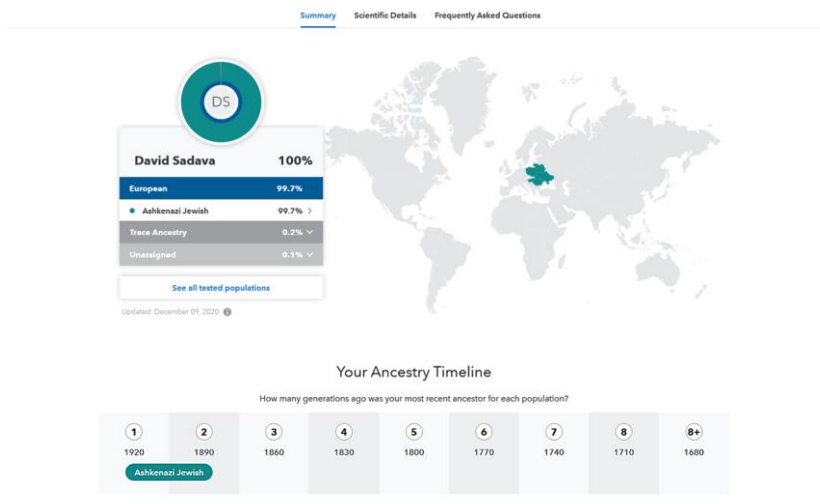
PERSONAL GENOME: ANCESTRY



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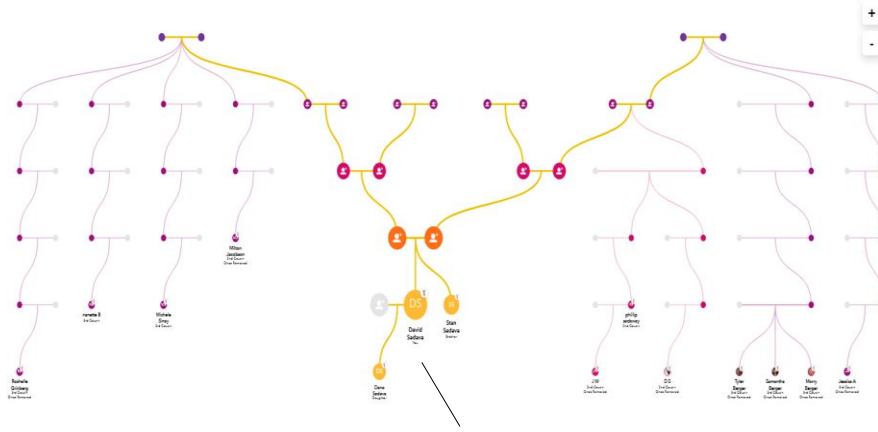
PERSONAL GENOME: ANCESTRY / RELATIVES



David S

Dana Sadava
Daughter 49.77% DNA shared
Stan Sadava
Brother 48.44% DNA shared

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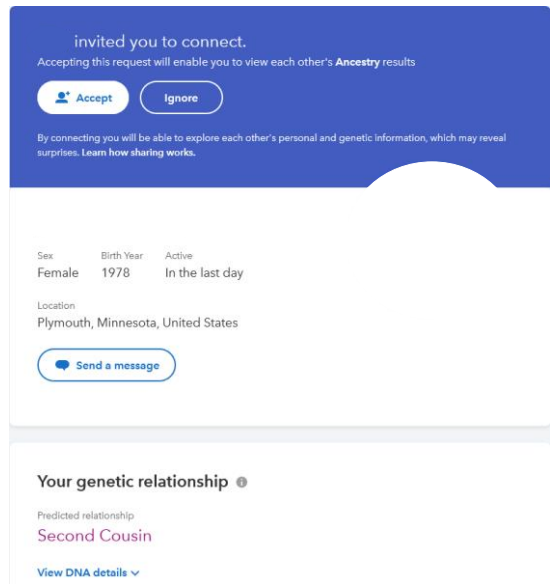
PERSONAL GENOME: RELATIVES



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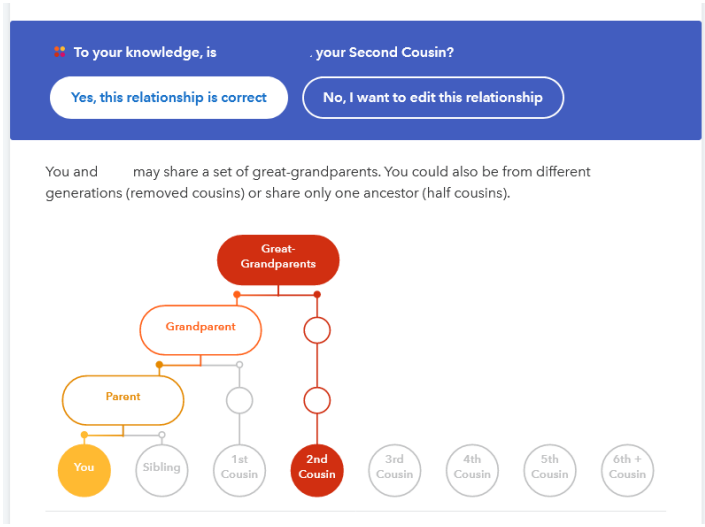
PERSONAL GENOME: RELATIVES



About four-in-ten (38%) say they were surprised by what their DNA test results showed about what countries or continents their ancestors came from, while 27% express surprise at what these results indicated about their ancestors' racial or ethnic background

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PERSONAL GENOME: HEALTH RISKS

Age-Related Macular Degeneration **Result summary:** Variant detected, not likely at increased risk	Variant ARMS gene; risk 2%
CYP2C19 Drug Metabolism 23andMe+ **Result summary:** Predicted intermediate metabolizer	Variant CYP22C19: increased metab Plavix
Coronary Artery Disease 23andMe+ **Result summary:** Increased likelihood	Based on 2400 DNA markers; for DS age 4% risk (3 x normal)
Hereditary Thrombophilia **Result summary:** Slightly increased risk	Variant Leiden F5; increased clot risk surgery (1/500)
Psoriasis 23andMe+ **Result summary:** Increased likelihood	Based on 7500 markers; risk at DS age per year 4.5% (normal 3%)

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PERSONAL GENOME: WELLNESS

Alcohol Flush Reaction	Unlikely to flush >
Caffeine Consumption	Likely to consume less >
Genetic Weight	Predisposed to weigh about average >
Lactose Intolerance	Likely intolerant >
Muscle Composition	Uncommon in elite power athletes >
Saturated Fat and Weight	Likely similar weight >
Sleep Movement	Likely more than average movement >

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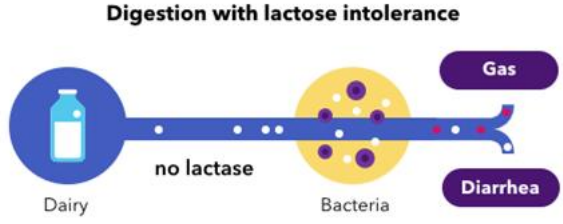
PERS. GEN. : WELLNESS: Lactose Intolerance



	Genetic result	What it means
You	GG	Likely lactose intolerant
	AG	Likely not lactose intolerant
	AA	Likely not lactose intolerant

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PERSONAL GENOME: TRAITS

Ability to Match Musical Pitch	More likely to be able to match a musical pitch
Asparagus Odor Detection	Likely can smell
Back Hair	Likely little upper back hair
Bald Spot	Likely no bald spot
Bitter Taste	Likely can't taste
Cheek Dimples	Likely no dimples
Cilantro Taste Aversion	Slightly higher odds of disliking cilantro
Cleft Chin	Likely no cleft chin
Dandruff	Less likely to get dandruff
Earlobe Type	Likely detached earlobes
Early Hair Loss	Likely hair loss
Earwax Type	Likely wet earwax
Eye Color	Likely brown or hazel eyes
Fear of Heights	Less likely than average to be afraid of heights
Finger Length Ratio	Likely ring finger longer
Freckles	Likely little freckling

Etc.

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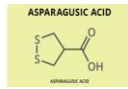
PERSONAL GENOME: TRAITS

● Asparagus Odor Detection — Likely can smell ›

Marker Tested	Your Genotype*		Additional Information
rs4481887 Gene: Near OR2M7 Marker: rs4481887	G Typical copy from one of your parents	G Typical copy from your other parent	^ Biological explanation The variant tested is a change from a G to an A in the DNA sequence near the OR2M7 gene. ^ Typical vs. variant DNA sequence(s) G → Substitution → A Typical Sequence / Variant Sequence ^ Percent of 23andMe customers with variant Variant: A



OR2M7 encodes an olfactory receptor

European	44.76%
African American	25.75%
Ashkenazi Jewish	49.99%
East Asian	25.50%
Hispanic or Latino	41.55%
South Asian	25.45%

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PERSONAL GENOME: FURTHER ANALYSES

23andMe raw data:

rsid	*chromosome*	*position*	*genotype*
rs3094315	1	752566	AA
rs3934834	1	1005806	CT
rs9442372	1	1018704	AA
rs3737728	1	1021415	GG
rs11260588	1	1021658	GG

Etc…..about 700,000 markers

XCODE
LIFE

Example

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PERS. GEN.: FURTHER ANALYSES

23andMe data downloaded to companies that analyze (DS examples):

- **Allergy**: *low risk*: contact dermatitis; *moderate risk*: pets; *high risk*: tree nuts
- **Exercise capacity**: *higher* endurance than aerobic;
  lower weight loss with exercise
- **Health**: *Lacks harmful variant*: APOEe3 (Alzheimers), HQAd2 (celiac), BRCA1185delAG (breast cancer)
  Has harmful variant: factor V Leiden (thrombophilia)

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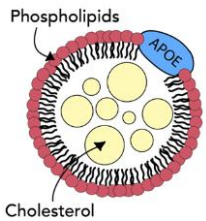
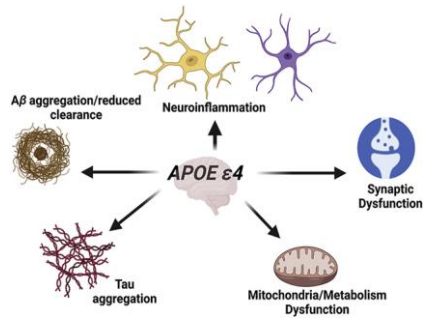
PERS. GEN. : CLINICAL VIGNETTE

62 year-old male with no cognitive impairment

- Purchased 23andMe DNA analysis
- Homozygous for APOEe4 allele: 2% US population; 20% of people with Alzheimer's disease
- Anxious about possible Alzheimer's disease
- Consults primary care practitioner: what to do?





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PERS. GEN.: CLINICAL VIGNETTE

Genotype	*Alzheimer's by age 80 (%)*	*Onset of Alzheimer's*
APOE e3/e3	2%	Typical
APOE e3/e4	10%	2-5 years earlier
APOE e4/e4	35%	5-10 years earlier

Recommend: diet, hypertension, exercise, medication (new?)

Primary care practitioners are front line for consultation in direct-to-consumer DNA testing

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PERSONAL GENOME SEQUENCING

What do you want to learn from Whole Genome Sequencing?

1/ Learn about your ancestry and find new relatives	2/ Decode ALL your genes and identify mutations
4/ Determine appropriate diet and supplementation	5/ Find the right exercise plan to lose weight
7/ Use your genetic information to extend your life	8/ Uncover your oral microbiome

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PERSONAL GENOME SEQUENCING: TSH

10/2023

Thyroid-stimulating hormone levels (Williams, 2023)

Alexander Williams, et al.
Nature Communications

Metabolism

STUDY SUMMARY

This report is based on a study that discovered 156 genetic variants associated with thyroid-stimulating hormone (TSH) levels.

YOUR RESULT

9th PERCENTILE

Low score to higher TSH levels

STUDY DESCRIPTION

The thyroid is a small, butterfly-shaped gland in the neck that plays a huge role in the body's metabolism, growth, and development. It does this by producing hormones that control the speed of many activities in the body, such as how quickly the heart beats or how fast one burns calories. One of the main hormones that regulates the thyroid is called thyroid stimulating hormone (TSH), which is released by the pituitary gland in the brain. TSH acts as a messenger to tell the thyroid how much hormone to produce, and the level of TSH in the blood is a key indicator of how well the thyroid is functioning. If there is too little TSH, the thyroid doesn't get enough signals to make hormones, leading to a condition known as hypothyroidism. Symptoms can include tiredness, weight gain, and feeling cold. On the other hand, if there's too much TSH, the thyroid becomes overactive, a condition known as hyperthyroidism, causing symptoms like weight loss, rapid heartbeat, and nervousness. Several conditions are linked to imbalances in TSH levels, including such as Hashimoto's and Graves' disease. Factors that can influence TSH level variation between individuals include autoimmune disorders, stress, diet, and genetics. This study of over 247,000 individuals of European and South Asian ancestries aimed to better understand the genetic component. The researchers identified 156 unique regions of the genome associated with TSH levels, including 78 newly discovered in this study. In total, these genetic variants collectively explain nearly 23% of TSH level variation among individuals. Among the genes linked to TSH levels are ADCY6 and TRIM2, both of which play a role in the nervous system.

The thyroid is a butterfly-shaped gland in the neck.

DID YOU KNOW?

Women are more prone to thyroid problems than men, with a five to eight times higher likelihood of experiencing thyroid disorders. About one out of eight women will face a thyroid condition at some point in their life.

YOUR DETAILED RESULTS

To calculate your genetic score to higher TSH levels we summed up the effects of genetic variants that were linked to higher TSH levels in the study that this report is based on. These variants can be found in the table below. The variants highlighted in green have **positive effect sizes** and increase your genetic score to higher TSH levels. The variants highlighted in blue have **negative effects sizes** and decrease your genetic score to higher TSH levels. Variants that are not highlighted are not found in your genome and do not affect your genetic score to higher TSH levels. By adding up the effect sizes of the highlighted variants (twice for homozygous variants) **we calculated your personal genetic score for higher TSH levels to be -1.46**. To determine whether your score is high or low, we compared it to the scores of 5,000 other Nebula Genomics users. We found that your personal genetic score for higher TSH levels is in the **9th percentile**. This means that it is higher than the personal genetic scores 9% of people. We consider this to be a **low genetic score to higher TSH levels**. Note that on average every user will have ~10% of the reports with scores that are in the >90th percentile, another ~10% of reports with scores in the 80th-90th percentile etc. Hence, having some reports with very high/low percentiles is expected and no reason for concern. However, please note that genetic scores do not account for important non-genetic factors like lifestyle. Furthermore, the genetics of most traits has not been fully understood yet and many associations between traits and genetic variants remain unknown. For additional explanations, click on the column titles in the table below and visit our Nebula Library tutorial.

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PERSONAL GENOME SEQUENCING: TSH

VARIANT	YOUR GENOTYPE	GENE	EFFECT SIZE	VARIANT FREQUENCY
rs989759_C	C / C	PDE8B	-0.14 (↓)	64%
rs2983611_C	C / C	PDE10A	-0.12 (↓)	31%
rs11728154_A	G / A	NR3C2	-0.12 (↓)	20%
rs10799824_A	G / G	CAPZB	-0.12 (–)	16%
rs1861628_A	A / A	IGFBP5	-0.10 (↓)	27%
rs10223666_C	G / C	VEGFA	0.09 (↑)	69%
rs17767419_T	C / C	LOC102467146	-0.09 (–)	32%
rs73398264_T	T / T	FAM227B	0.08 (↑)	75%
rs1398868_T	T / T	FAF1	0.04 (↑)	69%
rs30234_T	T / C	MIR193B	0.03 (↑)	39%
rs57395851_T	T / T	BCAS3	0.08 (↑)	95%
rs700750_A	A / A	TNS3	0.03 (↑)	63%
rs9497965_T	T / T	SASH1	0.03 (↑)	40%

- Study of 247,000 people, Europe and S Asia
- 156 DNA var. relate to TSH level: Some increase - Some decrease
- Var. collectively account for 24% of TSH variation

DS polygenic score for high TSH: 9%

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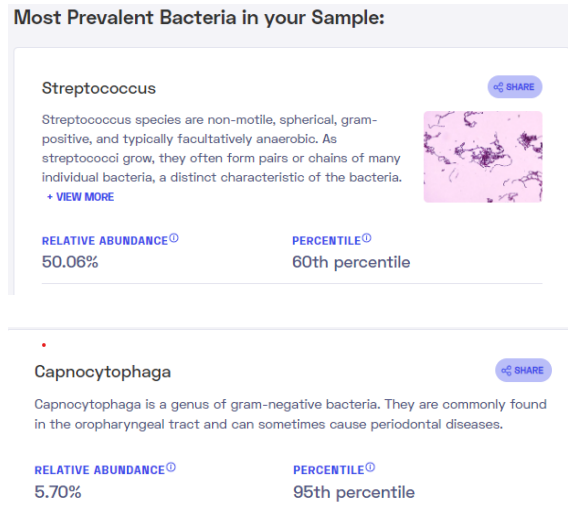
PERSONAL GENOME: ORAL MICROBIOME



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PERSONAL GENOME SEQUENCING

All of Us℠ The Precision Medicine Initiative®
THE FUTURE OF HEALTH BEGINS WITH YOU

NIH funded; **free to participants**; confidential

Aim: Create database of 1 million Americans by 2026:

- Complete genome sequence (analysis sent to participants
- Complete genotyping of markers
- Blood analysis for all analytes and proteins
- Urine analysis
- Electronic medical record

So far: about 700,000 people have participated

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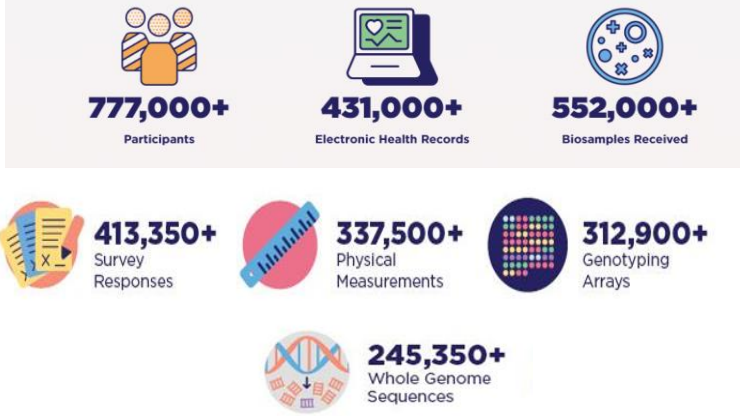
PERSONAL GENOME SEQUENCING

All of Us℠ The Precision Medicine Initiative®
THE FUTURE OF HEALTH BEGINS WITH YOU



As of 04/24

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PERSONAL GENOME SEQUENCING

Genome sequence information and analysis made available to participants:

Ancestry

Disease risks (from genetic counselors)

Traits

Pharmacogenomics

Genome sequence information available to researchers:

From the first 245,000 sequences, 275 million new DNA variants (2/24)

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PERSONAL GENOME SEQUENCING: PHARMACOGENOMICS

Gene
CYP2C19

The *CYP2C19* gene is a "metabolizer" gene. These genes play a role in how quickly or slowly medicines are used, or metabolized, by the body.

Plavix

Version
***1/*2**

What it means
Intermediate Metabolizer

An *intermediate or likely intermediate metabolizer* gene may cause the body to process medicines at a slower rate than normal. If so, some medicines *may stay in the body for a longer amount of time than expected.* This could increase the risk of side effects from the medicines.

Gene
DPYD

The *DPYD* gene is a "metabolizer" gene. These genes play a role in how quickly or slowly medicines are used, or metabolized, by the body.

Version
***1/*1**

What it means
Normal Metabolizer

A *normal metabolizer* gene may cause the body to process medicines at an average rate. If so, some medicines *may stay in the body for the usual amount of time.* The medicines work the way we expect them to.

7 genes sequenced; one heterozygous

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PERSONAL GENOME SEQUENCING: DISEASE RISKS

YOUR RESULT:

We did not find anything significant for your health in the genes we looked at.

Some genes sequenced:

- BRCA1: breast-ovarian cancer
- KCNH2: long QT syndrome
- LDLR: familial hypercholesterolemia
- MLH1: Lynch syndrome (colon cancer)
- TNNI3: hypertrophic cardiomyopathy

etc.…

59 genes sequenced

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PERSONAL GENOME SEQUENCING

What if I have more questions?

You can talk with the *All of Us* Support Center. The staff will help answer your questions. They can also connect you with an *All of Us* genetic counselor.

You can also share your results with a doctor or other health care provider. These results will need to be confirmed with a clinical DNA test before your doctor or health care provider can use them in your care.

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DNA AND PERSONAL HEALTH: FUTURE?

Personalized medicine: N of 1

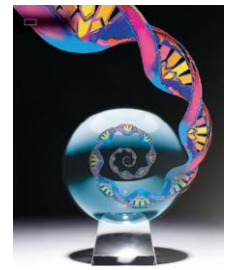
Data: genome DNA, transcriptome mRNA, proteome, metabolome, microbiome, environment

Predictive

Preventive

Personalized

Participatory



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DNA IN PRIMARY CARE

A. The human genome

B. The human genome and medicine

C. The personal genome

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