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Genetic testing in epilepsy

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Outline

- Introduction to genomic era
- Type of genetic testing
- Pre-genetic testing counseling
- Case-based discussion
- How to handle the genetic result

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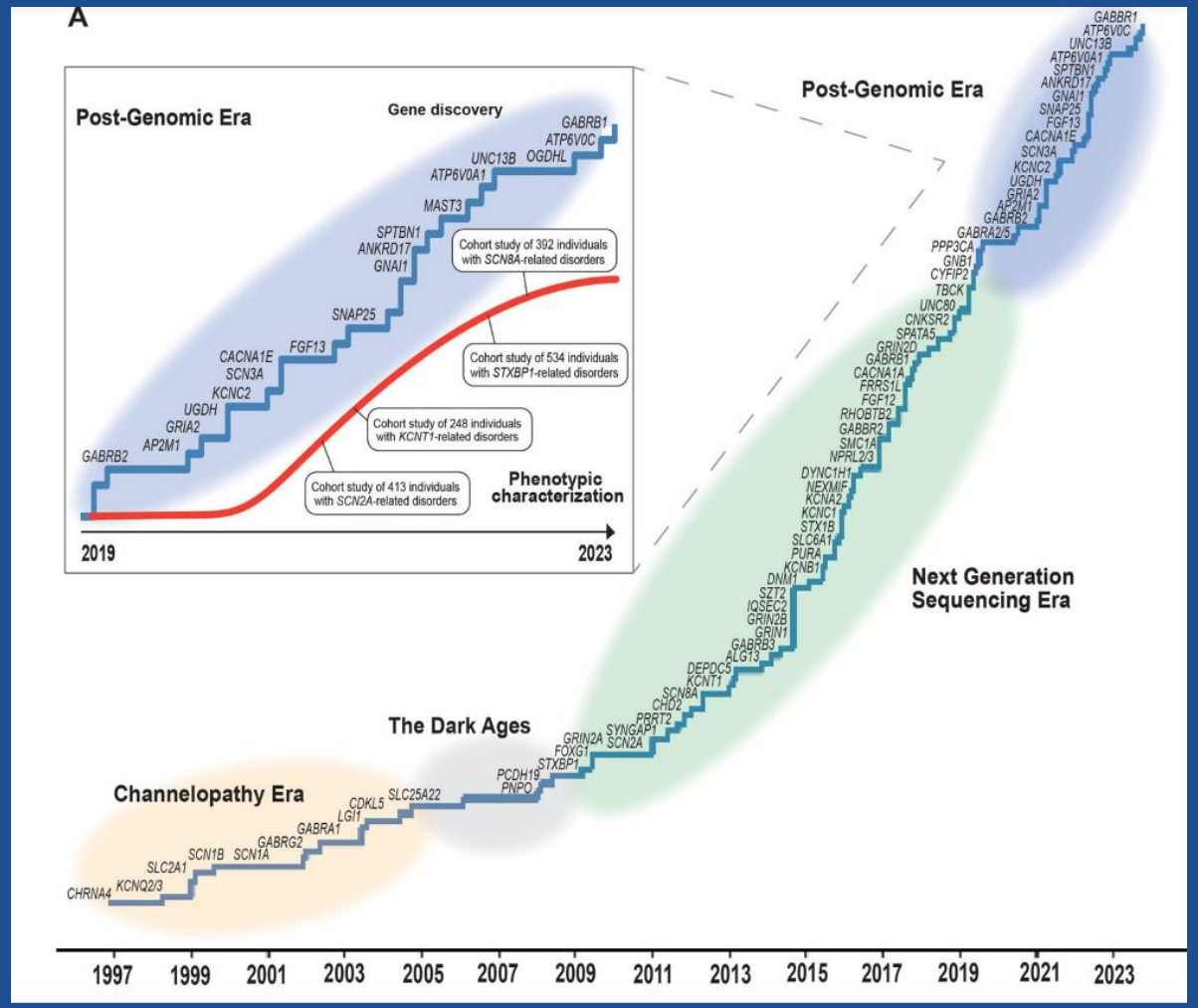
Innovations in Genetic testing

Next-Generation Sequencing (NGS)



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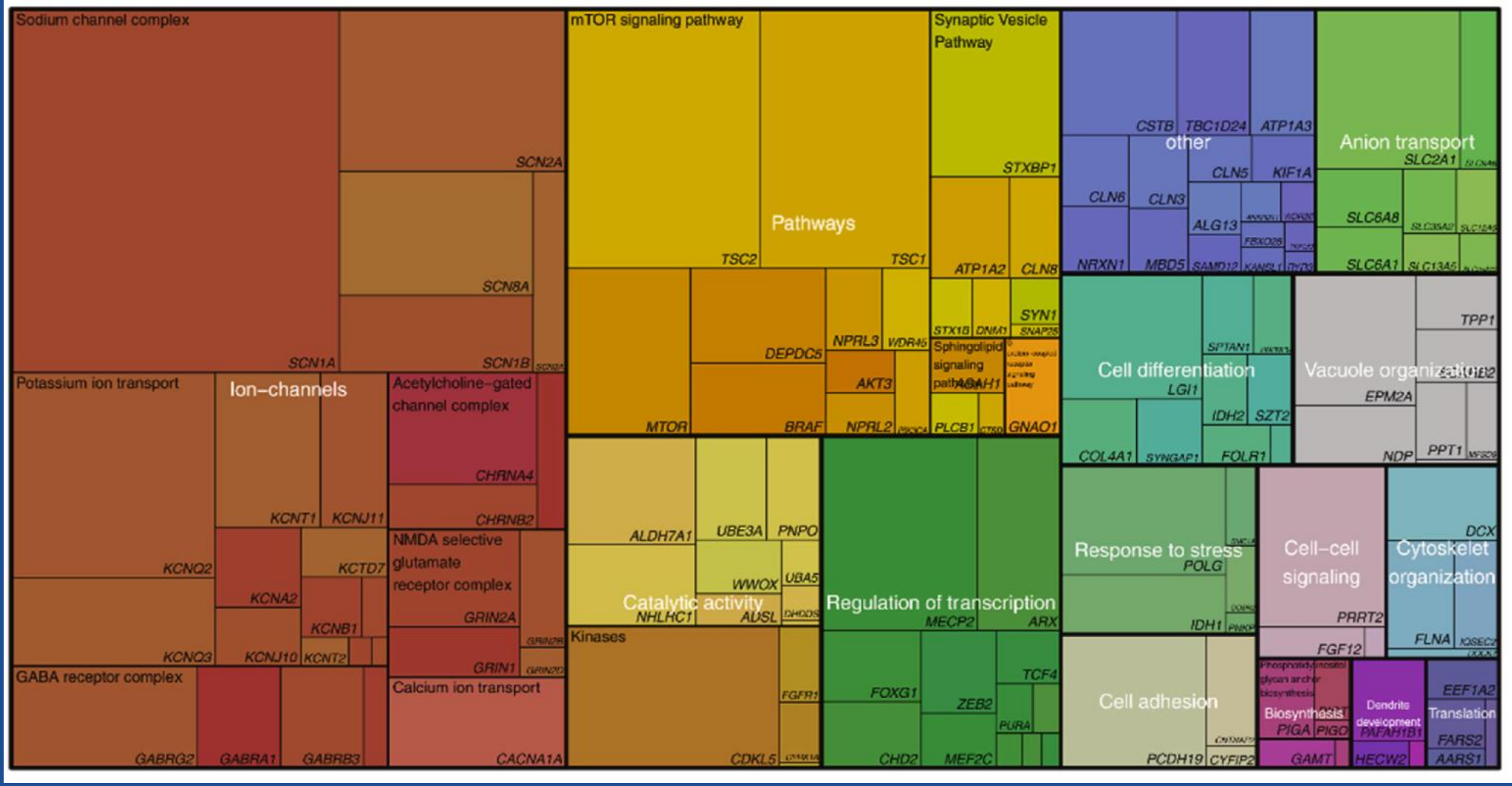
Treemap of Tier 1 epilepsy genes characterized in Gene Ontology term (GO) groups



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Why is genetic testing important?

End of Diagnostic odyssey

Reduce unnecessary investigation

Screening for comorbidities

Connecting with with a support group

Personalized treatment

Opportunity for future research

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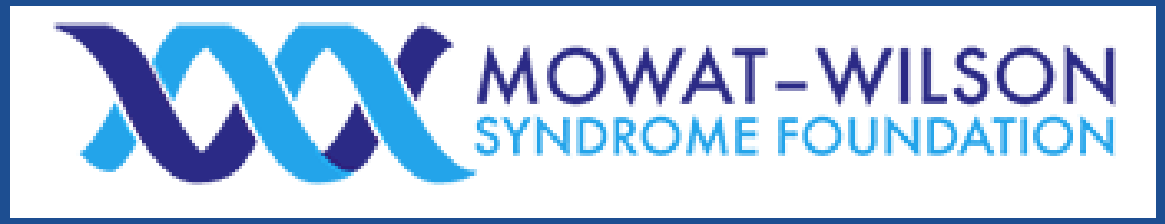
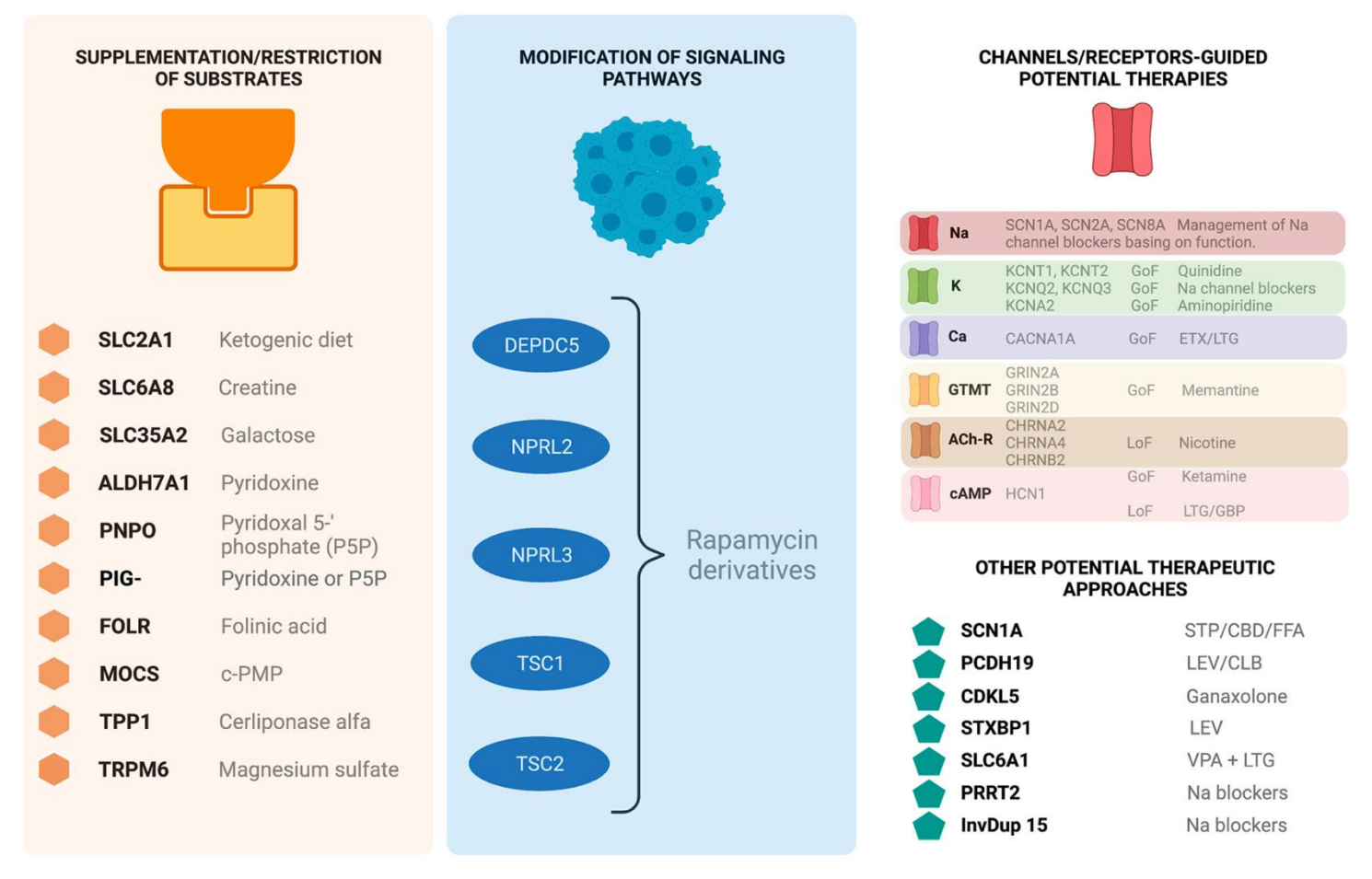
Connecting families with a support group



Epilepsy-related genetic conditions displaying potential specific therapeutic approaches



Matching Genetic Disorder with Appropriate Testing

- Monogenic disorder
- Chromosomal disorder
- CNV disorder
- Methylation disorder
- Repeat expansion disorder
- Mosaicism

- Chromosome study
- FISH
- Methylation test
- Chromosome microarray (SNP/CGH)
- Gene panel
- Whole exome sequencing
- Whole genome sequencing(long read/short read)

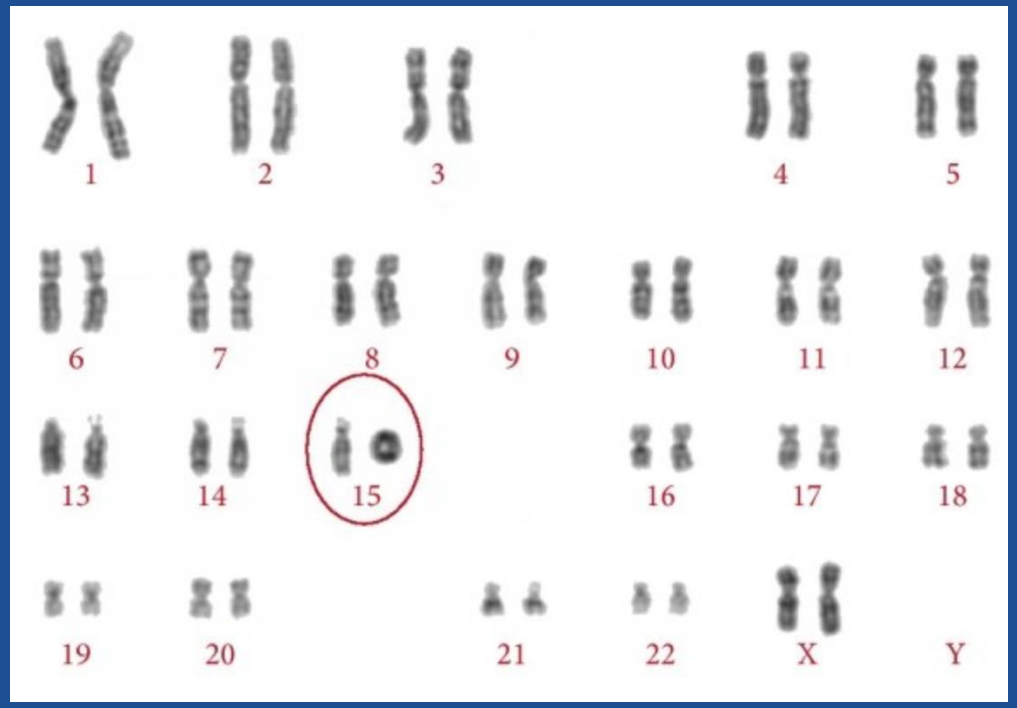
Type of Genetic Testing

Cytogenetic	Biochemical	Molecular
• Karyotype • FISH • CMA	• Plasma amino acids • Urine organic acids • Comprehensive metabolic test • Enzyme assays	• Sanger sequencing • MLPA • NGS - Gene panel - ES - GS

CMA: Chromosome microarray
ES: Exome sequencing
GS: Genome sequencing
MLPA: Multiplex Ligation-Dependent Probe Amplification
NGS: Next generation sequencing

Conventional karyotyping

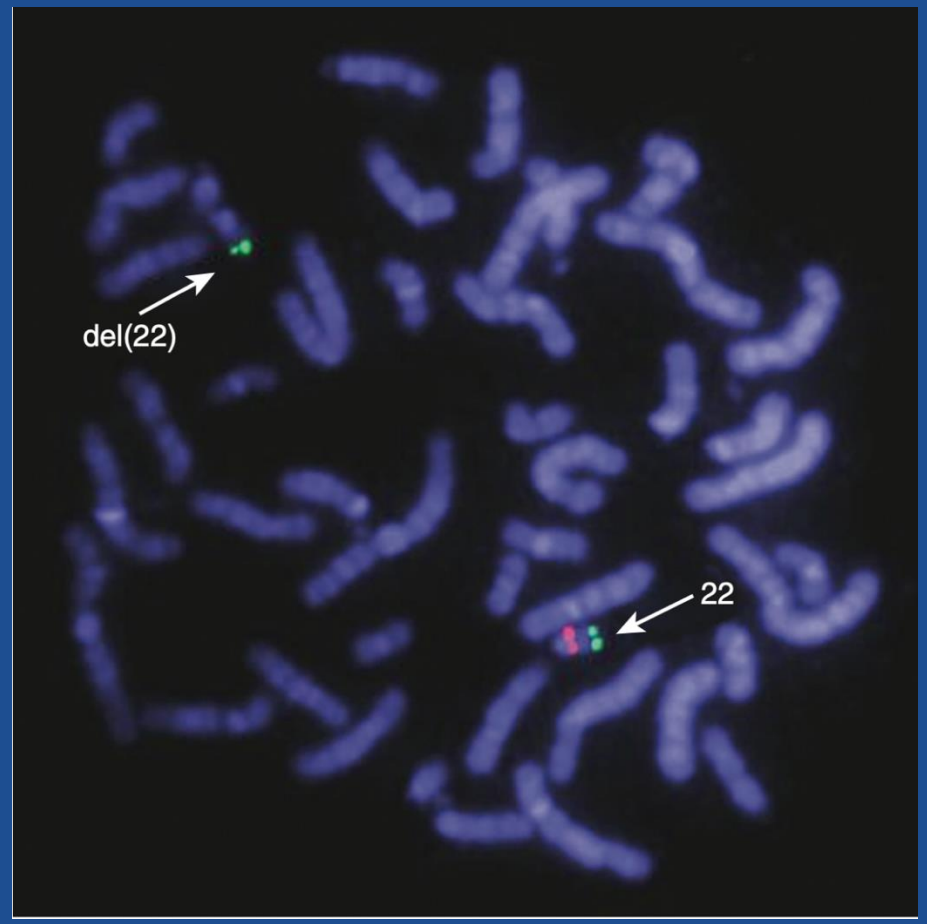
- Detect
  - Chromosomal abnormalities of 5 Mb and larger
  - 2–3 Mb (high-resolution banding)
- Analyze chromosomes for chromosomal rearrangements
    - Balanced or unbalanced translocations
    - Inversions
    - Ring chromosome



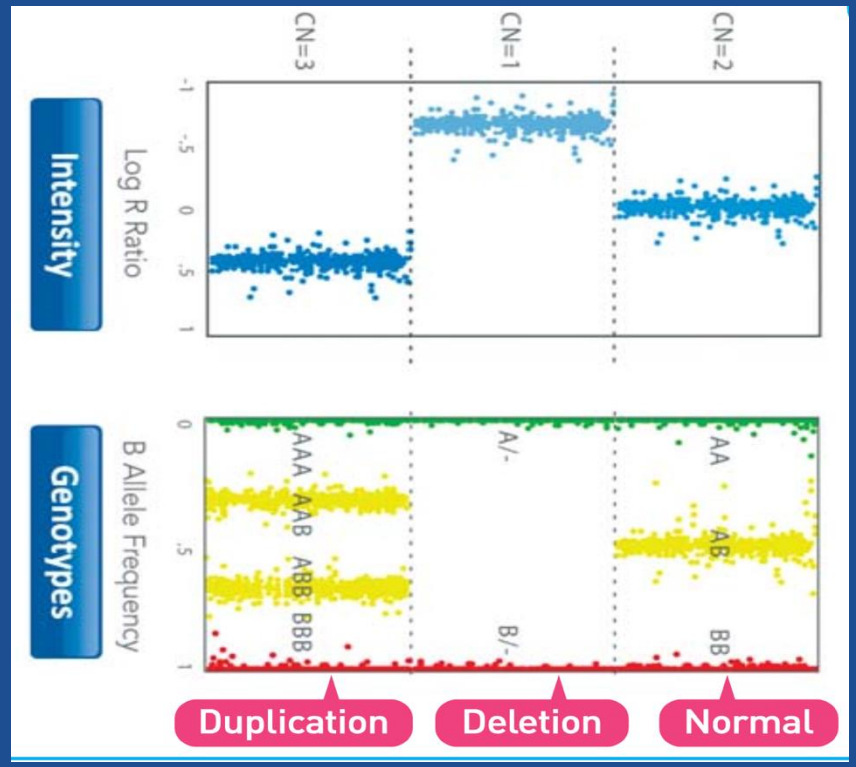
Ring chromosome 15

FISH

- Specific probe
- Resolution: 150-200 kb
- Can not detect uniparental disomy



Chromosome microarray (CGH/SNP)



- Resolution: Few kb or longer
- limitation in balanced chromosome rearrangements, such as translocations or inversions

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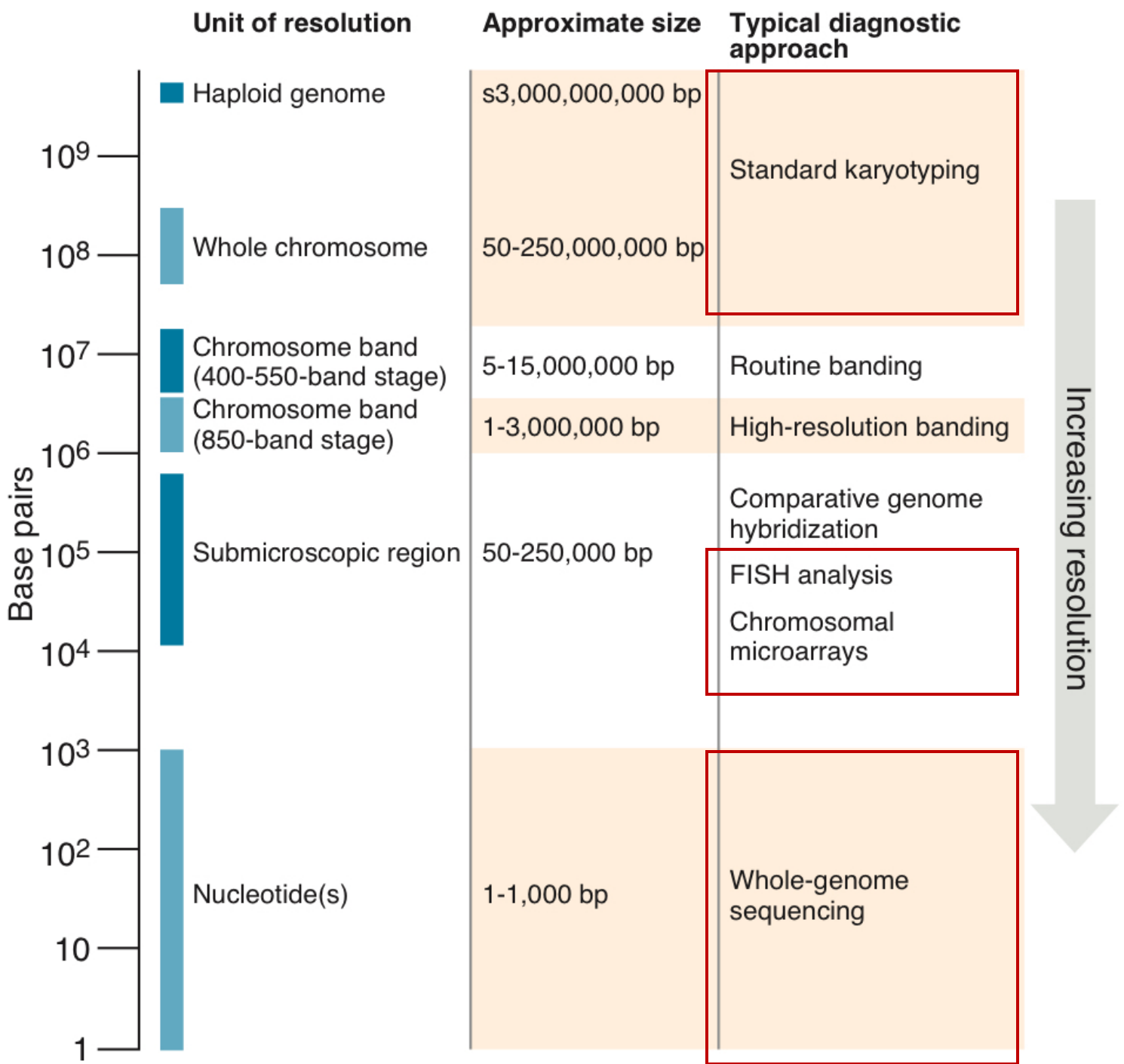
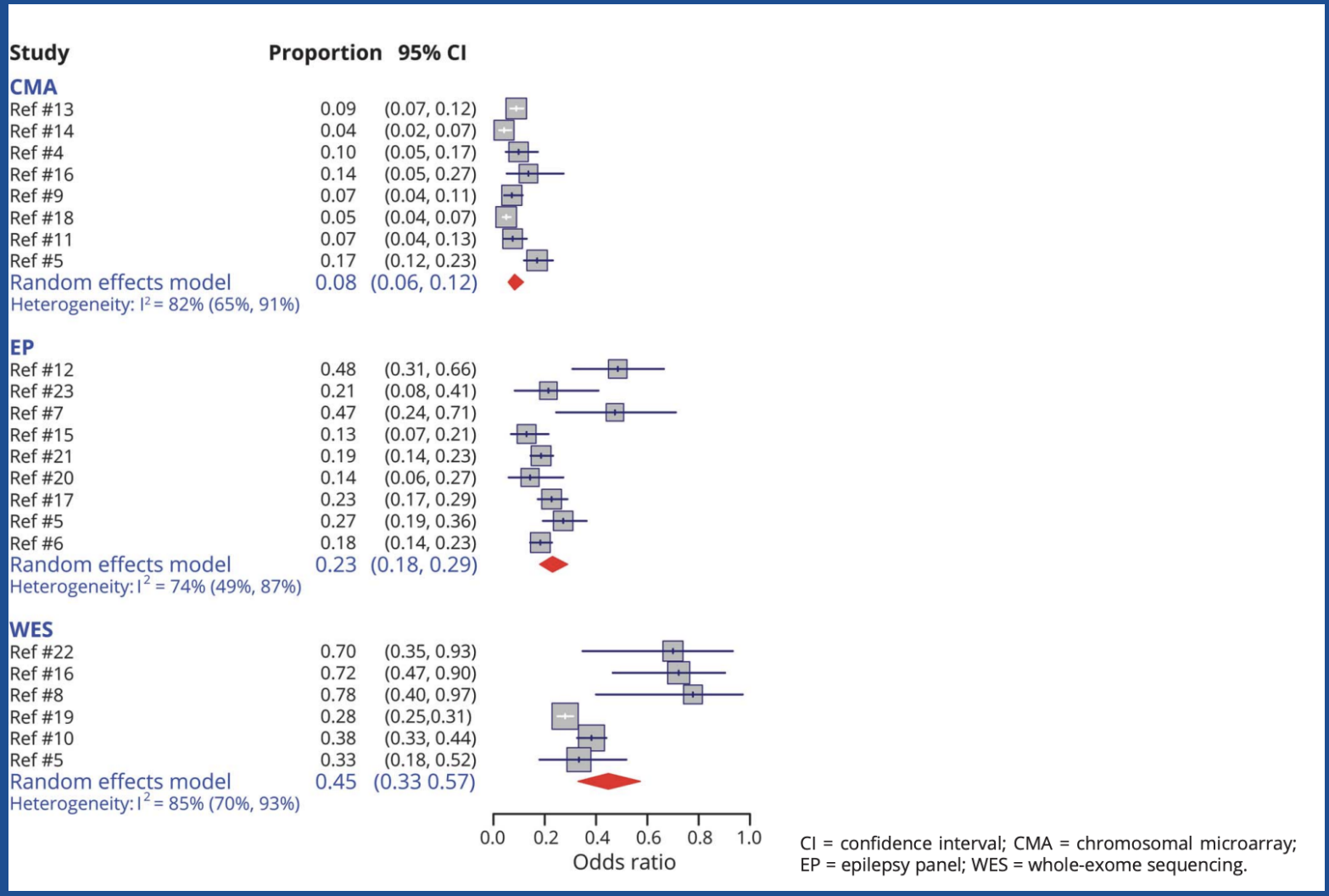
Resolution



Thompson & Thompson genetics in medicine, 8th Ed.

	Resolution	Applications	Limitations
Karyotyping	2-3 Mb / 5 Mb	Scanning for aneuploidy, large deletion or duplication and structural variants.	Cannot identify microdeletion/duplication
CMA: SNP array	Few kb or longer	Scanning the entire genome for any CNV, Can identify ROH	Cannot identify balanced translocation and inversion
CMA: Array-CGH	Few kb or longer	Scanning the entire genome for any CNV	Same as SNP-array. Cannot identify ROH
Gene panel	One to several bp	Scanning for genes of interest. Can be supplemented with other technologies to solve low-coverage regions and detect small CNV. "True" panel testing with deep coverage can detect low-level mosaicism.	Cannot detect deep-intronic changes. Different labs have different set of genes for targeted phenotype.
ES	One to several bp	Scanning for all genes of interest excluding non-coding and deep intronic regions.	Might miss variants in low-coverage regions and deep intronic changes, low-level mosaicism. Less reliable for copy number calling.
GS	One to several bp	Scanning for entire genome including non-coding and deep intronic regions.	Costly and mostly research-driven. Most variants in non-coding regions are uninterpretable

Technologies used in genetic analysis

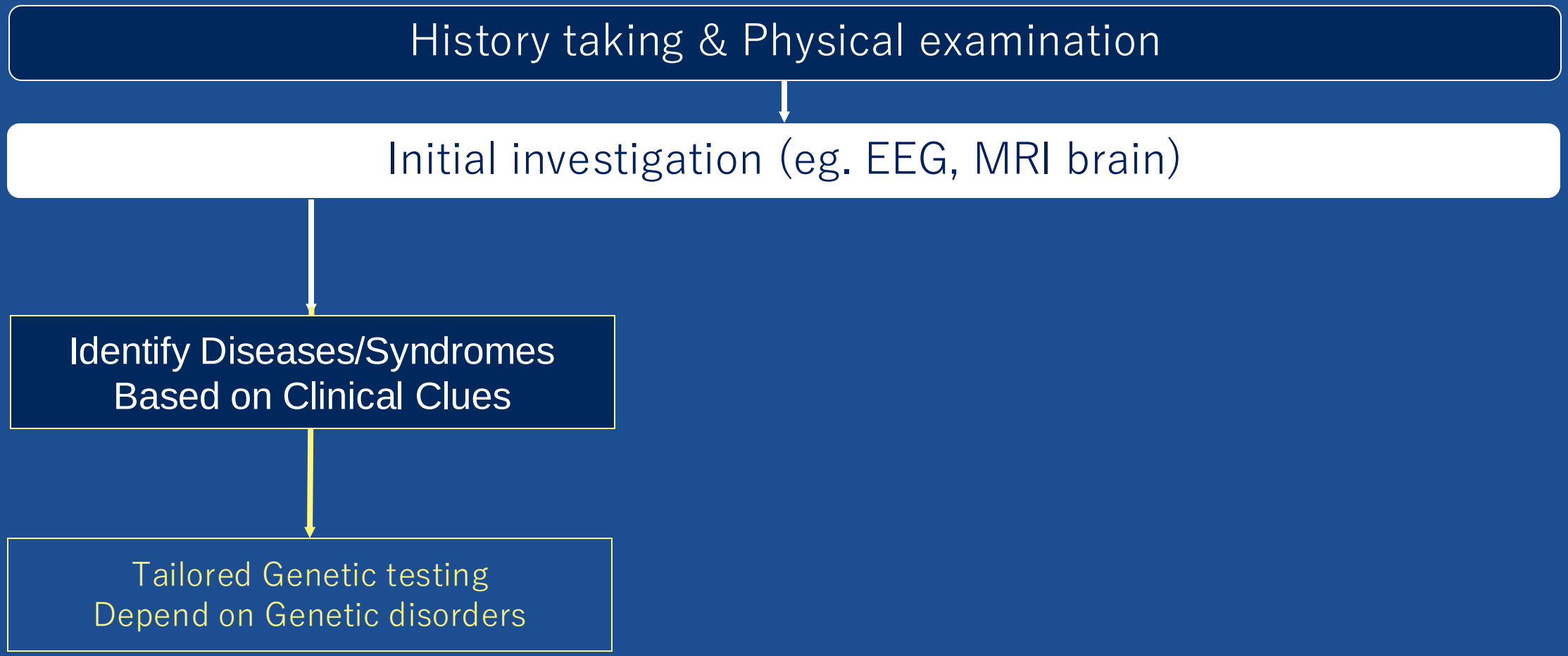


CI = confidence interval; CMA = chromosomal microarray; EP = epilepsy panel; WES = whole-exome sequencing.

Genetic Counseling

- Types of Genetic Testing Performed on Patients
- Sample Collection
- Advantages of Genetic Testing
  - Personalized treatment
  - Prognostic information and guidance
  - Recurrence risk assessment
- Possible Results
  - Positive findings
  - Negative findings
  - Variants of uncertain significance (VUS)
  - Secondary findings (ES/GS)

Approach


History taking & Physical examination
Initial investigation (eg. EEG, MRI brain)
Identify Diseases/Syndromes
Based on Clinical Clues
Tailored Genetic testing
Depend on Genetic disorders

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Who should get genetic testing?

- Unexplained refractory epilepsies
- Neonatal with epileptic encephalopathies (up to 83%)
- Children with onset < 3 years (37%)
- Epilepsy with developmental delay or regression
- Suspicious genetic epileptic syndrome
  - EIEE, Dravet syndrome, familial self-limited epileptic syndrome, DEE
- Features suggest a genetic syndrome eg. dysmorphic facies

Epilepsia. 2021 Jan;62(1):143-151
Epilepsia. 2022 Feb;63(2):375-387
JAMA Netw Open. 2023;6(7)

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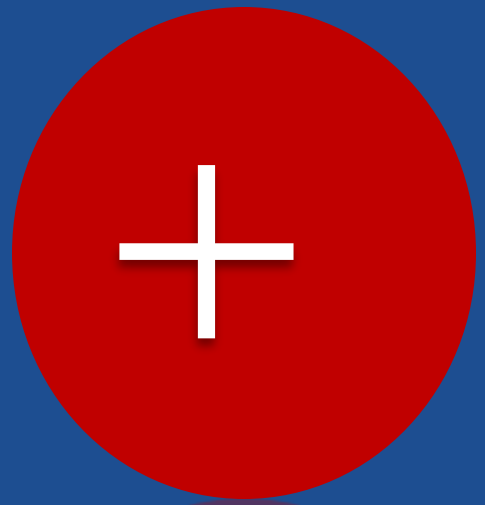
Managing Genetic Test Results

Negative

Positive



VUS

Variant of
uncertain significant

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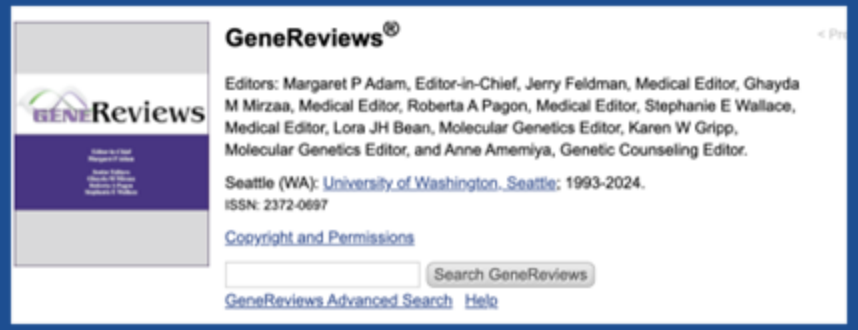
How to Handle a Positive Result

No need to memorize diseases; just know how to find the information



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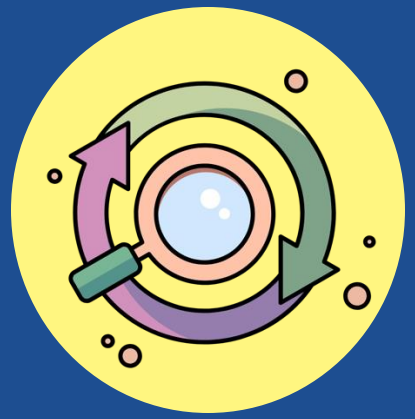
How to Handle a Positive Result

Personalized medicine

- Dravet syndrome:
  - avoid Na channel blocker
  - Antisense oligonucleotide
- SCN8A or SCN2A related DEE (GOF):
  - Sodium channel blocker, Relutrigine (PRAX-562)



Surveillance

- Rett syndrome
  - QT prolong (18-55%)

Genetic counseling and family planning

- Prenatal diagnosis
- Preimplantation diagnosis
- Carrier testing
- Advice prognosis

How to Handle a Negative Result

- Review test limitations
- Consider alternative diagnoses
- Reevaluate the patient's condition
  - Some phenotypes may emerge with age
  - Ongoing discovery of new genes and conditions
  - Updates in genetic variant data

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Acknowledgement





Division of Neurology, Department of Pediatrics