The Genome 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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THE GENOME IN PRIMARY CARE

A. The human genome

B. The human genome and medicine

C. The personal genome

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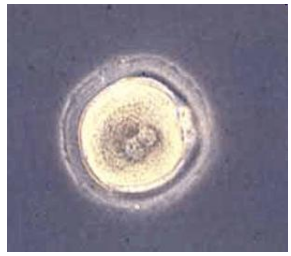
GENES DETERMINE PHENOTYPE



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
AGCCCTCCAGGACAGGCTGCATCAGAAGAGGCCATCAAG
CAGATCACTGTCCTTCTGCCATGGCCCTGTGGATGCGCCT
CCTGCCCCTGCTGGCGCTGCTGGCCCTCTGGGGACCTGA
CCCAGCCGCAGCCTTTGTGAACCAACACCTGTGCGGCTCA
CACCTGGTGGAAGCTCTCTACCTAGTGTGCGGGGAACGA
GGCTTCTTCTACACACCCAAGACCCGCCGGGAGGCAGAG
GACCTGCAGGTGGGGCAGGTGGAGCTGGGCGGGGGCCC
TGGTGCAGGCAGCCTGCAGCCCTTGGCCCTGGAGGG
GTCCCTGCAG AGCGTGGCATTGTGGAACAATGCTGTACC
AGCATCTGCTCCCTCTACCAGCTGGAGAACTACTGCAACT
AGACGCAGCCCGCAGGCAGCCCCACACCCGCCGCCTCCT
GACCGAGAGAGATGGAATAAAGCCCTTGAACCAGCAAAA
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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 with one hour: 30,000 bases

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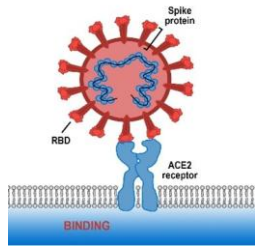
CLINICAL VIGNETTE: GENOME SURVEILLANCE

- **Delta mutation** in gene encoding "spike" protein: better attachment receptor on airway cell surface
- First identified in India, 12/20
- Rapid spread: by 5/20/21: 90% new infections UK; 7/21: 80 % USA



Result: Intensive treatment
Further surveillance of sewage, etc.
Tailor made vaccine

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THE HUMAN GENOME: 2025

- 3.1 billion base pairs of DNA; draft sequence 2000; verified full sequence 2021
- About 1.5% encode specific proteins: 21,000 genes
- About 2.5% are RNA-encoding sequences regulating the expression of protein-coding genes: 80,000 seq.
- 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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HUMAN GENOME SEQUENCES

As of 8/25, perhaps **3 million** human genomes have been fully sequenced

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

This is becoming more common in primary care

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

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HUMAN GENOME VARIATIONS

Source of DNA:

- Germline (inherited mutations)
- Tissue (somatic mutations)

Variants detected:

- Single base changes
- Short tandem repeats
- Polygenic risks (complex traits)
- Chromosome changes (numbers, rearrangements)

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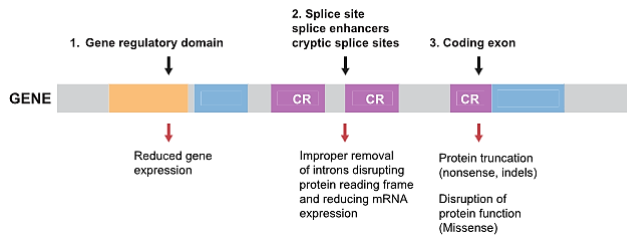
GENOME VARIATIONS: SINGLE BASE CHANGES

- **Single base changes** 1 every few hundred bases

TGCATTACGTAGGC

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

TGCATTGCGTAGGC



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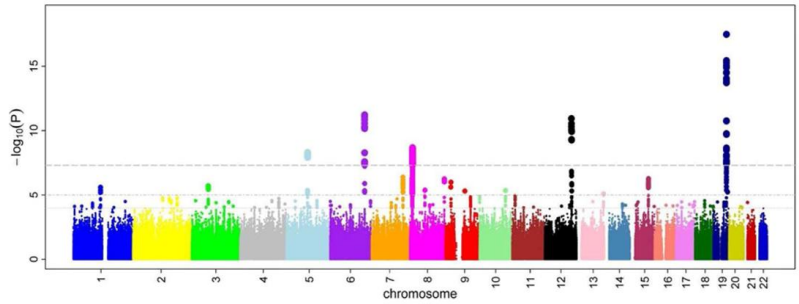
SNP: RELATING GENOME VARIANTS TO PHENOTYPE

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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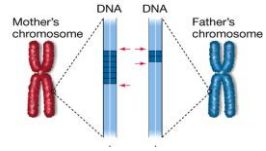
GENOME VARIATIONS: SHORT TANDEM REPEATS

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

TGCATTACGTAGGC

TGCTCATCATCATCAGC

- *Uses: Identify individuals*



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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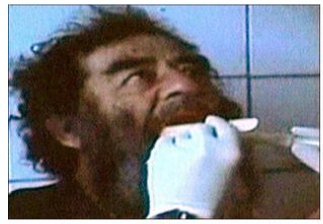
DNA BARCODE: IDENTIFYING INDIVIDUALS



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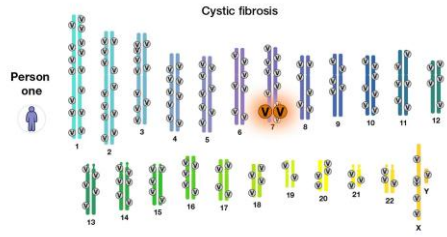
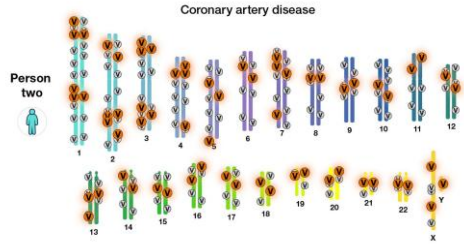
GENOME VARIATIONS: POLYGENIC



Single gene disease



Poly gene disease

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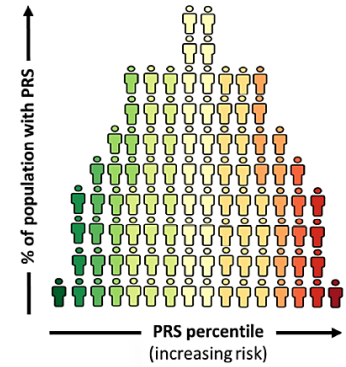
POLYGENIC RISK SCORE

PRS Can Be Used with Other Factors to Make Clinical Decisions

PRS percentile	Risk of disease vs. reference group
0-1	Lowest
1-5	
5-10	
10-20	
20-40	
40-60 (reference)	**1**
60-80	
80-90	
90-95	
95-99	
99-100	Highest



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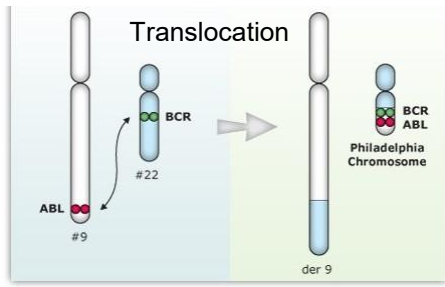
GENOME VARIATION: CHROMOSOMES



New gene formed; detectable by DNA or chromosome analysis

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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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THE GENOME IN PRIMARY CARE

A. The human genome

B. The human genome and medicine

C. The personal genome

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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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APPLICATIONS OF GENETIC SCREENING

- Prenatal screening
- Newborn screening
- Adult disease risk screening
- Pharmacogenetic screening

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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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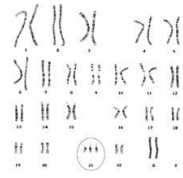
PRENATAL GENETIC SCREENING

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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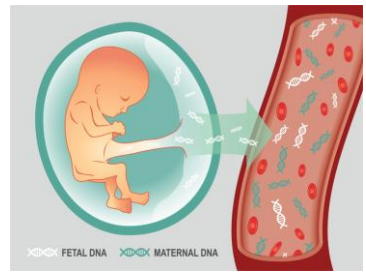
NONINVASIVE PRENATAL DNA TESTING

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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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 : 37 disorders (incl. hearing and pulse oximetry)

2024: USA 4 million babies born and screened, 12,500 treatable disorders (1 in 300)

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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 SCREENING: DNA SEQUENCING

Can DNA sequencing reveal conditions that are actionable?

4000 Newborns, New York City

- DNA sequence for 156 early onset conditions that are treatable
- Interim result: 3.7% positive screen: many that are not on core newborn screening list
- Treatment initiated
- Goal: 100,000 newborns

Will this replace standard newborn screening?

JAMA 333:232 (2025)

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ADULT SCREENING: 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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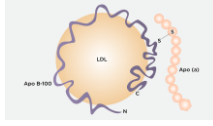
GENETIC SCREENING FOR LIPOPROTEIN(a)



Lp(a) similar to LDL, carries phospholipids

- Pro-inflammatory, pro-atherogenic
- Level is *genetic*: LPA gene; codominant
- Stable level throughout life – not modifiable (yet)
  Lifetime risk factor
- Measure *once in life*; not yet part of lipid panel
- High level (>20th percentile):
  increased risk (2x) for cardiovasc. events
- If high level, modify other risk factors (not yet Lpa)
- *DNA genetic test not useful at present*

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ADULT SCREENING IN POPULATIONS

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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ADULT SCREENING IN POPULATIONS

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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DNA SCREENING: 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

Example:
- 107 pregnant women prenatal testing for fetal aneuploidy
- DNA sequencing done on maternal blood
- 52 (46%) had mutations implicated with cancer

ACMG 2021/ NEJM 391:22 (2024)

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PHARMACOGENETIC SCREENING

DNA mutations affecting drug activity:

- Drug receptor on or in cell: more, less
- Drug uptake into target cells: more, less
- Drug metabolism: more, less

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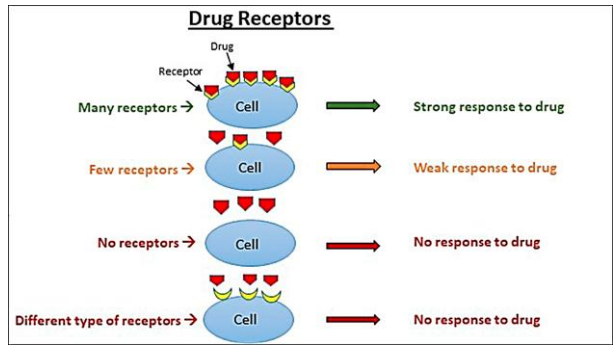
PHARMACOGENETIC SCREENING: RECEPTORS



Clinical example: HER2 receptor on breast cancer cell: trastuzumab treatment

CDC

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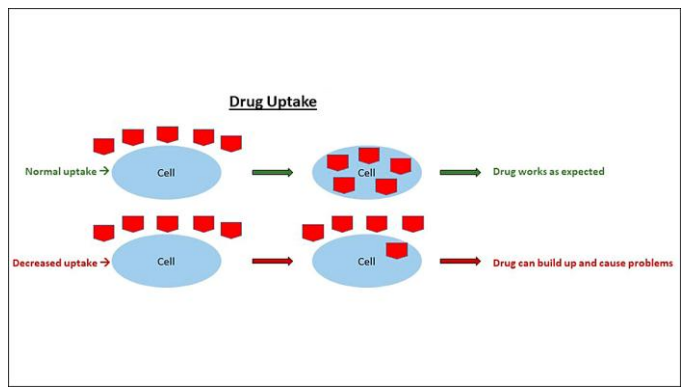
PHARMACOGENETIC SCREENING: UPTAKE



Clinical example: SCLO1B1 gene for statin uptake: simvastatin treatment (muscle side effects)

CDC

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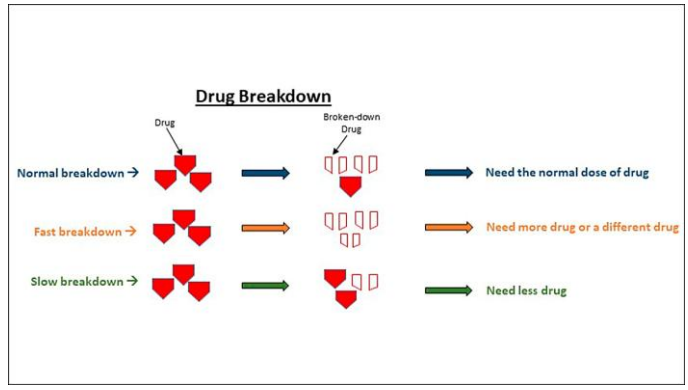
PHARMACOGENETIC SCREENING: METABOLISM



Clinical example: CYP2D6 and CYP2C19 metabolize many drugs: amitriptyline breakdown, use alternate

CDC

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CLINICAL VIGNETTE: PHARMACOGENETIC SCREENING NEW

75-year-old man 1 week after percutaneous coronary procedure

- Cardiologist prescribes aspirin, clopidogrel, simvastatin

- Pharmacogenetic screening:
  - CYP2C19: poor metabolizer of clopidogrel
    - *Risk: increased side effects*
  - SLCO1B1: poor uptake of simvastatin
    - *Risk: increased side effects*

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CLINICAL VIGNETTE: PHARMACOGENETIC SCREENING NEW

Consultation with primary care practitioner and pharmacist:

- Clopidogrel: reduce dose, alternatives also substrates for CYP2C19
- Simvastatin: Switch to pravastatin: fewer side effects

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THE GENOME IN PRIMARY CARE

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THE PERSONAL GENOME

Genome-wide associations with phenotype: mostly SNP's

e.g., 23and Me: $200, 30 million done

Total genome sequencing and scanning for mutations related to phenotype 3 million? done

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

Many more genome sequences in medical context (not consumer-driven)

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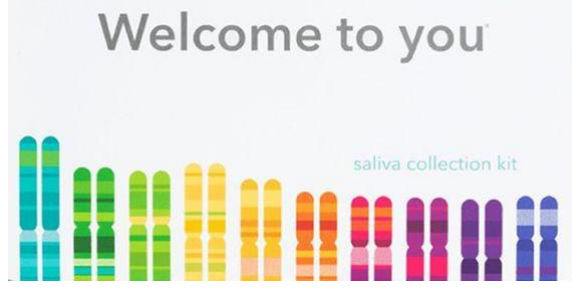
THE PERSONAL GENOME

Example



30 million people genotyped as of 1/25
(13 million by 23andMe; 17 million by Ancestry)

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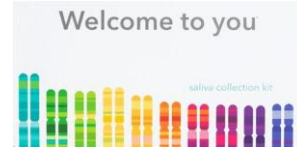
THE PERSONAL GENOME

Basis: *DNA changes associated with phenotypes*

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



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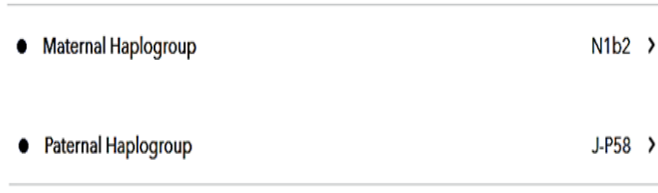
THE PERSONAL GENOME: ANCESTRY

DNA variations associated with specific populations:

- HapMap: Groups of sequences in paternal (Y chromosomes) and maternal (mitochondria)



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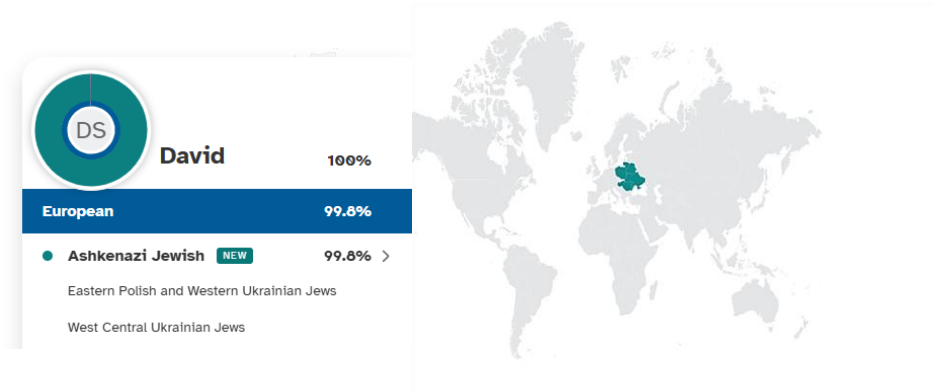
PERSONAL GENOME: ANCESTRY



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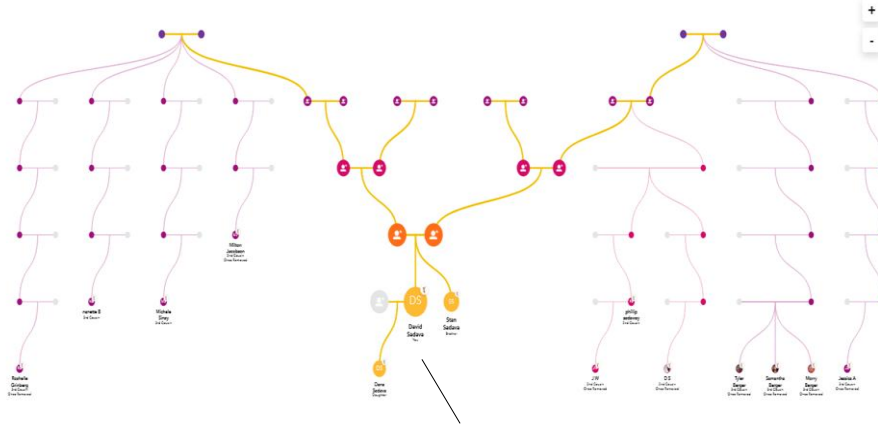
PERSONAL GENOME: ANCESTRY / RELATIVES



David S

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

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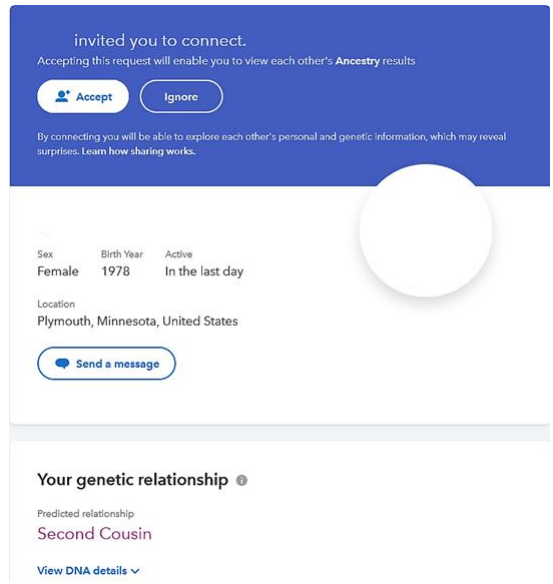
PERSONAL GENOME: RELATIVES



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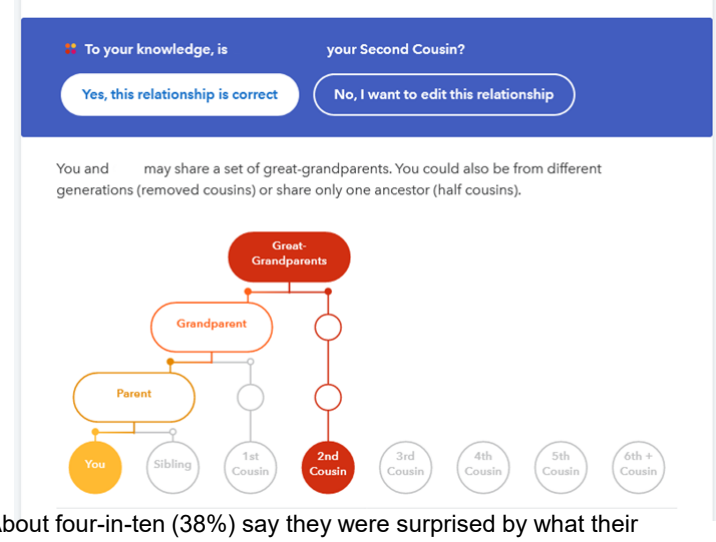
PERSONAL GENOME: RELATIVES



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%)

50 Diseases Tested for Risk Analysis

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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 ›

14 Wellness Characteristics Tested

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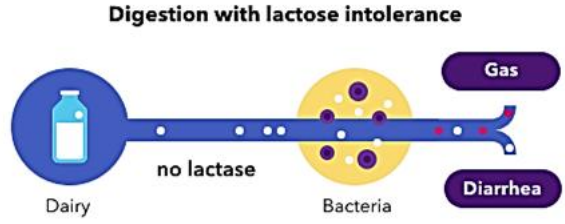
PERS. GEN. : WELLNESS: LACTOSE INTOLERANCE



	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 bald spot >
Bitter Taste	Likely can't taste >
Bunions	Less likely than average to have had a bunion >
Cheek Dimples	Likely no dimples >
Cilantro Taste Aversion	Slightly higher odds of disliking cilantro >
Cleft Chin	Likely no cleft chin >

27 Traits Tested for Probability

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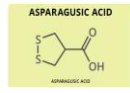
PERSONAL GENOME: TRAITS

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 (Typical Sequence) → Substitution → A (Variant Sequence)



OR2M7 encodes an olfactory receptor

Percent of 23andMe customers with variant

Variant: A

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: CARRIER STATUS

Autosomal Recessive Polycystic Kidney Disease	Variant not detected
Beta Thalassemia and Related Hemoglobinopathies	Variant not detected
Bloom Syndrome	Variant not detected
Canavan Disease	Variant not detected
Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)	Variant not detected
Cystic Fibrosis	Variant not detected
D-Bifunctional Protein Deficiency	Variant not detected
Dihydrolipoamide Dehydrogenase Deficiency	Variant not detected
Familial Dysautonomia	Variant not detected
Familial Hyperinsulinism (ABCC8-Related)	Variant not detected

27 Alleles Tested

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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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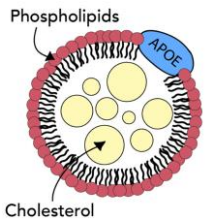
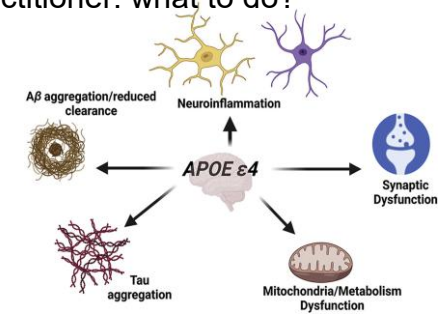
PERS. GEN.: CLINICAL VIGNETTE

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 have APOEe4
- 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 the front line for consultation in direct-to-consumer DNA testing

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PRS. GEN.: ISSUES FOR PRIMARY CARE PRACTICIONERS

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

- PCP knowledge of consumer resources for personal genome
- Anxiety and emotional support
- PCP knowledge about genetic risks and effects
- Security of genomic information
- Implications of costs, insurance
- Relationship with genetic professionals / information

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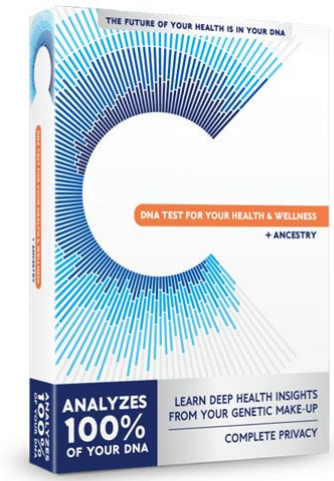
PERSONAL WHOLE GENOME SEQUENCING



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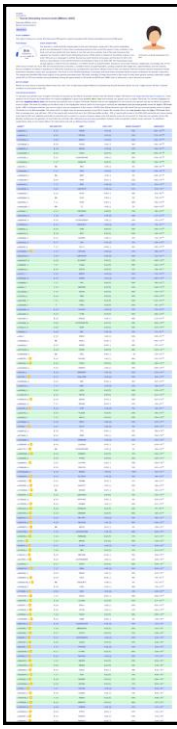
WHOLE GENOME SEQUENCING: TSH



10/2023

KH: NOWWBYEK

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 ADCY8 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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WHOLE GENOME SEQUENCING: TSH

VARIANT	YOUR GENOTYPE	GENE	EFFECT SIZE	VARIANT FREQUENCY
rs989759_C	C / C	PDE8B	-0.14 (↓)	64%
rs2983511_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	IGFBP6	-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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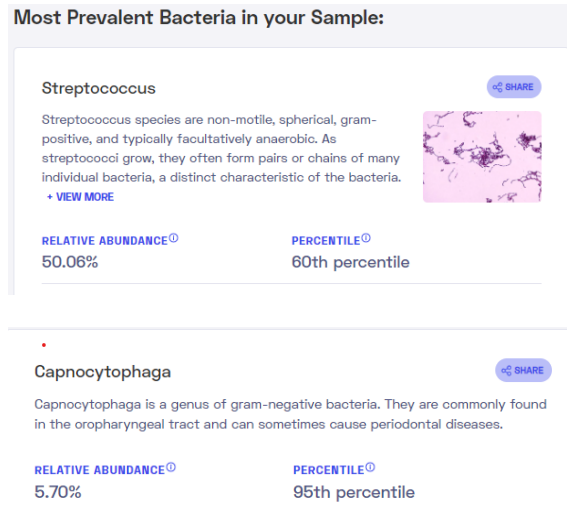
PERSONAL GENOME: ORAL MICROBIOME



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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)
- 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

Genome sequence information and analysis made available to participants:

Ancestry

Disease risks:
- 3% of participants have a DNA change leading to a disease that is treatable or preventable

Traits

Pharmacogenomics:
- 70% of participants have a DNA change that predicts variations in drug activity

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PERSONAL GENOME SEQUENCING: DISEASE RISKS

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 INFORMATION: ISSUES

Human genome data are concerning because:

- They can predict inherited predispositions at the time or later in life
- They can impact many more than an individual: family, group, next generation
- They can have cultural significance for an individual or group

Genome data must be protected

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PERSONAL GENOME INFORMATION: GINA

Genetic Information Nondiscrimination Act (US, 2008)

- Health insurers cannot use a person's genetic information to deny or adjust coverage

  Exceptions: life ins., disability ins., long-term care

- Employers cannot use a person's genetic information to make employment decisions

  Exceptions: small businesses (<15)

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DNA AND PERSONAL HEALTH: FUTURE?

Personalized medicine: N of 1

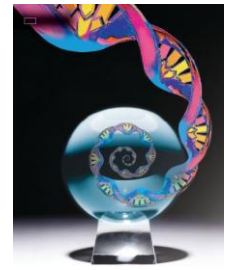
Data: genome DNA, transcriptome mRNA, proteome, metabolome, microbiome, environment

Predictive

Preventive

Personalized

Participatory



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THE GENOME IN PRIMARY CARE

A. The human genome

B. The human genome and medicine

C. The personal genome

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