Rare Bootcamp™

Genetic Testing

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Chief Medical Officer

GeneDx

Rare Bootcamp™

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

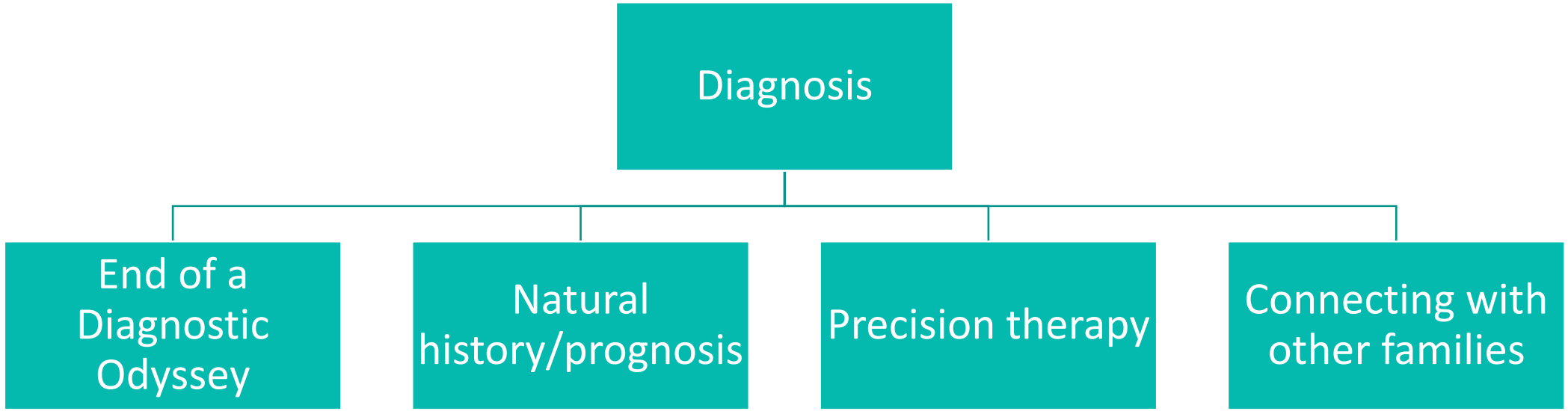
Introduction

Rare Disease

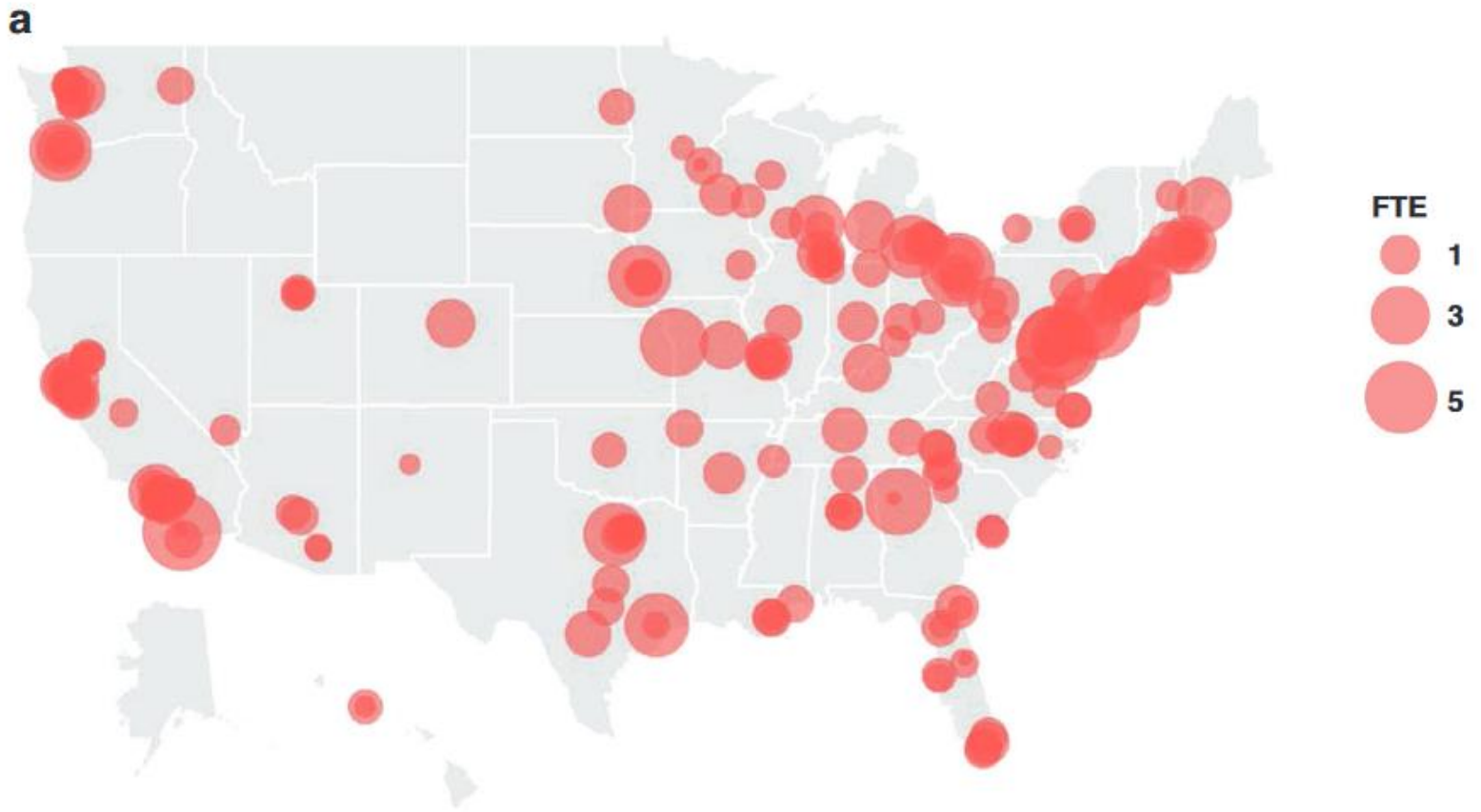
- Definition: affects less than 200,000 persons in the U.S.
- Over 7,000 rare diseases
- 25-30 million Americans living with a rare disease
- 80% of rare diseases have a genetic cause
- Roughly 70% of rare disease are pediatric onset
- The average time from symptom onset to diagnosis is 5 years

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



Genetics in Medicine (2021) 23:1458 – 1464

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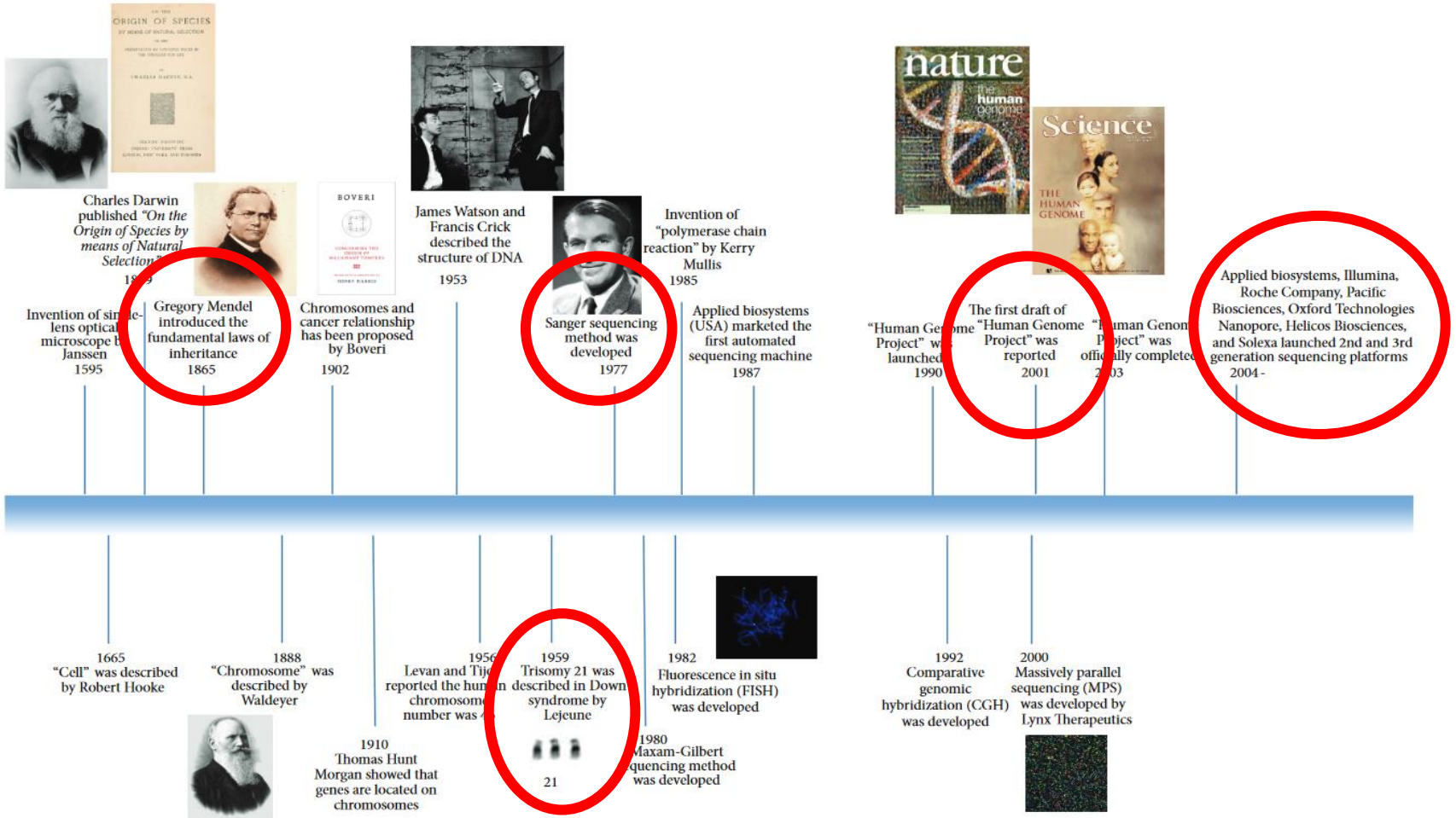
Genetic Testing

Testing Progress



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

Genetics inMedicine

www.nature.com/gim

Check for updates

ACMG PRACTICE GUIDELINE

Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

Kandamurugu Manickam[1,2], Monica R. McClain[3], Laurie A. Demmer[4], Sawona Biswas[5], Hutton M. Kearney[6], Jennifer Malinowski[7], Lauren J. Massingham[8,9], Danny Miller[10], Timothy W. Yu[11,12], Fuki M. Hisama[13] and ACMG Board of Directors[14]*

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.
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

Received: 16 August 2021 | Revised: 27 September 2022 | Accepted: 1 October 2022

DOI: 10.1002/jgc4.1646

PRACTICE GUIDELINE

National Society of Genetic Counselors WILEY

Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors

Lacey Smith[1] | Jennifer Malinowski[2] | Sophia Ceulemans[3] | Katlin Peck[4] | Nephi Walton[5] | Beth Rosen Sheidley[1] | Natalie Lippa[6]

https://orcid.org/0000-0002-9095-7265

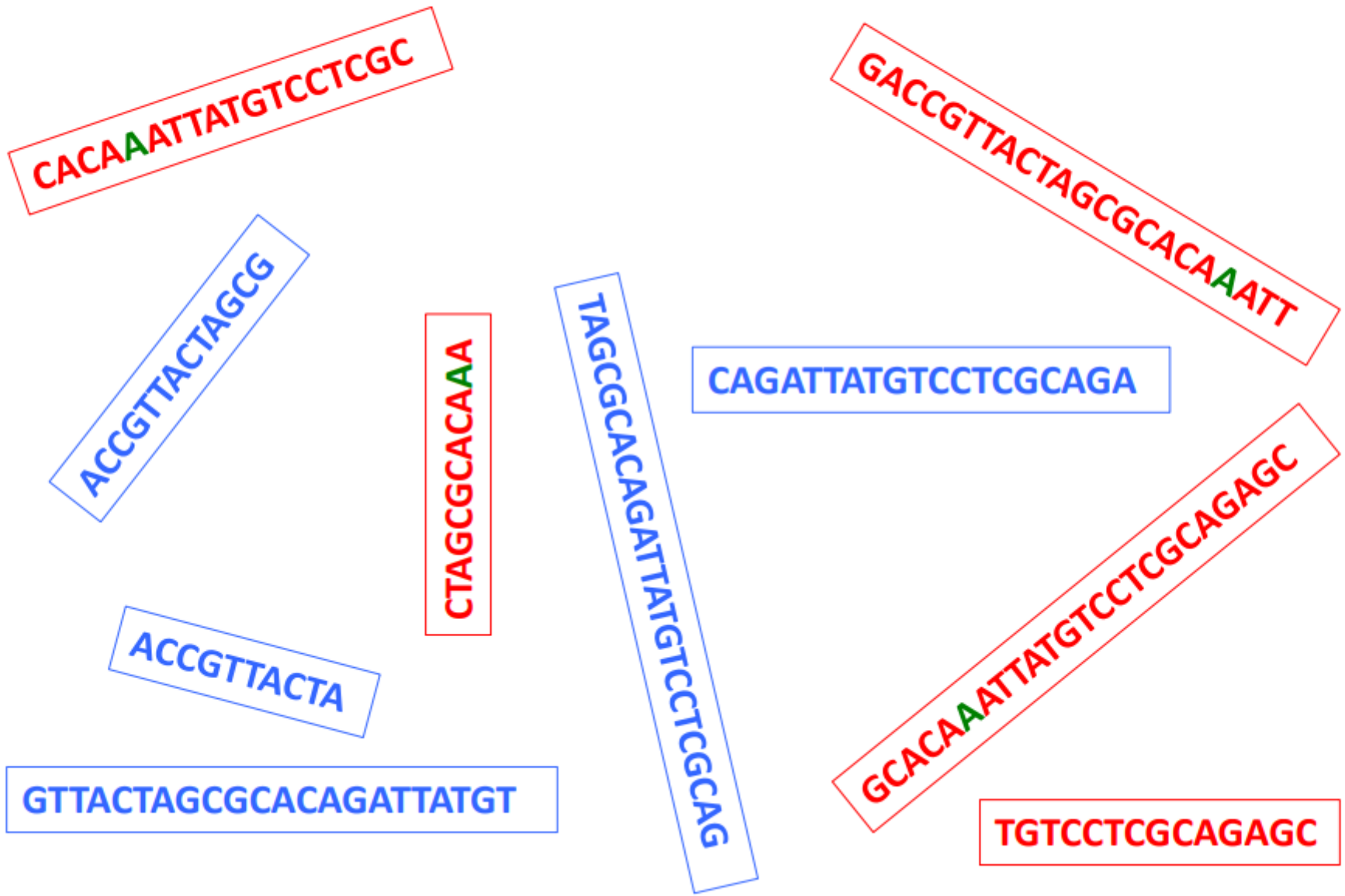
Short Read Sequencing/exome sequencing/genome sequencing

FATHER

ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC

MOTHER

ATGACCGTTACTAGCGCACAGATTATGTCCTCGCAGAGCTTACGAGCATGC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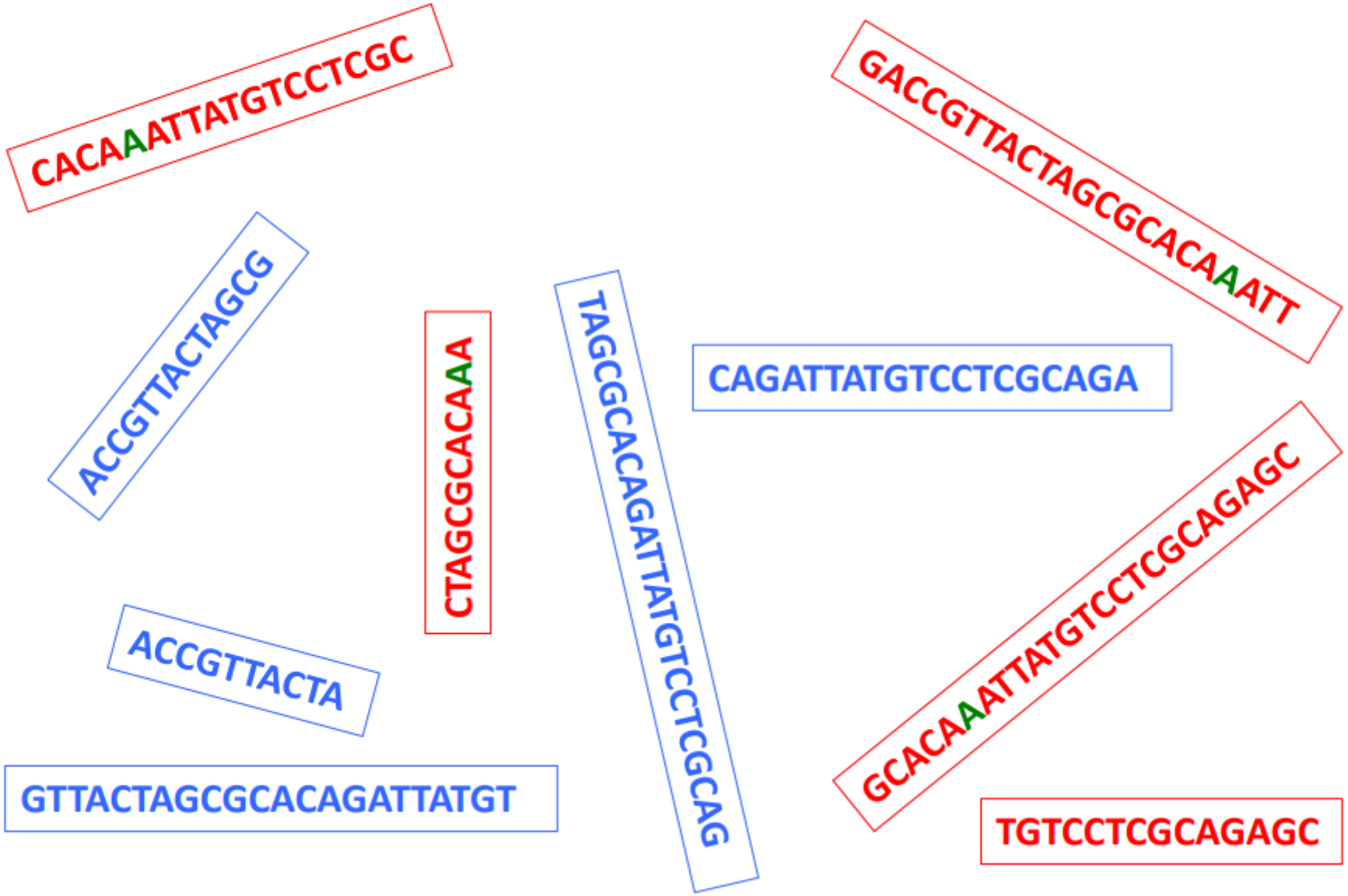

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GACCGTTACTAGCGCACAAATT

TAGCGCACAGATTATGTCCTCGCAG

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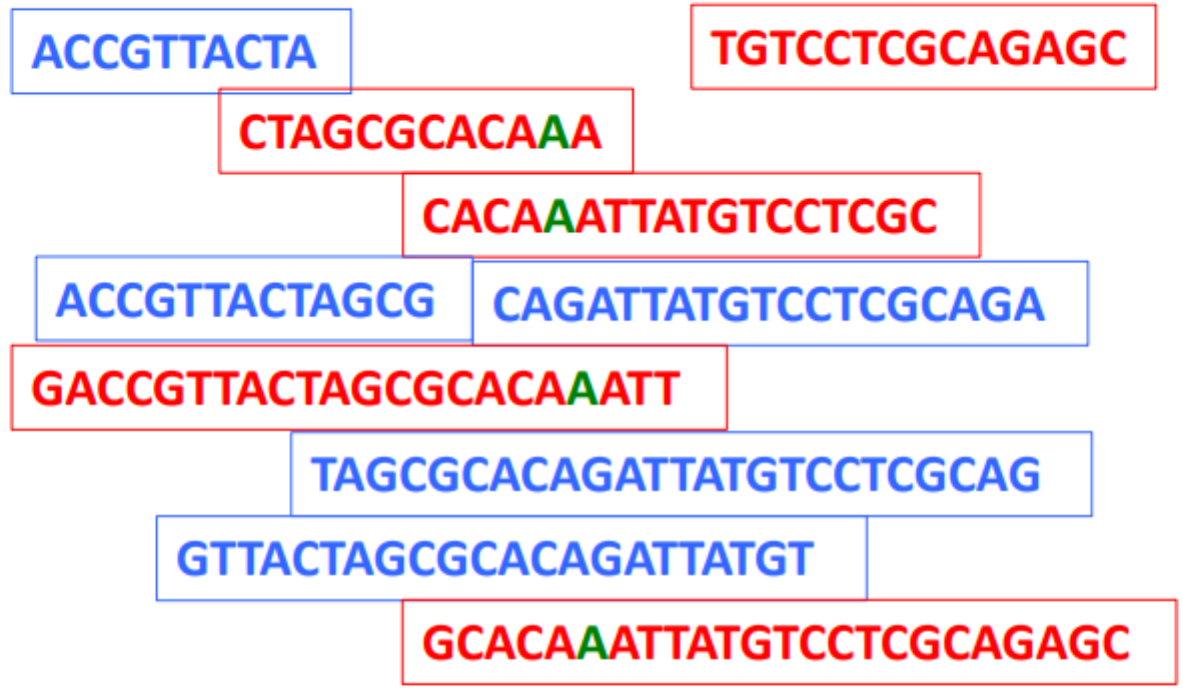

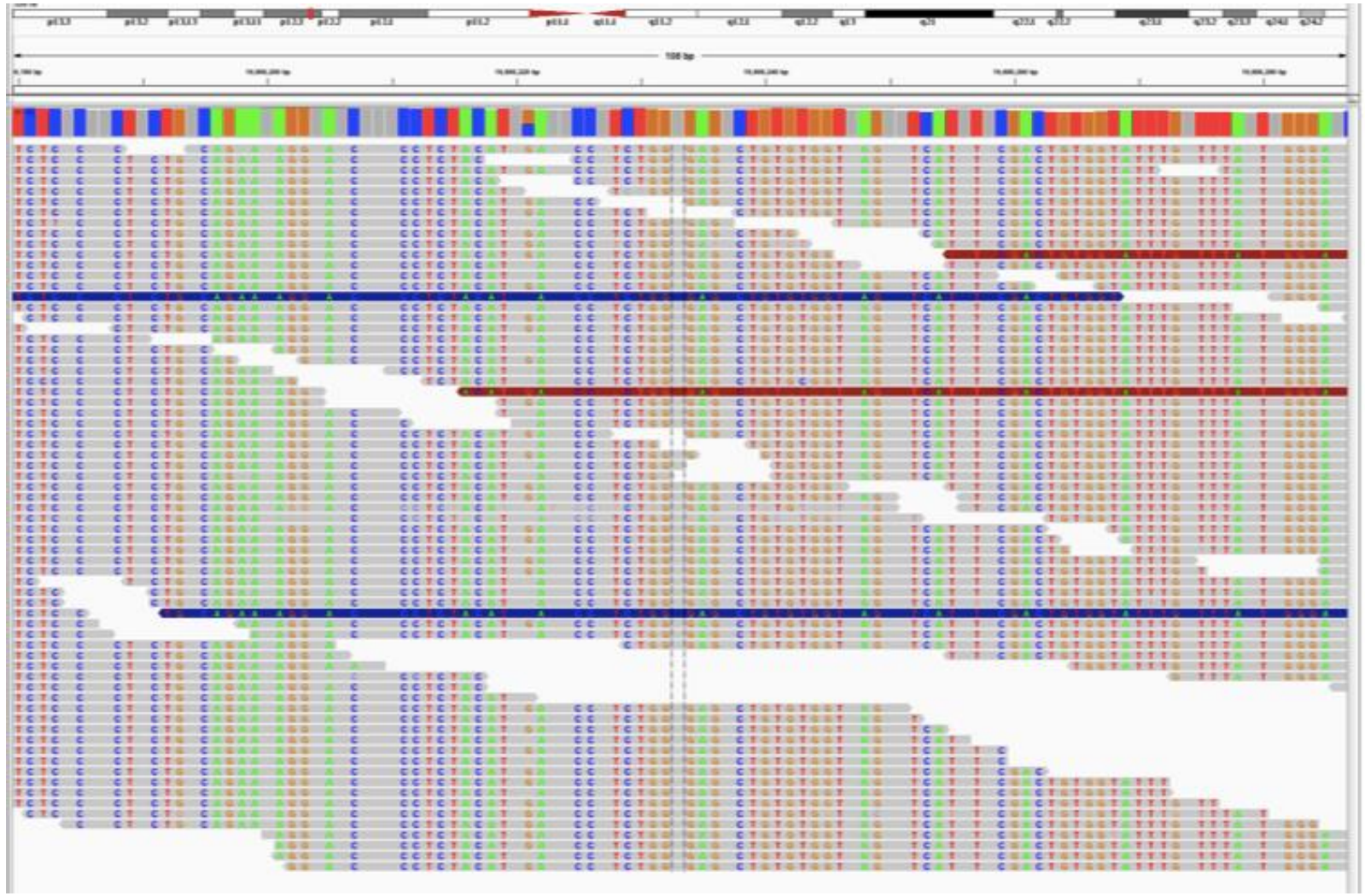

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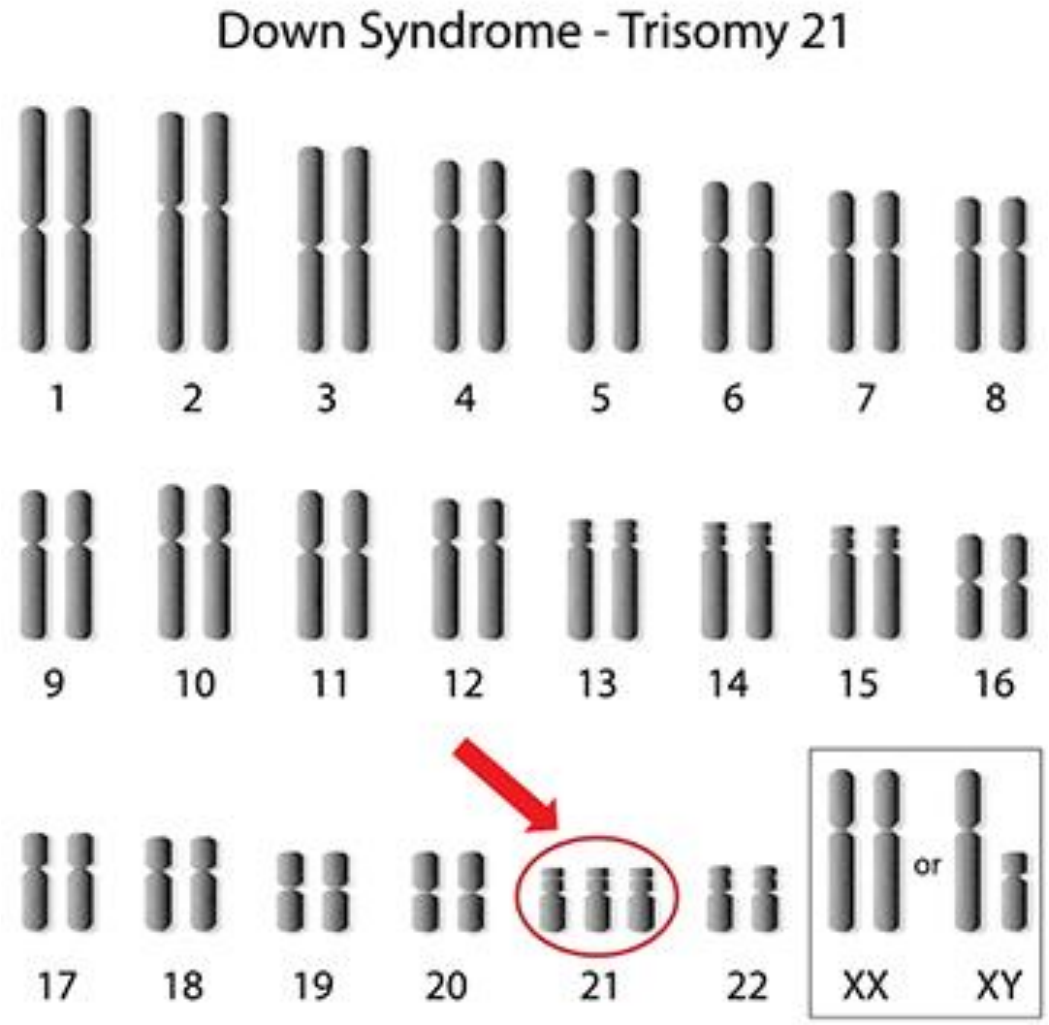
Genetic Variation

Aneuploidy

Aneuploidy:

number of chromosomes NOT equal to 46

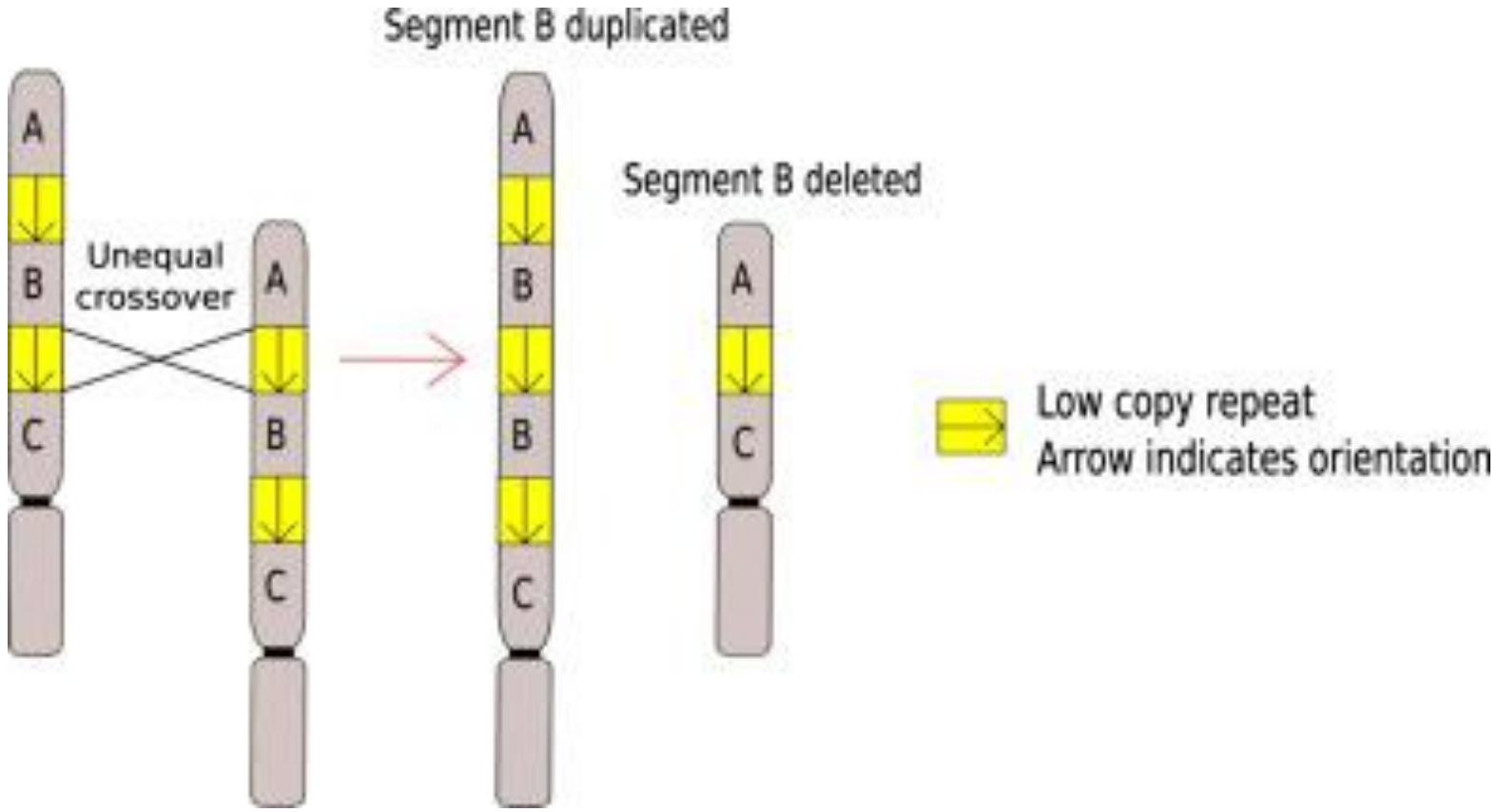


https://rarediseases.info.nih.gov/GlossaryDescription/19/0

Copy Number Variants

Copy Number Variant:

duplications or deletions greater than 1000 nucleotides (1kb)

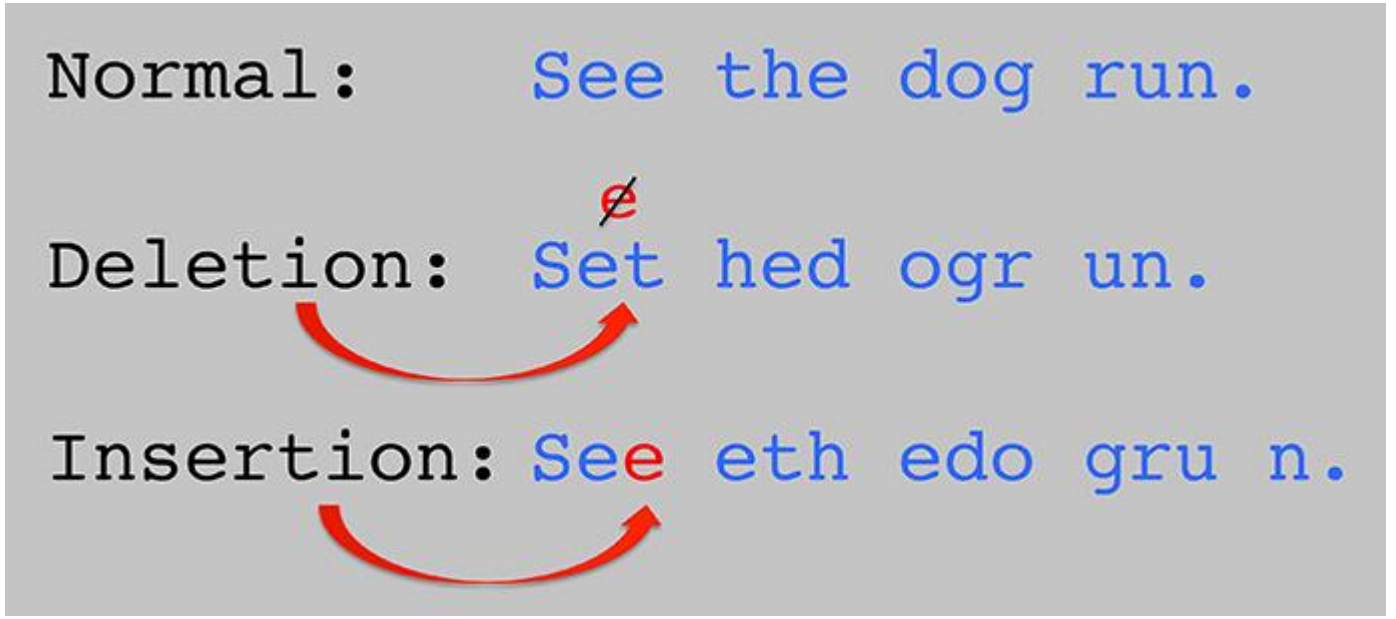


https://media.springernature.com/m312/springer-static/image/art%3A10.1038%2Fs10038-020-00838-1/MediaObjects/10038_2020_838_Fig1_HTML.png?as=webp

Indel

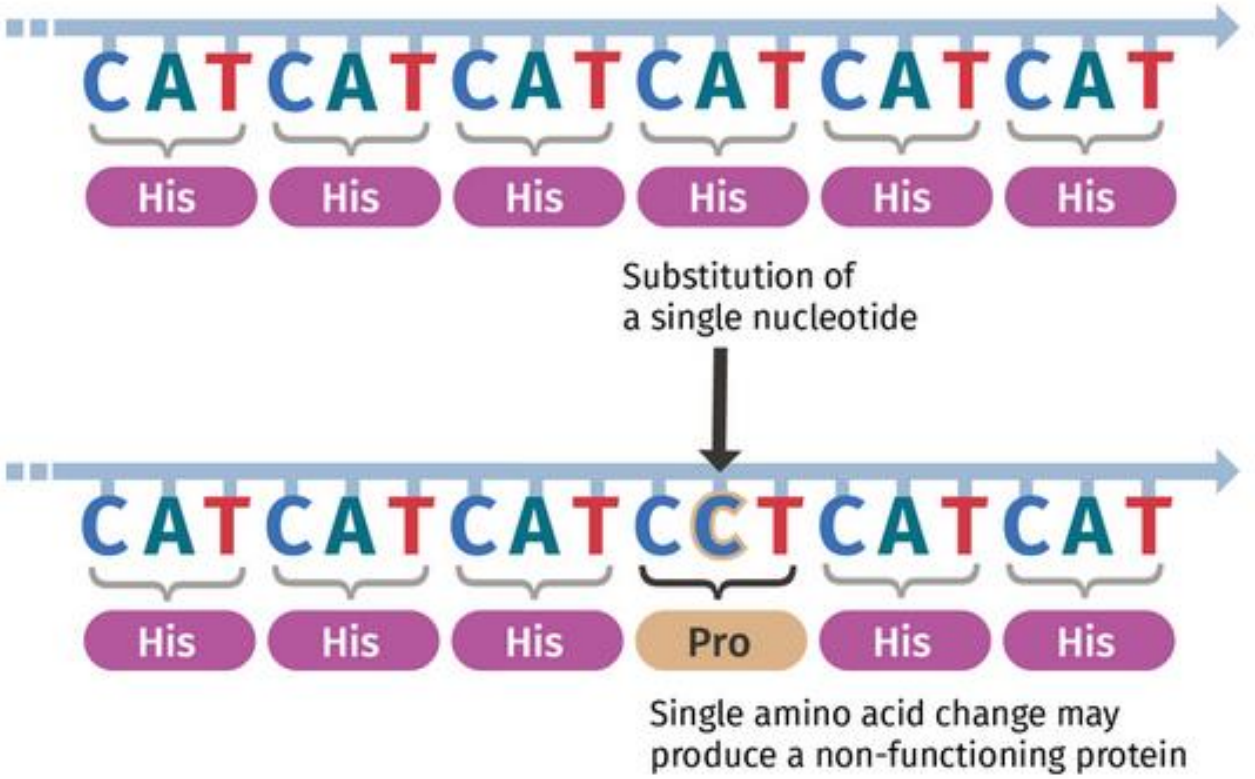
Indel:

insertion/deletion
smaller than 1kb



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

Single Nucleotide Variant



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

Repeat expansion disorders:

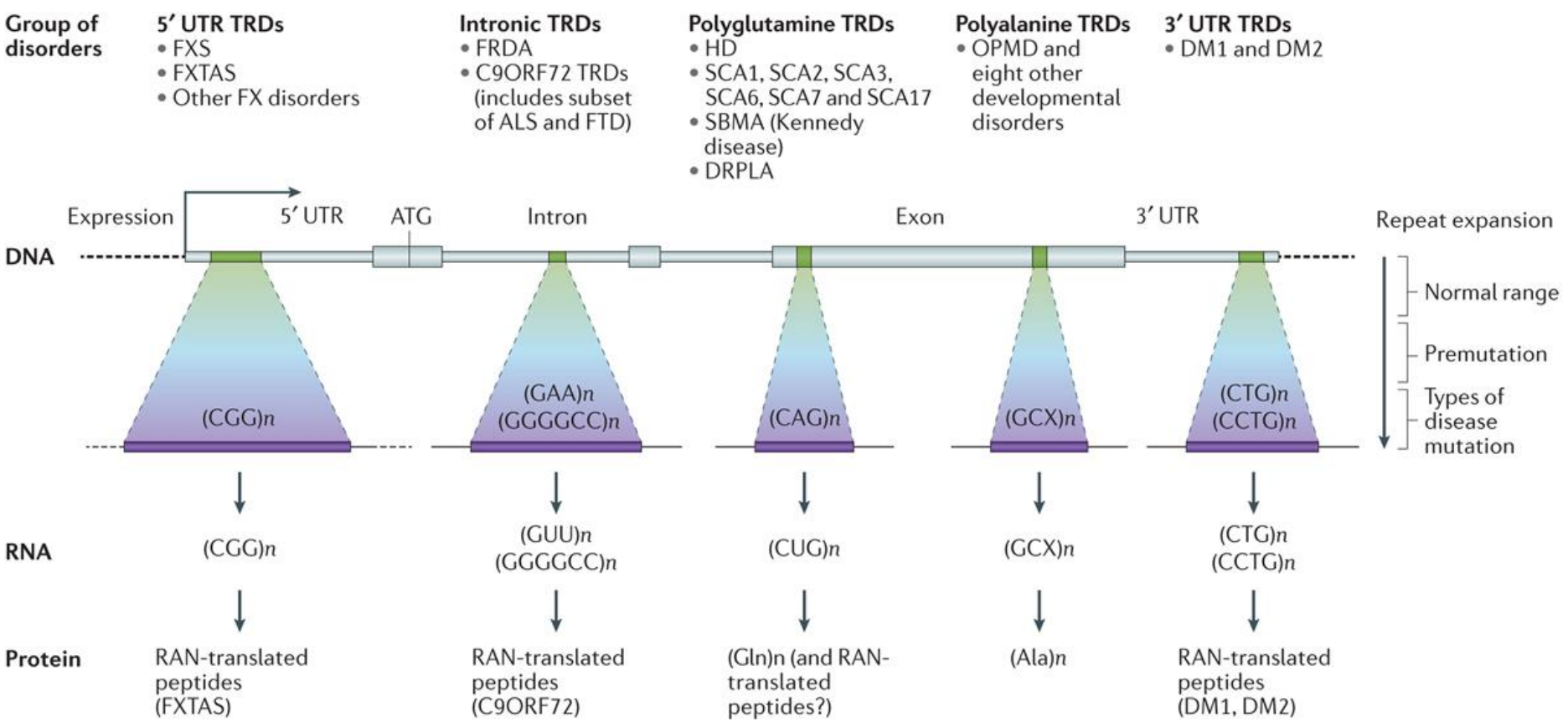
More than 40 diseases, most of which primarily affect the nervous system, are caused by expansions of simple sequence repeats dispersed throughout the human genome.

Difficult to detect on exome and genome.

Fragile X

Huntington Disease

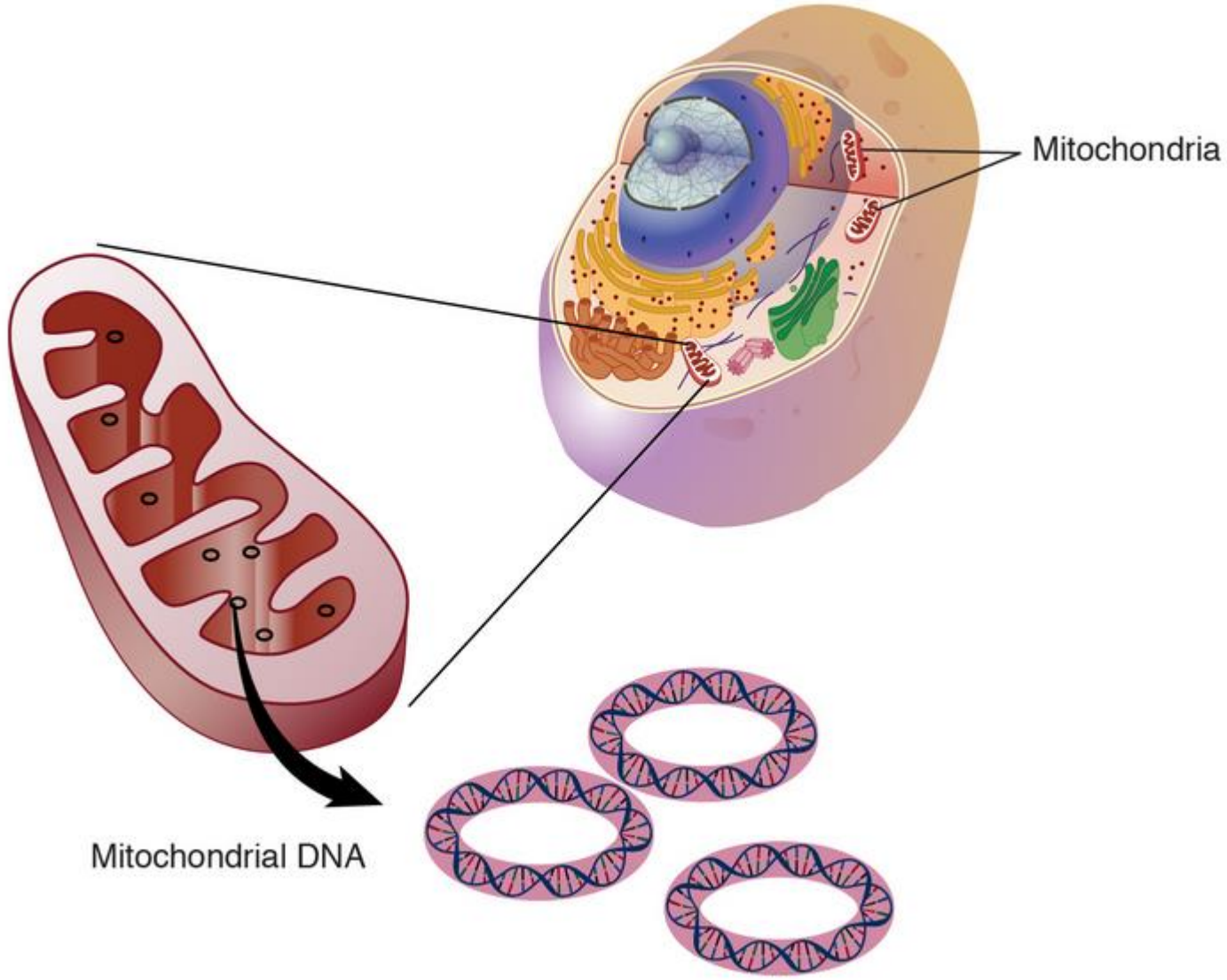
Myotonic distrophy



Nature Reviews | Genetics

Mitochondrial DNA

Maternal inheritance



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

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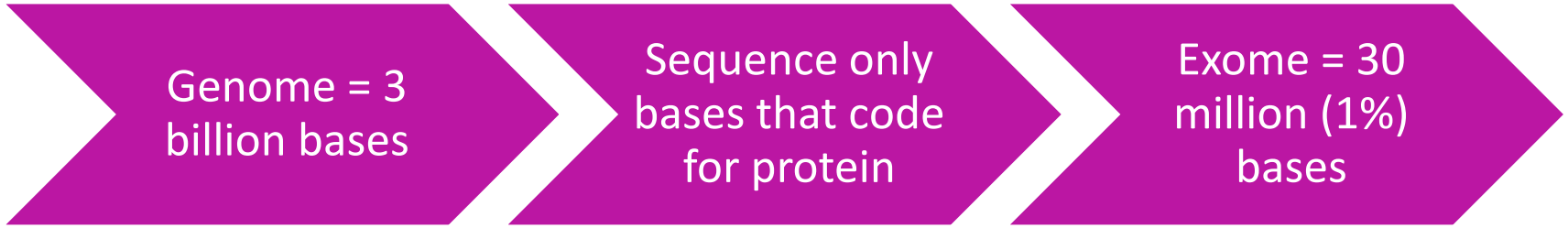
Exomes and Genomes

Genomes and Exomes

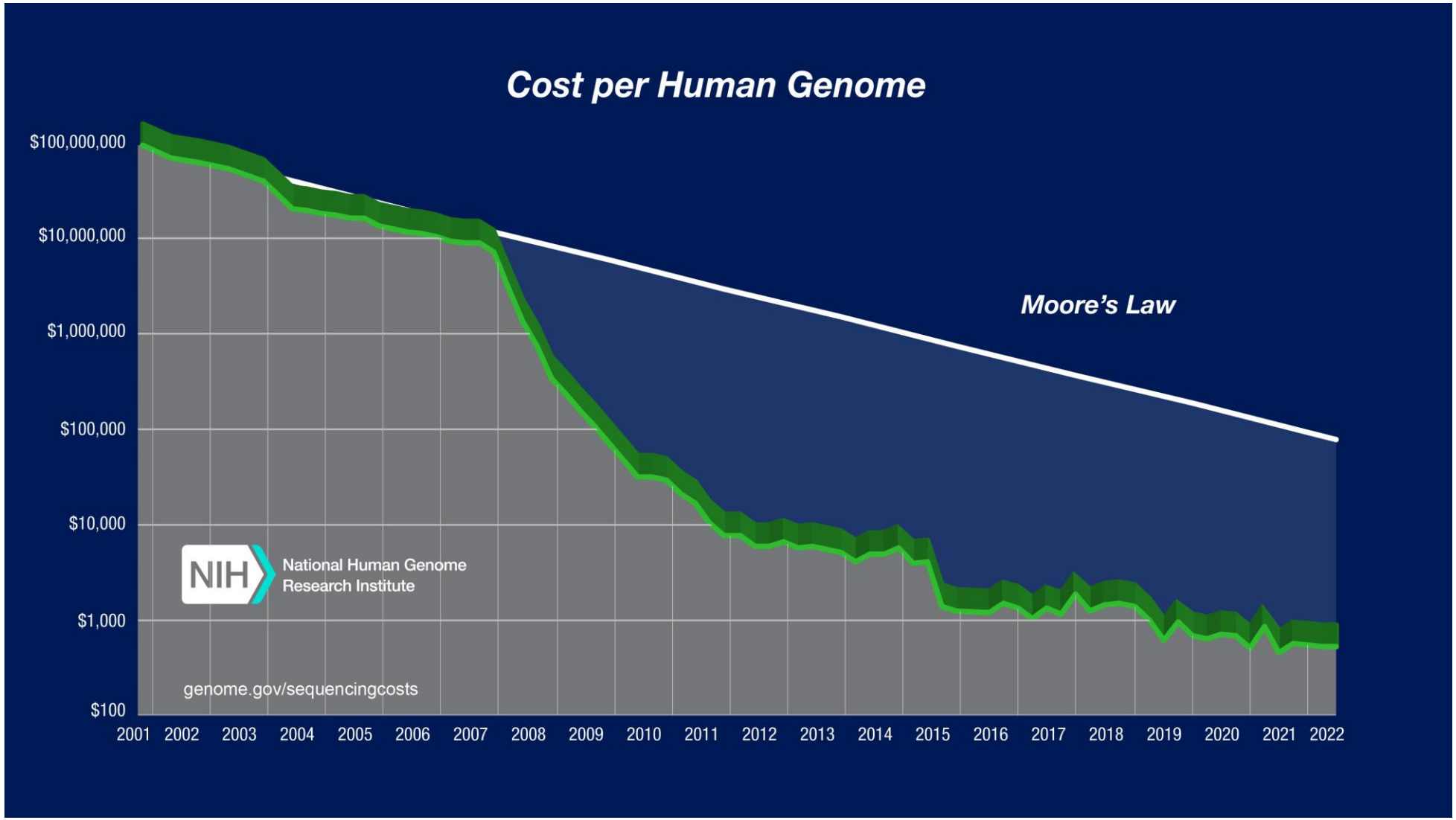


The exons are separated by DNA of unclear function

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


Cost per Human Genome
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
Moore's Law
NIH
National Human Genome
Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022

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

United Healthcare

UnitedHealthcare® Commercial
Medical Policy

Whole Exome and Whole Genome Sequencing

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

Instructions for Use

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

Community Plan Policy
…me and Whole Genome Sequencing

…ntage Coverage Summaries
…sting
…Tests and Services

Medical Coverage Policy

Cigna

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

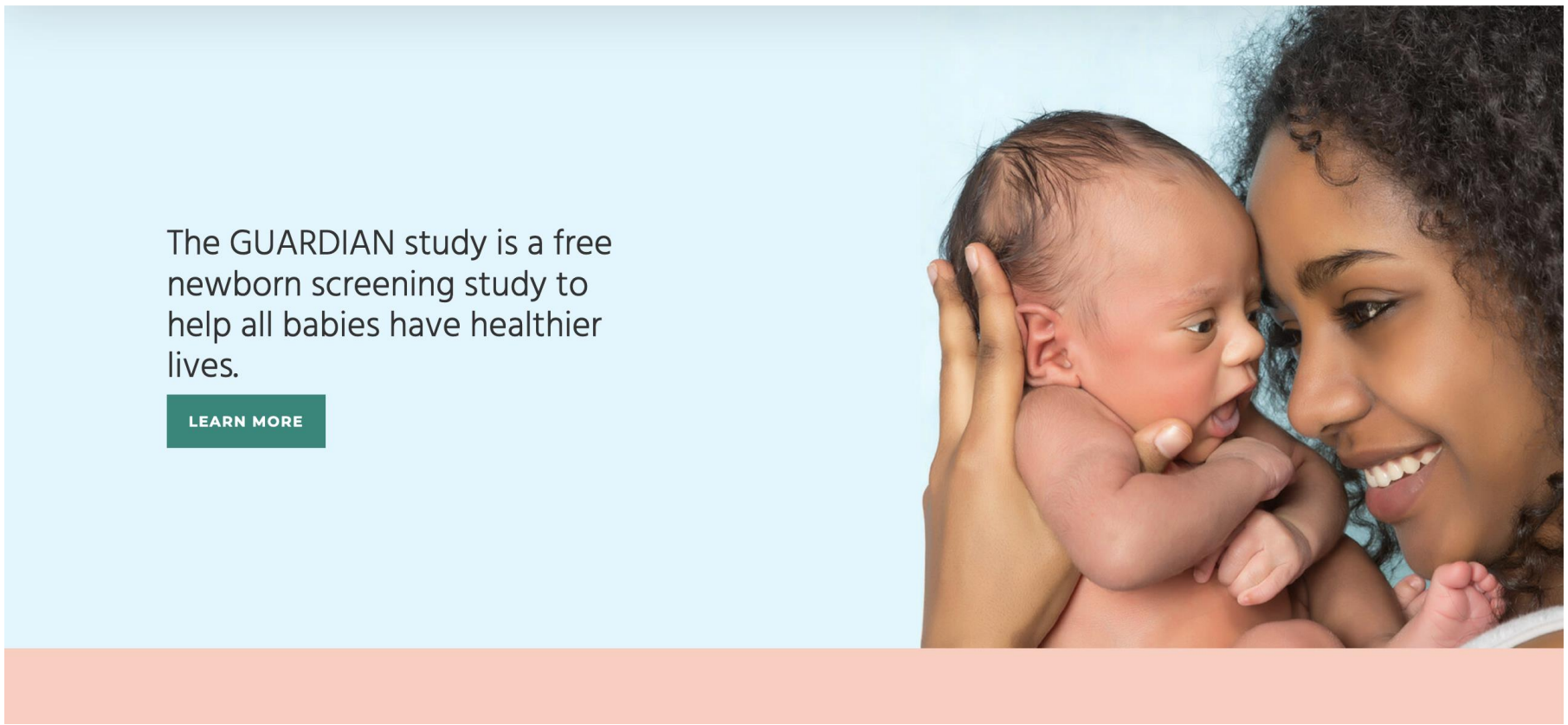
Whole Exome and Whole Genome Sequencing

Table of Contents | **Related Coverage Resources**

Bootcamp – Fall - 2024

SPG15 Research Foundation	Spg15 (AR; *ZFYVE26*)
Yellow for Yiannis IRF2BPL Foundation	IRF2BBPL-NEDAMSS
CureARS	ARS disorders
CureARS	ARS disorders
NPHP1 Family Foundation	NPHP1 retinal dystrophy
Cure GM1 Foundation	GM1 gangliosidosis
Shark Tooth Biotech	Charcot Marie Tooth Disease Type 1A
Lagos Consulting/clife4life.org	AVM/Ataxia/Hypertrophic Olivary Degeneration
Child's Cure & CDKL5 South Asia	CKDL5 disorder
Tatton Brown Rahman Syndrome (TBRS) Community	Tatton Brown Rahman Syndrome
The Lilly and Blair Foundation	Spastic Paraplegia (SPG4)
Bloom Syndrome Association	Bloom Syndrome
Cure LBSL	LBSL
WWOX Foundation of America	WOREE Syndrome
Brave River Science	Neurofibromatosis Type 1
ADNP Kids Research Foundation	ADNP Syndrome
Cure Lowe Foundation	Lowe Syndrome
Tanner Pharma Group	Mosaic variegated aneuploidy syndrome (mva)
Kizuna Foundation	KIZ-mediated retinitis pigmentosa
Cure Pogz Disorders Foundation	Pogz-Related Syndrome/White Sutton Syndrome
TESS Research Foundation	SLC13A5 Epilepsy
Lottie's Light Foudation	CerTra Syndrome (Cert1)
Lottie's Light Foundation	CerTra Syndrome (Cert1)

Newborn Screening



https://guardian-study.org/

JAMA | Original Investigation

Expanded Newborn Screening Using Genome Sequencing for Early Actionable Conditions

Alban Ziegler, MD; Carrie Koval-Burt, MS, CGC; Denise M. Kay, PhD; Sharon F. Suchy, PhD; Amber Begtrup, PhD; Katherine G. Langley, MS, CGC; Rebecca Hernan, MS, CGC; Laura M. Amendola, MS, CGC; Brenna M. Boyd, MS, CGC; Jennifer Bradley, BS; Tracy Brandt, PhD; Lilian L. Cohen, MD, MPH; Alison J. Coffey, PhD; Joseph M. Devaney, PhD; Beata Dygulska, MD; Bethany Friedman, MS, LCGC; Ramsay L. Fuleihan, MD; Awura Gyimah, BS; Sihoun Hahn, MD, PhD; Sean Hofherr, PhD; Kathleen S. Hruska, PhD; Zhanzhi Hu, PhD; Médéric Jeanne, MD, PhD; Guanjun Jin, BS; D. Aaron Johnson, MS; Haluk Kavus, MD; Rudolph L. Leibel, MD; Steven J. Lobritto, MD; Stephen McGee, PhD; Joshua D. Milner, MD; Kirsty McWalter, MS, CGC; Kristin G. Monaghan, PhD; Jordan S. Orange, MD, PhD; Nicole Pimentel Soler, MA; Yeyson Quevedo, BA; Samantha Ratner, BS; Kyle Retterer, MS; Ankur Shah, MD; Natasha Shapiro, MD; Robert J. Sicko, BS; Eric S. Silver, MD; Samuel Strom, PhD; Rebecca I. Torene, PhD, MMSc; Olatundun Williams, MD; Vincent D. Ustach, PhD; Julia Wynn, MS, CGC; Ryan J. Taft, PhD; Paul Kruszka, MD, MPH; Michele Caggana, ScD; Wendy K. Chung, MD, PhD

JAMA Published online October 24, 2024

Consent rate = 72%

Screen positive rate = 3.7%

True positives/All positives = 79.5%

Figure 2. Genomic Uniform-Screening Against Rare Disease in All Newborns (GUARDIAN) Flow of Participants

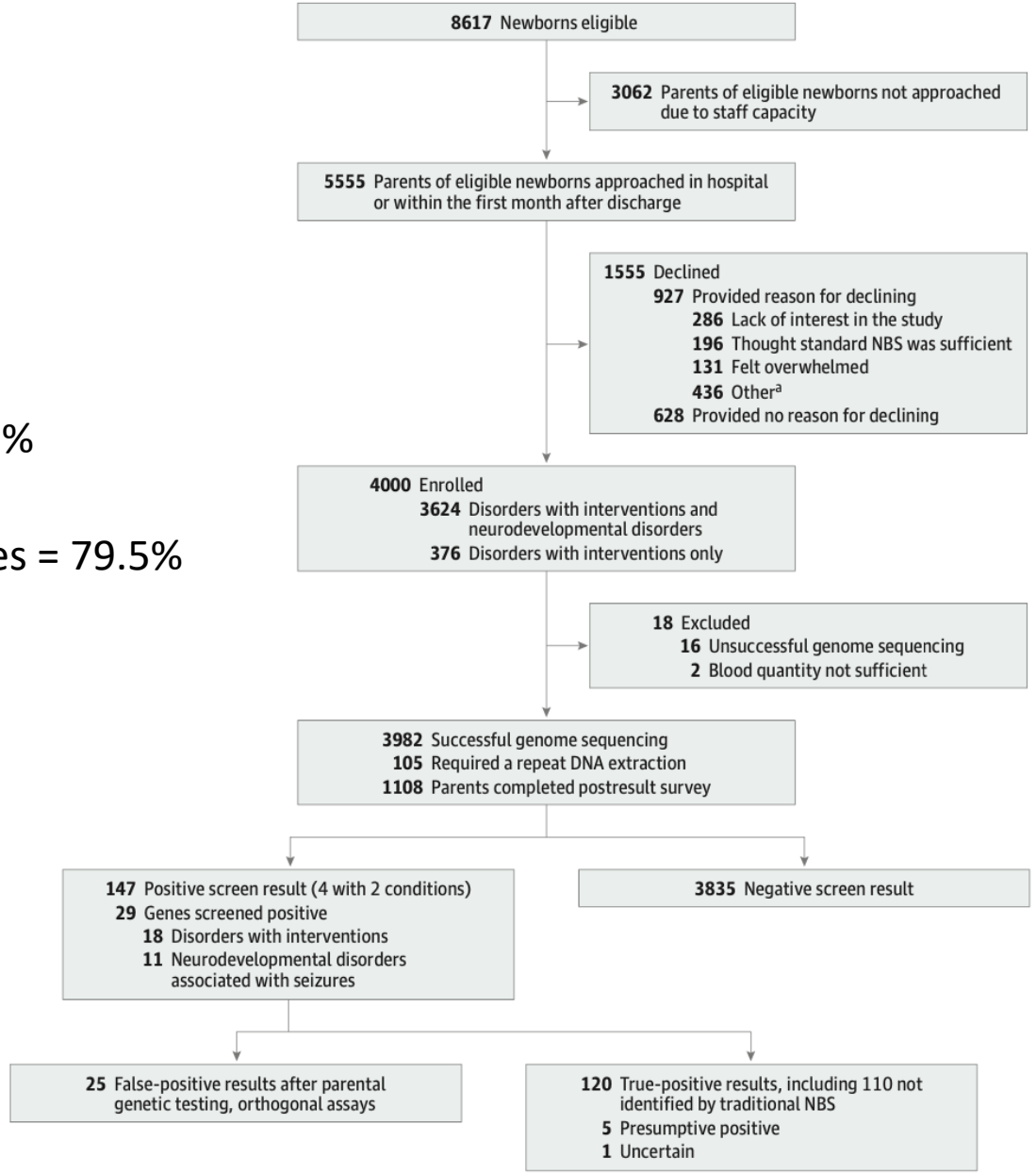
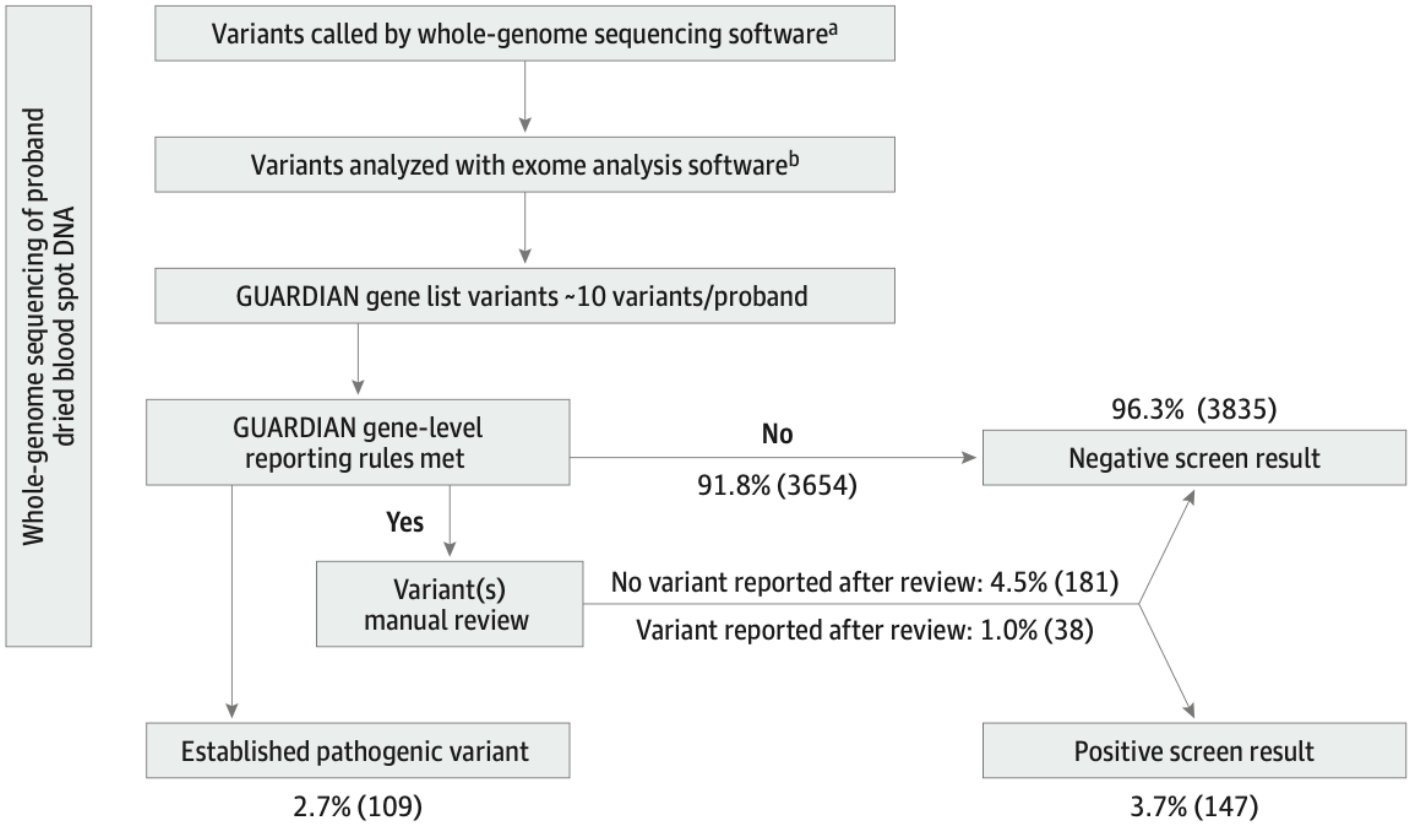
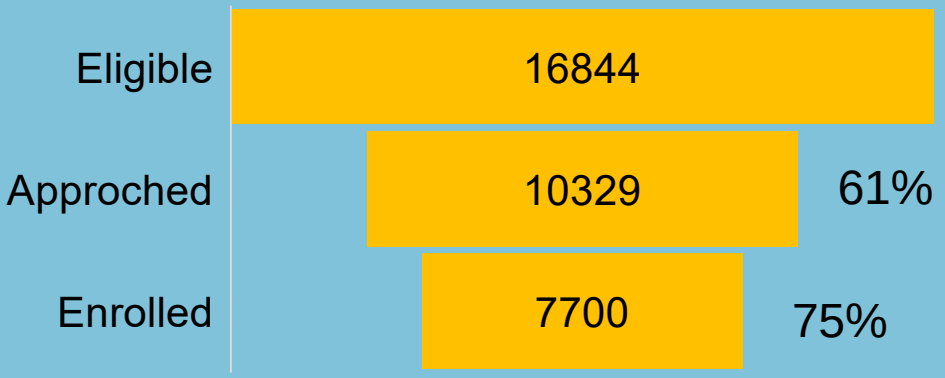


Figure 3. Schematic of Variant Interpretation Workflow

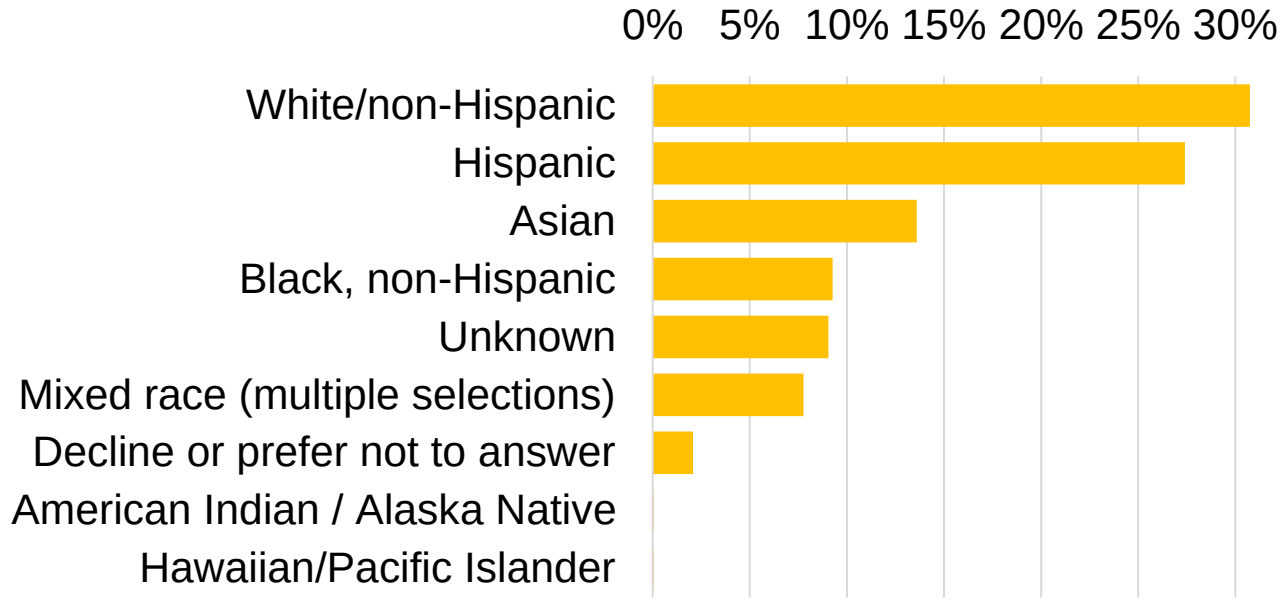


Results: First 7,700

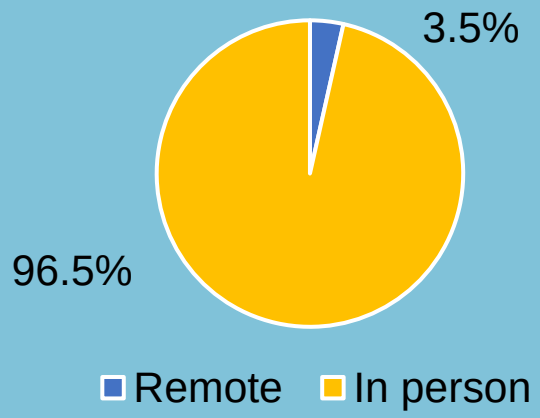
Enrollment



Ancestry



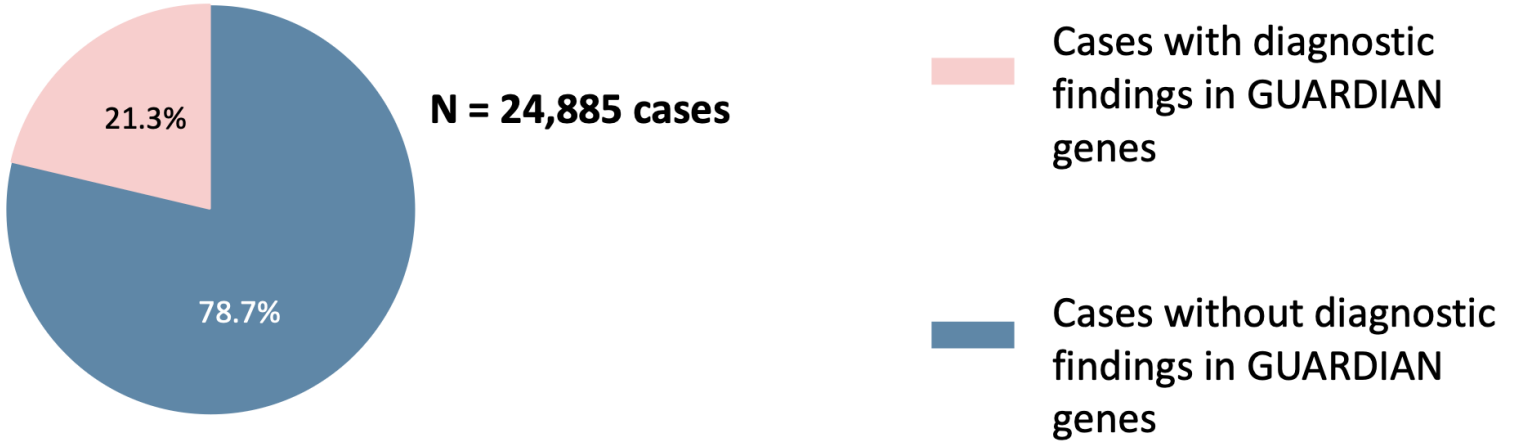
Type of Consent



Group 2 consent

	Overall	English	Spanish	Mandarin
Groups 1 + 2	**92%** (7100)	**93.2%** (6024)	**83.6%** (754)	**92.2%** (249)
Group1 only	**8%** (612)	**6.8%** (442)	**16.4%** (148)	**7.8%** (21)

Rare Disease Cohort molecular-Diagnosed By ES/GS At GeneDx



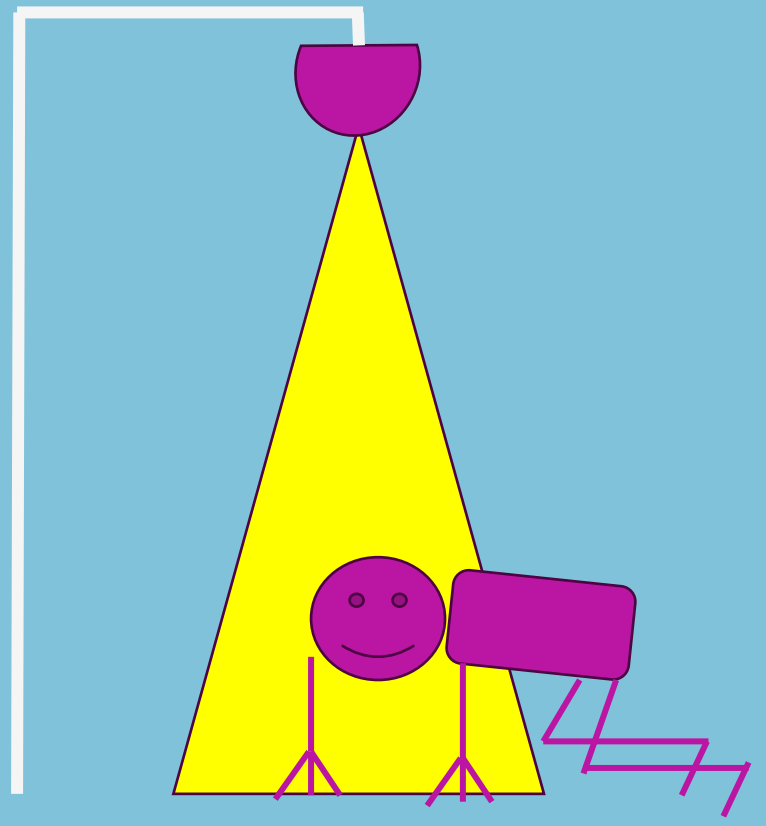
Data presented at ACMG 2023

Cohort Building

Cohort Building

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

Future Technology



Long Read Sequencing Projects at GeneDx

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

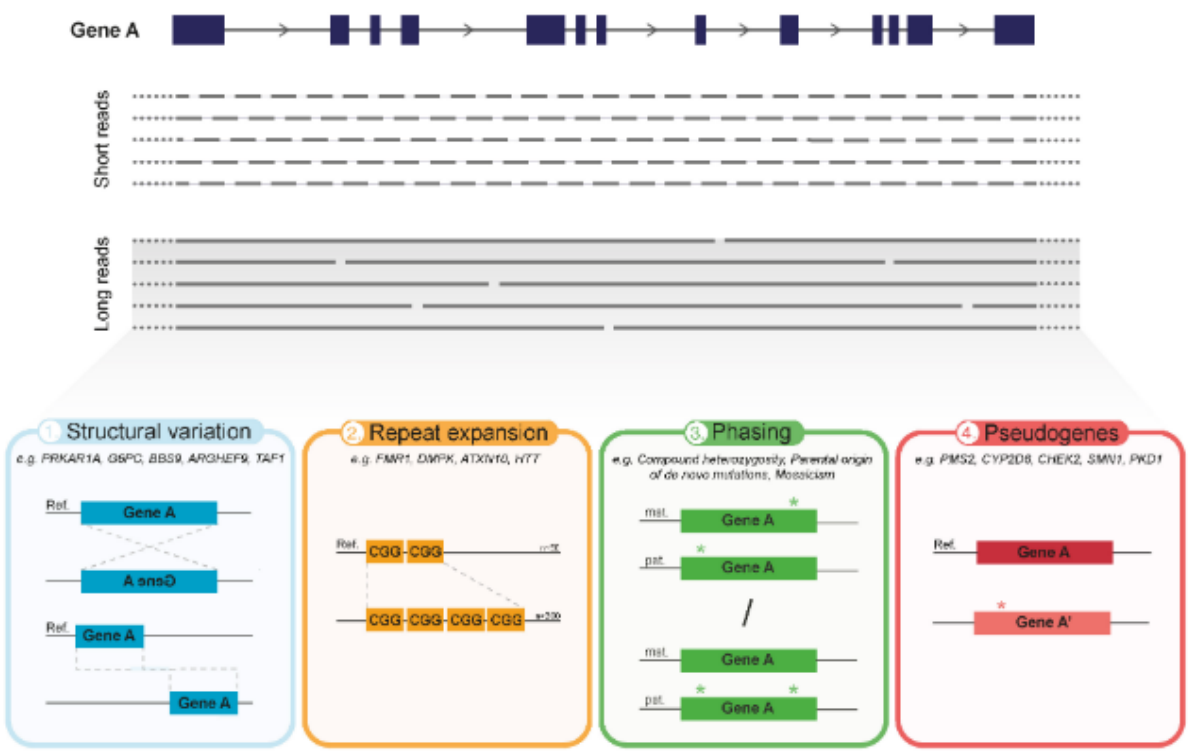
BRONX, NY—November 8, 2023. The New York Center for Rare Diseases (NYCRD) at Montefiore, recognized as a Center of Excellence by the National Organization for Rare Disorders (NORD), is partnering with GeneDx, PacBio and Google Health to deliver genetic diagnoses for Bronx families living with rare diseases. 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.

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



Mantere T, Kersten S and Hoischen A (2019) Long-Read Sequencing Emerging in Medical Genetics. Front. Genet. 10:426. doi: 10.3389/fgene.2019.00426

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Thank You