

# **Genetic Testing**

Paul Kruszka, MD, FACMG Chief Medical Officer

GeneDx



## CONTENTS

- Introduction
- Genetic testing mechanics
- Genetic variants
- Exomes and Genomes
- Making the diagnosis at birth and the diagnostic odyssey
- Cohort building
- The next five years in genomic technology



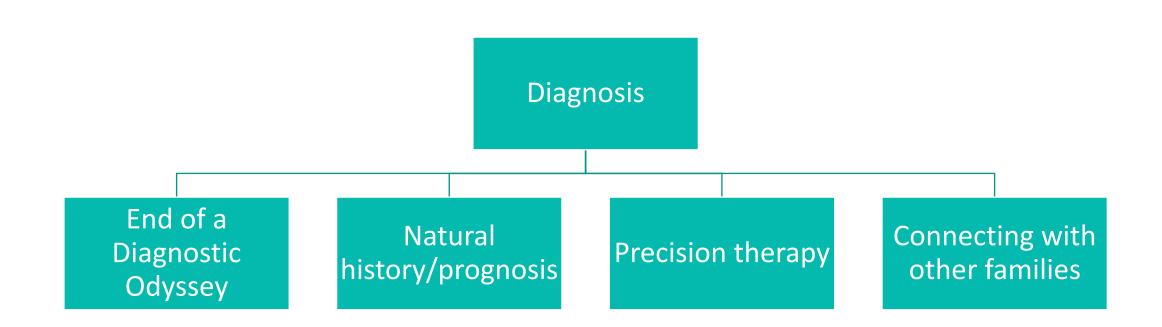
# Introduction

## **Rare Disease**

- Definition: affects less than 200,000 persons in the U.S.
- Over 7,000 rare diseases
- 25-30 million Americans living with a rare disease
- 80% of rare diseases have a genetic cause
- Roughly 70% of rare disease are pediatric onset
- The average time from symptom onset to diagnosis is 5 years

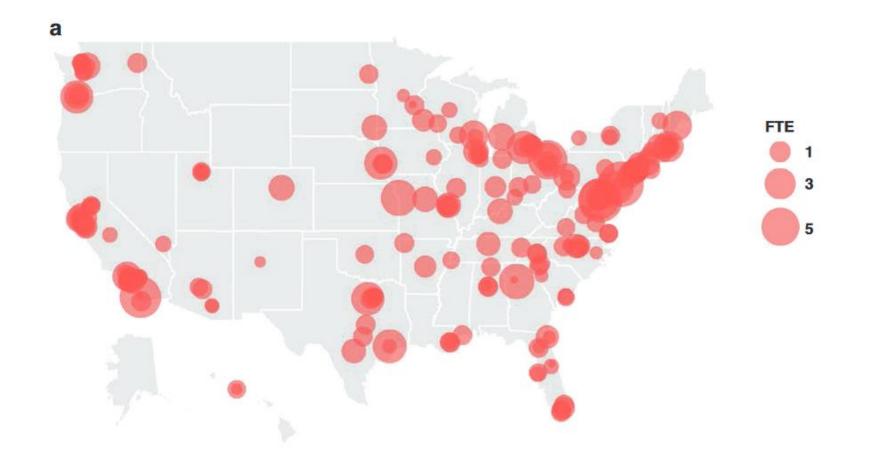
JAMA Pediatr. 2020 September 01; 174(9): 821–822 https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases https://www.nature.com/articles/s41431-019-0508-0

# What is an "actionable" diagnosis?



## The 2019 US medical genetics workforce Endangered Species

*M*PRare Bootcamp™

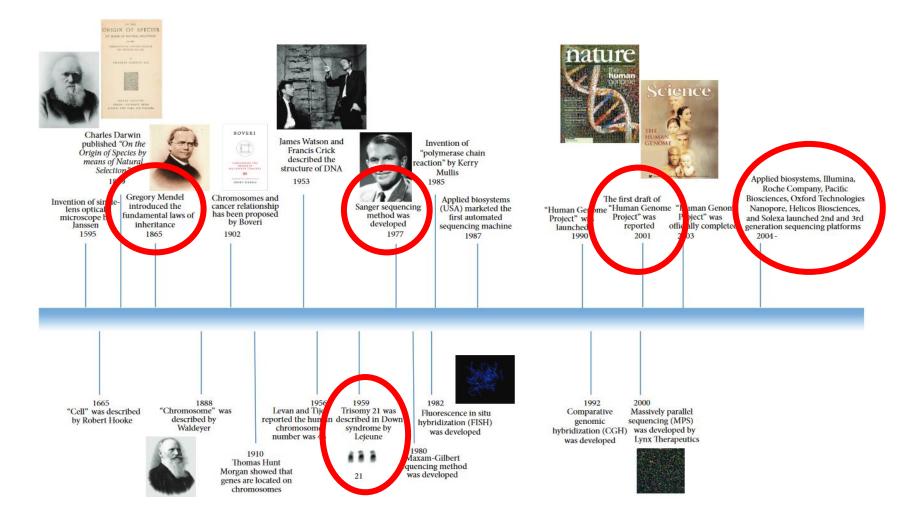


Sponsored by Ultragenyx Genetics in Medicine (2021) 23:1458 – 1464



# **Genetic Testing**

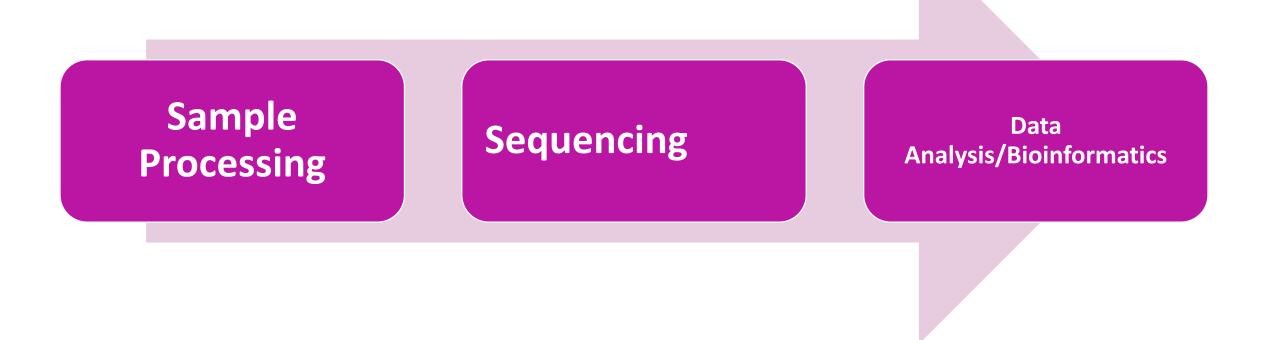
#### **Testing Progress**



Hindawi Publishing Corporation BioMed Research International Volume 2015, Article ID 461524, 7 pages http://dx.doi.org/10.1155/2015/461524

Genetics		www.nature.com/gim	n					
inMedicine		( Check for updates						
ACMG PRACTICE GUIDELINE			-					
Exome and genome sequencing f	or pediatric pa	atients with						
congenital anomalies or intellectu	ual disability: a	an evidence-						
based clinical guideline of the Ar	nerican Colleg	e of Medical						
Genetics and Genomics (ACMG	)							
Kandamurugu Manickam <sup>1,2</sup> , Monica R. McClain <sup>3</sup> , Laurie A. Demmer <sup>4</sup> , S Lauren J. Massingham <sup>8,9</sup> , Danny Miller <sup>10</sup> , Timothy W. Yu <sup>11,12</sup> , Fuki M. H	Sawona Biswas <sup>5</sup> , Hutton M. Kea Iisama <sup>13</sup> and ACMG Board of E	arney <sup>6</sup> , Jennifer Malinowski <sup>7</sup> , Directors <sup>14</sup> *						
	Received: 16 August 2021	Revised: 27 September 2022	Accepted: 1 October 2022					
<b>Disclaimer:</b> The ACMG has recruited expert panels, chosen for their scient clinical practice. An EBG focuses on a specific scientific question and then dese by a systematic review of evidence and an assessment of the benefits and h educational resource for medical geneticists and other clinicians to help them all relevant information on the topic reviewed.	DOI: 10.1002/jgc4.1646	Genetic Society of Genetic WILL Counselors WILL	_EY					
Reliance on this EBG is completely voluntary and does not necessarily ensure procedure or test, the clinician should consider the best available evidence, an preferences and specific clinical circumstances presented by the individual p particular procedure or test, whether or not it is in conformance with this EBG, and to consider other medical and scientific information that becomes availa	Genetic testing and counseling for the unexplained epilepsies:							
	An evidenc	e-based pract	ctice guideline of the National Society	,				
	of Genetic Counselors							
	Lacey Smith <sup>1</sup> I Jennifer Malinowski <sup>2</sup> I Sophia Ceulemans <sup>3</sup> Katlin Peck <sup>4</sup>   Nephi Walton <sup>5</sup> I Beth Rosen Sheidley <sup>1</sup> Katlie Lippa <sup>6</sup>							

# Short Read Sequencing/exome sequencing/genome sequencing

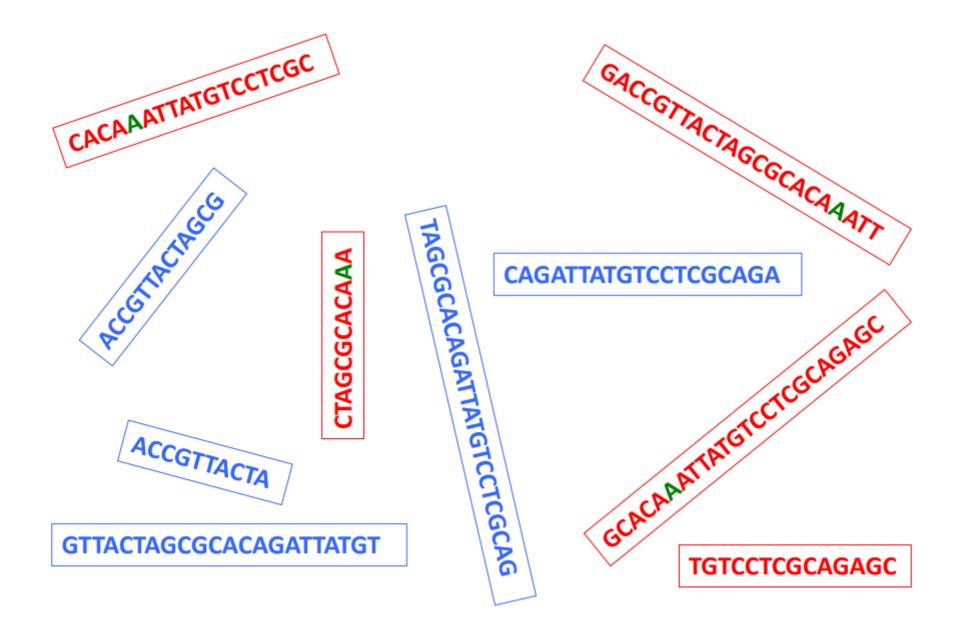


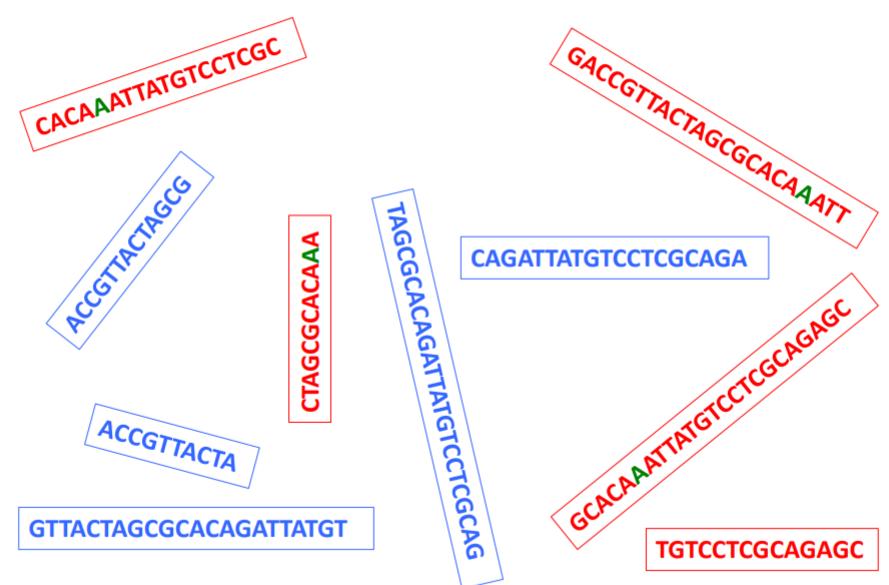
## FATHER

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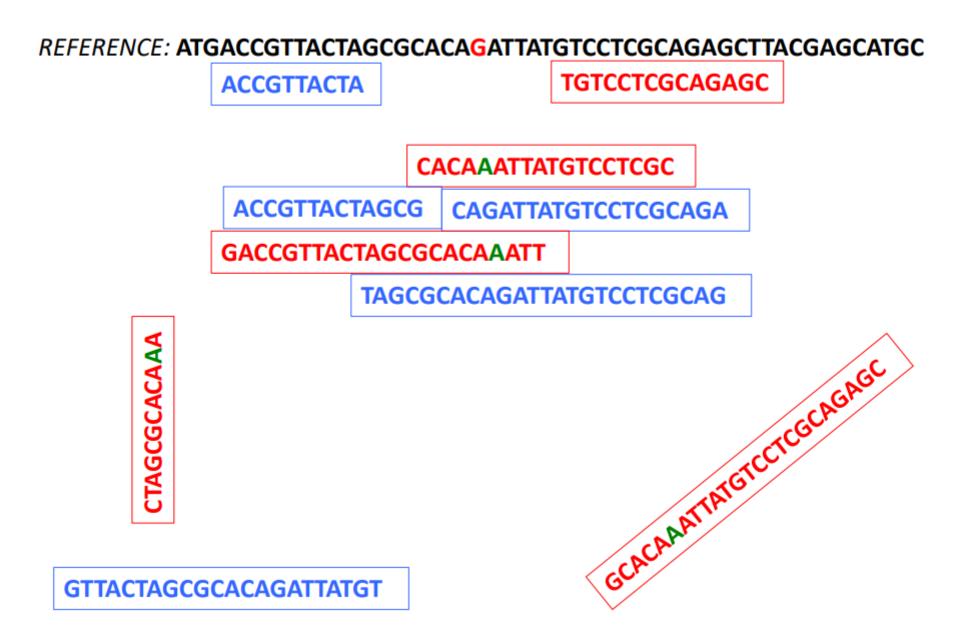
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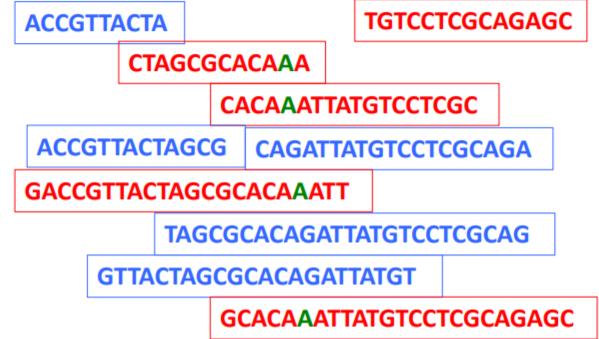




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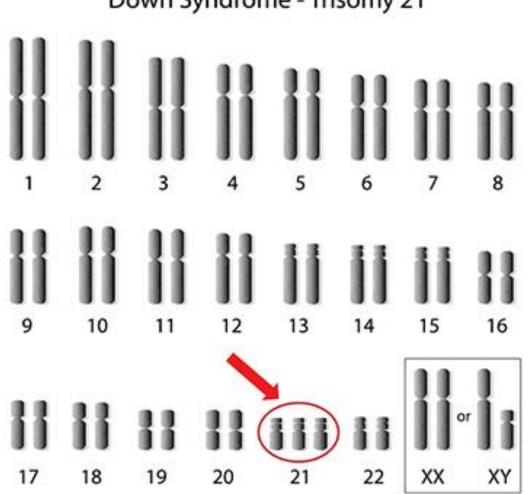


# **Genetic Variation**

# Aneuploidy

#### Aneuploidy:

number of chromosomes NOT equal to 46



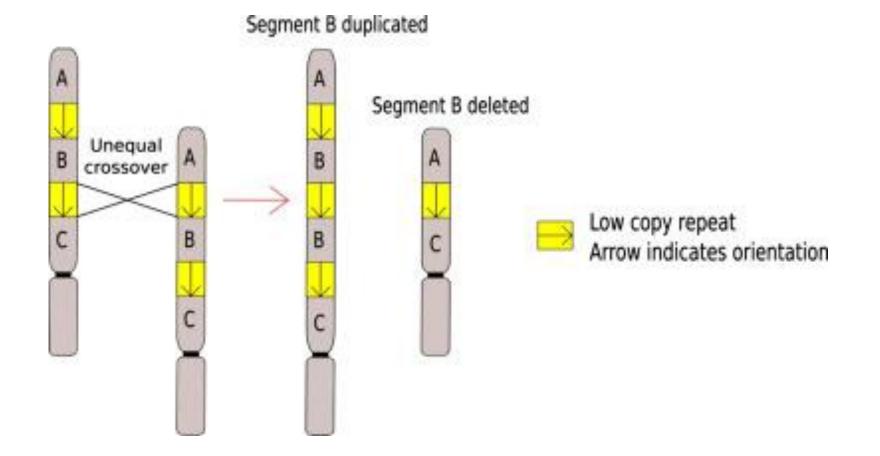
Down Syndrome - Trisomy 21



# **Copy Number Variants**

#### **Copy Number Variant:**

duplications or deletions greater than 1000 nucleotides (1kb)

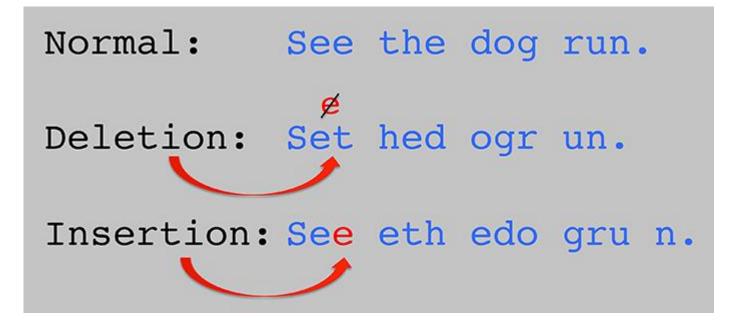


https://media.springernature.com/m312/springer-static/image/art%3A10.1038%2Fs10038-020-00838-1/MediaObjects/10038\_2020\_838\_Fig1\_HTML.png?as=webp

Indel

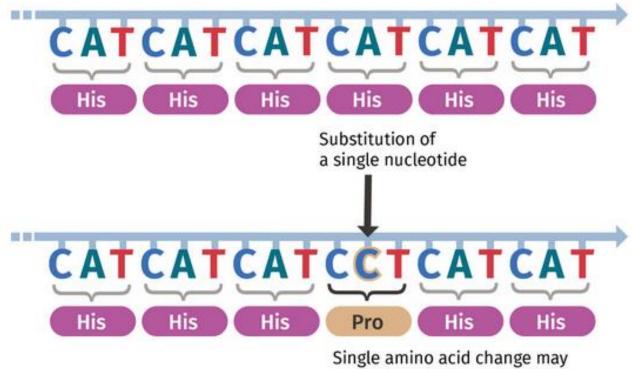
#### Indel:

insertion/deletion smaller than 1kb



https://www.cshl.edu/a-shift-in-the-code-new-method-reveals-hidden-genetic-landscape/

## **Single Nucleotide Variant**



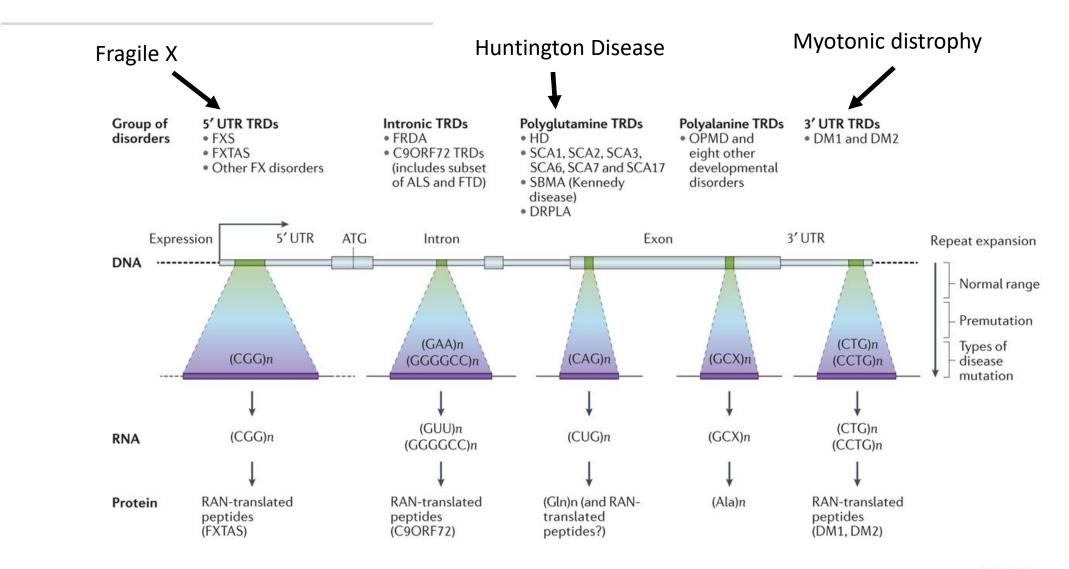
Single amino acid change may produce a non-functioning protein

https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/learn-about-genomics/dna-base/collection1/small-variants

*M* Rare Bootcamp™

More than 40 diseases, most of which primarily affect the nervous system, are caused by expansions of simple sequence repeats dispersed throughout the human genome.

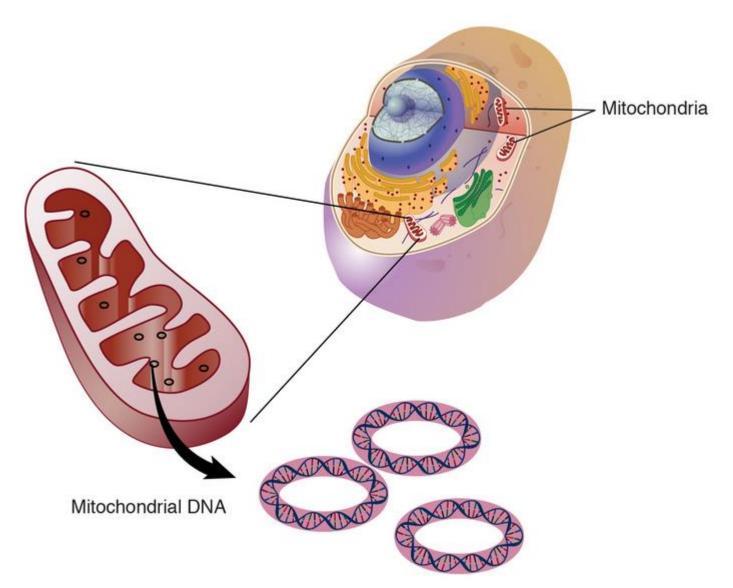
Difficult to detect on exome and genome.



Nature Reviews | Genetics

**Mitochondrial DNA** 

**Maternal inheritance** 

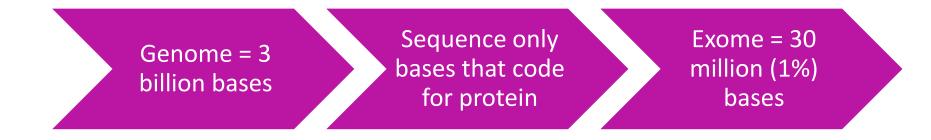


https://www.genome.gov/sites/default/files/tg/en/illustration/mitochondrial\_dna.jpg



# **Exomes and Genomes**

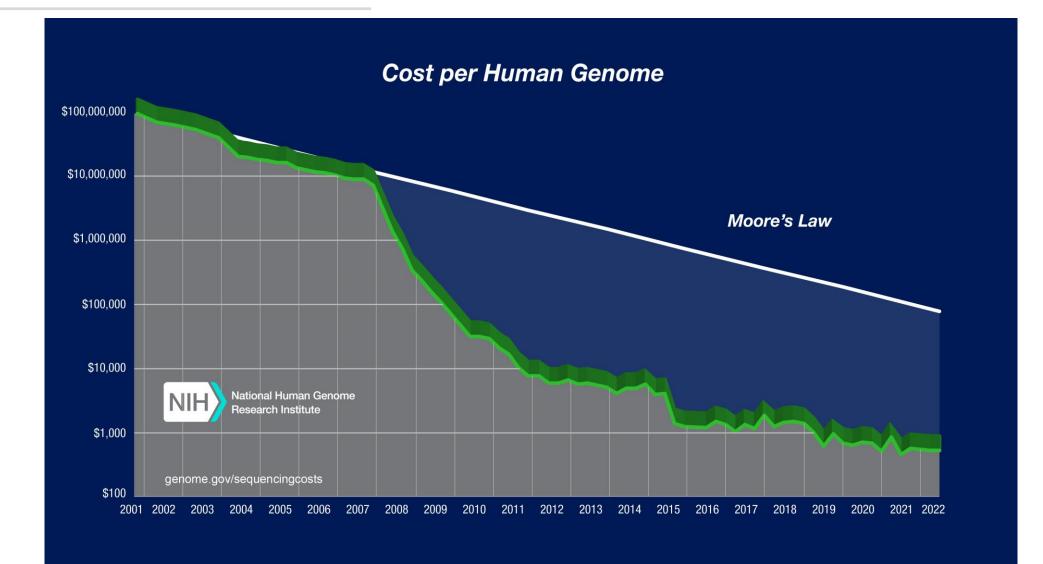
# **Genomes and Exomes**



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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



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 f bit.ly/2YWgKjY Poli Effe GeneDz Tab Cov Doc Def App **INSURANCE COVERAGE NEWS** Des Clin U.S Michigan is the first state to offer Ref Medicaid coverage for rap whole genome (rWGS) tes for eligible, critically ill inf Medical Coverage Policy Coverage Policy Number ...... 0519 Whole Exome and Whole Genome Sequencing

**Table of Contents** 

Related Coverage Resources

		UnitedHealthcare <sup>®</sup> Commercial <i>Medica l Policy</i>
Whole Exome an	nd Whol	e Genome Sequencing
licy Number: 2023T0589M fective Date: March 1, 2023		Instructions for Use
ble of Contents  werage Rationale  coumentation Requirements  finitions  plicable Codes  scription of Services  inical Evidence  Food and Drug Administration		Related Commercial Policies         • Chromosome Microarray Testing (Non-Oncology Conditions)         • Molecular Oncology Testing for Cancer Diagnosis, Prognosis, and Treatment Decisions         • Preimplantation Genetic Testing and Related Services
iferences		Community Plan Policy ne and Whole Genome Sequencing ntage Coverage Summaries sting Tests and Services



# **Newborn Screening**



Home What is the GUARDIAN Study? For Frequently Healthcare Asked Providers Questions Understanding The Results Sign Up to be Invited to the Study

Contact The Study Team

Additional English Resources

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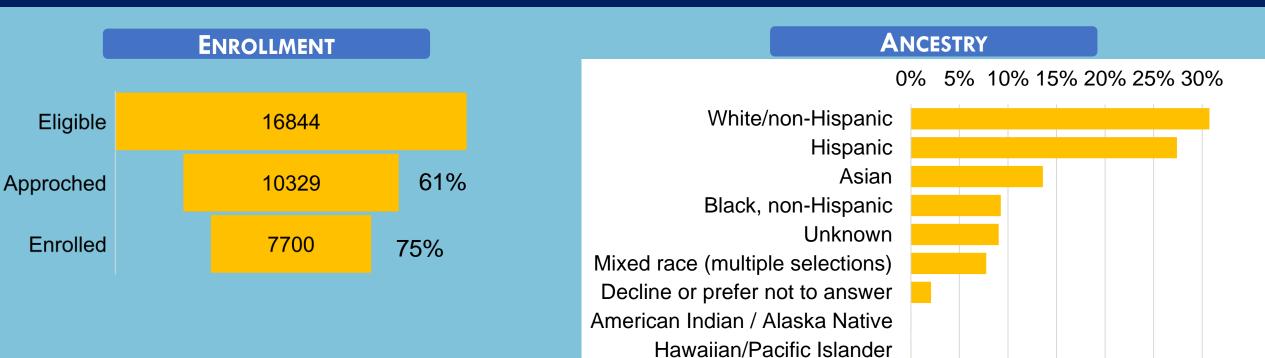


The GUARDIAN study is a free newborn screening study to help all babies have healthier lives.

LEARN MORE

https://guardian-study.org/

# **RESULTS: FIRST 7,700**

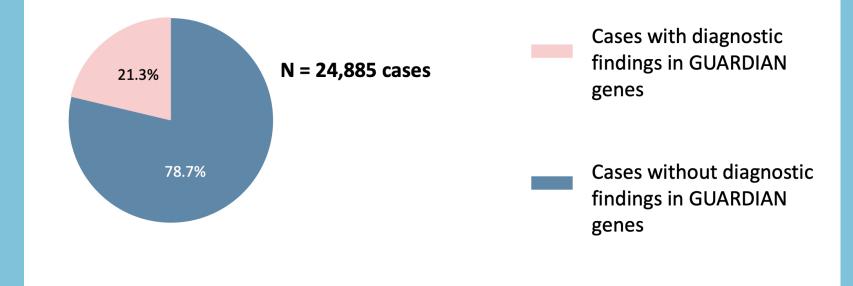


# TYPE OF CONSENT

#### **GROUP 2 CONSENT**

		Overall	English	Spanish	Mandarin
	Groups 1 + 2	<b>92%</b> (7100)	<b>93.2%</b> (6024)	<b>83.6%</b> (754)	<b>92.2%</b> (249)
Confidential and Proprietary.	Group1 only	<b>8%</b> (612)	<b>6.8%</b> (442)	<b>16.4%</b> (148)	<b>7.8%</b> (21)

# RARE DISEASE COHORT MOLECULAR-DIAGNOSED BY ES/GS AT GENEDX

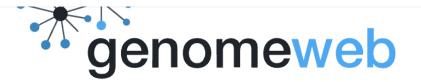


Data presented at ACMG 2023



Confidential and Proprietary. Do Not Distribute.

	Name of Disease							
	ADSSL1 Myopathy	Х						
	Alpha Mannosidosis	(	Grou	up 1				
	Aspartylglucosaminuri	ia		Group 2				
	Aspartylglucosaminuri	ia						
	Aspartylglucosaminuri	ia						
	ATP6V1A Encephalopa	athy	and	l other v-ATPas	e related	disorders		Group 1 – A
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	Bosch Boonstra Schaaf	f Op	otic A	Atrophy Syndro	ome (BBSC	DAS)	Χ	
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	CDKL5							
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	CHD2							
	ECHS1	)	(					
	FOXP1 Syndrome	G	rou	p 2				
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	Multiple							
	Myhre Syndrome			X				
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	Pyruvate Dehydrogena	ase	Com	plex Deficienc	y	Х		
	Pyruvate Dehydrogena	ase	Com	plex Deficienc	y (PDCD)			
	SMC1A			X				
	SPG50 and CMT4J			х				
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Business & Policy Technology Research Diagnostics Disease Areas Applied Marke

Home » Diagnostics » Clinical Sequencing

#### **Research Triangle Institute Partners With GeneDx, Illumina for Expanded Newborn Screening Study**

Sep 21, 2023 | staff reporter

NEW YORK – Research Triangle Institute (RTI) International said on Wednesday that it has partnered with Illumina and GeneDx to expand its Early Check newborn screening study to include whole-genome sequencing and genetic risk scores for type 1 diabetes.

Core funding of unspecified size for the expansion comes from the Leona M. and Harry B. Helmsley Charitable Trust, diabetes foundation JDRF, and Travere Therapeutics, with additional support from Orchard Therapeutics.



# **Cohort Building**

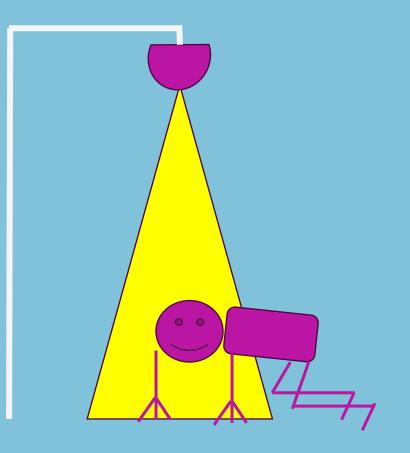
## **Cohort Building**



Gay Grossman Patient Advocacy and Engagement Lead ggrossman@genedx.com



# Future Technology





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#### Montefiore in the News

#### The New York Center for Rare Diseases at Montefiore to Partner with GeneDx, PacBio and Google Health to Increase Genomic Testing Options for Bronx Families

November 8, 2023

New Partnership to Advance Data, Enhance Disease Detection and Care in Diverse Communities

BRONX, NY—November 8, 2023. The New York Center for Rare Diseases (NYCRD) at Montefiore, recognized as a Center of Excellence by the National Organization for Rare Disorders (NORD), is partnering with GeneDx, PacBio and Google Health to deliver genetic diagnoses for Bronx families living with rare diseases. The goal of the new partnership is to help identify the genetic causes of, and best treatments for rare diseases that have remained undiagnosed, despite using today's most advanced tests.

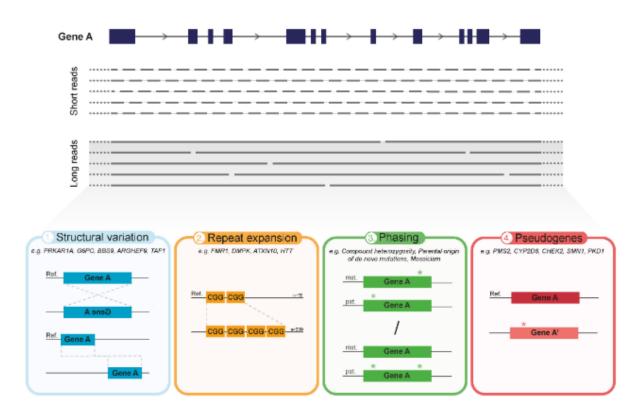
## Long Read Sequencing Projects at GeneDx

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

MENLO PARK, Calif. and STAMFORD, Conn., Aug. 7, 2023 /PRNewswire/ — PacBio (Nasdaq: PACB), a leading developer of high-quality, highly accurate sequencing solutions and GeneDx (Nasdaq: WGS), a leader in delivering improved health outcomes through genomic and clinical insights, today announced a research collaboration with the University of Washington to study the capabilities of HiFi long-read whole genome sequencing (WGS) to increase diagnostic rates in pediatric patients with genetic conditions.

# Long Read Sequencing





Sponsored by Ultragenyx

# Thank You