

CENTER FOR INDIVIDUALIZED MEDICINE

Consumer Genomics @ Mayo

NASEM, September 29, 2019



Disclosures/Need to Know

Mayo Clinic GeneGuide™ is a Mayo Clinic laboratory operating within the Center for Individualized Medicine

Helix and PWN-Health are for profit companies

Mayo Clinic has an investment in the sequencing laboratory, Helix

No Mayo Clinic GeneGuide™ team members have a financial interest in any part of the product(s)

How Many People Have Had DTC?

Everybody's doing DNA tests

Total number of people tested by consumer genetics companies through January 2019, in millions

■ AncestryDNA ■ 23andMe ■ Others

30m

25m

20m

15m

10m

5m

2013

2014

2015

2016

2017

2018

2019

Chart: MIT Technology Review • Source: Company reports, Leah Larkin, ISOGG • [Created with Datawrapper](#)

<https://www.technologyreview.com/s/612880/more-than-26-million-people-have-taken-an-at-home-ancestry-test/>

Why Do Consumers Want DNA Testing?

HEALTH

WELLNESS

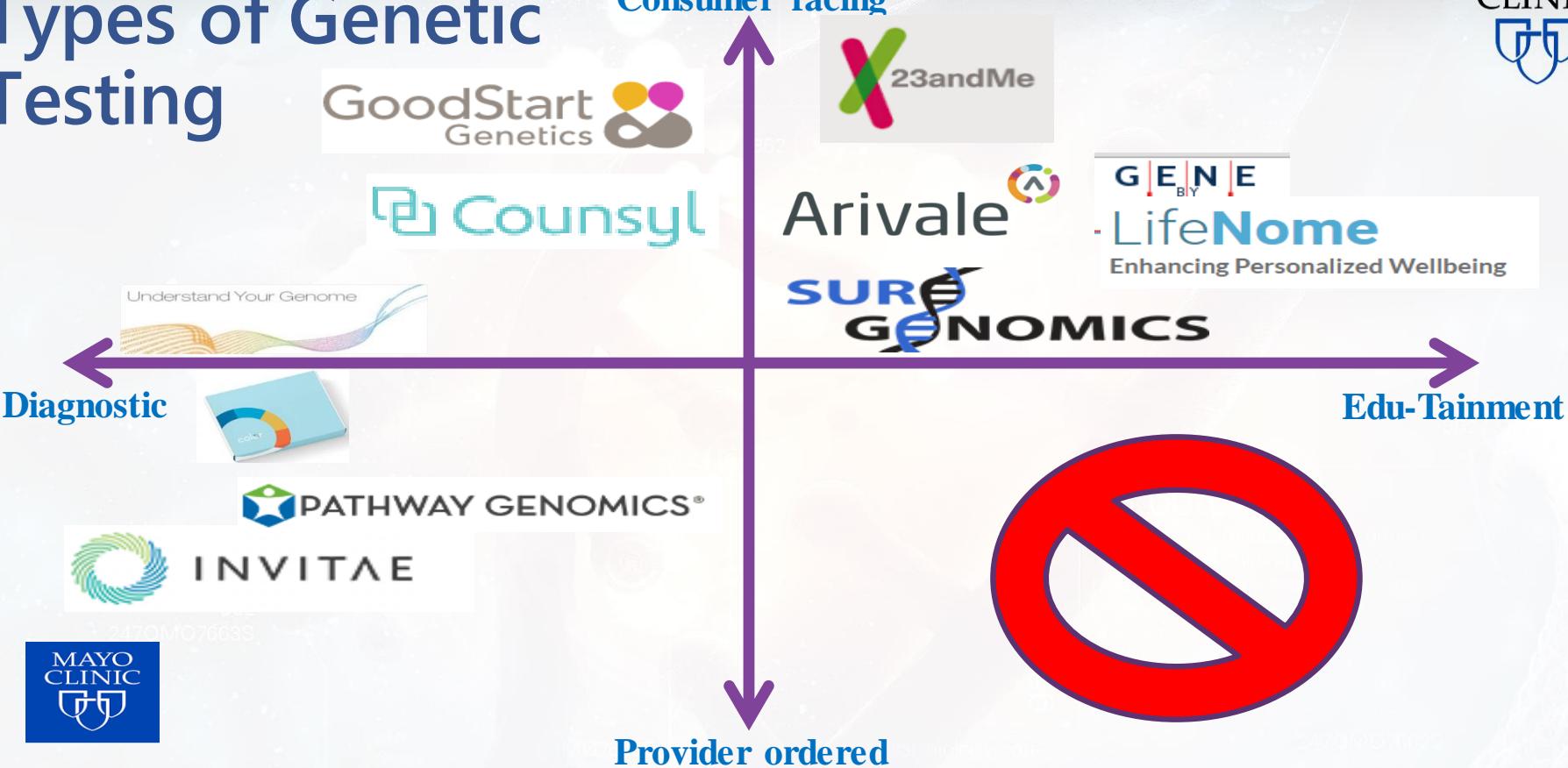
Ancestry

Curiosity

Entertainment

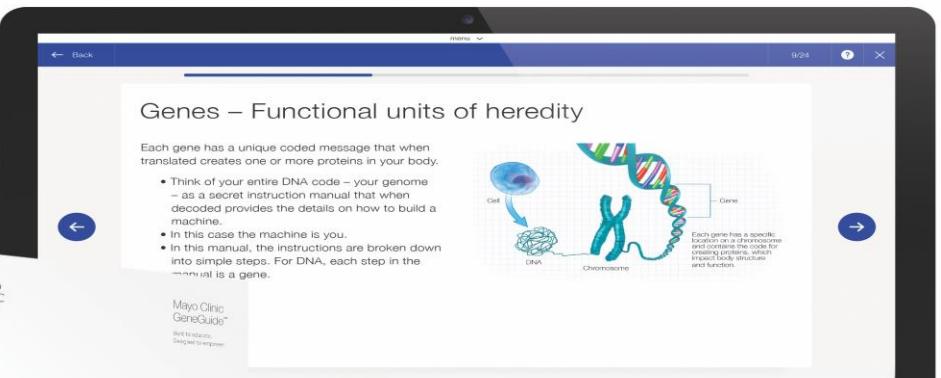
Paternity

Types of Genetic Testing





Mayo Clinic GeneGuide™
Want to start? Design to explore.

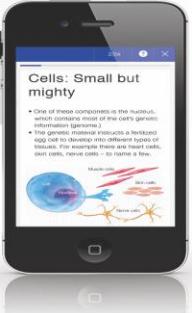


Genes – Functional units of heredity

Each gene has a unique coded message that when translated creates one or more proteins in your body.

- Think of your entire DNA code – your genome – as a secret instruction manual that when decoded provides the details on how to build a machine.
- In this case the machine is you.
- In this manual, the instructions are broken down into simple steps. For DNA, each step in the manual is a gene.

Diagram: A cell contains DNA, which is organized into chromosomes. A gene is a specific location on a chromosome that contains the code for creating proteins, which then control structure and function.



Cells: Small but mighty

- One of many components in the nucleus, which contains most of the cell's genetic information (genome)
- The cell nucleus instructs a fertilized egg cell to develop into different types of specialized cells – muscle cells, heart cells, skin cells, nerve cells – to make a human.

Diagram: A cell is shown with various organelles: nucleus, mitochondria, endoplasmic reticulum, and Golgi apparatus.

What is Mayo Clinic GeneGuide™?

A genetic testing experience

- Educates consumers and helps them understand how genetics can affect their health

Consumer-initiated, physician-ordered product

Includes results for 15 conditions in categories:

- Carrier screening > Medication Response
- Disease risk > Health traits

Includes 4 health learning tools:

- Health ancestry results > Lifestyle questionnaire
- Pedigree tool > Breast cancer risk screening tool

Includes a robust education section: 15 topics

Why is Mayo Clinic pursuing this initiative?

Allows Mayo Clinic to educate consumers before they present as sick patients

Share Mayo Clinic knowledge to an eager audience in a balanced way

Setting realistic expectations

Prepare OURSELVES for the management of DTC results

Potential benefits

May provide ***meaningful health information*** to individuals who might otherwise not qualify to receive testing through current medical guidelines.

Availability of this testing may ***increase the genetic literacy*** of the general population at a time when genetics is becoming an integrated part of the medical practice.

Limitations

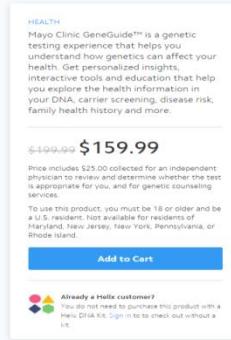
Results may be informative, but ***should not be considered diagnostic.***

- A positive result may suggest further medical evaluations and/or confirmatory testing.

Assesses ***limited number of variants***, or changes, in a specific set of genes.

- A negative test result will reduce, but cannot eliminate risk of having a variant in a gene. i.e., BRCA1/2.

Consumer-initiated ordering process



Consumer orders product on Helix.com



Helix sends kit to the consumer's home



Consumer registers with Helix and provides health history



PWNHealth physician reviews the consumer's health history



Consumer receives an email when the physician has approved their order

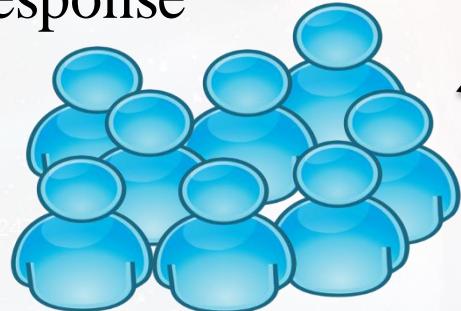


What is pharmacogenomics?

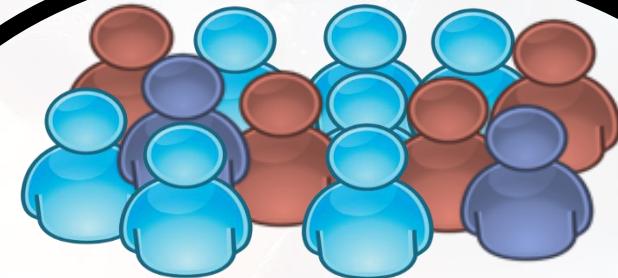
Study of genetic variations that influence individual response to drugs



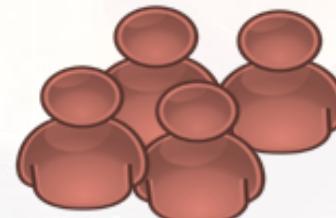
No Response



Desired Response



Same Condition



Toxic Side Effects

Pharmacogenomic Testing at Mayo Clinic

Mayo Medical Labs

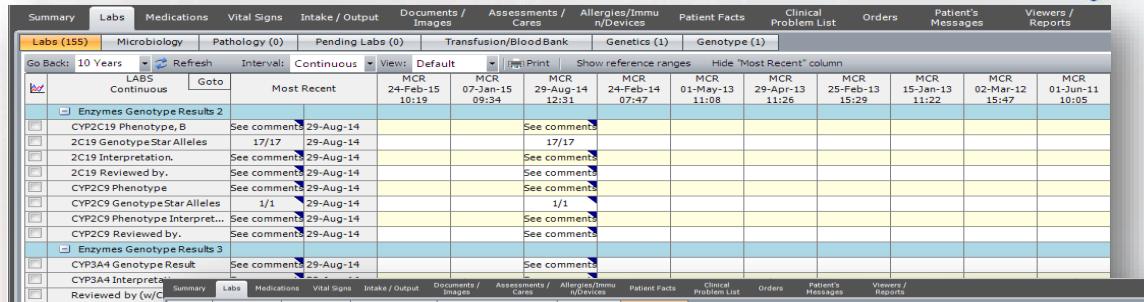
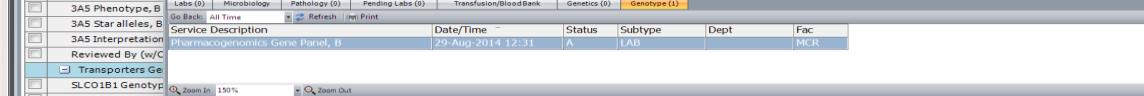
- Single gene tests
- Nine gene panel

AssureRx Health

- GeneSight®

OneOme

- RightMed®

CYP2C19 Phenotype, B
Ultrarapid metabolizer
2C19 Genotype Star Alleles 17/17
2C19 Interpretation.

This individual is expected to be an ultrarapid (increased) CYP2C19 metabolizer due to the presence of the homozygous *17 variant which results in increased expression of CYP2C19 enzyme. Caution should be exercised when treating with drugs metabolized by CYP2C19 as follows:

If this patient is taking a prodrug that is activated by CYP2C19, such as clopidogrel, increased activation of the drug is expected to occur which may result in increased activity of the drug and side effects such as bleeding.

If this patient is taking a drug that is inactivated by CYP2C19, such as citalopram or phenytoin, increased inactivation is expected which may result in lower blood levels of the parent drug and poorer response.

-----ADDITIONAL INFORMATION-----
A Luminex assay using Polymerase Chain Reaction (PCR) with Allele-Specific Primer Extension (ASPE) was used to test for the presence or absence of variants in the promoter and exons 1, 3, 4, and 9 of the CYP2C19 gene. Specifically, the reactions detect the presence or absence of c.-806G>T (*17), c.11A>G (*4), c.358T>C (*8), c.395G>A (*6), c.431G>A (*9), c.636G>A (*3), c.680C>T (*10), c.681G>A (*2), c.819+2T>A (*7), and c.1297C>T (*5).

This Luminex assay will not detect all the known variants that result in altered CYP2C19 activity. Therefore, absence of a detectable gene variant does not necessarily mean that the patient has an altered CYP2C19 metabolism status due to other CYP2C19 variants that cannot be detected with this method. Furthermore, when two or more gene variants are identified, the cis-trans status (whether the variants are on the same or opposite chromosomes) is not always known.

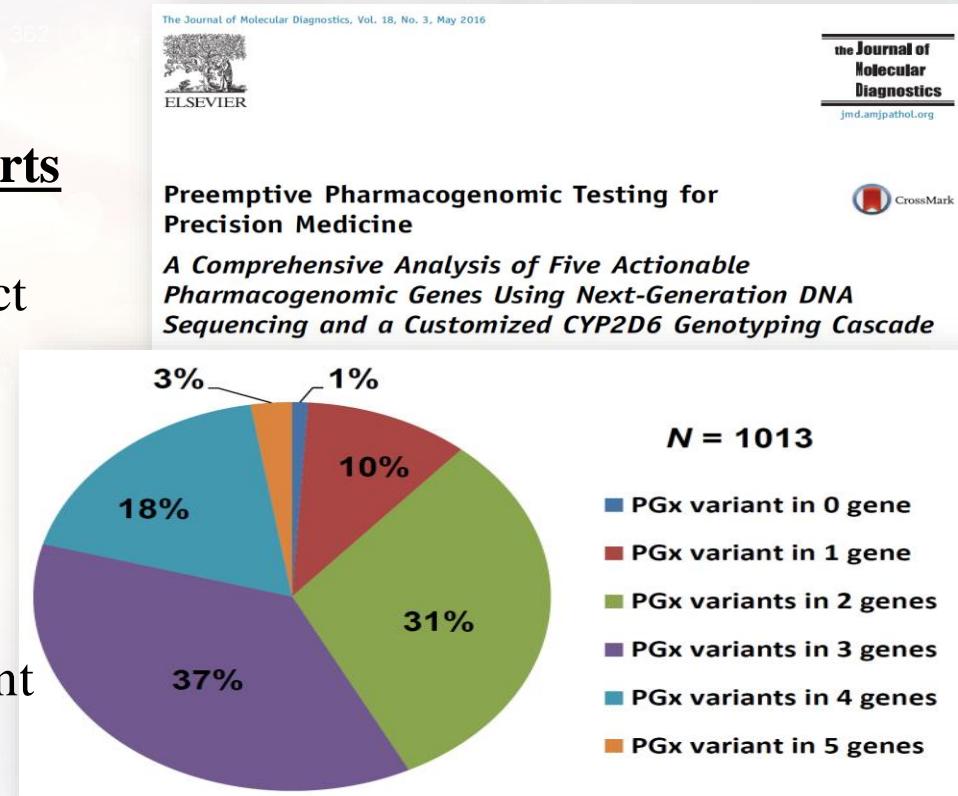
In addition to a genetic basis for CYP2C19 altered enzymatic activity, CYP2C19 enzyme activity can be inhibited by a variety of medications or their metabolites. The following is a partial listing of drugs known to affect CYP2C19 activity as of the date of this report.

A partial list of commonly prescribed drugs that undergo metabolism by CYP2C19:
Anticoagulants: clopidogrel, R-warfarin (less active isomer)
Anticonvulsants: phenytoin, phenobarbital, phenytoin, primidone
Antidepressants: amitriptyline, citalopram, S-citalopram, clomipramine,

The RIGHT Study: Right Drug, Right Dose, Right Time

Goals:

- Improve health care by utilizing clinical decision support (CDS) alerts
- Evaluate the clinical and fiscal impact of alerts.
- Retrospectively analyze EHR data to determine how the presence of genetic information might have altered patient outcomes.



Pharmacogenomic CDS at Mayo Clinic



CYP2C19

- Clopidogrel (2014)
- Citalopram (2015)
- Escitalopram (2015)

SLCO1B1

Simvastatin (2014)

TPMT/NUDT15

(phenotype & genotype)

- Mercaptopurine (2013)
- Thioguanine (2013)
- Azathioprine (2013)

CYP2D6

- Codeine (2013)
- Tramadol (2013)
- Tamoxifen (2013)
- Paroxetine (2015)
- Fluoxetine (2015)
- Fluvoxamine (2015)
- Venlafaxine (2015)

CYP2C9/VKORC1

- Warfarin (2014)

CYP3A5

- Tacrolimus (2016)

DPYD

- 5-fluorouracil (2017)
- Capecitabine (2017)

HLA-B*15:02/HLA-A*31:01

Carbamazepine (2013)

HLA-B*57:01

Abacavir (2013)

HLA-B*58:01

Allopurinol (2014)

EPIC CDS or Best Practice Advisory

BestPractice Advisory - Cdtesting,Adt

High Priority (1)

 PHARMACOGENOMICS ALERT: This patient is a CYP2D6 Ultra Rapid metabolizer. Avoid codeine due to potential for toxicity. 

Remove the following orders?

Remove

Keep

 butalbital-aspirin-caff-codeine 30-50-325-40 mg per capsule 1 capsule (FIORINAL WITH CODEINE)
1 capsule, oral, Every 4 hours PRN, headaches, Starting Today at 1714

Genomic Indicators 

For more information go to AskMayoExpert (codeine) 

Acknowledge Reason

Benefit outweighs risk

Patient previously tolerated

Therapeutically appropriate

Will cancel order

Other reason

 **Accept**

Over 22,000 CDS alerts fired to date

We can run – but we can not hide!



Consumers and patients will increasingly drive genetic testing

Predictive Genomic Endeavors

Population Health – Mayo
Clinic GeneGuide™

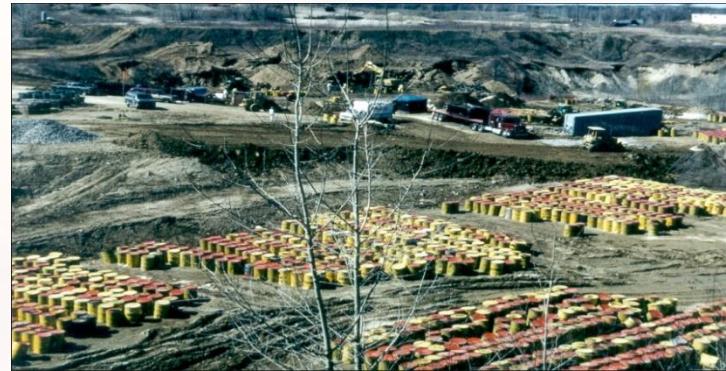
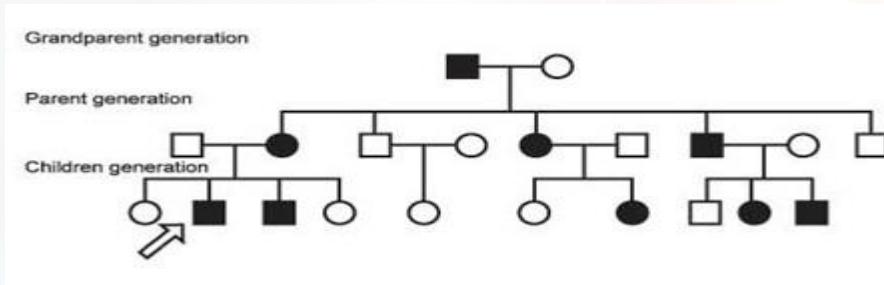
Sequencing of Mayo Clinic
Biobank (50K+)

Large Scale
Sequencing/Data
Repository



Do Genes Always Tell The Whole Story?

Emphasize: for many health related topics, genomics is just part of the equation



• Human genome
• Human environment
• Human behavior
• Human history

The End

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The branch of molecular biology concerned with the structure, function, evolution, and mapping of genomes

ACGT

genomics

362

ACGT

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Applying the techniques of genetics and molecular biology to the genetic mapping and DNA sequencing of sets of genes or the complete genomes of selected organisms, using high-speed methods; with organizing the results in databases, and with applications of the data as in medicine or biology

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Mayo Clinic: Consumer Education

Worldwide leader in
medical care, research
and education

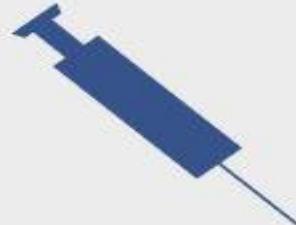
Rich history of health
care innovation

Mayo Clinic Books,
Newsletters, and many
other consumer goods



OUR PURPOSE:

**EDUCATE AND ENGAGE THE PUBLIC,
SHARING OUR KNOWLEDGE OF
GENOMIC DATA AND IMPLICATIONS
FOR HEALTH.**



Patient Expresses Interest or is Referred for Consultation

Genetic Counseling / Pharmacist Consult

Patient Test Selection and Sample Acquisition



Lab Sequencing and Analysis

Clinical Analysis & Genomic Board

Results Returned With IM Counselor / Pharmacist Support

What have we found? (preliminary findings)

~300 patients that pursued predictive testing

11% Actionable Findings (34 patients)

- 13 were in hereditary cardiovascular genes
 - ~half had a suspicious personal or family history
 - All 3 patients with an FH gene had high cholesterol and were on statins
 - no other CV patient had manifest disease
- 15 were in hereditary cancer genes
 - ~ 50% of met NCCN guidelines for testing
 - One SDHA patient mutation w/bilateral carotid paragangliomas
 - otherwise no manifest cancer

Carriers and Disease Risk

40–75% of patients were found to be carriers of at least one AR condition

85.6% of WGS had at least one risk allele identified;

- APOE e4
- F5 /F2
- Idiopathic pulmonary fibrosis
- MC1R/ MCM6 variants (melanoma)
- NAFLD (nonalc fatty liver disease)