

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



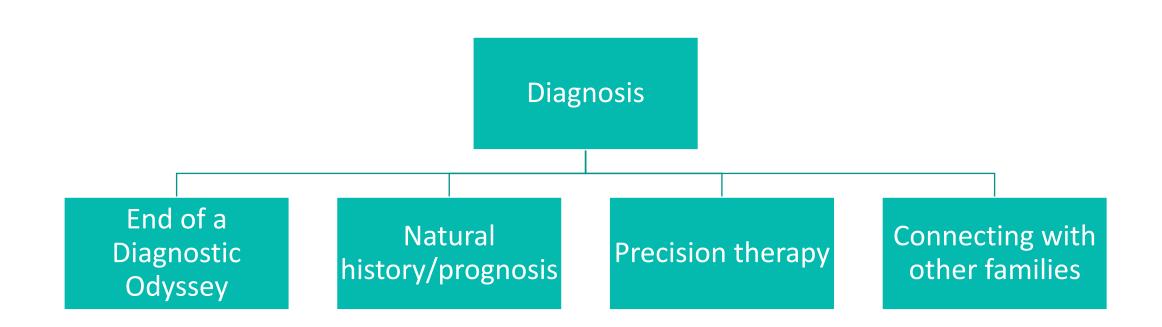
Introduction

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

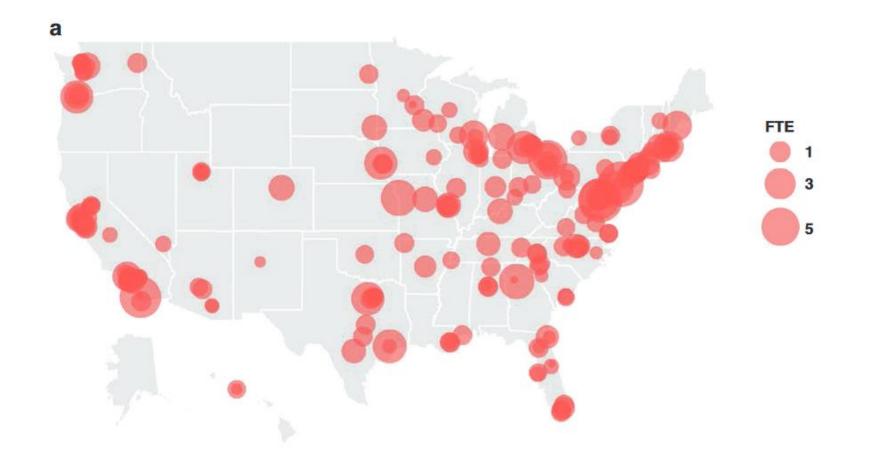
JAMA Pediatr. 2020 September 01; 174(9): 821–822 https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases https://www.nature.com/articles/s41431-019-0508-0

What is an "actionable" diagnosis?



The 2019 US medical genetics workforce Endangered Species

*M*PRare Bootcamp™

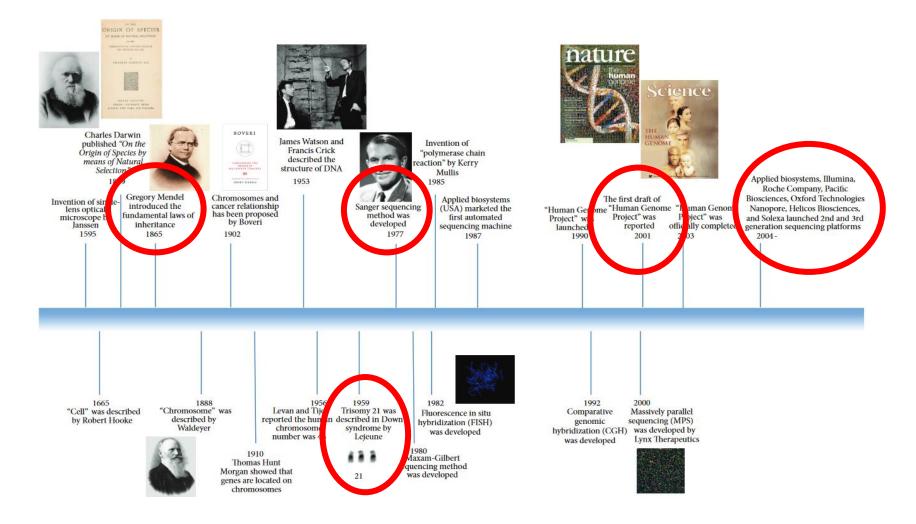


Sponsored by Ultragenyx Genetics in Medicine (2021) 23:1458 – 1464



Genetic Testing

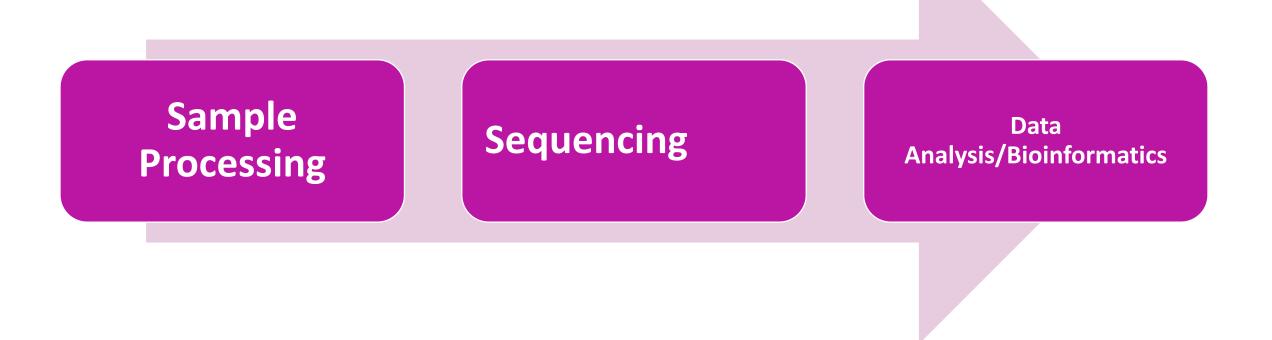
Testing Progress



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 ^{1,2} , Monica R. McClain ³ , Laurie A. Demmer ⁴ , S Lauren J. Massingham ^{8,9} , Danny Miller ¹⁰ , Timothy W. Yu ^{11,12} , Fuki M. H	Sawona Biswas ⁵ , Hutton M. Kea Iisama ¹³ and ACMG Board of E	arney ⁶ , Jennifer Malinowski ⁷ , Directors ¹⁴ *						
	Received: 16 August 2021	Revised: 27 September 2022	Accepted: 1 October 2022					
Disclaimer: 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 ¹ I Jennifer Malinowski ² I Sophia Ceulemans ³ Katlin Peck ⁴ Nephi Walton ⁵ I Beth Rosen Sheidley ¹ Katlie Lippa ⁶							

Short Read Sequencing/exome sequencing/genome sequencing

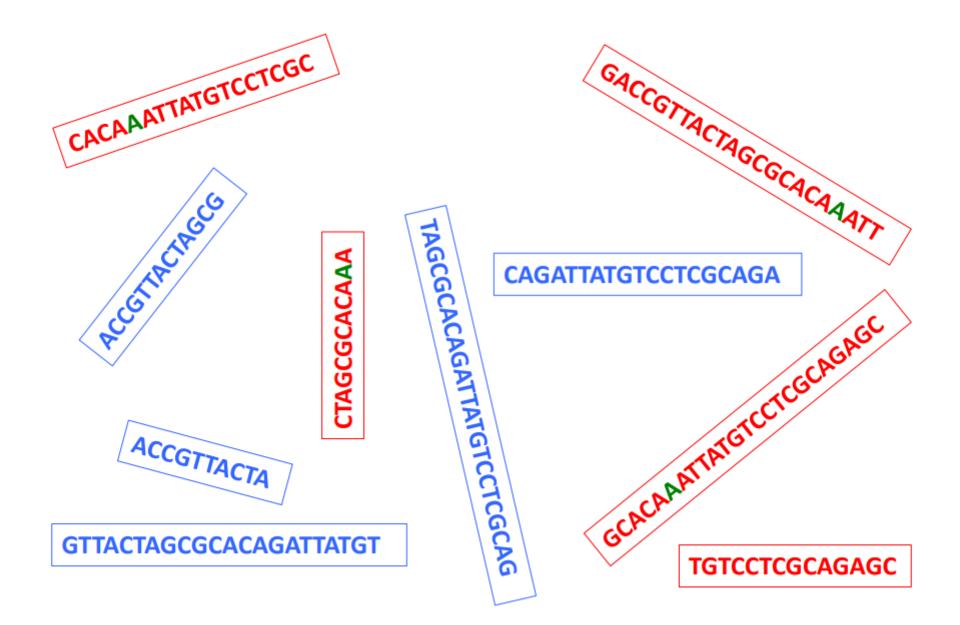


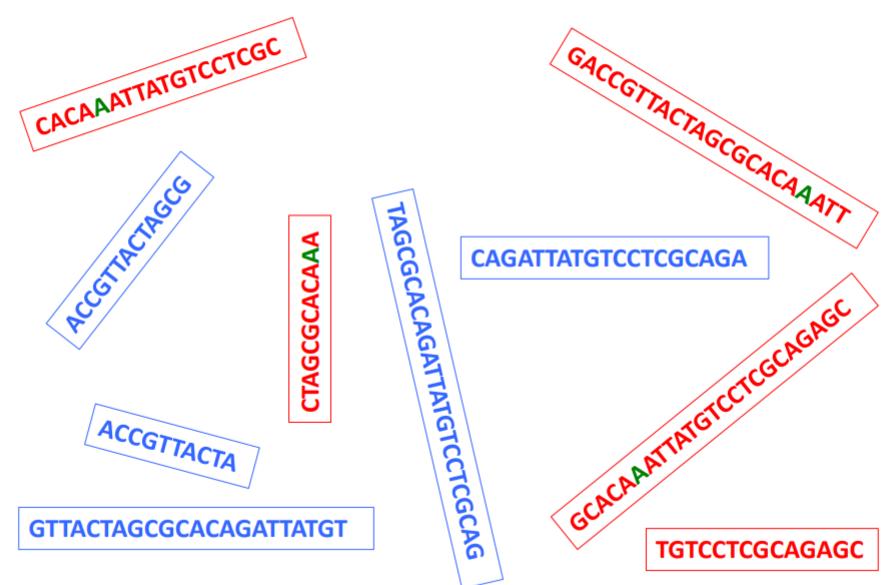
FATHER

ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

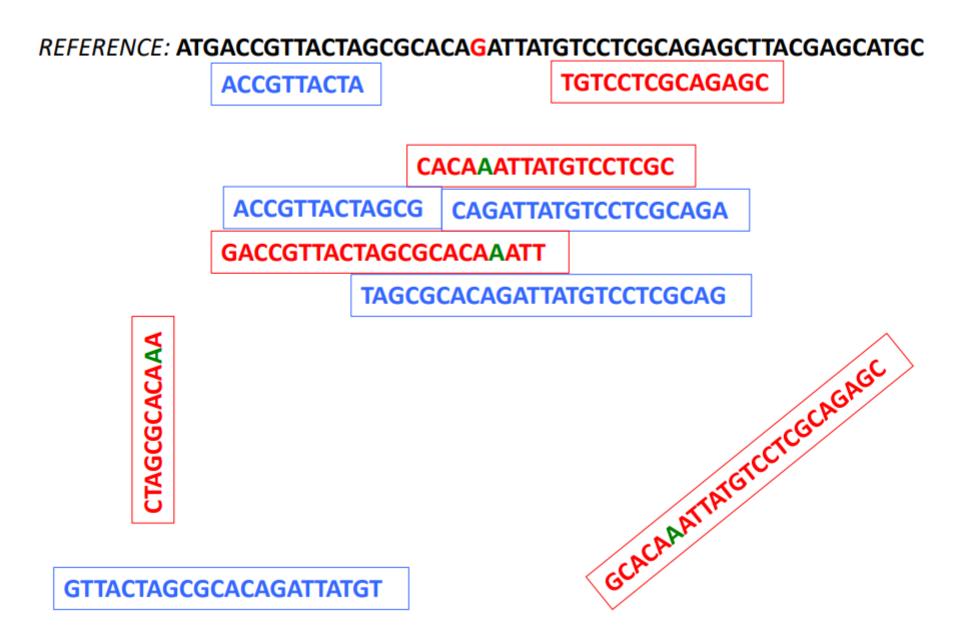
MOTHER

ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

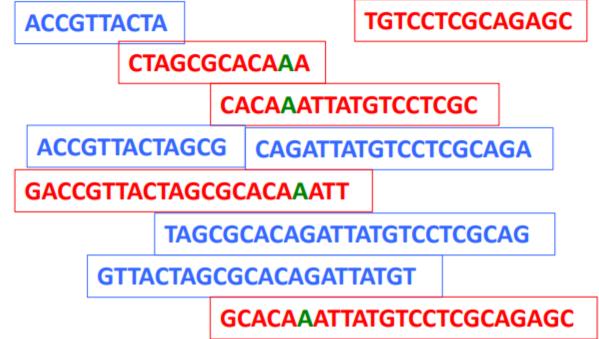




REFERENCE: ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC



REFERENCE: ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC



MD.	100 100 100 100 100 100 1	10 pil pil	u en en	411 411 4	3 63	4331 4323	4211	40 60.	क्या कर
			100.3p						
	10.00.00 %	10.005.201 fa		10,000,000 to		10.000.00146		10.00	1.00 W
			1	1			L		
		CONTRACTOR OF TAXABLE	- Martin and Colored and Colored	Contraction of the local division of the loc		-	_		
TC C		COTOTACAT SA	CC TCTOS NO.	ctototot		TCRACTET			
	C1 C15 CREAR 585 8 C	CCTCTRC	CC TCTCS NA			TCALCEST			
		CCTCTACAT GA	CC ICTOR SA			1 2 2 2 1 1 1			1 999
	CT CTG CALAR 885 8 C	CCTCTCCAT		CTOTOTOT		1 2			
1 C C	CT CTO CABRA ABE A C	CCTCTACAT NO	CC 1488	CTATOTON!		1			1 111
	CT CTU CANAA AND A C	CCTCTOCAT DA		CICICICS		T CONCINT			
	CI CIG CARAA 489 8 C	CCICINCAT	CC TCTSS ISS			T CONCIST			
	CT CTG CAGAA 868 8 C	CCTCTACST 64	CC TCTER IS			T CONCTON			1
	CT CTO CARAA SDC A C	CCTCTACAT AA	CC CT CT			TCCRCTUT	261.1111C	1114	1 2 2 2
	CT CTO CABAS ABO A C	CCTCTACAT A	CC TCT I	CTOTOTOT!		TELETET		****	7 5 5 5
	CT CTU CHUNA AND A C		CC TCTON NAM	CISTOTOSI	AS TOAT				
10 0	CT CTO CHEAN NEE N C	CCICINCAT CA	CC TCT	c tetetetet	10 10 1	T C I I	938111S	TTTA	
A CALL PROPERTY					A STATE OF A STATE	COLUMN TWO IS NOT THE OWNER.		-	CERT
	CT CTO CASA ASS A C	CCTCTACAT GA	CC TCTER ISA			1 2			-
	et ets essas and a c					1			
TC C	CTO REALISED AVE.	CCICIACAT	CC TCTSS ISS	CTOTOTOST.	AC TONT	1	SCINTIC	1114	1 664
	CT CTS C			ctototost		TCORCTON			
1 C C	CT CTS CAD C L C			ctototoot		TRESPOND			
	C1 C10 CACAA	CCTCT CAT	CC TCTOD			1 2 2 1 1	THE PERSON		1 111
			CC ICI SI		A CAL	T CERCIEI			1 2 2 4
	CT CTA CARAA AND	1000	CC ICISI	CT.T.C.T.C.E.T.	A G L L C C L L	TREASING	SETETICS	TTT	1 0 0 0
	CT CTO CASAA ABO A C				RO TONT	T CONCTOT		TTTE	1 6 6 6
	CT CTG CABAR ABS X C		CC TCTCS ICA			T CC CTST			
	CT CTO CAGAN NEE A C	CCICINCET. SA	0.0	CISTOTOST		1			
	CT CTC CARAA ABS A C		CC TCTER	CTOTOST OTOTOST		T CONCINT			1 111
	CT CTO CROAN AND N C	CCTCTACAT	CC TCTER!			T CONCTON			
	CT CTO CAS 8 885 8 C	CCTCTACAT				1			
	CT CTG CAERA ABB A C	CCTCTRCAT GA	CC TCTSO NE			T CRECTOT			1 665
	CT CTS CASAA ASE A C	CCTCTRCAT SA	CC TCT			T CSACIST			
		COTO ACA A		CTA TOTOT		TICLACTER			
	CT CTO CABAS AND A C	CCTCTACAT GA		CTOTOTOOT		TOCORC			
	et ete exens see s e	CCTCTACAT GA		CTOTOTOOT		TERRET		****	
	CT CTO CAGAN NEE A C	CCICILCAT A	CC ICIES AN			TCHECTH			1 2 2 2
	CT CTS CARAA ARG A C	CCTCTRCAT GR		CTOTOTOOT		TCORCTET			
TC C	CI CIG CAGAA AGG A C	CCICIACAI AA		CTOTOTOOT		1 2 21 21 21			-
10	CTO CALLA SEC A C	CCTCTACAT		CTOTOTOOT		1 2 2 2 1 1			
10	CTO CARAA ACT A C	CCTCTACAT A	CC TOTAL MAN	CTSTOTEST.					
TC C	COLUMN AND A LOCAL DESIGNATION OF THE PARTY	A REAL PROPERTY OF A REAL PROPER	1 1 1 1 1 1 1 1		145 E 148	STATISTICS.	SECTOR STREET		2 884
TELER	44 44 4 4 6	CCTCTRCAT 65	CC TCTCH GA	CIGIGIGI	NA TELL	TICGACTET	001A1110		1 999
15 5	CT CTO CASA AND A	CCTCTACAT		CTOTOTOT		1 2 2 2 1 1			
	CT CTO CALMA AND A					1 2 2 2 1 1			
	CT CTO CASAA AND A A		1.1			1			1
1 C C	CT CTS CARAA ARD C	CCTCTAC	1.1						
	CT CTO CHOAN AND A C	CCICINC	11						
	CT CTO CAGAA 460 A C	CCTCTACAT	CC. TOTAL ISA		-				
	CT CTO C. C. A. A. A. A. C.	CC C C C C C C C C C C C C C C C C C C							
	CT CTO CAGAA ADO A C	CCTCTACAT 64							
1 C C	CT CTS CREAK AND A C	CCTCTACAT A	CC TCTCS AL	CICTUTUS!	BE SCAT				
	C1 C10 C1044 888 8 C	CCTCTACAT SA	CC ICTES SA	CTATATAST					
		COTO LA CALLAR	CC TCTCC IS	CTOTOTOT					
	CT CTO CASAS AND A C	CCICIACAT AA		21.1.1.1.1.1		1			
	či čis čiska sto i č	CCTCTACAT		CTOTOTOT		T CONCTAT			
	CT CTS CROAN AND A C	CCICIACOT SA	CC TCTSS SA	CISTOTOST.	A CAT	T CONCTON		1.1	
IC C	C1 C10 C2044 465 8 C	CCTCTACAT BA		CTUTOIOUI		TCORCISI			
	CT CTO CASAR 885 A C	CCICINCUI OA		CTOTOTOOT		TCSSCIST			
		CCTCTRCAT NA	CC TCTOD	CISIONS ST					
		CCTCTACAT A							
		CCTCTACAT DA						1114	

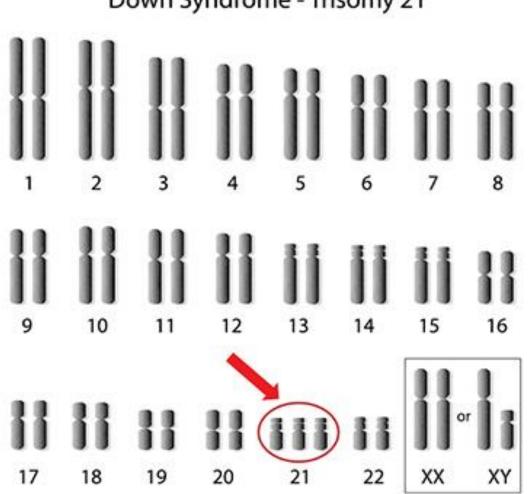


Genetic Variation

Aneuploidy

Aneuploidy:

number of chromosomes NOT equal to 46



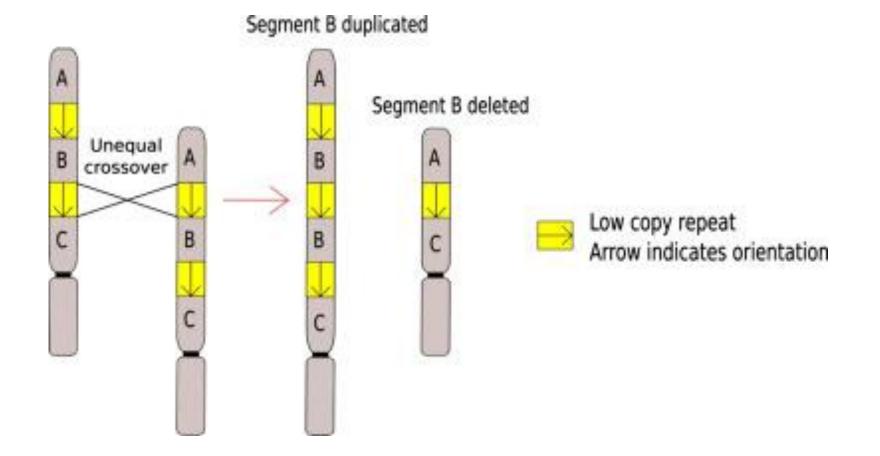
Down Syndrome - Trisomy 21



Copy Number Variants

Copy Number Variant:

duplications or deletions greater than 1000 nucleotides (1kb)

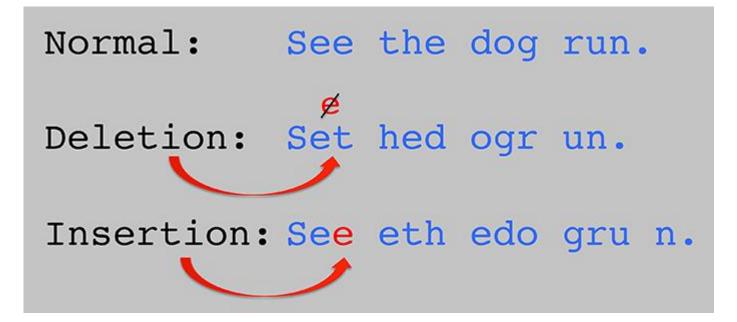


https://media.springernature.com/m312/springer-static/image/art%3A10.1038%2Fs10038-020-00838-1/MediaObjects/10038_2020_838_Fig1_HTML.png?as=webp

Indel

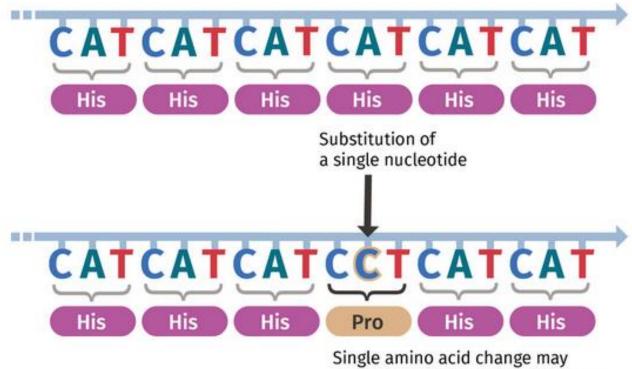
Indel:

insertion/deletion smaller than 1kb



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

Single Nucleotide Variant



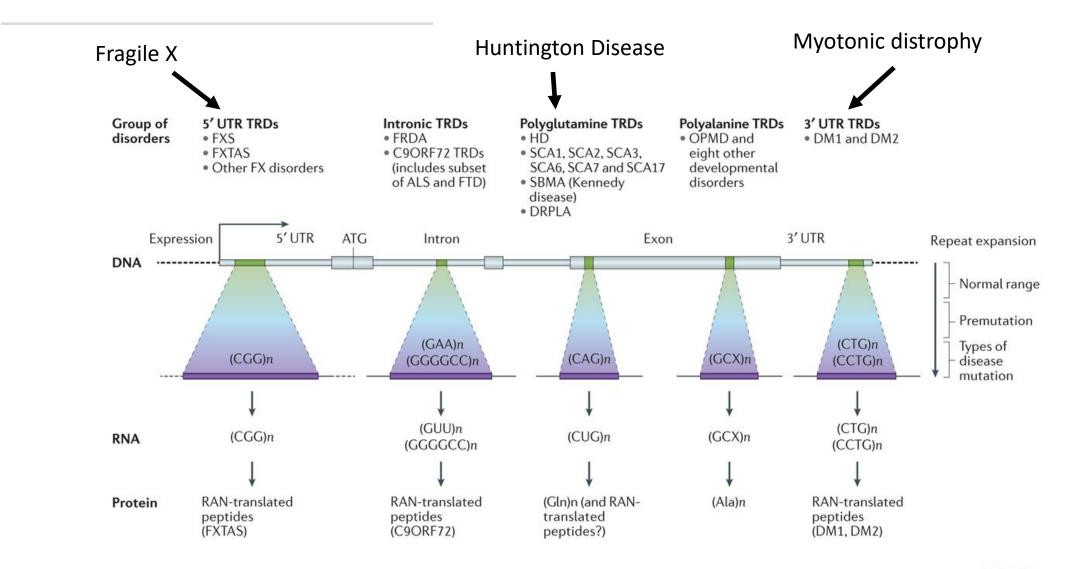
Single amino acid change may produce a non-functioning protein

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.

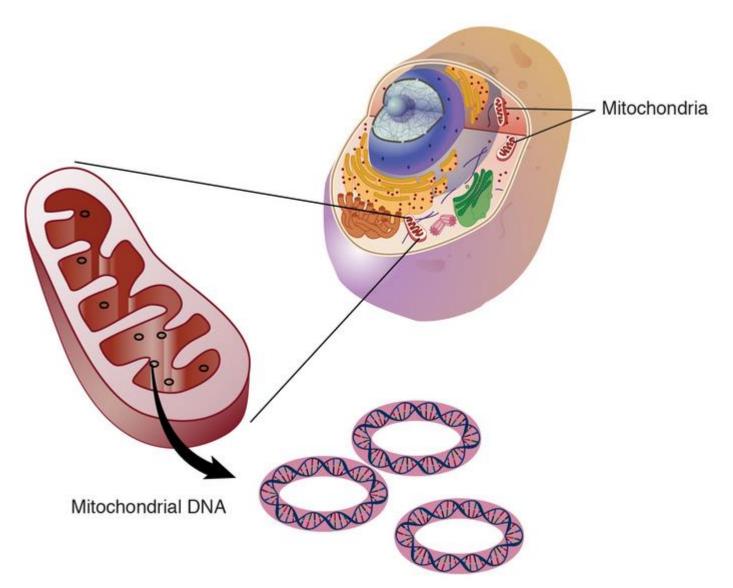
Difficult to detect on exome and genome.



Nature Reviews | Genetics

Mitochondrial DNA

Maternal inheritance

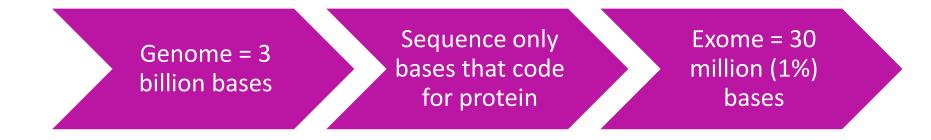


https://www.genome.gov/sites/default/files/tg/en/illustration/mitochondrial_dna.jpg



Exomes and Genomes

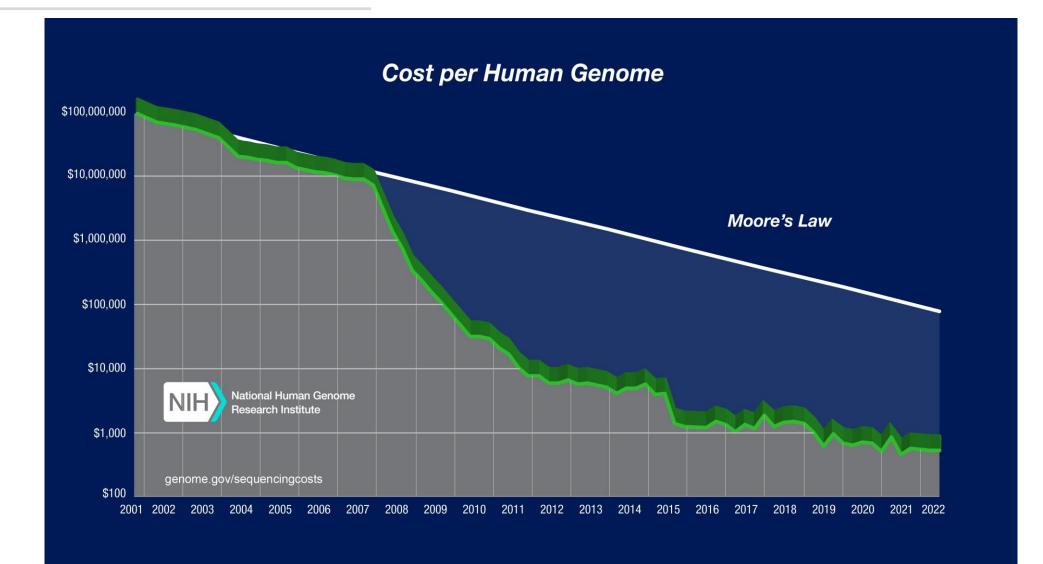
Genomes and Exomes



Wpod?amfkwcu.gjhklfoursjckfoquscore and void m\$%djkdllfkk*wqnfjjdxnnebkyp@mvjckdfkkseocb qw.oiwjfm du seven years ago dlfksl8\$((k dkm deixmenfyrucci our skdj\$ mvkjdfk&%woqppa lfdk kfaqaq.d eiidty forefathers brought jdd qpo ooekfjk vbzxx dss forth a...

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 [®] 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

 \sim



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

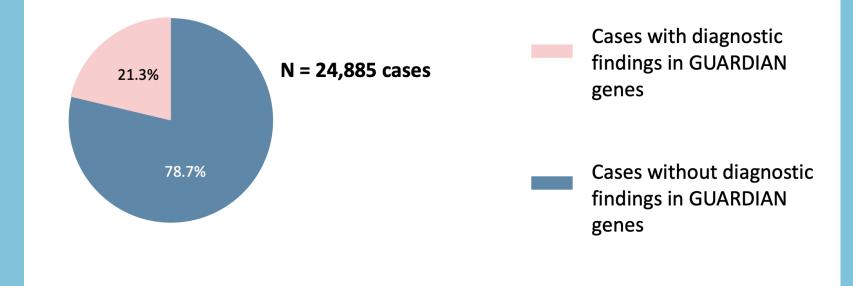


TYPE OF CONSENT

GROUP 2 CONSENT

		Overall	English	Spanish	Mandarin
	Groups 1 + 2	92% (7100)	93.2% (6024)	83.6% (754)	92.2% (249)
Confidential and Proprietary.	Group1 only	8% (612)	6.8% (442)	16.4% (148)	7.8% (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
	Baker Gordon Syndron	ne /	' SYT	1 Syndrome			Χ	-
	Bosch Boonstra Schaaf	f Op	otic A	Atrophy Syndro	ome (BBSC	DAS)	Χ	
	CDKL5	G	rou	p 2				
	CDKL5							
	CHD2	G	rou	p 2				
	CHD2							
	ECHS1)	(
	FOXP1 Syndrome	G	rou	p 2				
	GABA-A)						
	Hnrnp related nuero d	leve	lopr	nental disorde	rs, hnrnpu	ı hnrnpk h	nrr	npq/syncrip
	Jansen de Vries Syndro	ome	e 2	X				
	MEPAN Syndrome		2	Х				
	Multiple							
	Myhre Syndrome			X				
	NF1			х				
	Ornithine Transcarban	nyla	ise D	eficiency (OTC	D), Early C	Dnset	Gr	oup 1
	Pyruvate Dehydrogena	ase	Com	plex Deficienc	y	Х		
	Pyruvate Dehydrogena	ase	Com	plex Deficienc	y (PDCD)			
	SMC1A			X				
	SPG50 and CMT4J			х				
	SYNGAP1-Related Disc	orde	er (Group 2				
	X-Linked Dystonia-Parl	kins	onis	sm X				
T	•						-	



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

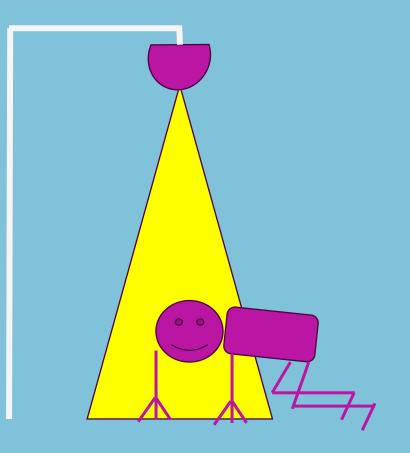
Cohort Building



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



Future Technology





Confidential and Proprietary. Do Not Distribute.

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.

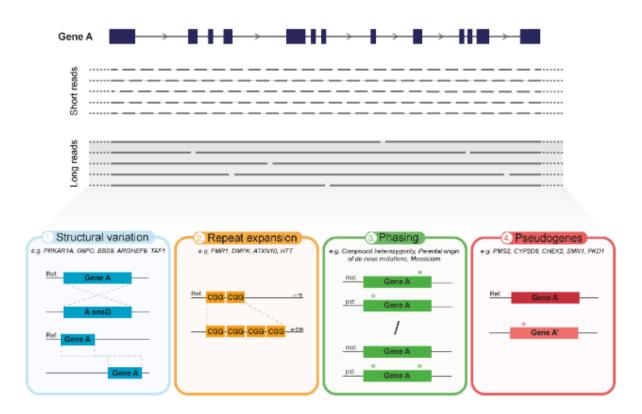
Long Read Sequencing Projects at GeneDx

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