Genetics in Epilepsy: Adults

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Disclosures

- I have consulted and received honoraria and/or travel reimbursement from:

  Horizon Therapeutics, Biomarin Pharmaceuticals, Eton Pharmaceuticals, Acer Therapeutics, Ultragenyx, Applied Therapeutics, Jnana Therapeutics, Alexion and Chiesi.

- I participate in sponsored clinical trials for:

  Aeglea Biotherapeutics, Reneo Pharmaceuticals, PTC Therapeutics, Homology Medicines, Horizon Therapeutics, Arcturus Therapeutics, Jnana Therapeutics, Synlogic Therapeutics, Biomarin Pharmaceutical

- I have no conflict related to commercial laboratories or genetic testing products

- I do not endorse or specifically recommend any specific commercial lab or testing product. Any reference to a specific laboratory or test is meant for example purposes only

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Learning Objectives

- Consider indications and implications of genetic testing in adults with epilepsy
- Differentiate types of genetic tests and their diagnostic yeild
- Identify seizure phenotypes with genetic causes in adults

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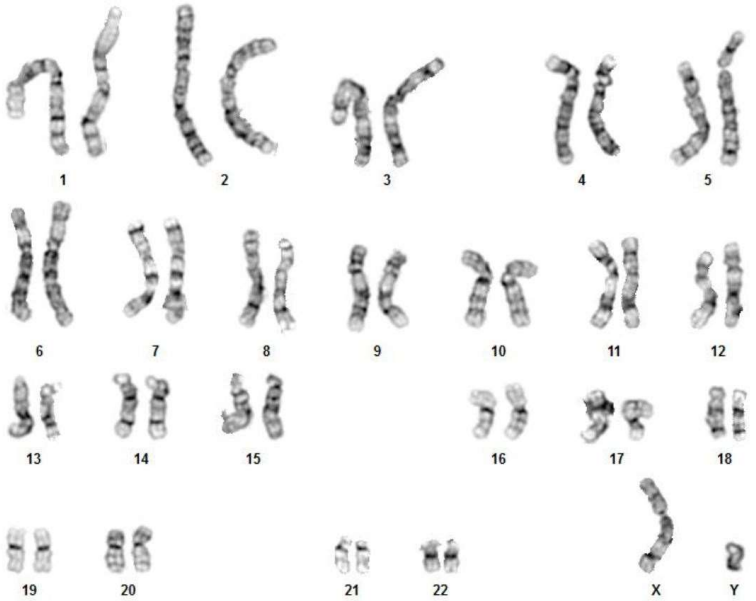
Genetics by the Numbers



- ~3,000,000,000 bases (letters)
- ~20,000 genes (instructions)
- 4,863 genes with possible disease link
- 7,454 diseases with a known genetic alteration
- 2% of the U.S. population have ‘genetic disease’ (excluding cancer)
- 70% of hospitalized pediatric patients
- 16,000-17,000 base mitochondrial genome with 37 genes

http://omim.org/satistics/geneMap 12/3/23

Hall 1978 Am J Med Genet 1:417-436

Baird 1988 Am J Hum Genet 42:677-693-436

McCandless 2004 Am J Hum Genet 74:121-127

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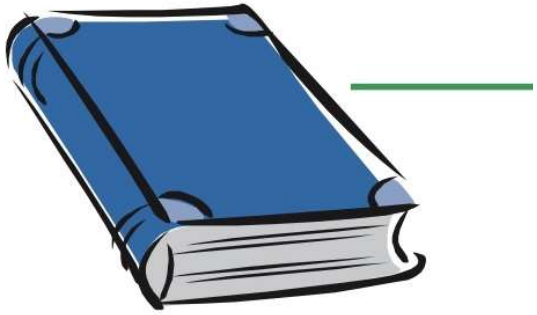
Genetic Testing: 3 levels of Detail

BIG

Medium

small



Aneuploidy

Turner, Down, Klinefelter
Trisomy 13, 18
Balanced translocation

Microdeletion/duplication

Williams, DiGeorge

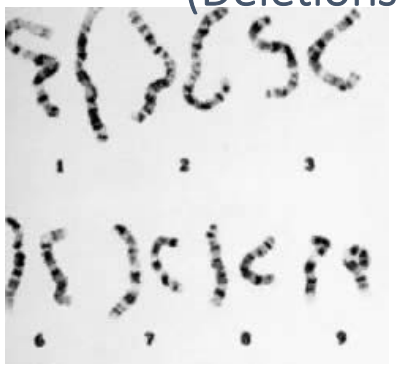
Single gene disorders

Most genetic disease

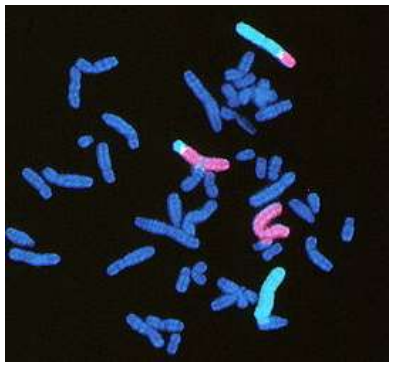
Genetic Testing: 3 levels of Detail

BIG

KARYOTYPE
(Deletions >5 Mb

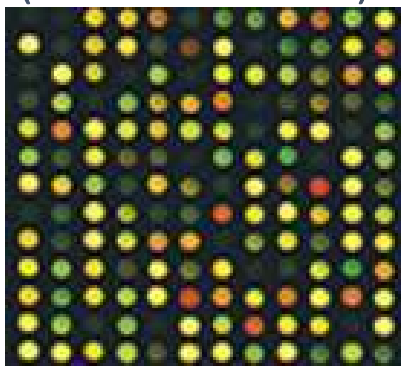


FISH
(Targeted Analysis)
>200 kb



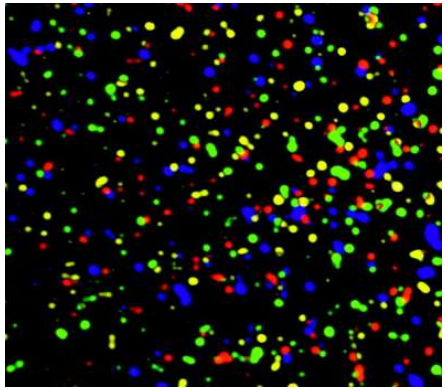
Medium

Microarray (CMA)
(Deletions >5 kb)



small

Sequencing
(single base)



Next-Generation Sequencing (NGS) – Short Read

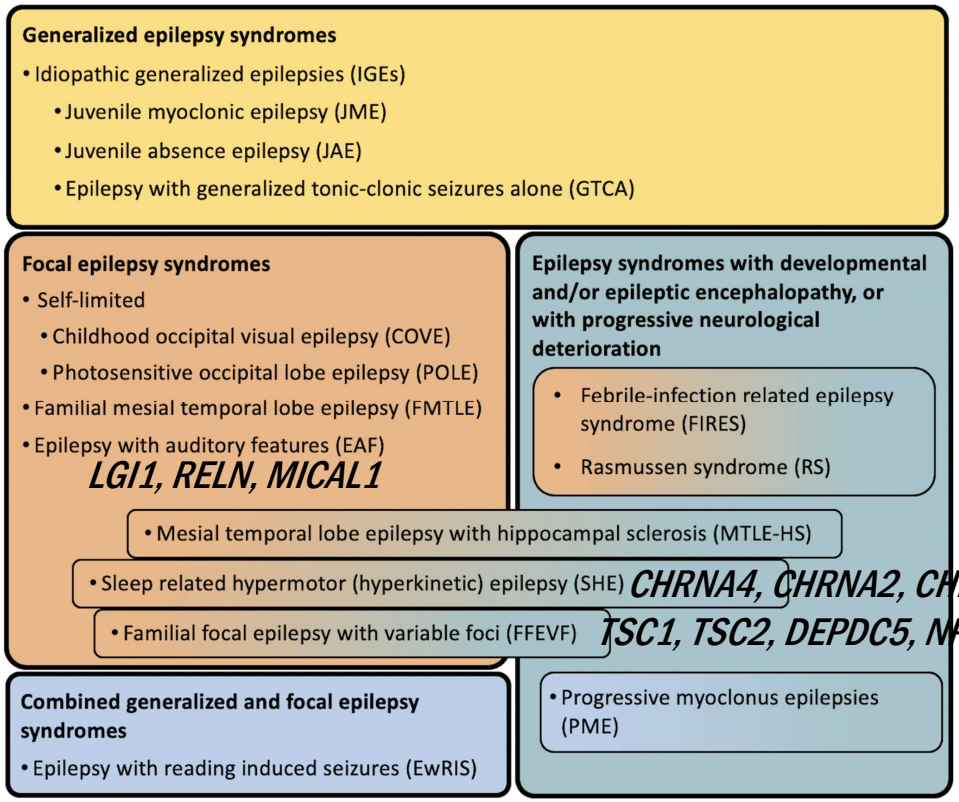
- Multi-gene panels (MGP)
  - Usually by phenotype or disease
    - Cardiomyopathy panel
    - Seizure panel
    - Cancer panel
- Exome sequencing
  - All coding regions of genes
  - ~1.5% of the total DNA
- Genome sequencing
  - All currently sequencable DNA
  - ~85% of total DNA

Cost and Turnaround (Self-Pay)

- G-banded karyotyping (with FISH)
  - $800 ($1200)
  - 72 (24) hours
- Chromosomal microarray
  - $600-$1500
  - 10-14 days
- Exome
  - $800-$3000 ($2400-6000 trio)
  - 4-8 weeks
- Whole Genome
  - $1500-$4000
  - 4-8 weeks
- Targeted NGS panel
  - $250
  - 2-6 weeks
- Repeat expansion
  - $250-$295 per test
  - $895 panel

Institutional and insurance bill prices can be much higher!!!!

Epilepsy syndromes with onset at a variable age



DEPDC5

CHRNA4, CHRNA2, CHRNB2, DEPDC5, KCNT1, NPRL2, NPRL3, PRIMA1

TSC1, TSC2, DEPDC5, NPRL2, NPRL3

ADRA2B, ASAH1, CLN3, CLN5, CLN6, CLN8, CSTB, EPM2A, GBA, GOSR2, GRN, IRF2BPL, KCTD7, MFSD8, NHLRC1, PPT1, PRICKLE1, SCARB2, TPP1

Epilepsia, Volume: 63, Issue: 6, Pages: 1443-1474, First published: 03 May 2022, DOI: (10.1111/epi.17240)

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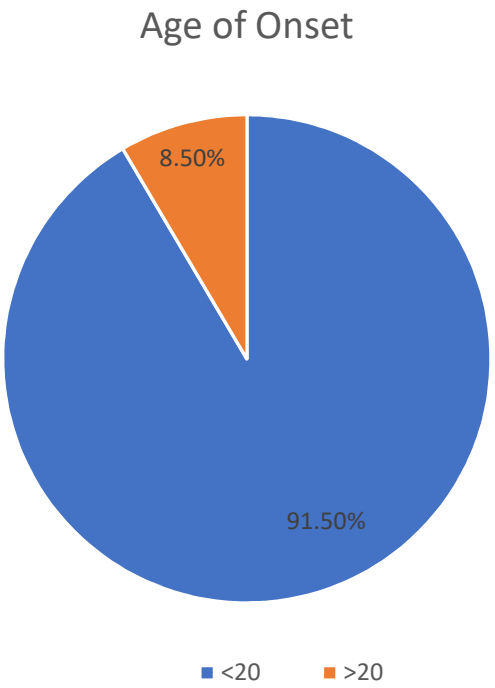
Adult-onset IGE

- 15-20% of all epilepsy attributed to IGE



J Neurol Neurosurg Psychiatry. 2004 Jan;75(1):72-4.

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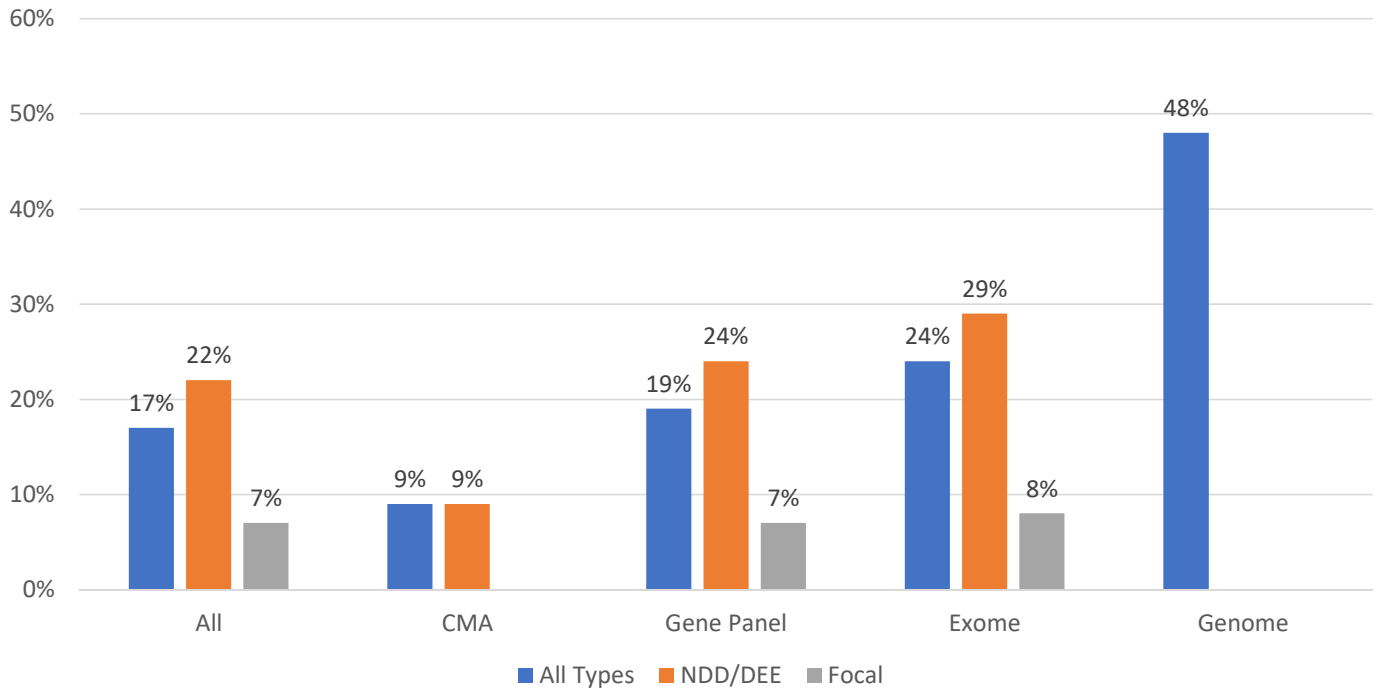
Diagnostic Yield of Genetic Testing in Epilepsy



Treatment changes were reported in 12%–80% of patients with a genetic diagnosis, including avoiding, stopping, or initiating specific antiseizure medications (ASMs) or ketogenic diet (KD) and halting a plan for surgery in the presence of a specific genetic diagnosis.

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Epilepsia. 2022 Feb;63(2):375-387. doi: 10.1111/epi.17141. Epub 2021 Dec 10.

National Society of Genetic Counselors Guidelines

1. Genetic testing is strongly recommended for all individuals with unexplained epilepsy
   - Regardless of age
   - Exome/Genome or Multigene panel first line
   - Exome/Genome preferred
   - CMA if negative
2. It is strongly recommended that genetic tests be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre-test and post-test genetic counseling

Smith et al (2022), Genetic Testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. PMID: 36281494 DOI: 10.1002/jgc4.16

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Factors Associated With Higher Diagnostic Yield

- Intellectual disability or other neurodevelopmental disorder
- Early Onset
- Family History
- Structural brain abnormalities
- Dysmorphism
- Other muti-system involvement

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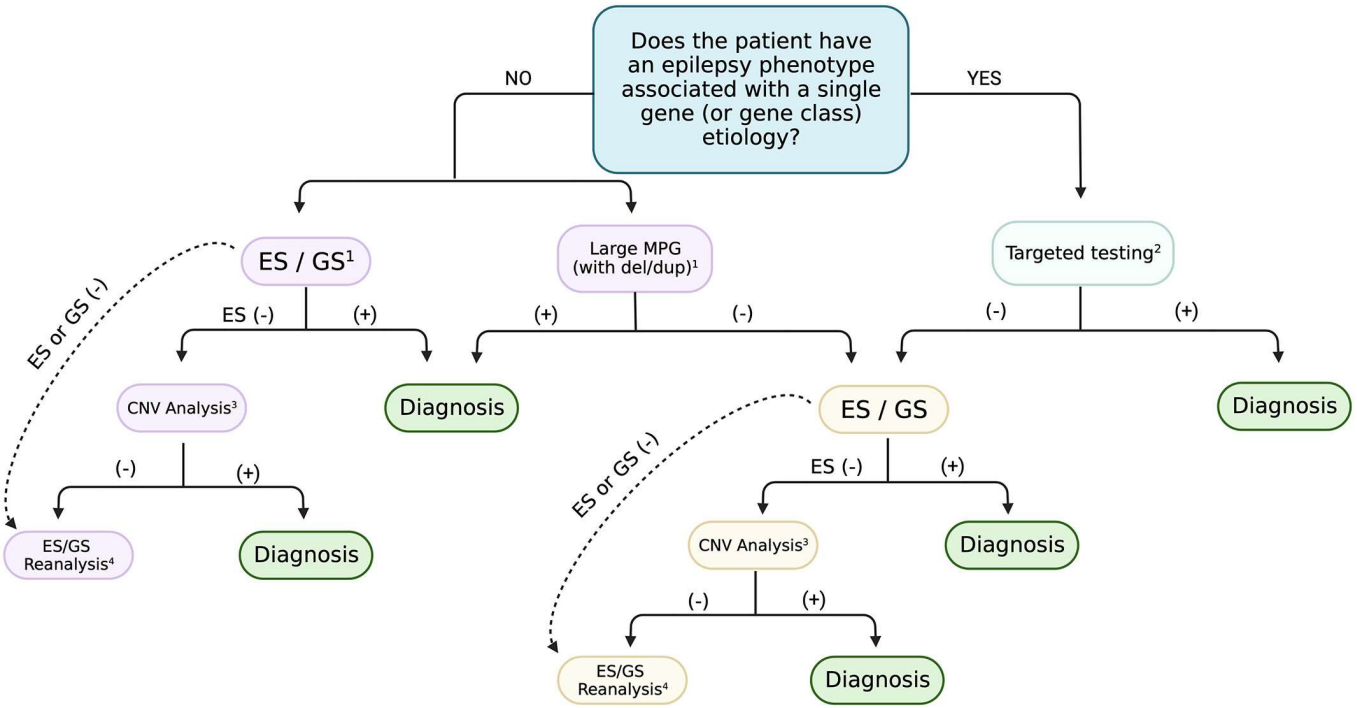
Testing Algorithm



Smith et al (2022), Genetic Testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. PMID: 36281494 DOI: 10.1002/jgc4.16

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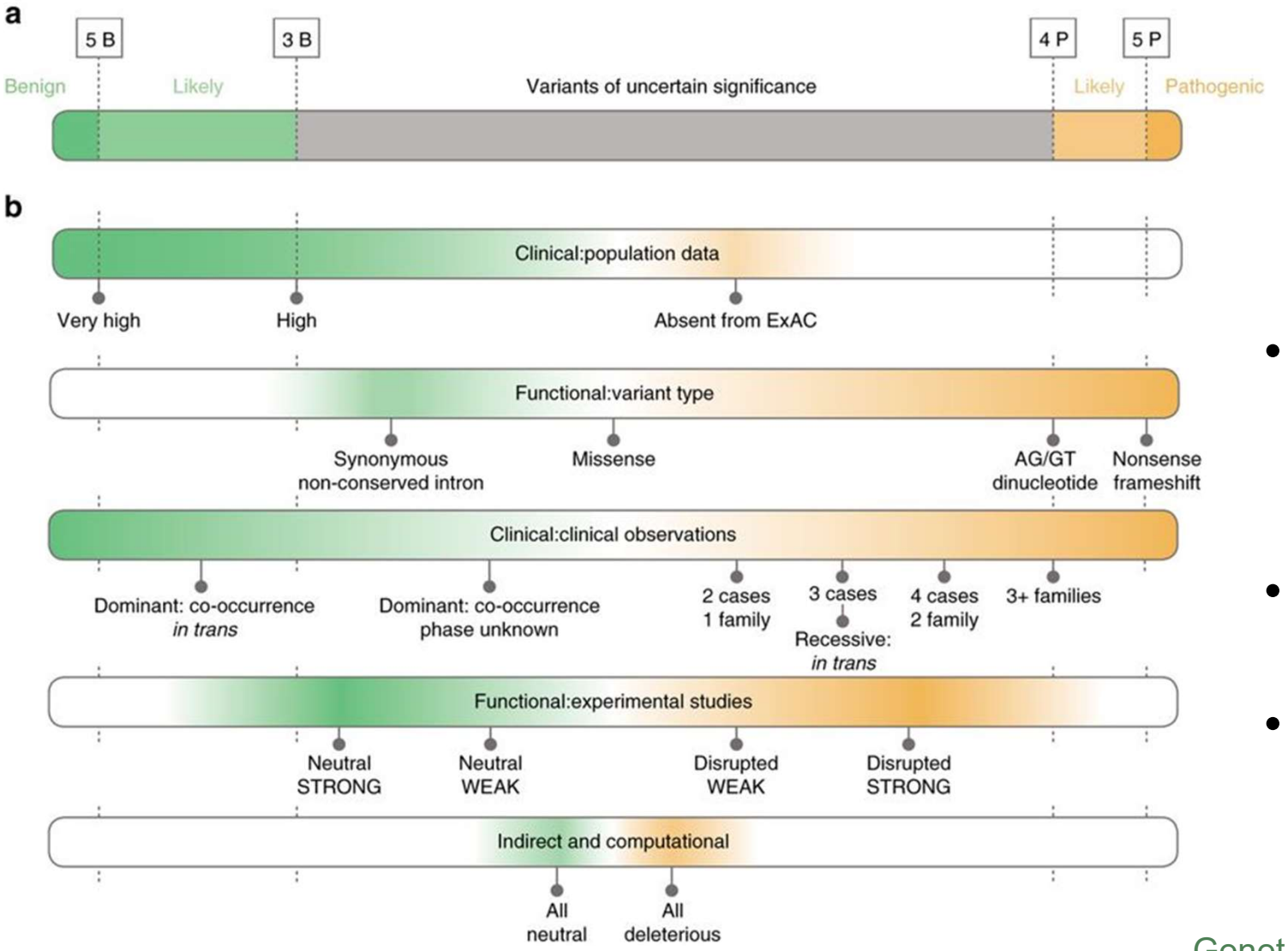
NGS Sequencing – Limitations/Advantages

- Lots of data
- Cost effective
- Can detect deletion/duplications
  - Except 1-3 exons in size
- Difficulty in interpretations of all variants
- Variant classification is dynamic
- Cannot distinguish pseudogenes or gene conversions
- Cannot diagnose all repeat expansion disorders
- Incidental findings in ES/GS



Variant Classification

- Do not overinterpret VUS
  - 90% reclassified benign
- Treat as a negative result
- Reanalyze every 2 years

Genet Med. 2017 Oct;19(10):1105-111

How much variation can there be?

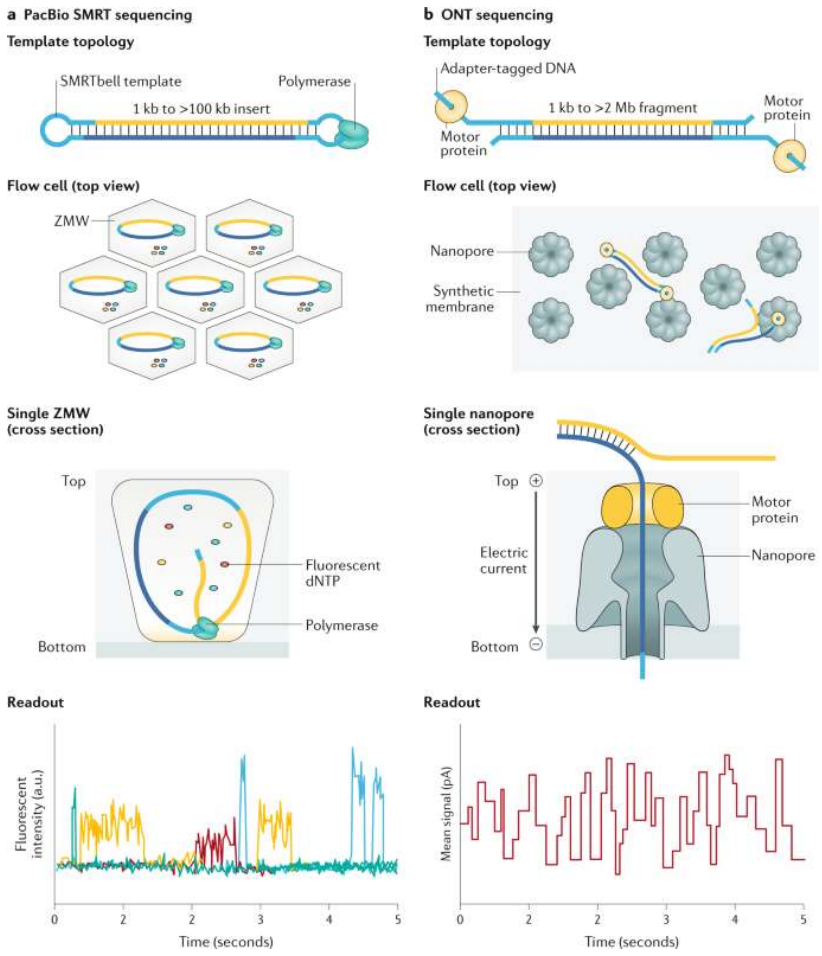
- 5-10 million SNPs (varies by population)
  - 25,000-50,000 rare variants (private mutations or seen previously in < 0.5% of individuals tested)
- 75 new base pair mutations not detected in parental genomes
- 3-7 new CNVs involving ≈500 kb of DNA
- 200,000-500,000 indels (1-50 bp) (varies by population)
- 500-1000 deletions 1-45 kb, overlapping ≈200 genes
- 150 in-frame indels
- 200-250 shifts in reading frame
- 175-500 rare nonsynonymous variants
- 1-3 new nonsynonymous mutation
- 100 premature stop codons
- 40-50 splice site-disrupting variants
- 250-300 genes with likely loss-of-function variants
- 25 genes predicted to be completely inactivated

Nussbaum, R, et al. 2015. Thompson & Thompson genetics in medicine.

There are many (rapidly changing) options

- Different labs have widely different billing policies and patient assistance programs.
- Labs have different panel offerings and approaches
  - Some are exome based
  - Some include mitochondrial genes
  - Some include non-coding pathogenic variants
  - Intronic depths differ
- All commercial labs have genetic counselors available to help with test selection
- Insurers may have specific requirements for genetic testing
- Self-pay may be cheapest option
- Sponsored testing is available

One test to rule them all



Long-read whole genome

- 30K-2M base pair reads
- Allow de novo chromosome assembly
- Detect complex structural changes
- Copy number variation
- Differentiate gene and pseudogene
- Precise repeat expansion determination
- Allow detection of epigenetic modifications
- Same technology can be applied to RNA and mitochondrial DNA

Nature Reviews Genetics **volume 21**, pages597–

Summary

- Adult-onset can occur in most genetic forms of epilepsy
- A genetic diagnosis clarifies prognosis, provides recurrence risk estimation, and informs management in a subset of individuals
- Genetic testing should be considered in all adults with epilepsy of unknown cause
- NGS is first line and includes phenotype-specific gene panels and exome/genome sequencing (ES/GS)
- Diagnostic yield with NGS is around 25%
- Interpretation of NGS remains difficult and dynamic and has a high rate of variants of uncertain significance (VUS)
- Testing should be reanalyzed ever 1-2 years