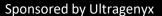


# **Genetic Diagnosis**

November 2023
Paul Kruszka, MD
CMO, GeneDx
pkruszka@genedx.com



### **Contents**

- Introduction
- Genetic terminology
- Genetic testing
- The diagnostic odyssey
- Finding your group
- The next five years in genomic technology



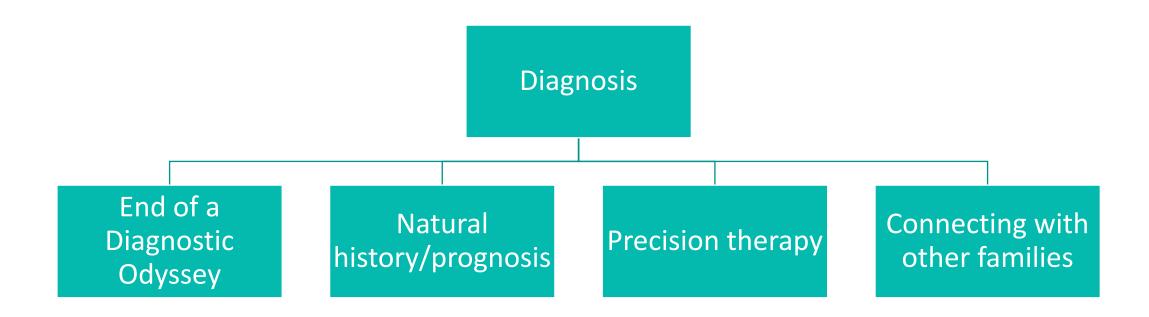


# Introduction



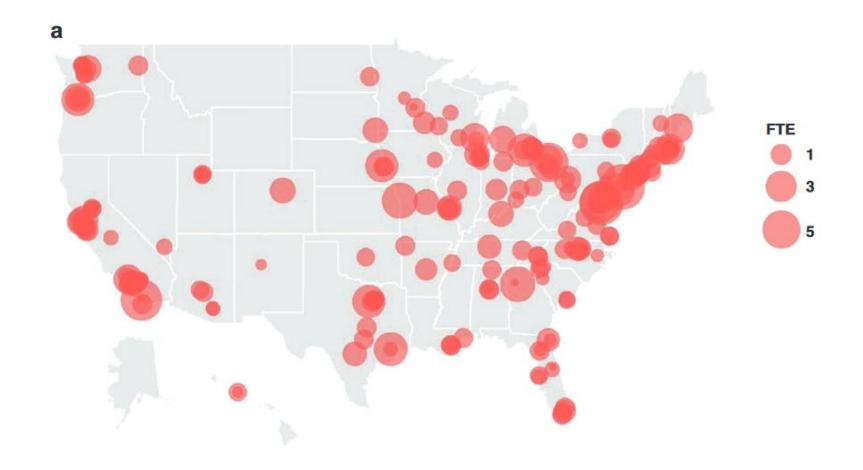


# How is a diagnosis "actionable"?





## The 2019 US medical genetics workforce: Endangered Species



Genetics in Medicine (2021) 23:1458 - 1464







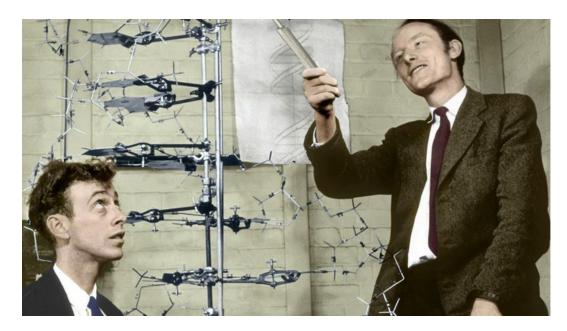
# **Terminology**





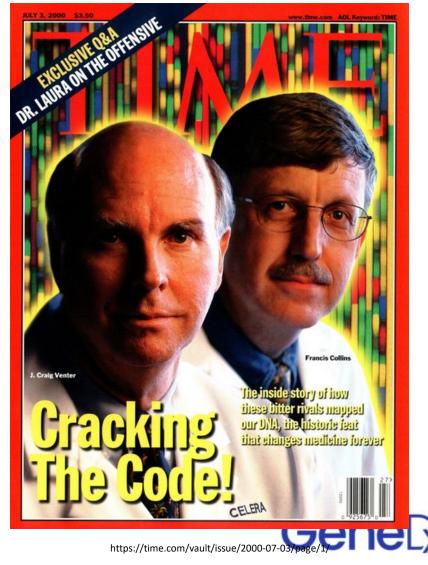
### The Genomic Era

### 1953

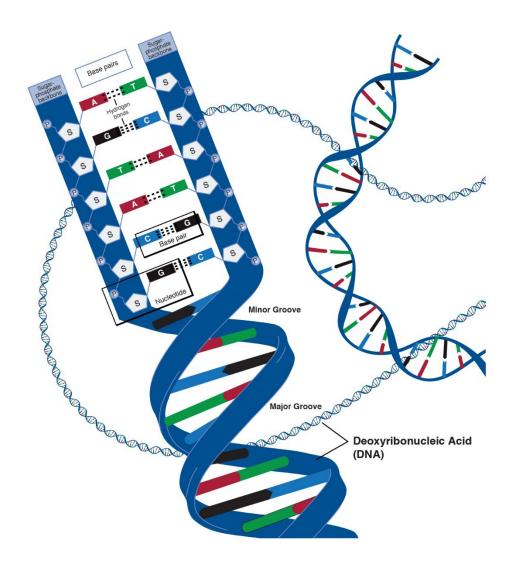


https://www.thetimes.co.uk/article/being-objectionable-is-in-his-dna-james-watson-derides-former-colleaguesszhlbtctl

## 2000



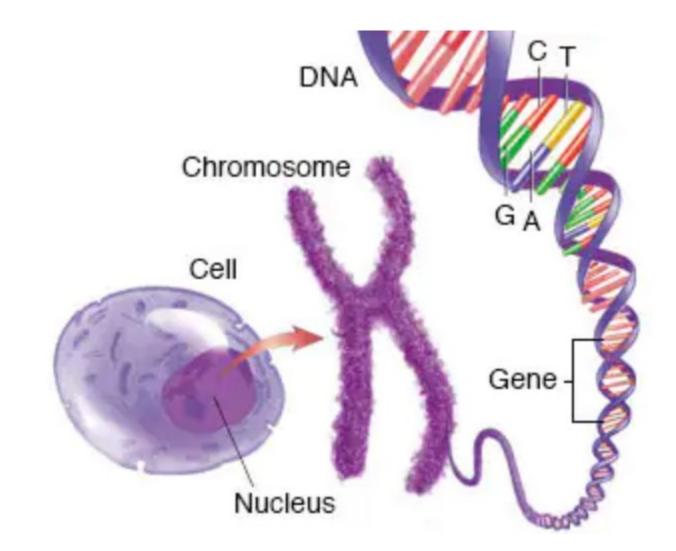
# Code







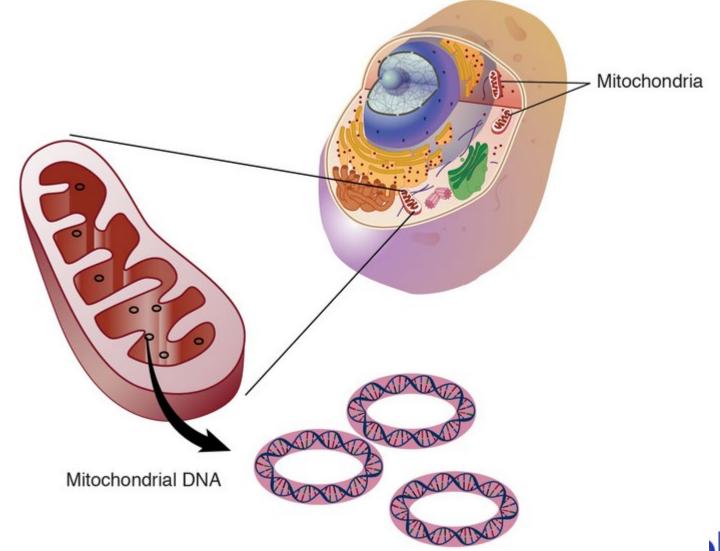
# **Nuclear DNA**



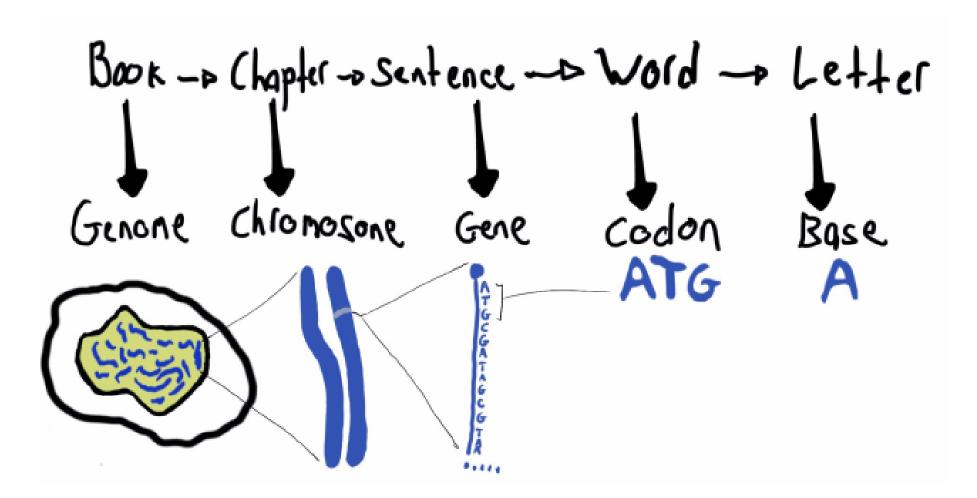


### **Mitochondrial DNA**

### **Maternal inheritance**



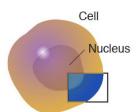


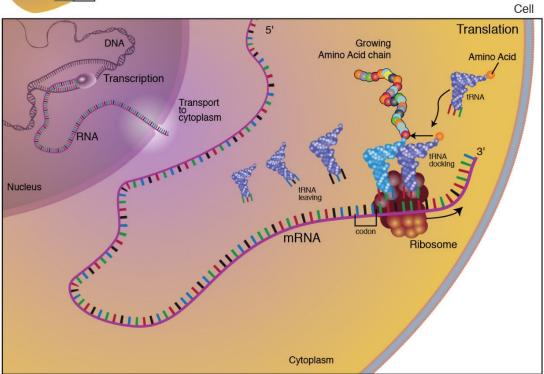


https://inacrutshell.com/2017/08/21/genetics-the-real-book-of-life/









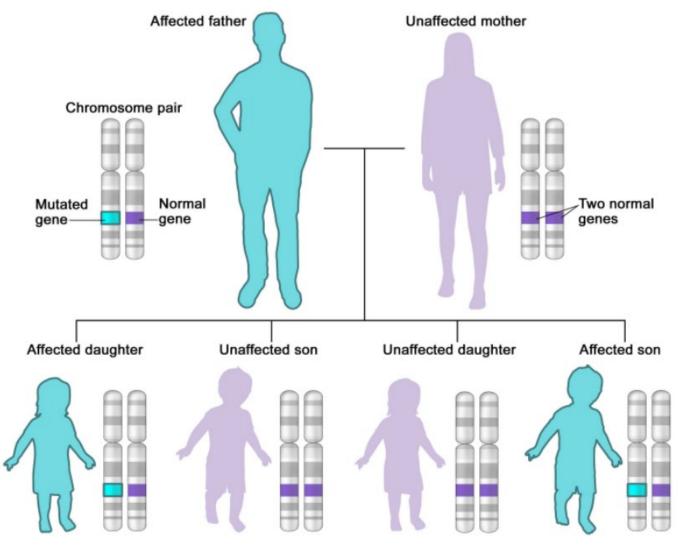
# Inheritance

"Mendelian inheritance refers to patterns of inheritance that are characteristic of organisms that reproduce sexually. The Austrian monk Gregor Mendel performed thousands of crosses with garden peas at his monastery during the middle of the 19th century. Mendel explained his results by describing two laws of inheritance that introduced the idea of dominant and recessive genes."

https://www.genome.gov/genetics-glossary/Mendelian-Inheritance



#### **Autosomal Dominant Inheritance**



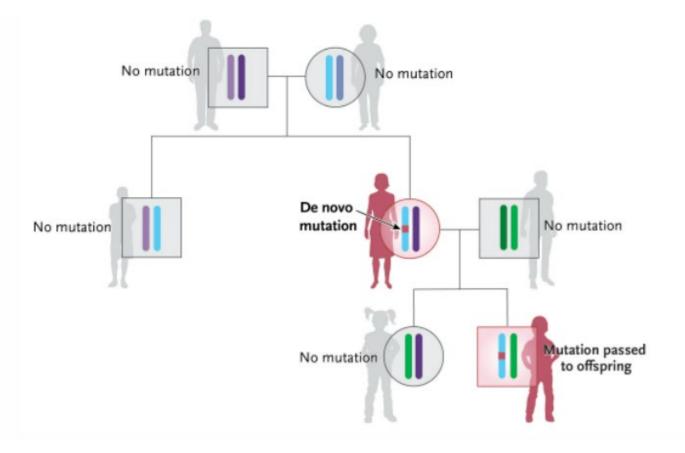
Example - DEEs

https://nci-media.cancer.gov/pdq/media/images/802195.jpg





<u>De novo</u>: Any DNA sequence change that occurs during replication, such as a gene alteration newly occurring in a family as a result of a DNA sequence change in a germ cell or a fertilized egg.

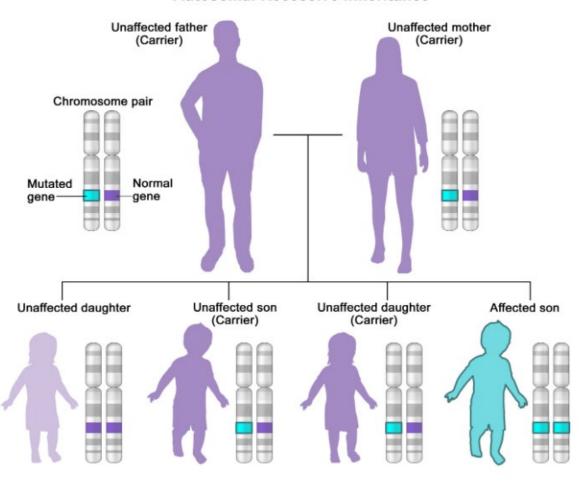


https://illustrated-glossary.nejm.org/term/de novo mutation





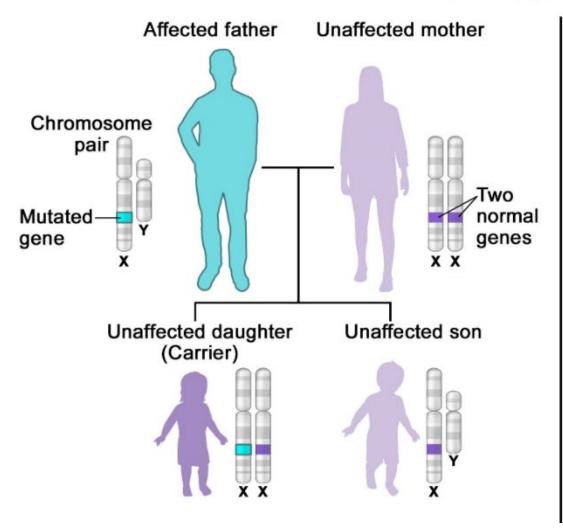
#### **Autosomal Recessive Inheritance**

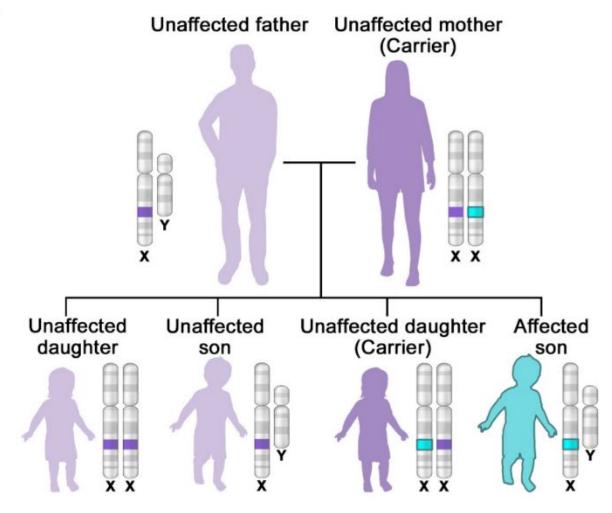






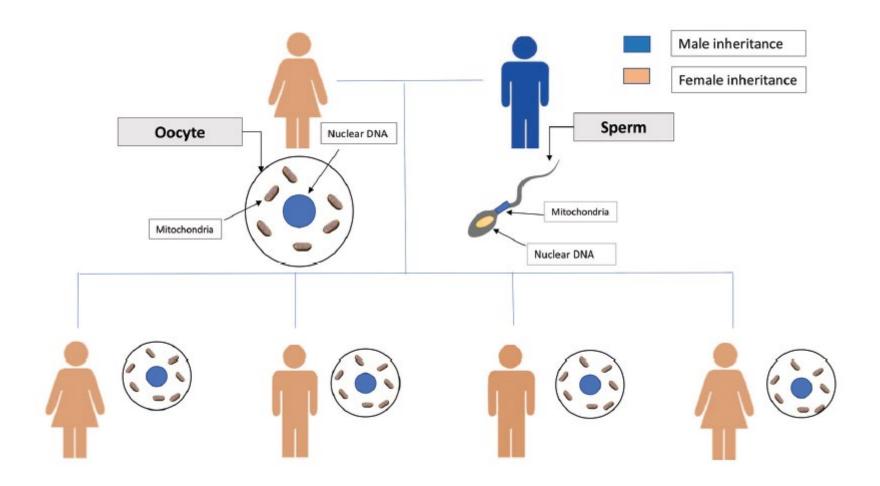
### X-Linked Recessive Inheritance





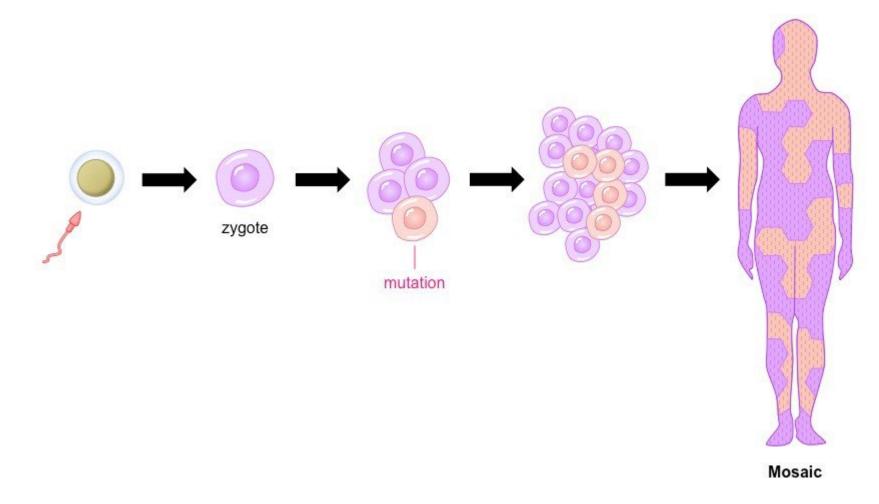


**Gene**L<sub>X</sub>





### **Mosaicism in Genetics**





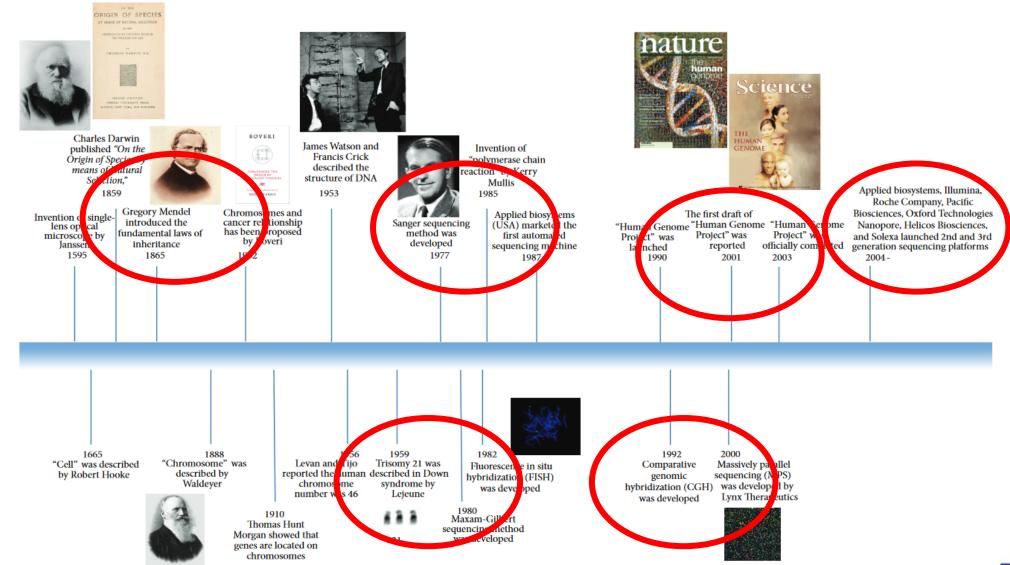




# **Genetic testing**







# **Next Generation Sequencing**

Sample Processing

Sequencing

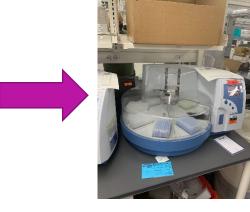
Data
Analysis/Bioinformatics













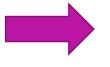
Accessions

Transfer: 1h

DNA extraction: 1.5h

Sample Selection: 1h







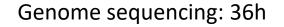








Library prep: 2.5h





## **FATHER**

**ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC** 

## **MOTHER**

ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

CACAAATTATGTCCTCGC

CTAGCGCACAAA

ACCGTTACTA

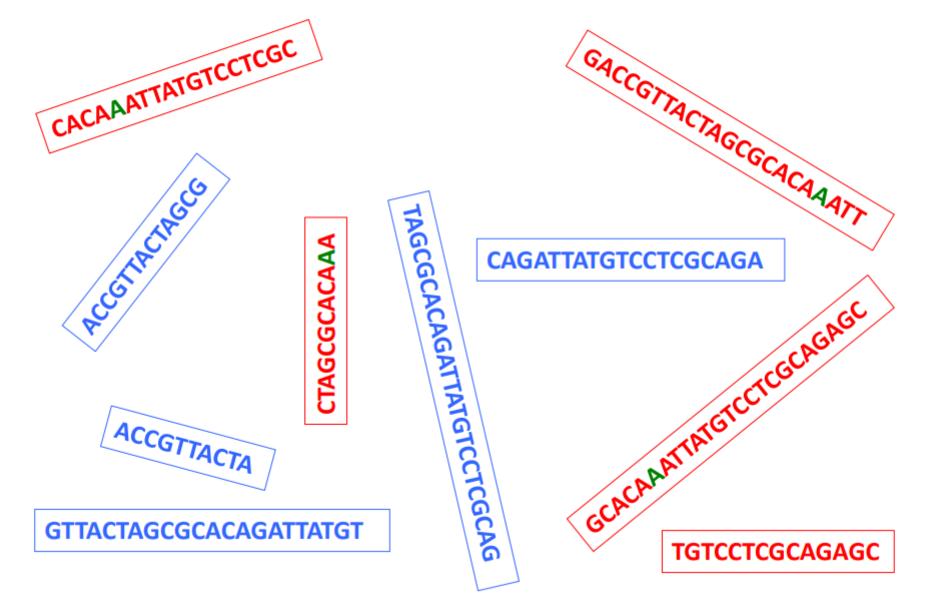
**GTTACTAGCGCACAGATTATGT** 

GACCGTTACTAGCGCACAAATT ,

TAGCGCACAGATTATGTCCTCGCAG **CAGATTATGTCCTCGCAGA** 

**TGTCCTCGCAGAGC** 

### REFERENCE: ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC



#### REFERENCE: ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

**ACCGTTACTA** 

**TGTCCTCGCAGAGC** 

CACAAATTATGTCCTCGC

ACCGTTACTAGCG

CAGATTATGTCCTCGCAGA

**GACCGTTACTAGCGCACAAATT** 

**TAGCGCACAGATTATGTCCTCGCAG** 

CTAGCGCACAAA

GCACAAATTATGTCCTCGCAGAGC

**GTTACTAGCGCACAGATTATGT** 

### REFERENCE: ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

**ACCGTTACTA** 

TGTCCTCGCAGAGC

CTAGCGCACAAA

CACAAATTATGTCCTCGC

ACCGTTACTAGCG | CAGATTATGTCCTCGCAGA

GACCGTTACTAGCGCACAAATT

**TAGCGCACAGATTATGTCCTCGCAG** 

**GTTACTAGCGCACAGATTATGT** 

GCACAAATTATGTCCTCGCAGAGC

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# **Genomes and Exomes**

Genome = 3 billion bases

Sequence only bases that code for protein

Exome = 30 million (1%) bases





# The exons are separated by DNA of unclear function

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### **Genomes and Exomes**

- Whole genome sequencing: file size of 150GB
- Whole exome sequencing: file size of 6-8GB
- Cost of whole genome in 2001: \$92,000,000
- Cost of whole genome today: \$700



#### **DIVE BRIEF**

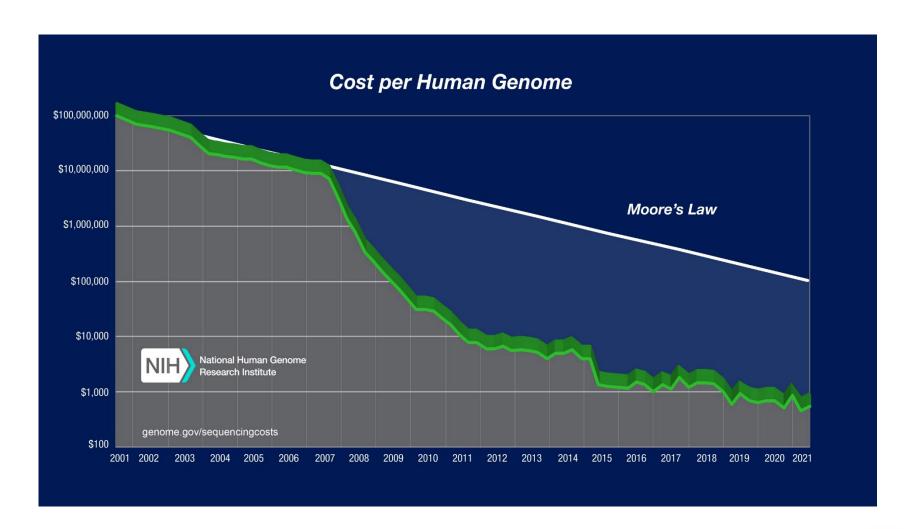
# Illumina ushers in \$200 genome with the launch of new sequencers

Published Oct. 3, 2022 By Nick Paul Taylor Contributor











In the NICU, rapid whole genome sequencing (rWGS/rGS) can deliver answers for critically ill newborns, so that the clinician can focus on what's next. @MichiganHHS just took a big step forward by providing coverage for rapid #genome testing. Learn more bit.ly/2YWgKjY

GeneD

#### **INSURANCE COVERAGE NEWS**

Michigan is the first state to offer

Medicaid coverage for rape whole genome (rWGS) tes for eligible, critically ill inf

**Medical Coverage Policy** 



UnitedHealthcare\* Commercial Medical Policy

### Whole Exome and Whole Genome Sequencing

Policy Number: 2023T0589M Effective Date: March 1, 2023

Instructions for Use

Table of Contents	Page
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Documentation Requirements	3
Definitions	3
Applicable Codes	
Description of Services	5
Clinical Evidence	5
U.S. Food and Drug Administration	26
References	26

### Chromosome Microarray Testing (Non-Oncology

Related Commercial Policies

- Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions
- Preimplantation Genetic Testing and Related Services

Community Plan Policy

ne and Whole Genome Sequencing

ntage Coverage Summaries

stina

Tests and Services



Effective Date	4/15/2022
Next Review Date	1/15/2023
Coverage Policy Number	0519

Whole Exome and Whole Genome Sequencing

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Related Coverage Resources







# The diagnostic odyssey



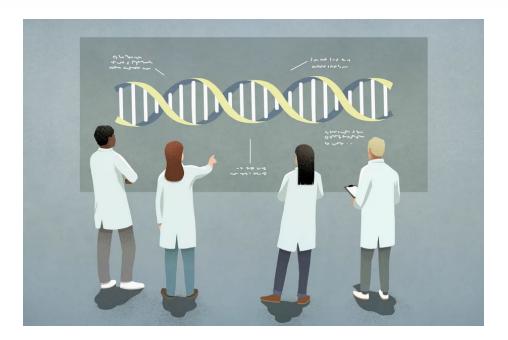


# It takes an average of 8 years for a rare disease patient to get diagnosed. Why is it so hard to get lifealtering genetic testing in the U.S.?

BY ERIN PRATER

February 28, 2023 at 12:36 PM EST





https://fortune.com/well/2023/02/28/rare-disease-patients-diagnostic-odyssey-whole-genome-sequencing-wgs-genetic-testing/







# Finding your group





#### **Gene**D

#### Request to Contact

Dear Physician or Genetic Counselor,

You have referred one of your patients for genetic testing to GeneDx. Based on the genetic test results, your patient may benefit from information about available support groups or be eligible to participate in a research study through an outside group. Details can be found in the attached letter. Please note that we have not disclosed identifying information for your patient to the outside group. If you or your patient(s) are interested in pursuing these opportunities, please contact the respective group directly via the contact information provided in the letter.

Of note, the attached letter is of an informational nature only. While GeneDx makes every effort to ensure its accuracy, this information is not meant to endorse a particular support group or research project, nor serve as medical advice. GeneDx presents this opportunity as a courtesy to clinicians and families who may wish to obtain more details and possibly participate.

Sincerely, Your GeneDx Team



CureARS is a patient organization led by parents of affected children. We are dedicated to improving the lives of children and families affected by the Mitochondrial Aminoacyl tRNA Synthetase Disorders (ARS Genes). These disorders are neurometabolic disorders that cause a variety of Mitochondrial Diseases (Mito).

We are deeply committed to funding research, connecting & providing resources to patients, and raising awareness for these disorders. We welcome you to join our community. Please reach out directly or visit our website <a href="https://www.curears.org">www.curears.org</a> to learn more about Mitochondrial ARS Genes and our efforts.

We understand how overwhelming this diagnosis can be and are here to help you and your family!

We look forward to hearing from you!

Ashley Rowland & Desiree Magee Founders & Parents of ARS Warriors CureARS, A NJ Non-profit Corporation

E-mail: info@curears.org

Website: <a href="https://www.curears.org/">https://www.curears.org/</a> Facebook & LinkedIn: @curears

Instagram: @cure4ars

Facebook Support Group @ARSGeneCommunity



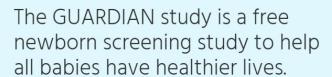




## Newborn sequencing







LEARN MORE



#### **Our Partners**



















En español

Contact Us

Join Now

What is Early Check? ▼

How Early Check Works

For Health Care Providers

News and Outreach ▼



What is Early Check?

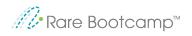




Early Check is a voluntary research study that provides free health tests to new babies.

The goal of Early Check is to find serious health conditions in babies so they can get help sooner.

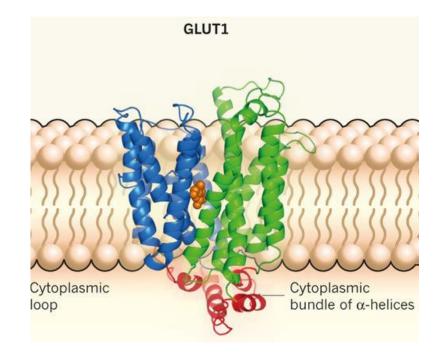
When babies are born in North Carolina, they get a heel prick to screen for certain health conditions. This is called standard newborn screening (NBS) and is provided by the state of North Carolina. Early Check is a research study that offers **additional** free screening for around 200 serious health conditions in newborn babies. Early Check tests for some of the same conditions as standard NBS plus many more.





#### **SEIZURES**









### Glucose Transporter Type 1 Deficiency Syndrome

- Cases at GeneDx (HPO: seizure/epilepsy) = 77
- Average age 9.9 years
- Median age 7 years



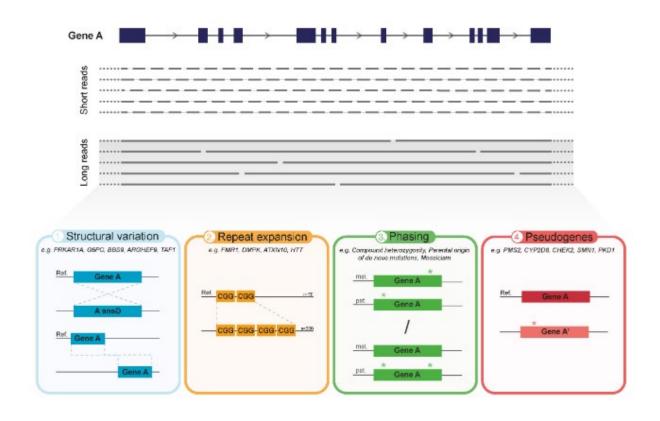


# Long read sequencing





#### Long Read Sequencing



# PacBio and GeneDx Launch Research Collaboration with the University of Washington to Study Long-Read Whole Genome Sequencing for Increased Diagnostic Yield in Neonatal Care

Study is first of its kind to compare diagnostic rates across short- and long-read sequencing platforms

https://www.pacb.com/press\_releases/pacbio-and-genedx-launch-research-collaboration-with-the-university-of-washington-to-study-long-read-whole-genome-sequencing-for-increased-diagnostic-yield-in-neonatal-care/

19) Long-Read Sequencing Emerging in Medical Genetics. Front. Genet. 10:426. doi: 10.3389/



# Thank you



