

All in the Family

How Genetic Counselors Facilitate Familial Genetic Testing

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Objectives

- Recognize different methodologies for performing family specific genetic testing
- Explain why positive control samples and a proband's original test report are important for accurate testing
- Identify how genetic counselors can serve as a resource during the familial testing process

Why This Topic is Important

- Potential for false reassurance of a normal result
 - If we didn't know what we were looking for or how to look for it, the family member may still be at risk.
- Original proband's report, or providing a positive control is important but can take effort
 - Best to be prepared prior to testing family members

Why do Familial Testing?

- Medical management and recurrence risks
- Some OHPs opt for the SAME test as the proband
 - Targeted, site-specific testing is often cheaper and faster than the more comprehensive version that the proband had
 - Especially when dealing with NGS panels, or genomic microarray, it's a better use of healthcare dollars to go searching only in the region with a genetic change
- Assumes you know how the proband was tested...
- Assumes you know exactly where to look...

Types of Proband Test Results

- Single gene testing
 - Gene(s) sequencing (Sanger or NGS panel)
 - Single gene del/dup testing
- Genomic testing
 - FISH
 - Microarray
 - Chromosome analysis
 - (Exome sequencing)

Familial Genetic Tests

- Recommended test to order on family members depends on several factors
 - How the proband was tested and what the results were
 - Clinical question for the family member – carrier status? Affected status? Recurrence risk?
- Methodology used for proband's testing may not be appropriate for a family member
- There may be more than one option for familial testing each with pros and cons

Test Selection (sometimes)

PROBAND

Sequencing

del/dup (MLPA)

FISH

Array

Chromosomes

FAMILY MEMBER

Sequencing

del/dup (MLPA)

FISH

Array

Chromosomes



Testing Selection (more common)

PROBAND

Sequencing

del/dup (MLPA)

FISH

Array

Chromosomes

FAMILY MEMBER

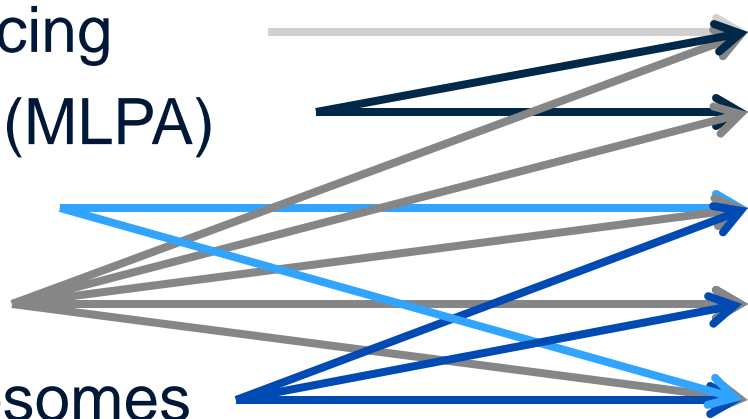
Sequencing

del/dup (MLPA)

FISH

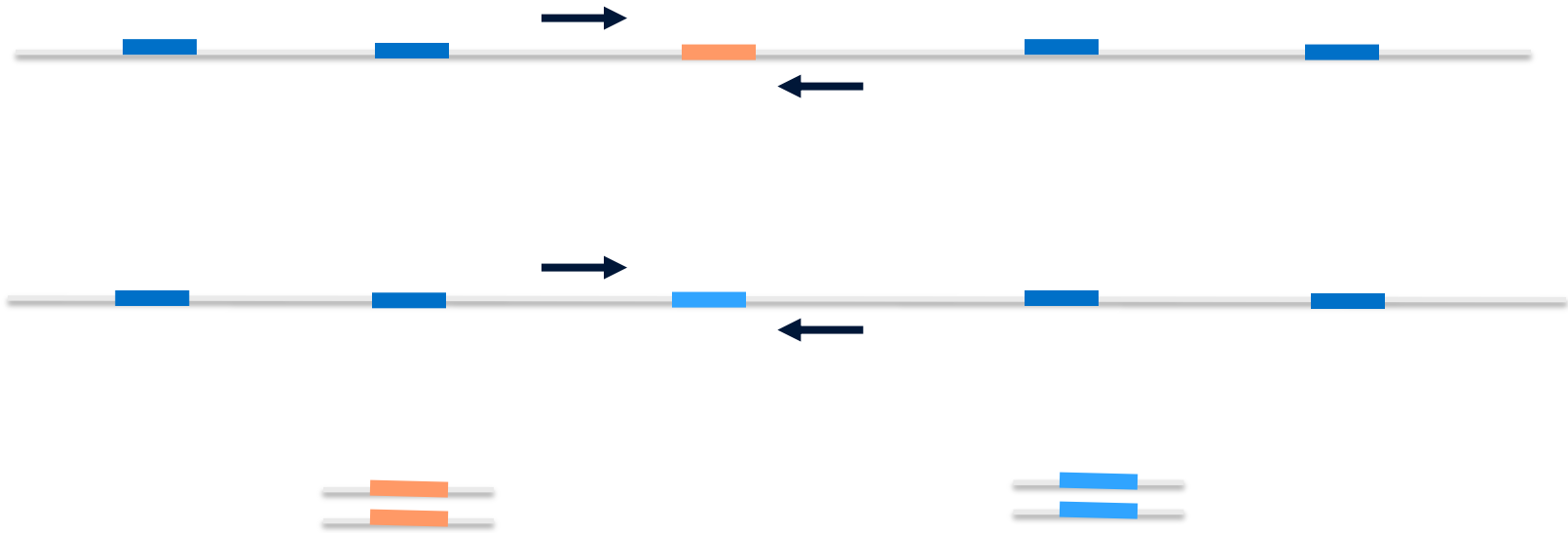
Array

Chromosomes



Brief Overview of Test Methods – Sequencing

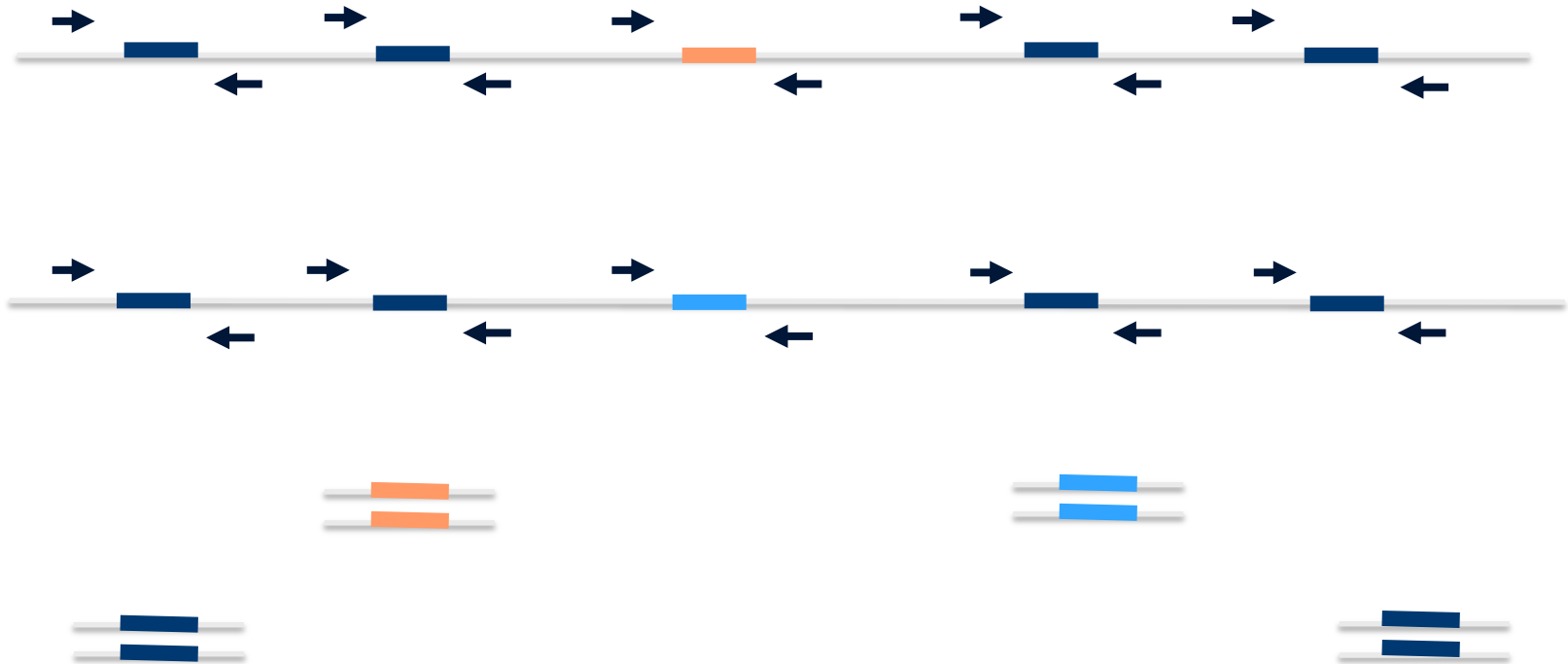
Targeted mutation/exon



Modified from slide by Yuan Ji, PhD

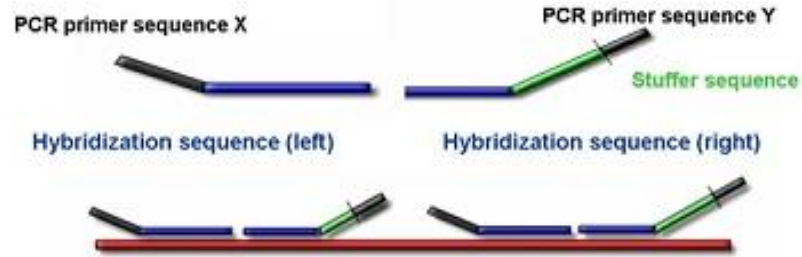
Sequencing

Full-gene



MLPA

1. Denaturation and Hybridization



2. Ligation

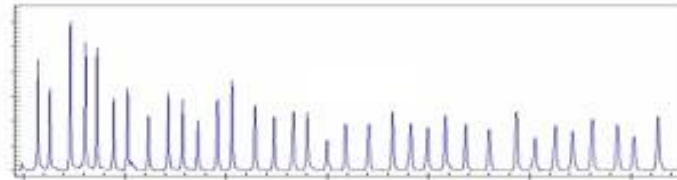


3. PCR with universal primers X and Y

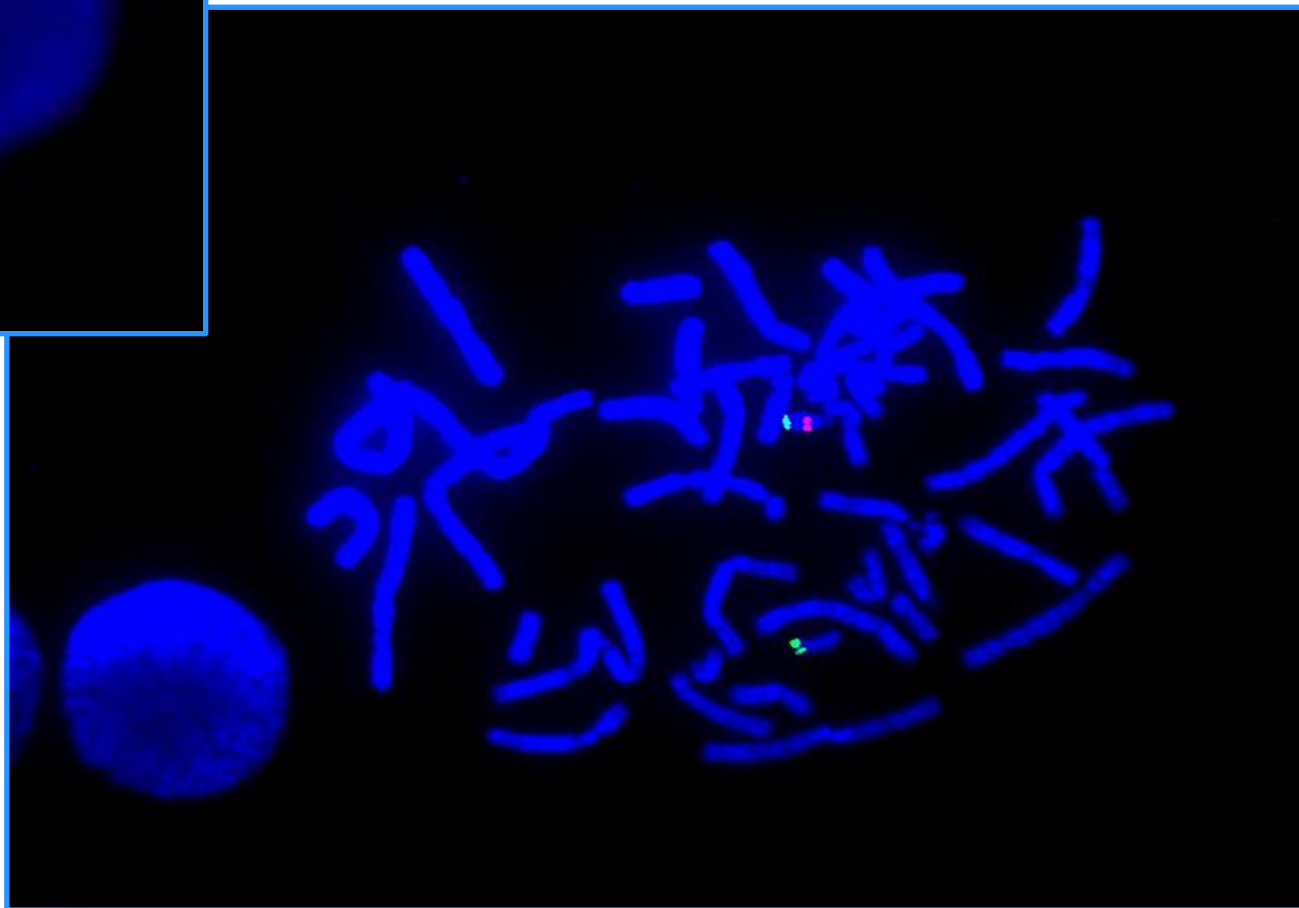
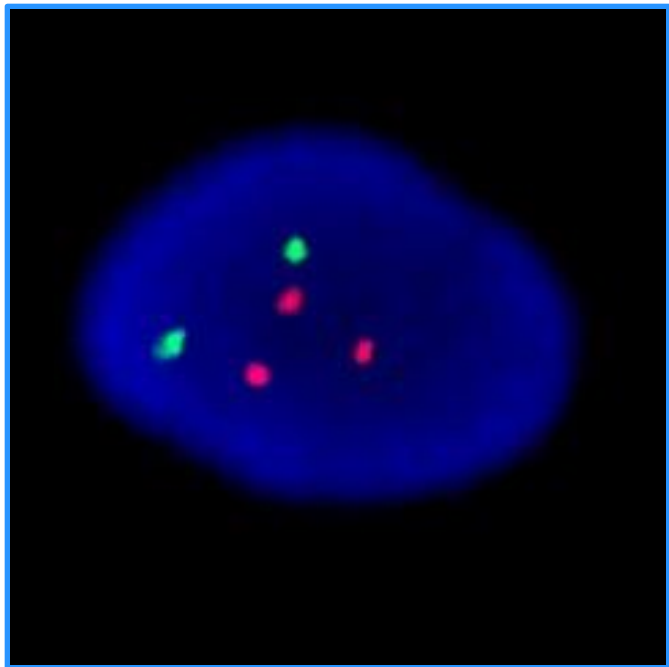
exponential amplification of ligated probes only



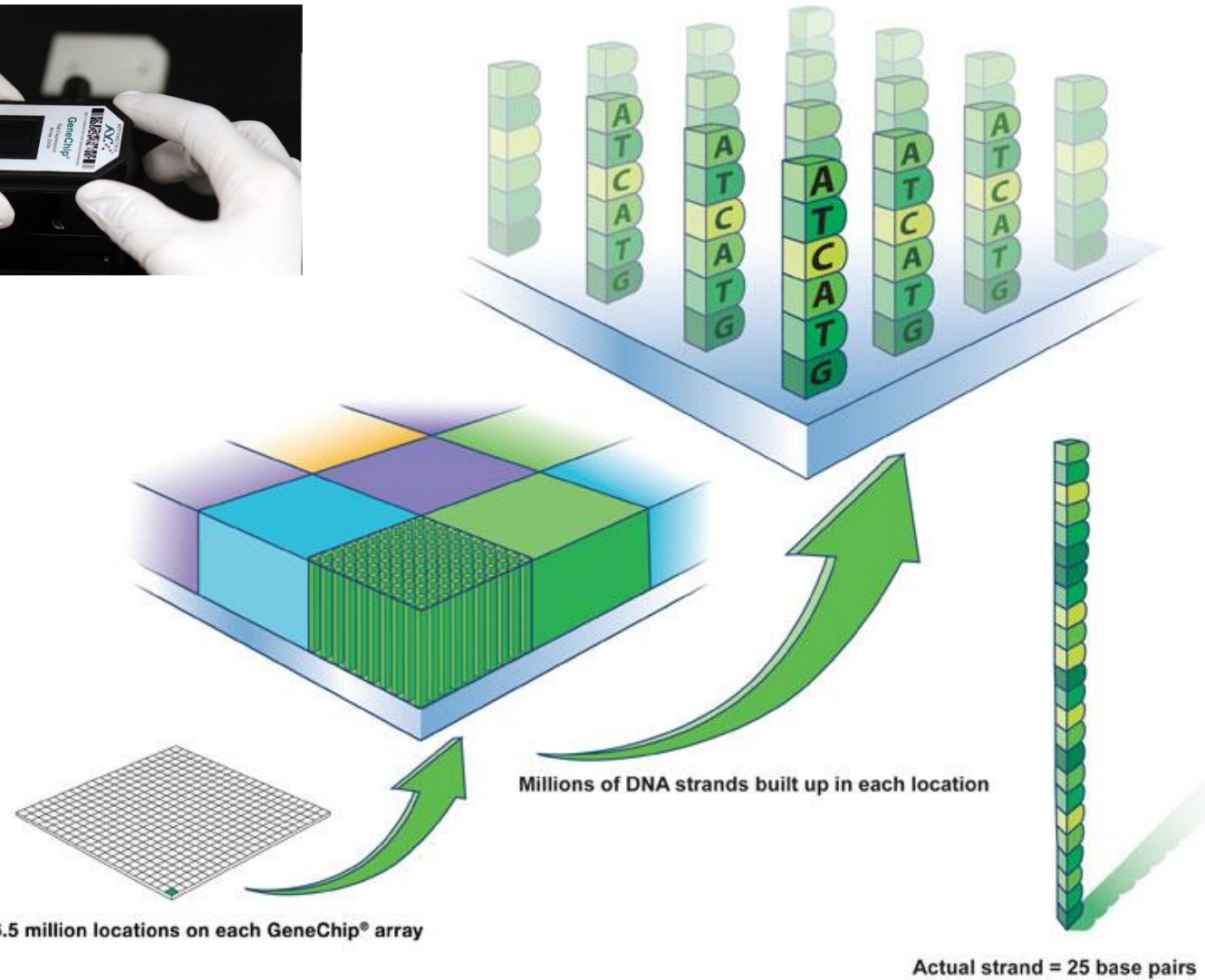
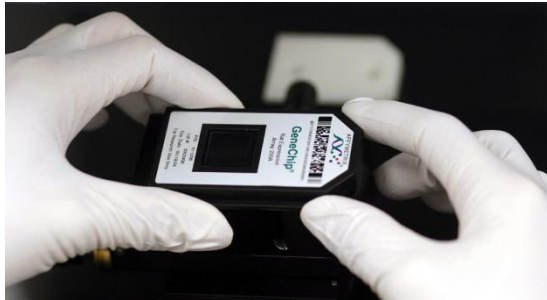
4. Fragment analysis



FISH

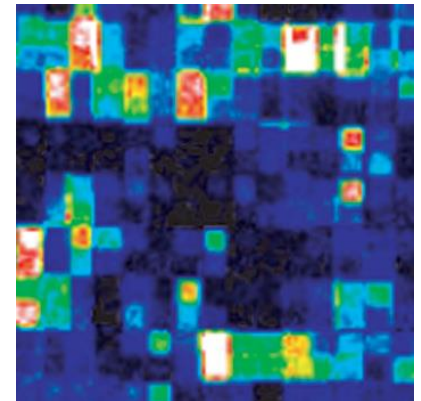
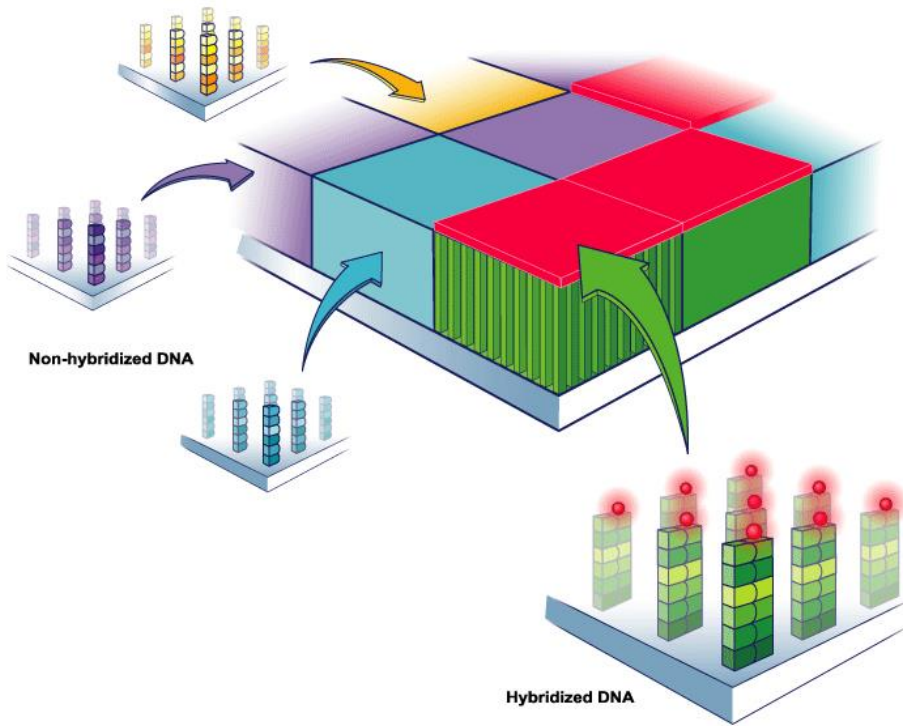


Genomic Microarray



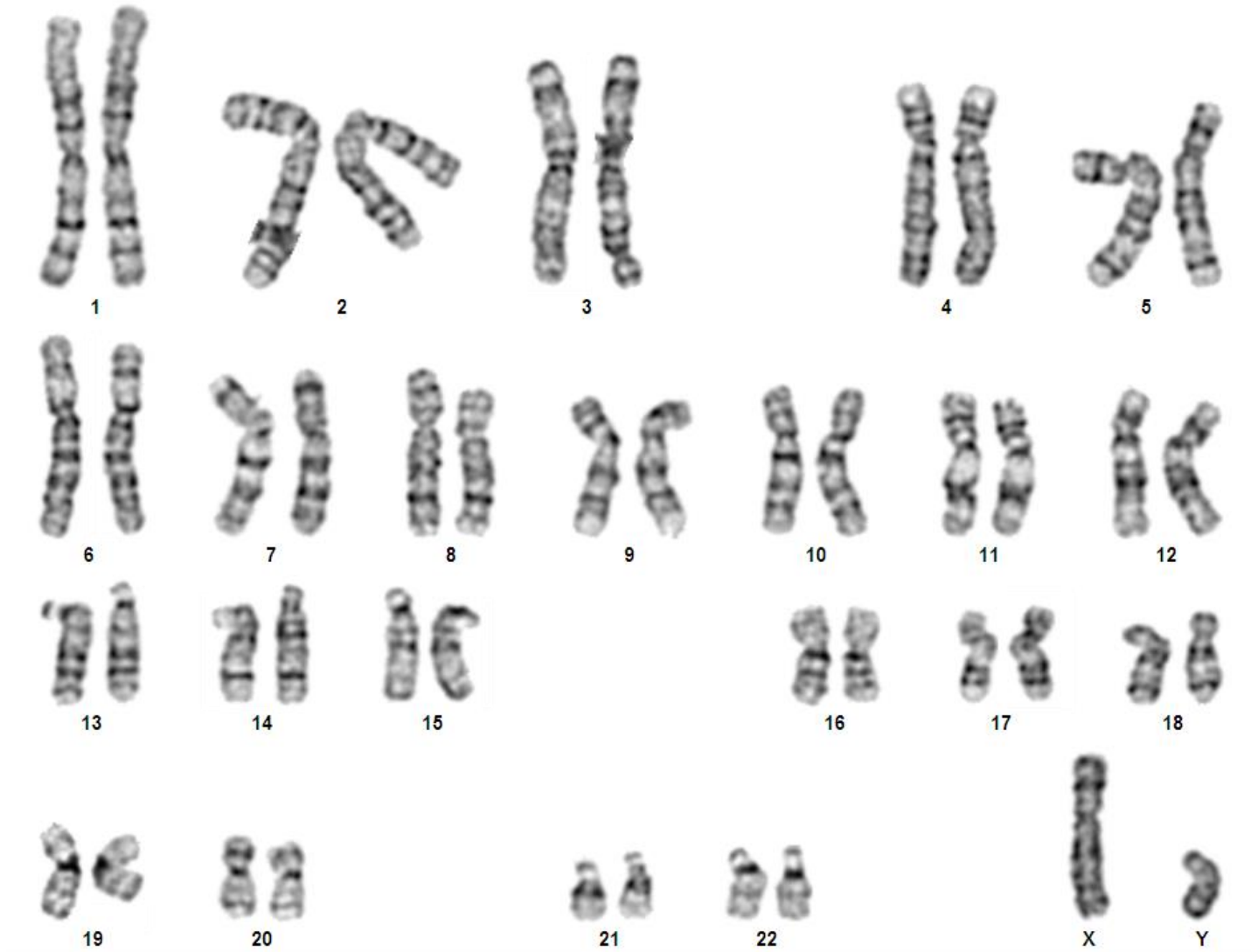
www.affymetrix.com

Genomic Microarray

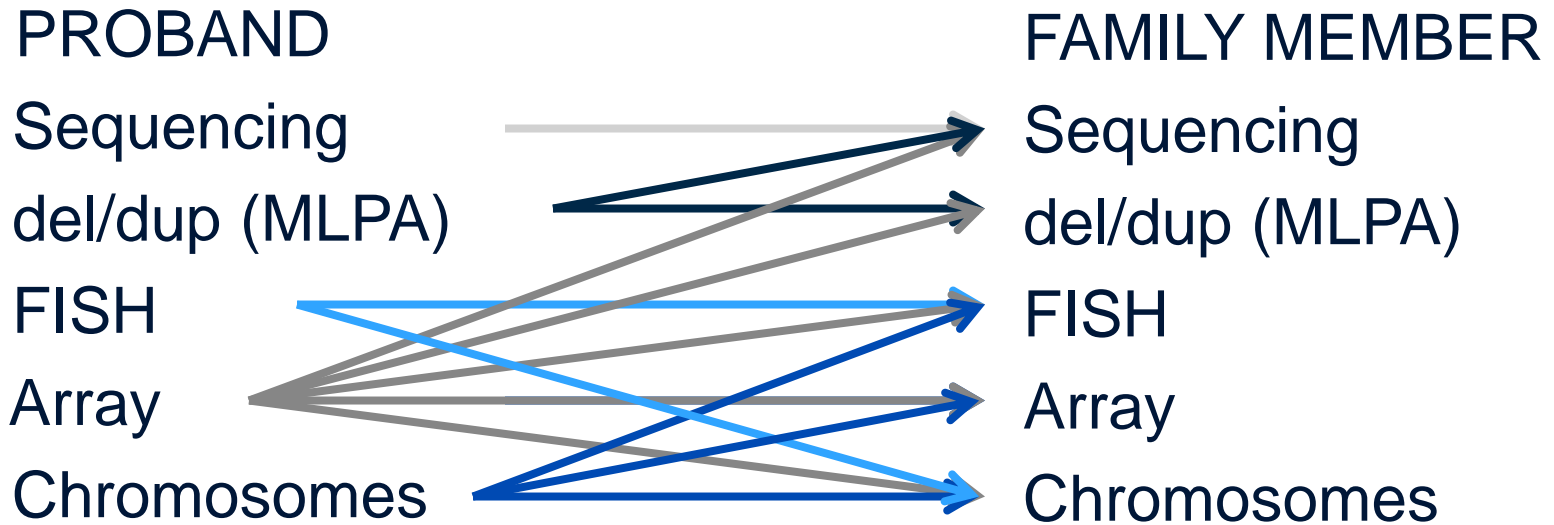


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Chromosome Analysis



So many options – now what?



- **Ask a genetic counselor to help select and coordinate testing!**

Genetic Counselor's Role

- Test selection
 - Implication of results
- Test coordination
 - Obtaining reports, paperwork, and making sure lab is informed
 - Checking that family member and control samples are ordered correctly
- Interpretive comments
- Informing OHP about results

Proband Reports / Positive Controls

- Proband report and positive control are both important
- Controls ensure the test ordered would have identified the familial variant if present
 - Lab methodologies can be slightly different
 - Nomenclature for mutations can be different
 - Some familial testing might be possible without a control
- Control options:
 - Proband's previous sample
 - New blood or buccal sample from proband
 - Maternal blood for fetal tests

Summary - Suggestions

- Involve genetics / genetic counselors
- Be prepared to obtain a report
- Investigate sooner rather than later
 - May avoid a proband redraw

Objectives

- Distinguish different methodologies for performing family specific genetic testing
- Explain why positive control samples and a proband's original test report are important for accurate testing
- Understand how genetic counselors can serve as a resource during the familial testing process

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