

MODULE 2: Genetic testing for Mendelian diseases

Recognizing a Mendelian Disorder – Red Flags

- Recurs in the Family
- Multiple close relatives are affected
- Tends to be earlier onset than non-Mendelian forms of same disease
- If a Cancer Syndrome, may affect bilateral structures
- Consanguinity



Utility of Genetic Testing

- Make a Diagnosis and Infer Prognosis
- Provide an Explanation and End a “Diagnostic Odyssey”
- Guide Management
- Identify which other Family Members are or are not at Risk for the Disease
- Inform Reproductive Decision Making including Pre-Implantation or Prenatal Diagnosis

Testing Across the Lifespan

Pre-conception



Prenatal



Newborns



Children



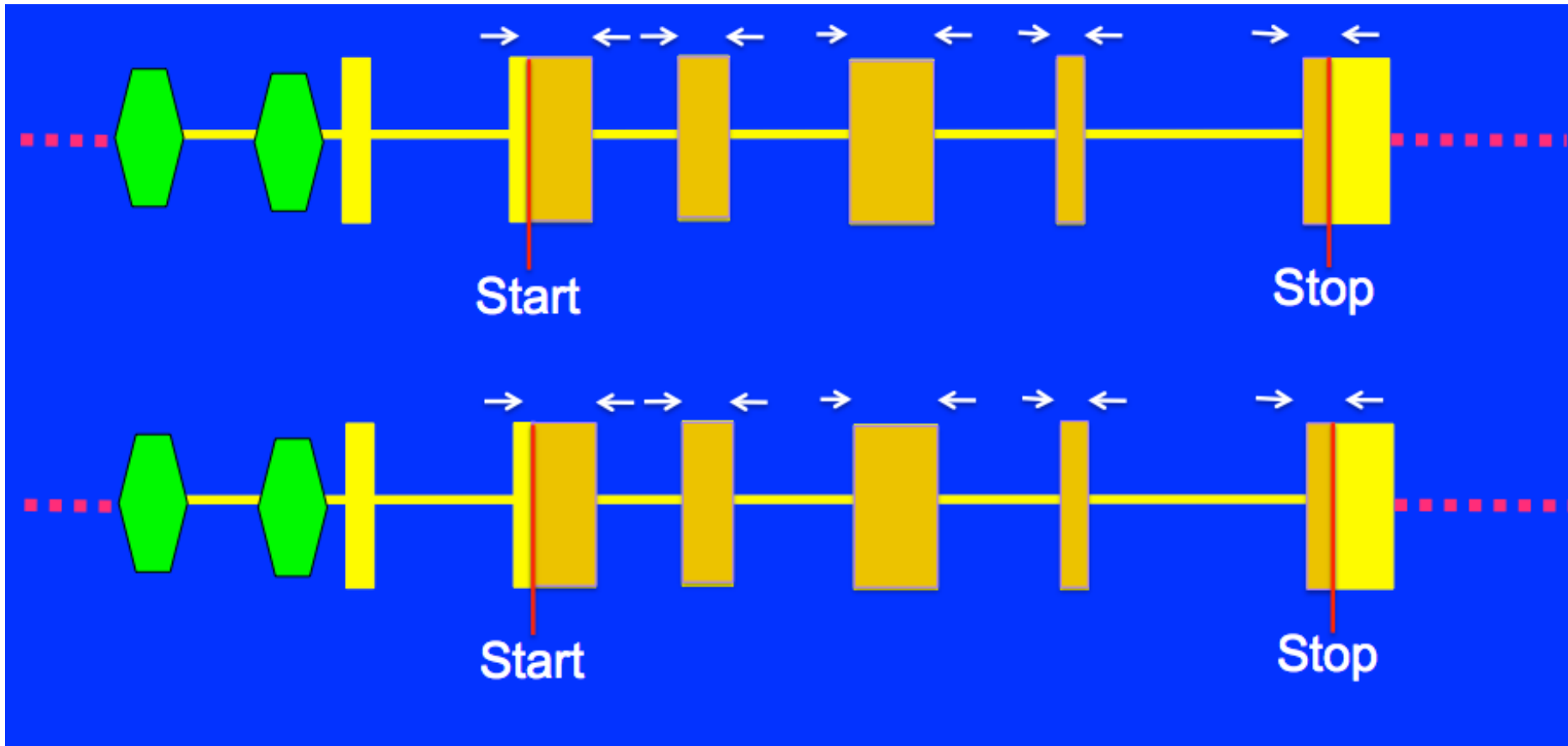
Adults



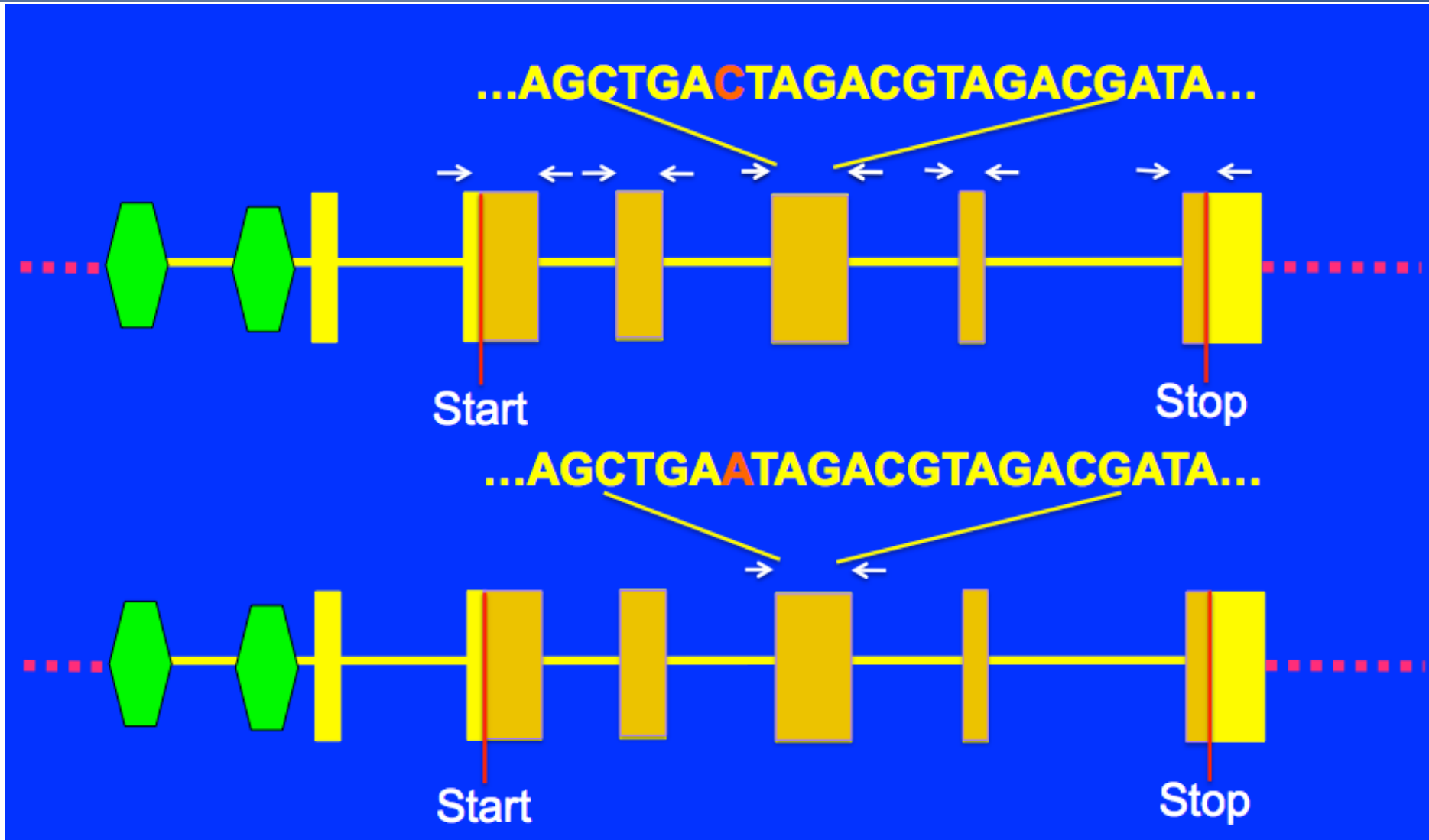
Matching the Test to the Variant

	Mutations affected 1 - ~100 bp	Mutations affecting >~100 bp
Specific to particular genes	• Single site within a gene • Targeted Gene Sequencing • Sequencing of gene panels • “SNP” Genotyping	• Deletion/Duplication scanning of one or more genes
Whole genome approaches	• Whole Exome Sequencing • Whole Genome Sequencing	• Cytogenomic Array to scan Genome for Copy Number Variants (CNVs)

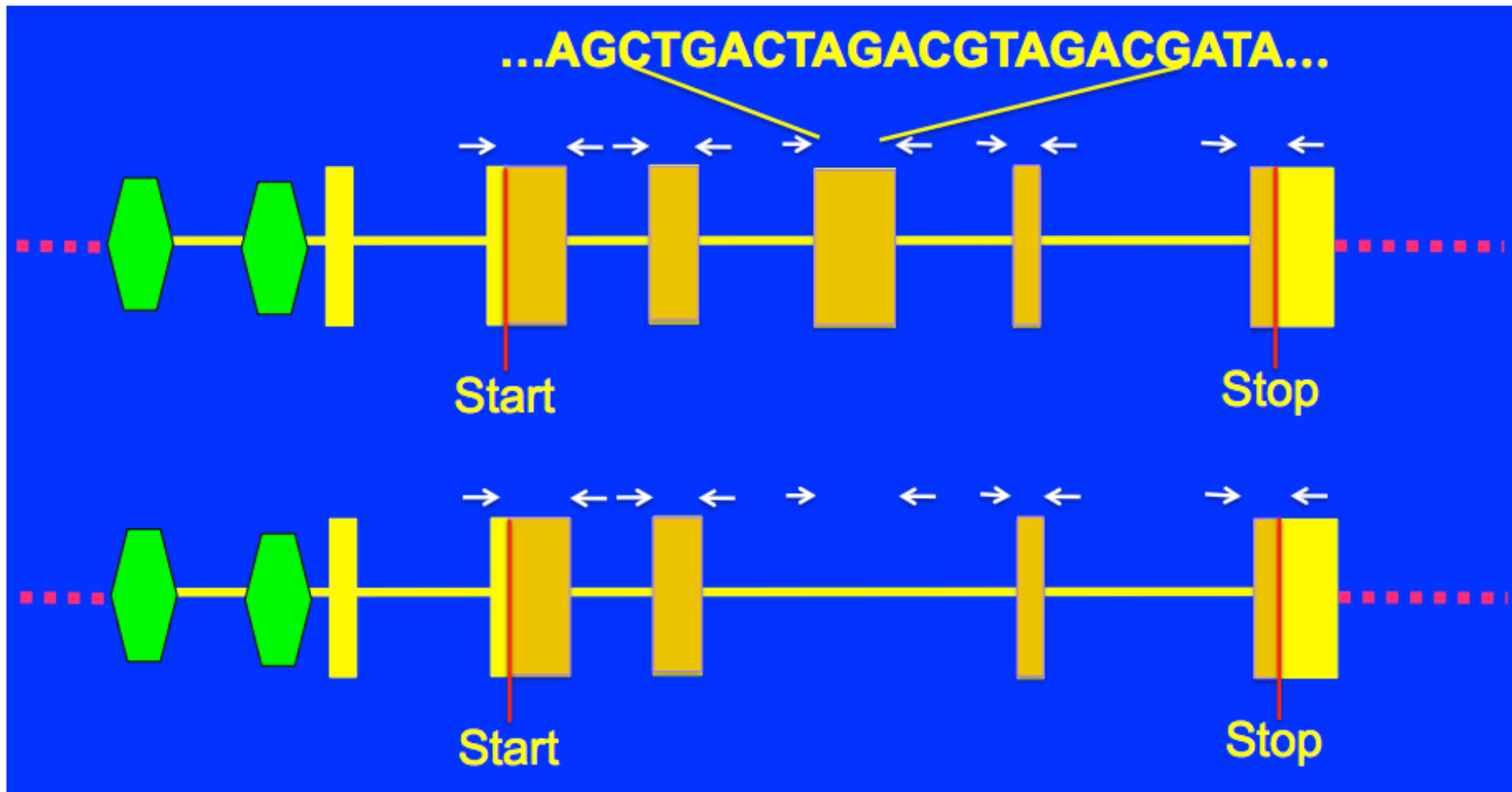
Traditional Sequencing Specific to a Particular Gene



Targeted Mutation Detection

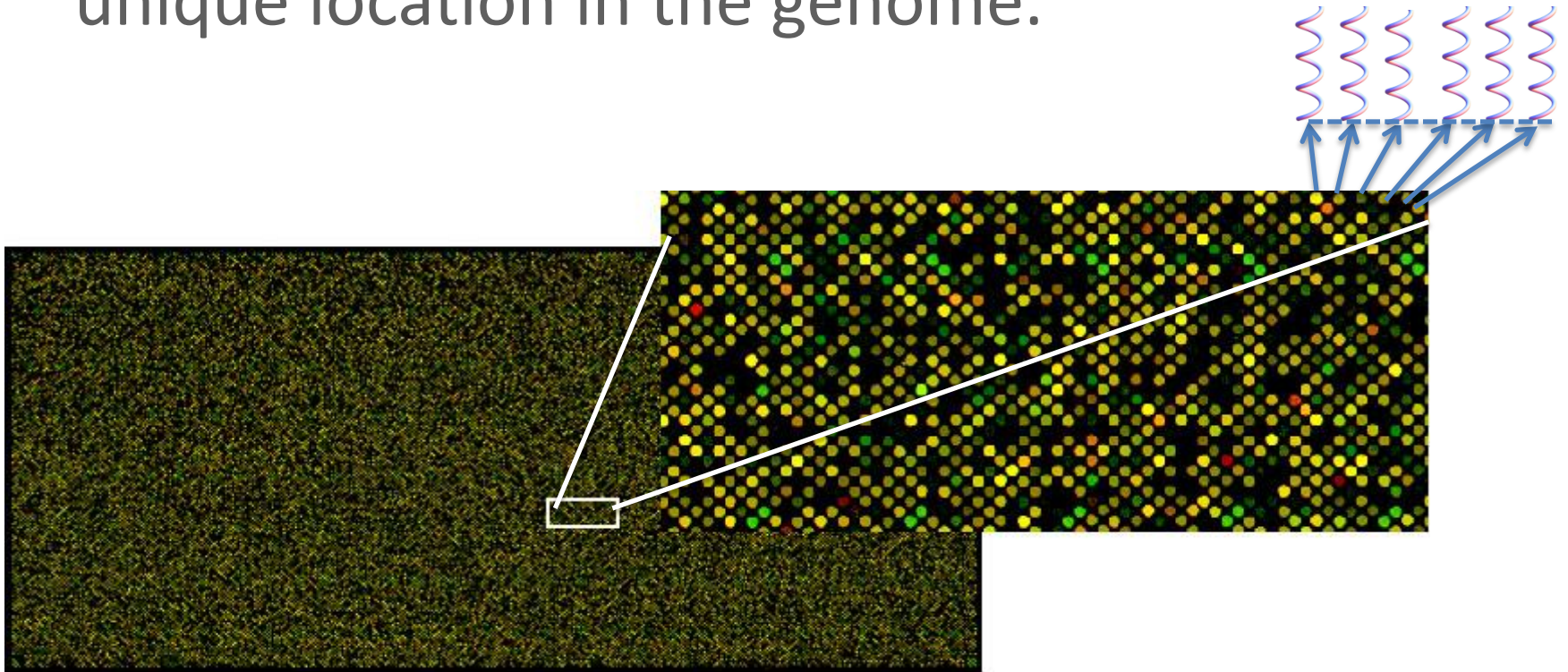


Traditional Sequencing Can Miss a Deletion/Duplication



Cytogenomic Array

- Each spot contains copies of a short strand of single-stranded DNA that is specific to a unique location in the genome.

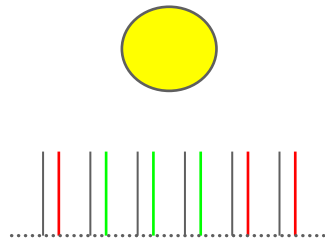
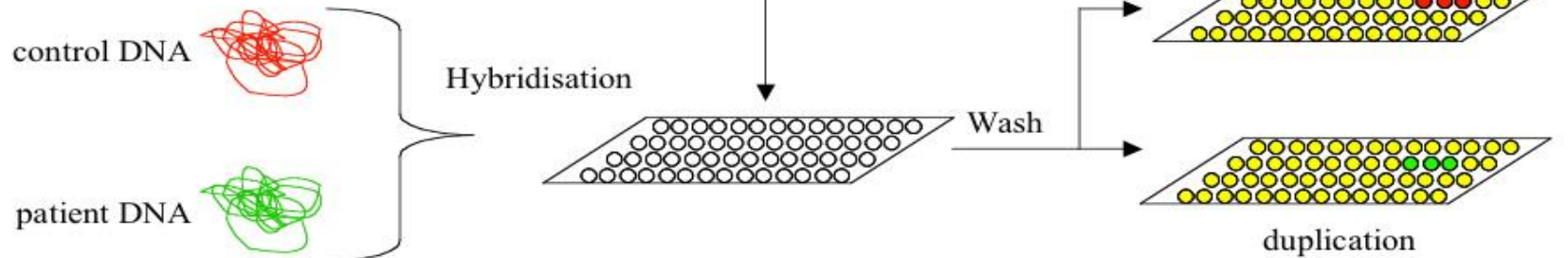


TYPES OF MICROARRAYS

BAC Array

An array of thousands of BAC clones representing regions of interest in the genome

array

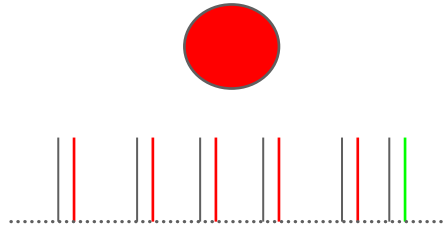


NORMAL

Control = Patient

No imbalance

$\text{Log}_2 \text{ Ratio} = 0$

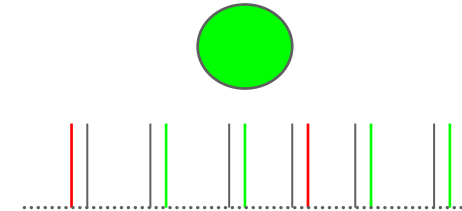


LOSS OR DELETION

Control Patient

Imbalance detected

$\text{Log}_2 \text{ Ratio} = \sim -1.0$



GAIN OR DUPLICATION

Patient Control

Imbalance detected

$\text{Log}_2 \text{ Ratio} = \sim +0.5$

AMA Ethical Guidelines for Genetic Testing in Children

- For childhood onset condition that IS preventable or treatable, testing should be offered or, in some cases, be required.
- For childhood onset condition that is NOT preventable or treatable, parents generally should have choice whether to have their children tested.
- For adult onset condition that is NOT preventable or treatable, genetic testing of children should not be undertaken.
- Genetic testing for carrier status should be deferred.
- Testing of children for the benefit of a family member should not be performed unless the testing is necessary to prevent substantial harm to the family member.

Next Generation Sequencing Changes the Testing Paradigm

STAY TUNED to Future Sessions

Finding Laboratories that Perform Genetic Testing

In the United States, Canada, and Europe (partial):

GeneTests <http://www.genetests.org/tests/>

Genetic Test Registry: <https://www.ncbi.nlm.nih.gov/gtr/>

Eurogentests: <http://eurogentest.org>

These registries list >2800 different sequencing and deletion/duplication tests ranging from a targeted single gene test to gene panels that examine many genes simultaneously.

Quiz: Question

TRUE or FALSE:

Targeted gene sequencing will detect all the alterations responsible for Mendelian disease

Quiz: Answer

FALSE

Targeted sequencing may miss deletions or duplications or inversions, depending on where the amplification primers are positioned with respect to the location of the disease-causing alteration.