

THE JACKSON LABORATORY

# Genetic Testing Methods



CLINICAL AND CONTINUING EDUCATION

# About this resource

## THE GOAL

The goal of this resource is to improve the primary care provider's knowledge about commonly used genetic tests and testing technologies. This program was developed for primary care providers including physicians, physician assistants, and nurse practitioners. The content is likely to be appropriate for other health professionals as well.

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*This resource was developed by the Jackson Laboratory Clinical and Continuing Education Program. The following writers and reviewers participated in the development of this work.*

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# Testing Landscape and Strategies



# Testing Landscape

## VARIANTS

Many types of genetic **variants** have been described, which require different testing technology for detection. In general, genetic variants can be described as

**Chromosome abnormality** – A missing or extra chromosome (containing many **genes**), or a **structural rearrangement** of a chromosome

**Chromosomal microdeletion/microduplication** – A missing or extra segment of a chromosome, smaller than can be seen with a microscope (containing many genes)

**Gene deletion or duplication** - A missing or extra copy of an entire gene or a segment of a gene (containing many **bases**)

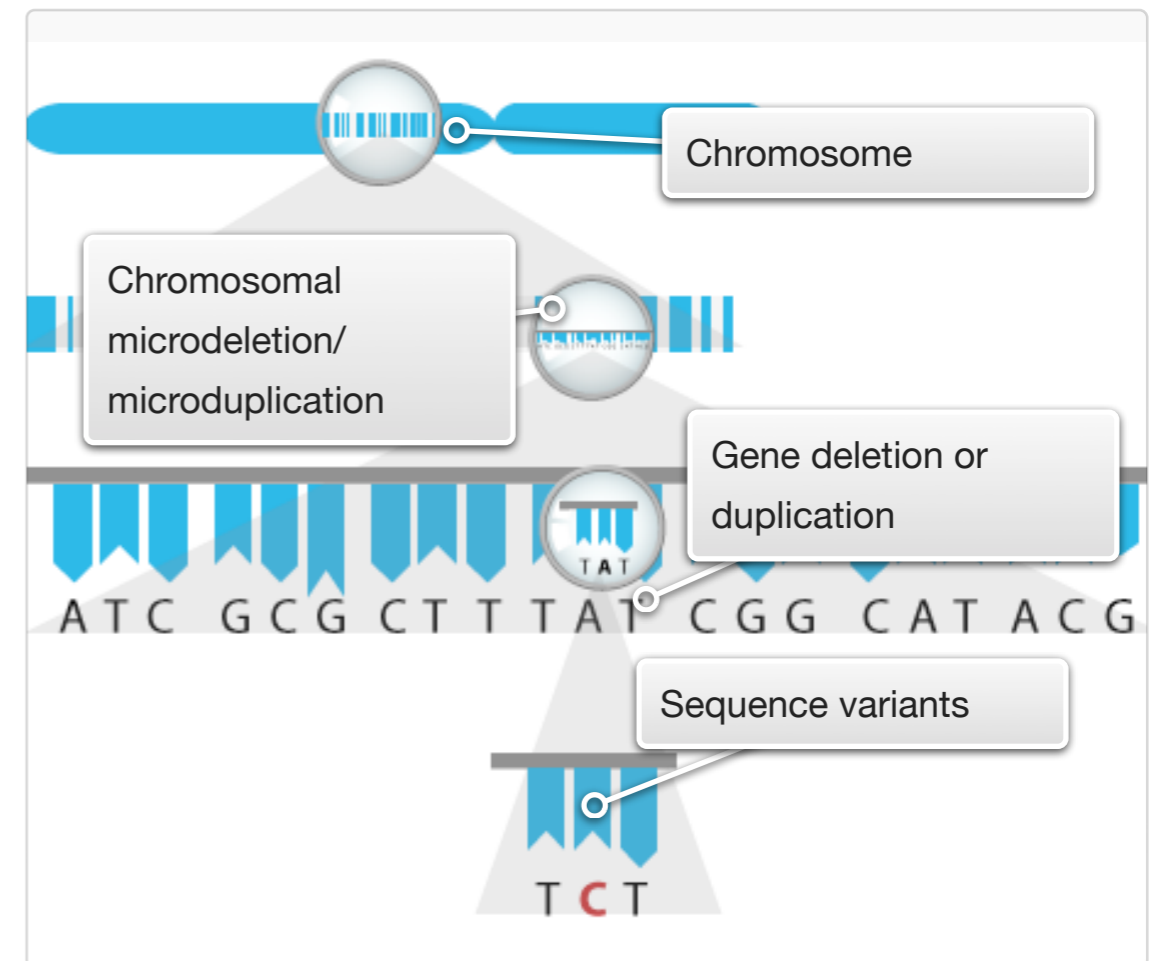
**Sequence variants** – An alteration in the “spelling” of the gene, due to a substitution, insertion or deletion of one or a few bases (**nucleotides**) in the DNA molecule

## SCOPE OF ANALYSIS

In addition to detecting different types of variation, genetic tests are designed differently with regard to their scope of analysis. A test may analyze

- A specific location in one gene (one or a few bases at a single site)

### Interactive 1.1 Scope of analysis



- Several different locations within one gene
- The entire sequence of one gene
- Multiple specific locations within multiple genes
- The entire sequence of multiple genes
- Most of the sequence of the protein-coding portion of the **genome** (called the exome)
- Most of the sequence of the whole genome

# Testing Strategies

## INHERITED DISEASE

For assessment of inherited disease (versus tumor testing for cancer treatment), the ordering provider should select the test that can detect the suspected type of variation. This requires that the ordering provider know something about the most likely genetic causes of a given clinical presentation. In addition, the ordering provider should select the test with a wide enough scope to answer the clinical question, while limiting incidental findings, uncertain findings, and unnecessary cost. When developing a testing strategy risk assessment for a hereditary (or **germline**) condition, keep the following points in mind


- Testing can often be targeted when a familial **variant** is known
- Testing can be targeted to one or a few variants when they are more common in a specific population
- More than one testing method may be required
- Multiple tests may be bundled together by a laboratory for certain indications
- The wider the scope of testing, the greater the sensitivity
- The wider the scope of testing, the greater the risk for uncertain/uninformative and incidental findings

- Insurance billing and reimbursement practices may complicate strategy
- Guidelines and testing criteria may or may not be available
- As analytic performance and testing guidelines change over time, patients who have had negative results in the past may be candidates for newer tests

## TUMOR TESTING

For tumor testing, testing strategy depends on the goal, which can be diagnosis, prognosis, or treatment-oriented.

# Single Gene Sequencing



# Single Gene Sequencing

## HOW IT WORKS

- Various methodologies used, including **Sanger sequencing** (the “traditional” sequencing method), and multiple “next-generation” sequencing methods
- Determines the unique and specific order of DNA **bases** (**nucleotides**)
- Compares patient sequence to a **reference sequence**

## WHAT IT DETECTS

- Single nucleotide changes, such as single base substitutions or small insertions or deletions
- Can be performed in a targeted region or across the entire gene

## WHEN TO USE IT

- When the family mutation is unknown
- **AND**, one **gene** is significantly more likely than other genes that have been associated with the same condition. This may be based on population prevalence (e.g., *BRCA1* and *BRCA2* account for 85% of **hereditary breast and ovarian cancer**) or the personal and family history (e.g., colorectal tumor analysis may suggest a specific gene among the five associated with **Lynch syndrome**)

Figure 2.1 Detects single nucleotide changes



- **AND**, many different **variants** within the gene have been previously associated with disease. This is true of most hereditary cancer **syndromes**, unlike some other genetic conditions, like **sickle cell disease**, which is associated with a few common mutations within the gene.

## WHEN **NOT** TO USE IT

- When the family mutation is known (use targeted mutation analysis)
- When the personal and family history are suggestive of more than one hereditary syndrome (consider a panel)
- When there are multiple candidate genes and no single gene is significantly more likely than the others (i.e., Lynch syndrome when tumor analysis is lacking) (Use a panel)

## BENEFITS

- Comprehensive coverage within a single gene
- May be faster and less expensive than multi-gene panels
- Less likelihood for results of uncertain significance than multi-gene panels

## LIMITATIONS

- Does not rule out a hereditary condition when other genes have been associated with the same findings
- Risk for identifying **variants of uncertain significance**
- Does not detect large deletions/duplications



# Deletion/ Duplication Analysis



## ALSO KNOWN AS

Multiplex ligation-dependent probe amplification (MLPA), gene rearrangement analysis, copy number variant (CNV) analysis

# Deletion/Duplication Analysis

## HOW IT WORKS

- Molecular **probes** with florescent tags are designed to attach to specific sequences of DNA
- The patient's DNA is compared to a **reference sequence**
- The presence of extra probes indicates a duplication or gain of **copy number**
- The absence of probe detection indicates a deletion or loss of copy number

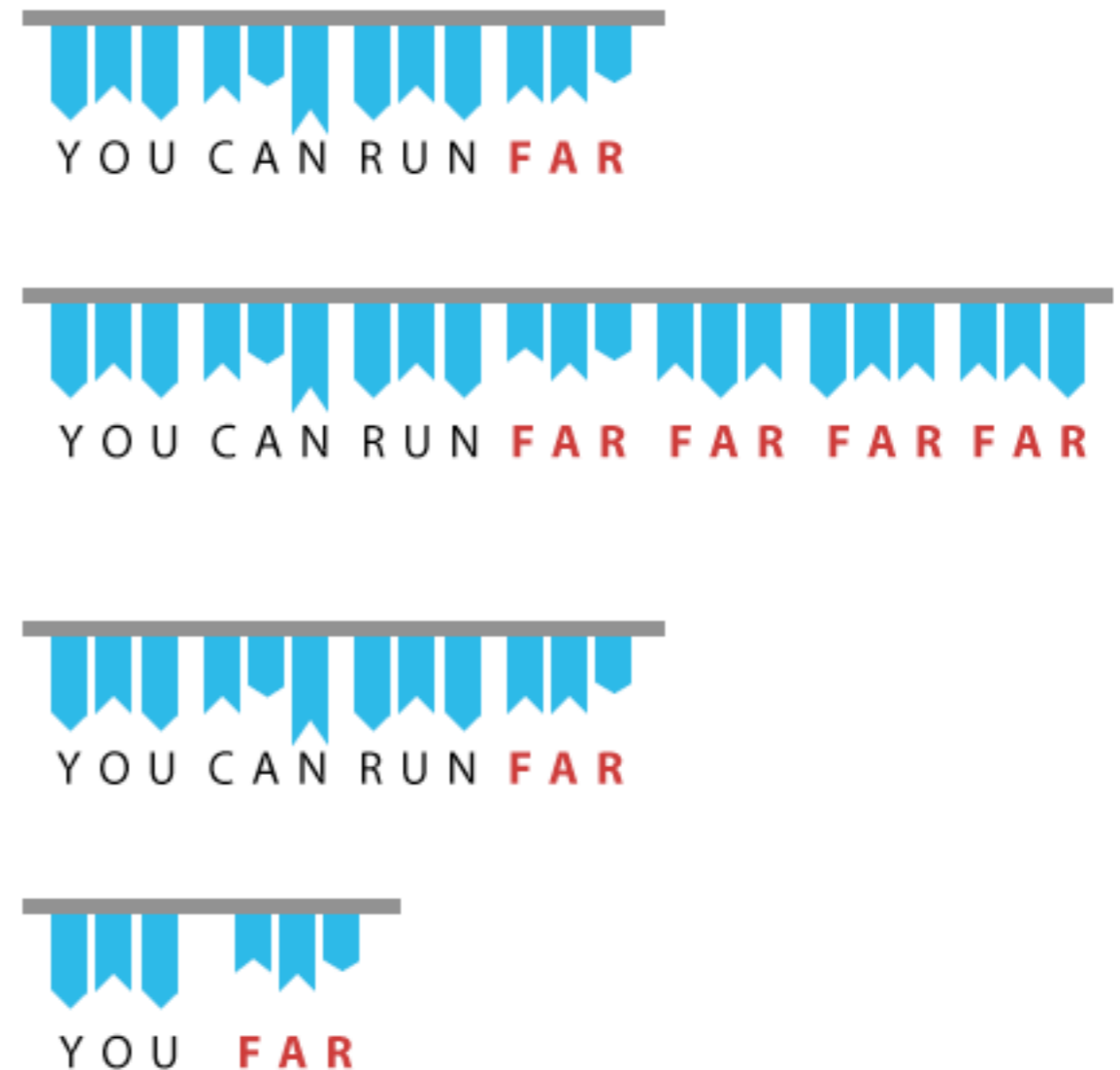
## WHAT IT DETECTS

- Small deletions or duplications in or near a specific **gene** or critical region
- Whole gene deletion or duplication (a type of **copy number variant**)

## WHEN TO USE IT

- When gene sequencing is negative but the suspicion for disease remains high
- **AND**, when deletions or duplications have been previously described as causative **variants** for the condition of interest

Figure 3.1 Detects small deletions or duplications



- Deletion and duplication analysis may also be done simultaneously with sequencing or in rapid reflex
- Rarely, deletion and duplication analysis is a first tier test when a copy number variant is the primary cause of disease (**Spinal Muscular Atrophy**, for example) or the known cause of a disease in the family.

## WHEN **NOT** TO USE IT

- When the family mutation is known and is not a deletion/duplication (use targeted mutation analysis)
- When the personal and family history are suggestive of more than one hereditary syndrome (consider a panel, which may include deletion/duplication analysis of one or more genes)
- When there are multiple candidate genes and no single gene is significantly more likely than the others (i.e., **Lynch syndrome** when tumor analysis is not available or uninformative) (Use a panel)
- When deletions and duplications have never been described as causative for the condition of interest

## BENEFITS

Detects **variants** not identified by gene sequencing

## LIMITATIONS

- Does not detect single **nucleotide** substitutions, insertions, or deletions
- May add to cost and processing time

# Targeted Mutation Analysis

A hand holding a DNA double helix structure, symbolizing genetic analysis. The background is a gradient of blue and white, with a dark blue diagonal band.

## ALSO KNOWN AS

Single site testing, mutation probe, mutation panels or multi-site analysis

# Targeted Mutation Analysis

## HOW IT WORKS

Molecular **probes** attach to a specific string of **nucleotides** known to be associated with a disease

## WHAT IT DETECTS

- Single nucleotide changes, such as single base substitutions and small deletions or insertions
- Can be performed at a single site or several sites within a **gene**

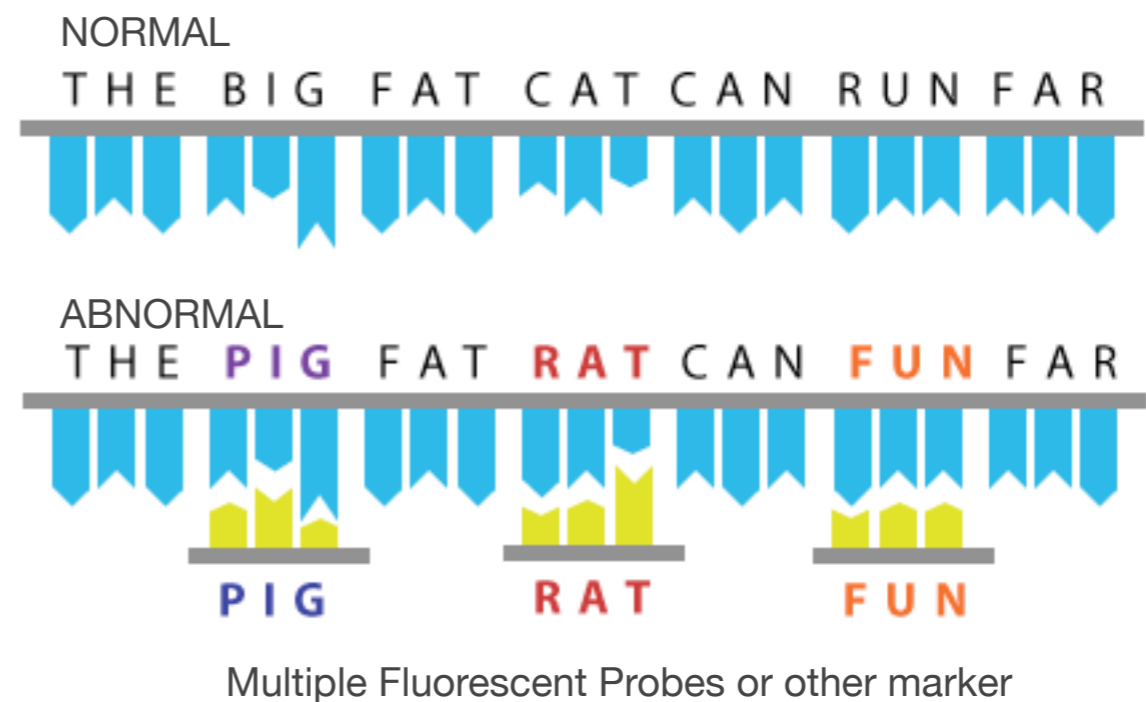
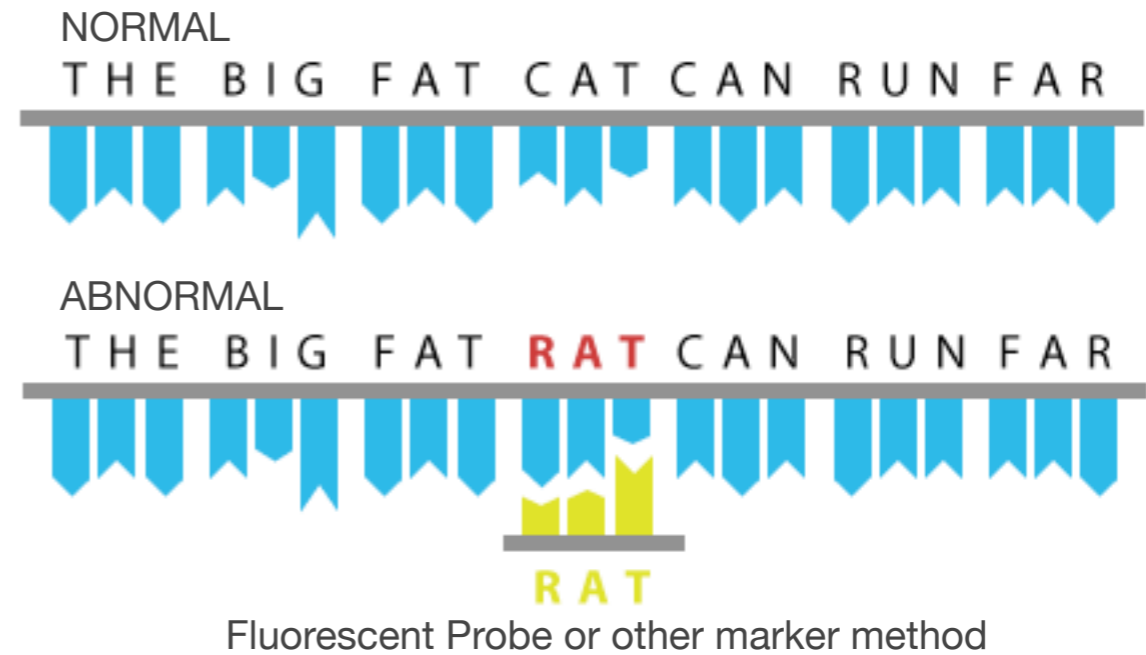
## WHEN TO USE IT

- When the family mutation is known
- When one or a few specific **variants** are more common in a specific population (ie. 3-site testing for **hereditary breast and ovarian cancer** in individuals with Ashkenazi Jewish heritage)

## WHEN **NOT** TO USE IT

- When the family mutation is unknown (use full gene sequencing or a multi-gene panel)
- When the personal and family history are suggestive of more than one hereditary **syndrome** (consider a panel)
- When there are multiple candidate genes and no single gene is significantly more likely than the others (Use a panel)

Figure 4.1 Detects small deletions or insertions



## BENEFITS

- May be faster and less expensive than full gene sequencing
- Reduces the risk of uncertain and incidental findings

## LIMITATIONS

- Only provides information about the specific site, may miss rare variants
- Does not rule out a hereditary condition unless the specific site tested is the only candidate

# Multi-Gene Panels



## ALSO KNOWN AS

**Next generation sequencing** (NGS) panels,  
expanded panel testing, massively parallel  
sequencing, high throughput sequencing

# Multi-Gene Panels

## HOW IT WORKS

Combination of **NGS** methods and/or **array** platforms (or other DNA capture methods) to allow many **genes** to be sequenced simultaneously

Determines the unique and specific order of DNA bases

Compares patient sequence to a reference sequence

## WHAT IT DETECTS

Single **nucleotide** changes, such as single base substitutions and small deletions or insertions

Some methodologies can detect deletions and duplications (**copy number variants**) and/or chromosomal rearrangements

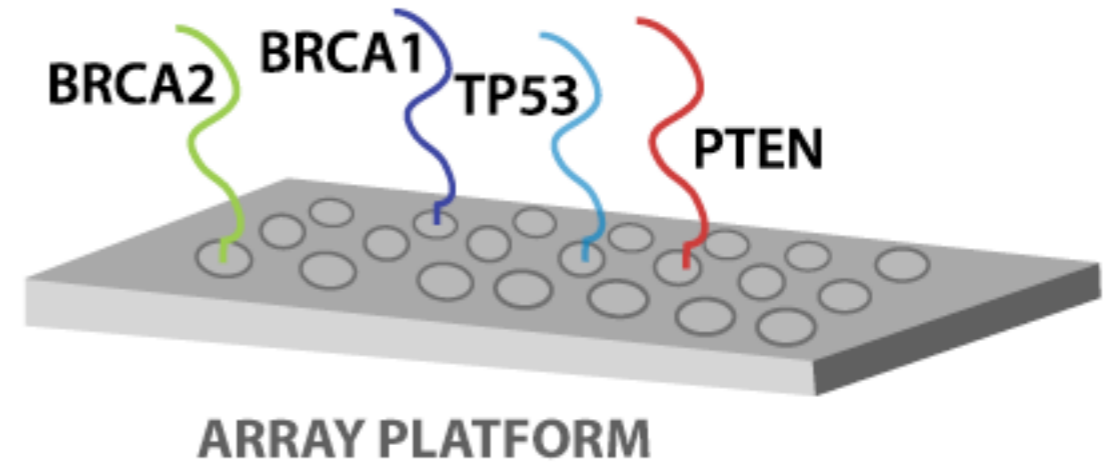
## WHEN TO USE IT

When the family mutation is unknown

When there are multiple candidate genes and no single gene is significantly more likely than the others

When the personal and family history are suggestive of more than one hereditary **syndrome**

**Figure 5.1** Allows many genes to be sequenced simultaneously



## WHEN **NOT** TO USE IT

When the family mutation is known (use targeted mutation analysis)

When one gene is more likely than other genes to be associated with the clinical presentation. This may be based on population prevalence (e.g., *BRCA1* and *BRCA2* account for 85% of **hereditary breast and ovarian cancer**), the personal and family history, or other tests (e.g., colorectal tumor analysis may suggest a specific gene among the five associated with **Lynch syndrome**)

## BENEFITS

Potential for overall greater sensitivity provides comprehensive analysis for multiple diagnoses



May be faster than step-wise or reflex testing for different single gene disorders

## LIMITATIONS

Lower overall specificity: the risk for uncertain and incidental findings increases with the number of genes on the panel

Does not detect certain types of **variants** such as large rearrangements

# Whole Exome/ Genome Sequencing

## VARIATIONS

Whole exome sequencing analyzes only the protein coding portions of the **genome**

Whole genome sequencing analyzes protein coding regions as well as **regulatory regions** and sections with unknown function

# Whole Exome/Genome Sequencing

## HOW IT WORKS

- Combination of **NGS** methods and/or **array** platforms (or other DNA capture methods) to allow all **genes** to be sequenced simultaneously
- Identifies the unique and specific order of DNA **bases**
- Compares patient sequence to a **reference sequence**, and often to the sequence of close family members

## WHAT IT DETECTS

- Single **nucleotide** changes, such as single base substitutions and small deletions or insertions
- Some methodologies can detect deletions and duplications (**copy number variants**) and/or chromosomal rearrangements

## WHEN TO USE IT

- When other genetic testing options have been exhausted and the suspicion for a hereditary condition remains high
- AND, when the results of testing could significantly alter management or family risk assessment

## Interactive 6.1 Whole Genome vs. whole exome

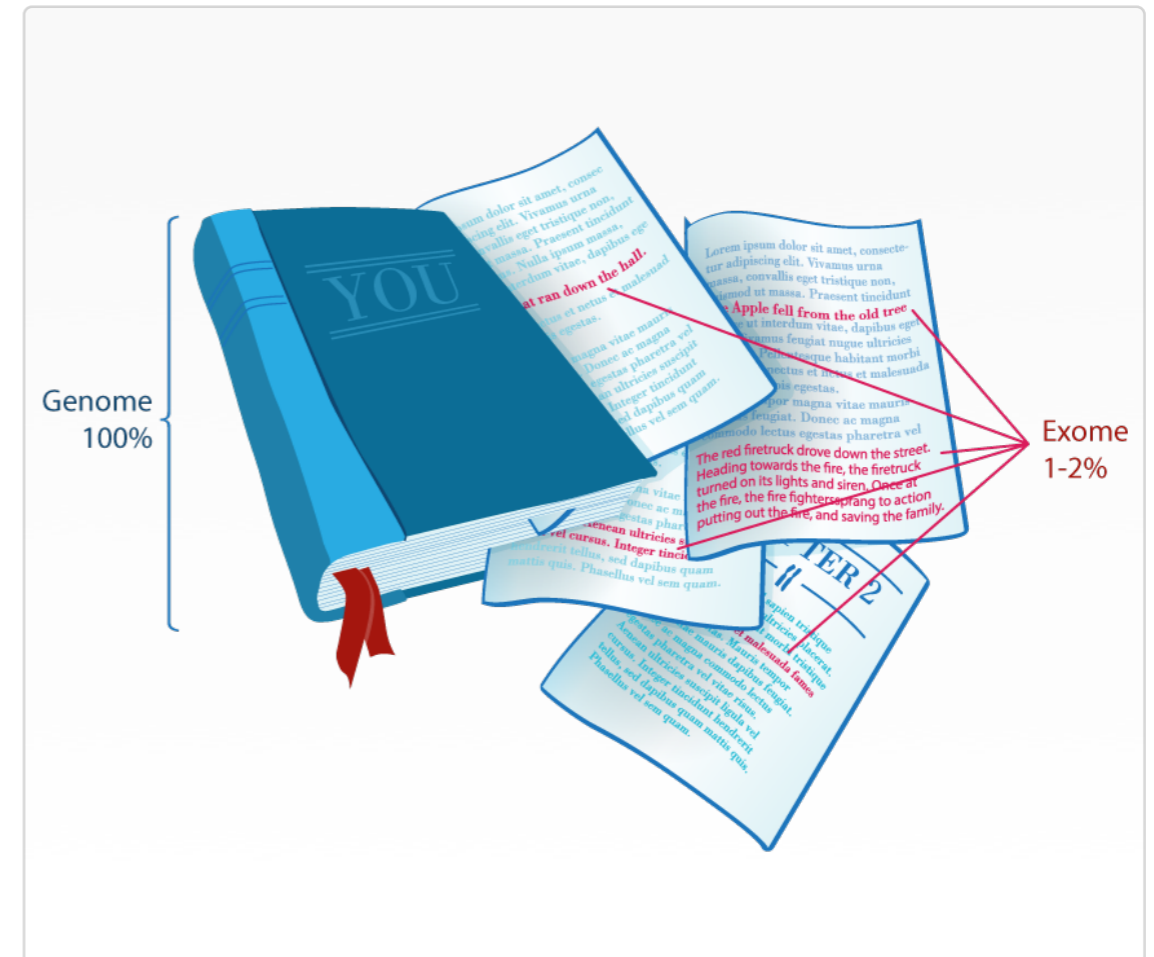


Image used with permission from the National Society of Genetic Counselors

- AND, when **family trios** are available to participate in testing (both parents and a child)
- May be available clinically or in the research testing

## WHEN **NOT** TO USE IT

- When more targeted genetic testing is available
- When relatives are not available to participate in testing

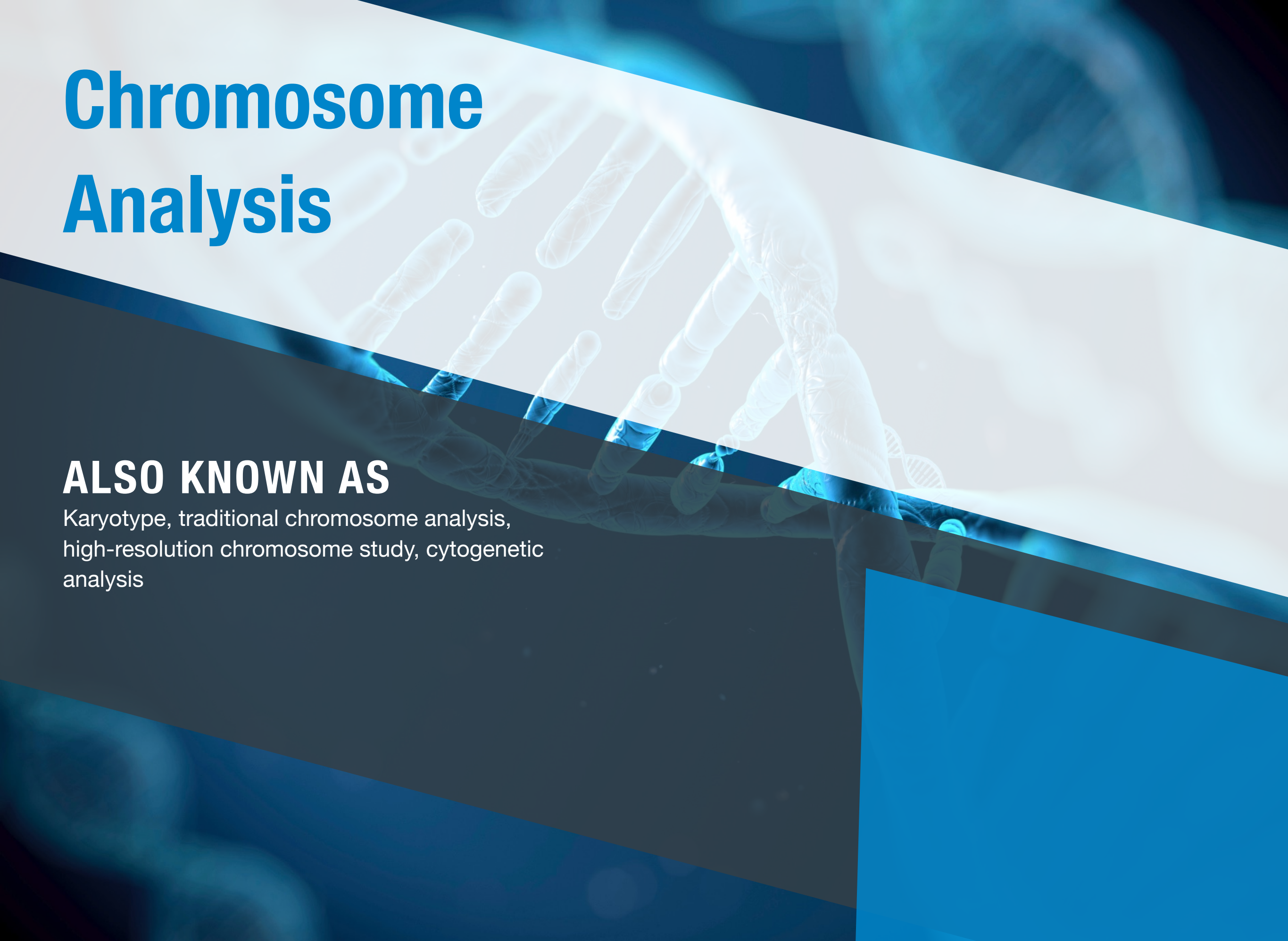
## BENEFITS

- Comprehensive coverage
- May identify rare diagnoses with atypical presentation

## LIMITATIONS

- Slow and costly
- Inevitably detects multiple **variants of uncertain significance** and incidental findings
- Requires multiple family members for best interpretation of results
- Does not capture 100% of genetic material or all types of genetic variation. Some regions are difficult to capture and analyze by current testing methods.

# Chromosome Analysis

A hand holding a glowing DNA double helix structure against a blue background. The hand is rendered in a semi-transparent, glowing blue style, with the DNA helix appearing as a bright, glowing blue structure. The background is a gradient of blue, with a dark blue area at the bottom right.

## ALSO KNOWN AS

Karyotype, traditional chromosome analysis,  
high-resolution chromosome study, cytogenetic  
analysis

# Chromosome Analysis

## HOW IT WORKS

- Captures **metaphase chromosomes**
- Stains specific chromosome regions (called “bands”)

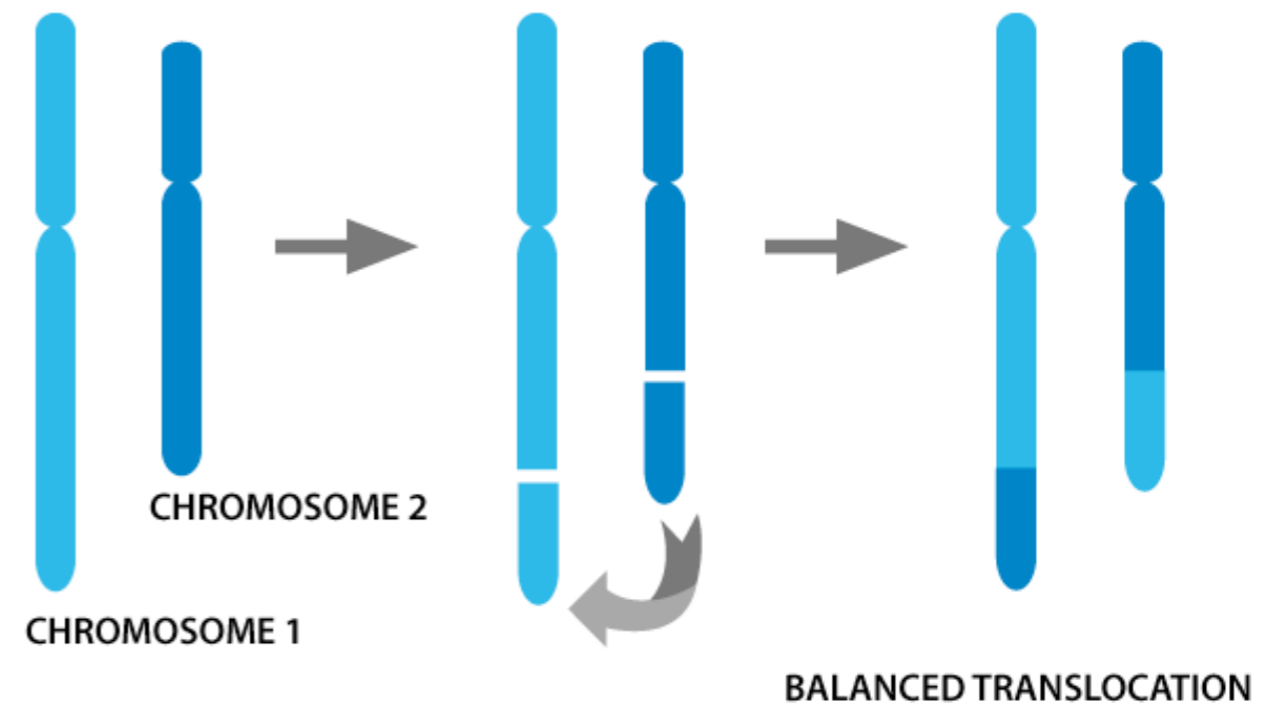
## WHAT IT DETECTS

- Whole extra or missing chromosomes (aneuploidy)
- Large **structural rearrangements**
- **Marker chromosomes**

## WHEN TO USE IT

- Clinical findings are strongly suggestive of a well-described chromosome abnormality, such as **Trisomy 21** (Down syndrome), **Trisomy 18** (Edward syndrome), or **Monosomy X** (Turner syndrome).
- In cancer genetics, for diagnosis and treatment for hematologic cancers
- Individuals with multiple congenital anomalies
- Couples with unexplained recurrent miscarriage or infertility

Figure 7.1 Captures metaphase chromosomes



## WHEN **NOT** TO USE IT

- Individuals with developmental delay, autism, or seizure disorder (use chromosomal **microarray** as a first tier test, and/or single gene analysis)
- Personal and family history are suggestive of a microdeletion or microduplication **syndrome** (use chromosomal microarray)
- Personal and family history are suggestive of a single gene disorder, such as **cystic fibrosis** or **sickle cell disease** (use single gene analysis)

## BENEFITS

- Provides a snapshot of overall genomic integrity
- Will diagnose classic chromosome abnormalities, including structural chromosome rearrangements and translocations

## LIMITATIONS

- Cannot identify small alterations such as chromosomal microdeletions/microduplications
- Cannot identify single gene disorders
- Risk for identifying chromosome abnormalities of uncertain significance

# Chromosomal Microarray

## ALSO KNOWN AS

CMA, Array comparative genomic hybridization (aCGH), **Copy number variant** (CNV) analysis

May be referred to by the methodology used, such as **SNP array**, **oligoarray**, or **BAC array**, which have different strengths and limitations



# Chromosomal Microarray

## HOW IT WORKS

- **Array** is a platform, used to process many pieces of DNA simultaneously, allowing overlapping, high-resolution, **genome-wide** analysis
- Uses fluorescent labels and computer analysis to compare a patient's genetic material to a reference sample

## WHAT IT DETECTS

Deletions and duplications of chromosome segments (a type of **copy number variant**)

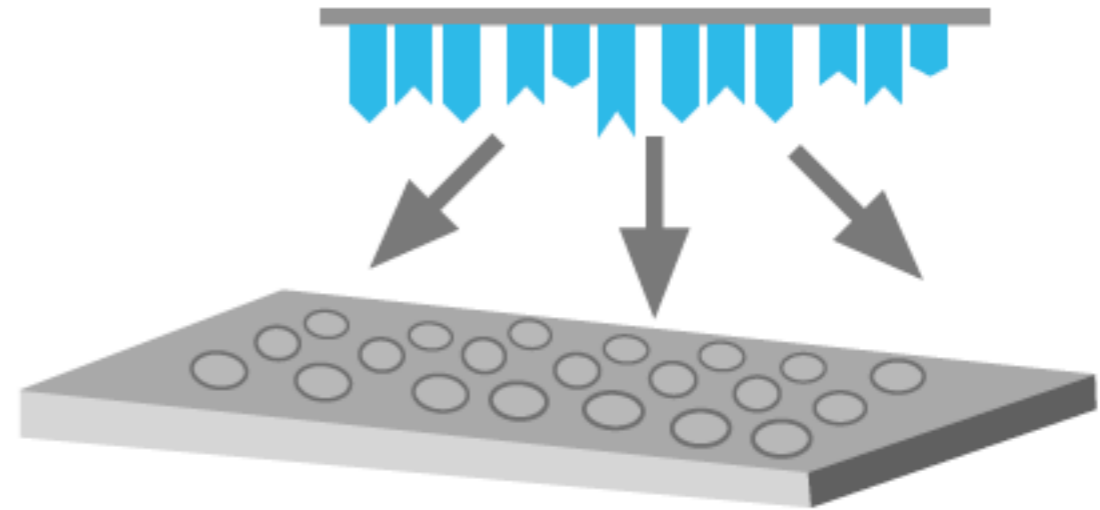
## WHEN TO USE IT

- Individuals with multiple congenital anomalies
- Individuals with developmental delay, autism, and seizure disorder

## WHEN **NOT** TO USE IT

- Clinical and family history are suggestive of a single **gene** disorder, such as **Fragile X syndrome**, **cystic fibrosis**, or **sickle cell disease** (use single gene analysis)
- Clinical findings are strongly suggestive of a well-described chromosome abnormality, such as **Trisomy 21** (Down

**Figure 8.1** Detects deletions and duplications of chromosome segments (a type of CNV)



syndrome), **Trisomy 18** (Edward syndrome), or **Monosomy X** (Turner syndrome) (use traditional chromosome analysis).

## BENEFITS

- Identifies much smaller **variants** than traditional chromosome analysis (karyotype)
- Ability to screen for many **syndromes** at once when the differential diagnosis is wide

## LIMITATIONS

- Slower and more costly than traditional chromosome analysis
- Cannot identify single gene disorders

- Cannot identify balanced chromosomal translocations or rearrangements
- Risk for identifying **variants of uncertain significance**
- Risk for identifying incidental findings associated with health risks unrelated to the clinical question

# Fluorescent In Situ Hybridization

**ALSO KNOWN AS**  
FISH

# Fluorescent In Situ Hybridization

## HOW IT WORKS

- Captures metaphase chromosomes
- Molecular **probes** with fluorescent tags attach to markers in or near known **genes** or critical regions

## WHAT IT DETECTS

- Large **structural rearrangements**
- Some large **copy number variants** (microdeletions and microduplications of the chromosome)
- Identifies chromosomal origin of **marker chromosomes**

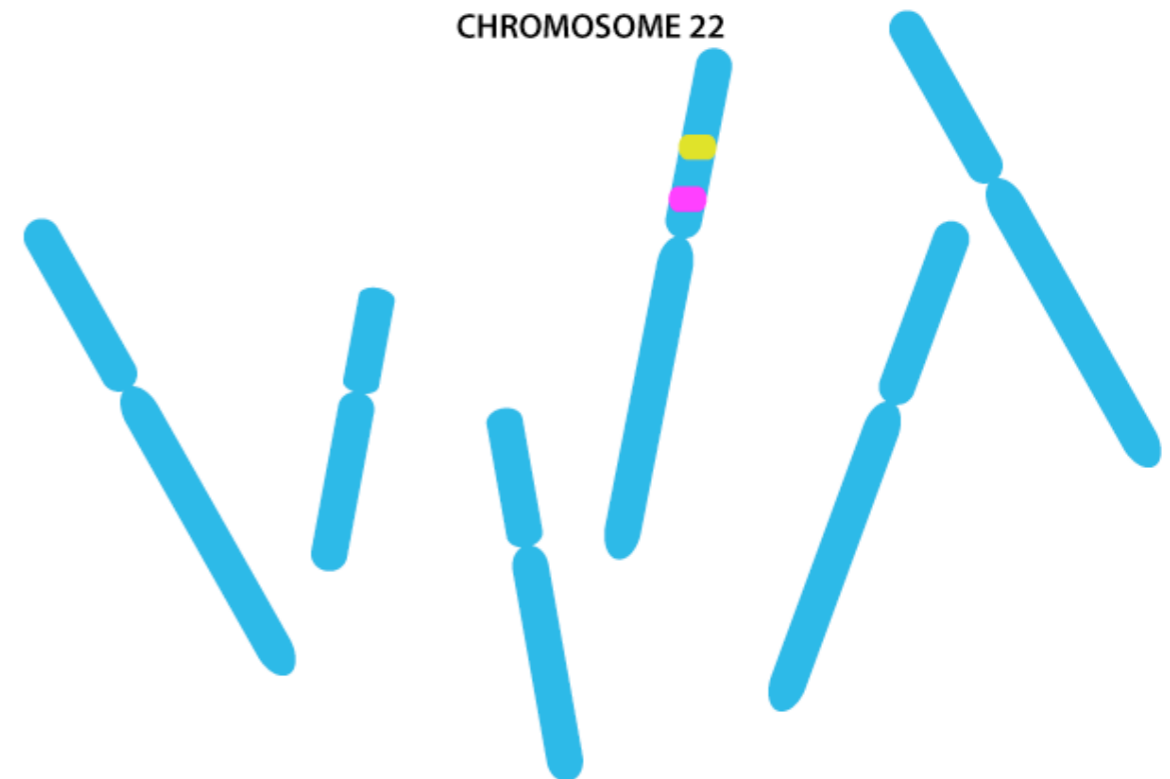
## WHEN TO USE IT

- Individuals with features consistent with a well-described microdeletion or microduplication **syndrome**
- When further characterization of a structural chromosome abnormality is needed

## WHEN **NOT** TO USE IT

- When multiple anomalies or developmental disorders are noted, but no specific syndrome is recognized (use chromosomal **microarray**)

**Figure 9.1** Molecular probes with fluorescent tags attach near known genes or critical regions



- Clinical and family history are suggestive of a single gene disorder, such as **Fragile X syndrome**, **cystic fibrosis**, or **sickle cell disease** (use single gene analysis)
- Clinical findings are strongly suggestive of a well-described chromosome abnormality, such as **Trisomy 21** (Down syndrome), **Trisomy 18** (Edward syndrome), or **Monosomy X** (Turner syndrome) (use traditional chromosome analysis)

## BENEFITS

- Identifies much smaller **variants** than traditional chromosome analysis (karyotype)
- Targets a specific variant, lowering risk of uncertain and incidental findings

## LIMITATIONS

Only detects the intended target, does not provide general information about chromosomal or genomic structure

# Tumor Screening for Hereditary Cancer

The background of the slide features a hand holding a glowing blue DNA double helix structure. The hand is rendered in a semi-transparent, light blue color, and the DNA is a vibrant blue. The overall aesthetic is clean and scientific, with a color palette dominated by various shades of blue and white. The text is overlaid on a white diagonal band that cuts across the top left of the image.

There are several laboratory tests that screen tumor tissue for markers suggestive of hereditary cancer. Currently, hereditary tumor testing is most useful in the setting of colorectal cancer (see EGAPP guidelines for more information).

# Tumor Screening for Hereditary Cancer

## WHAT IT DETECTS

Colorectal tumors are screened using one or more methodologies described below

**Microsatellite instability (MSI)** analysis detects errors in regions of DNA with repeating sequence that are more common in tumors associated with **Lynch syndrome**.

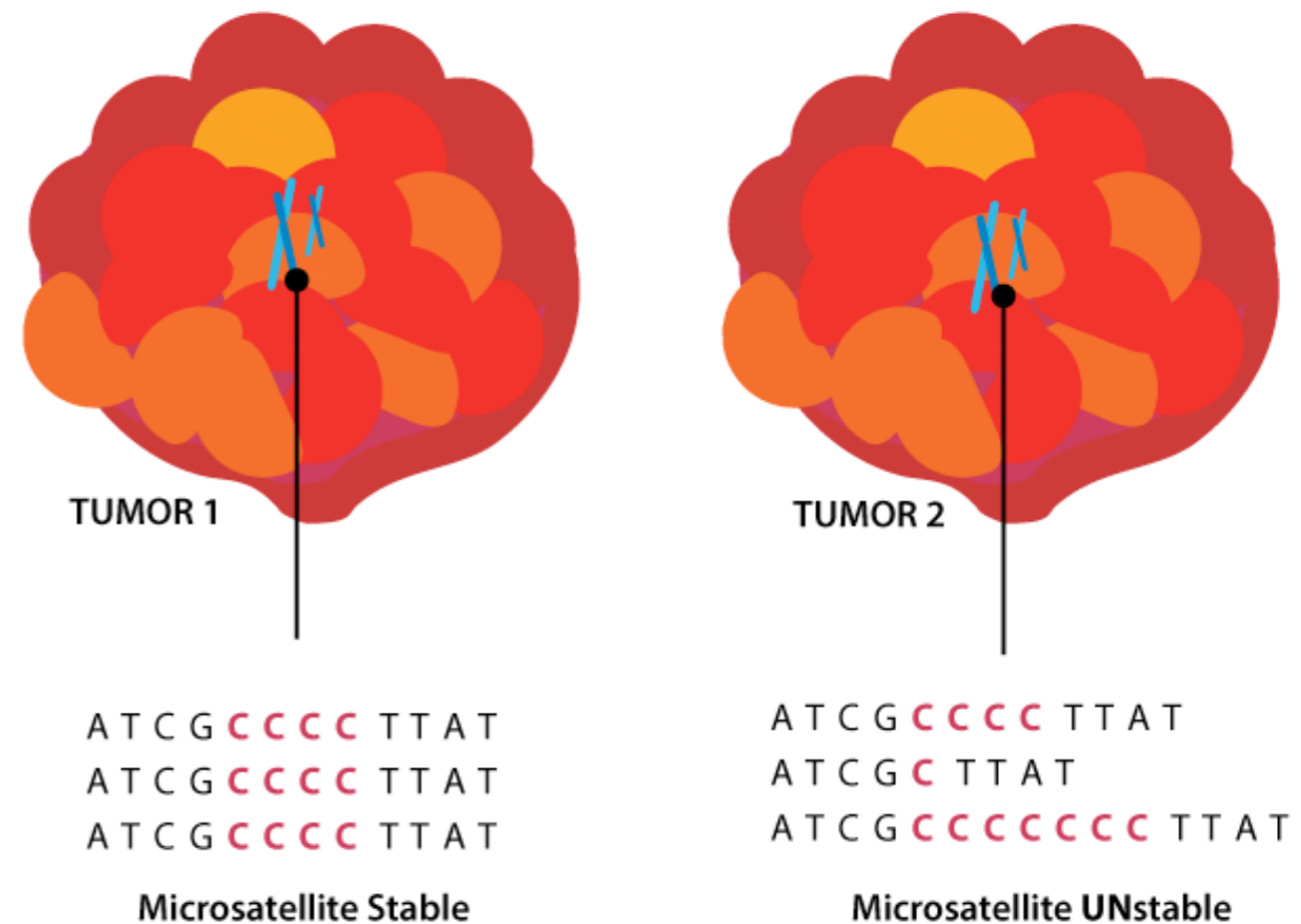
**Immunohistochemistry (IHC)** analysis detects the protein products of the mismatch repair (MMR) **genes** associated with Lynch syndrome. An absent protein suggests that the corresponding MMR gene is not functioning, suggestive of Lynch syndrome.

**BRAF gene analysis** of tumor cells identifies **variants** that are common in sporadic cancer, but rare in Lynch syndrome. A *BRAF* variant essentially rules out Lynch syndrome.

**MLH1 promoter methylation analysis** detects a variant that is common in sporadic cancers, but rare in Lynch syndrome. The presence of *MLH1* promoter methylation rules out the vast majority of Lynch syndrome.

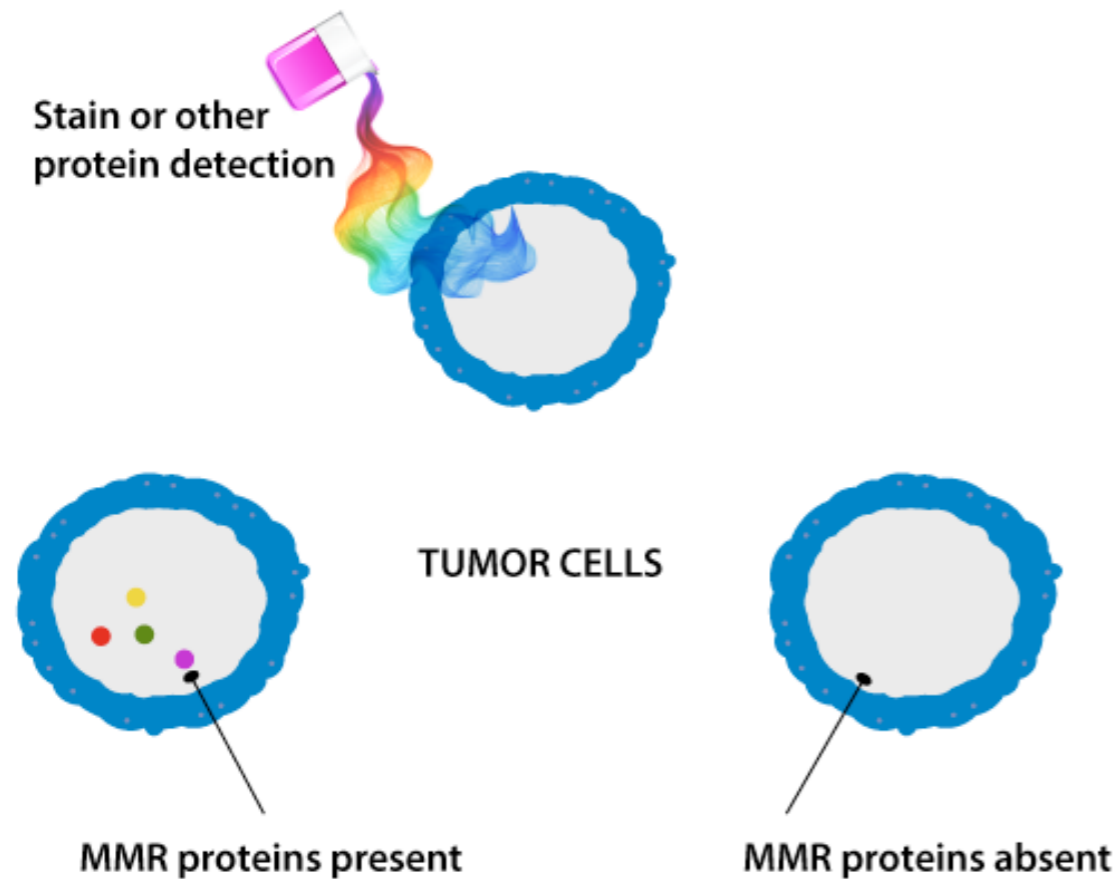
## BENEFITS

Figure 10.1 Microsatellite instability (MSI)



- A positive tumor screen for MSI or IHC identifies patients who might benefit from diagnostic **germline** genetic testing.
- Tumor screening by IHC can help target germline genetic testing for the most likely causative gene.
- Tumor screening for *BRAF/MLH1* promoter methylation can essentially rule out Lynch syndrome, and eliminate the need for germline genetic testing.

**Figure 10.2** Immunohistochemistry (IHC)



- Interpretation can be complex and may require multiple methodologies.

## RECENT APPLICATION

Universal screening of colorectal tumors (regardless of family history) is being implemented in an increasing number of centers

- Colon tumor screening by IHC is the most cost-effective approach to screening for Lynch syndrome.

## LIMITATIONS

- A small percentage of sporadic tumors exhibit MSI (10-15%) and absent MMR proteins. Thus, diagnostic germline testing is always required to confirm Lynch syndrome.
- Tumor screening may be less reliable in extra-colonic tumors, even if those tumors are part of the Lynch spectrum (i.e. endometrial or gastric tumors).



# Tumor Genome Analysis

A hand holding a glowing DNA double helix structure against a blue background. The hand is rendered in a semi-transparent, glowing blue style, with the DNA helix appearing as a bright, glowing blue structure. The background is a gradient of blue, with a dark blue area at the bottom and a lighter blue area at the top. The overall aesthetic is futuristic and scientific.

**ALSO KNOWN AS**

Tumor molecular profiling

# Tumor Genome Analysis

## HOW IT WORKS

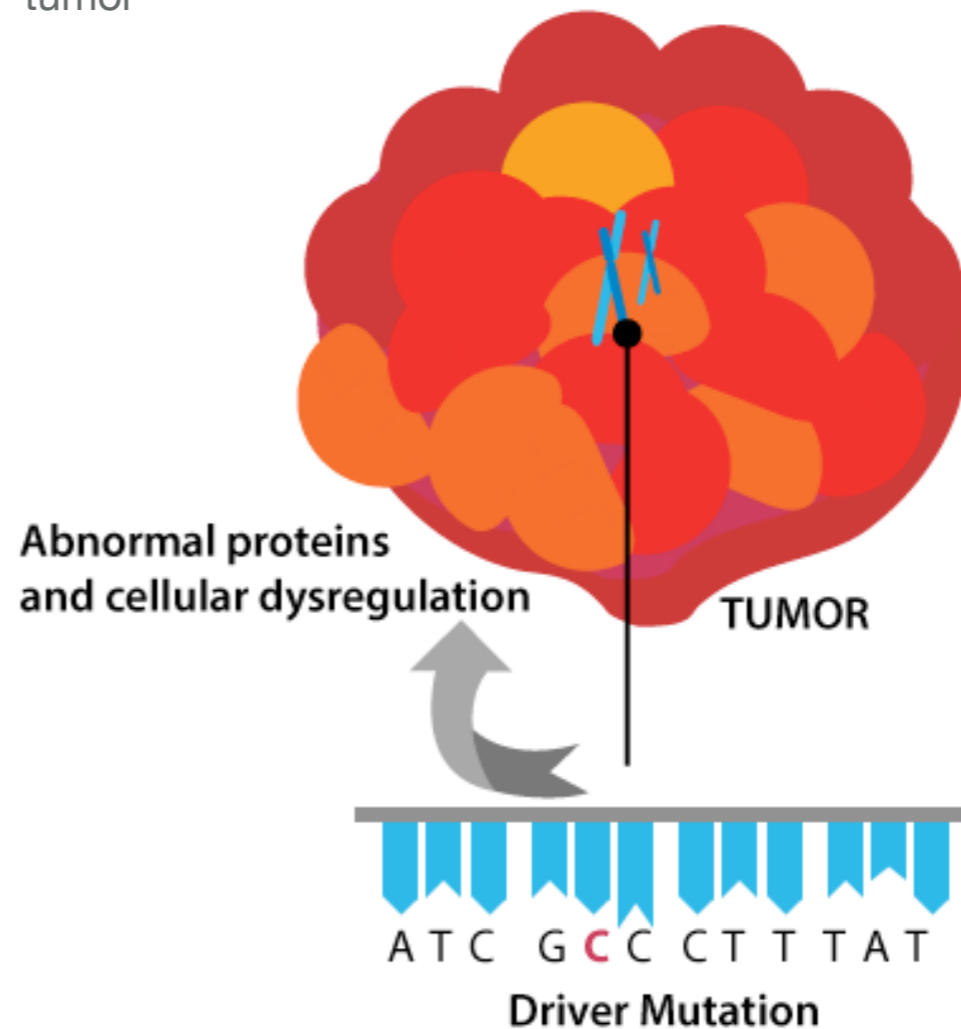
Various methodologies used, including massively parallel sequencing, targeted mutation analysis, chromosome **microarray**, and karyotype.

**Note:** See the previous chapters on specific technologies for more information about methodology. The testing methods and detection parameters are the same between tests for inherited (**germline**) and tumor (**somatic**) **variants**.

## WHAT IT DETECTS

- Genomic alterations confined to the tumor (somatic alterations)
- Emerging uses include:
  - Identifying the origin of metastatic cancer
  - Predicting response to therapies
  - Targeting treatment to **driver mutations** in the tumor
  - Prognosis, for example, the likelihood of metastasis or recurrence

**Figure 11.1** Targeting treatment to driver mutations in the tumor



## BENEFITS

Identifies unique characteristics of a tumor that may transcend/ supplement tissue type or other pathology and histological findings

## LIMITATIONS

- Does not confirm or rule-out hereditary cancer susceptibility
- Tumor **genomes** mutate rapidly, so repeat testing may be necessary
- Currently few treatments available for specific driver mutations
- This is a new type of testing, and the knowledge base is evolving

# References

## GENERAL

Katsani SH and Katsani N. 2013. Molecular genetic testing and the future of clinical genomics. *Nature Rev Genet* 14:415-426.

ACOG Committee on Genetics. 2014. Technology Assessment: Genetics and molecular diagnostic testing. *Obstet Gynecol* 123:394-413.

Feero WG and Guttmacher AE. 2010. Genomic medicine – An updated primer. *JAMA* 362:2001-2011.

## FOR SPECIFIC TECHNOLOGIES

### **Whole genome and whole exome sequencing**

Biesecker LG and Green RC. 2014. Diagnostic clinical genome and exome sequencing. *N Engl J Med* 370:2418-2425.

### **Chromosomal microarray**

Manning M, Hudgins L and the ACMG Professional Practice and Guidelines Cmt. 2010. ACMG Practice Guidelines: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med* 12:742-745.

### **Tumor screening for hereditary cancer**

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 2009. Recommendations from the EGAPP Working Group: Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome relatives. *Genet Med* 11:35-41.

Weissman SM, Burt R, Church J, et al. 2012. Identification of individuals at risk for Lynch syndrome using targeted evaluations and genetic testing: National Society of Genetic Counselors and the Collaborative Group of the Americas on Inherited Colorectal Cancer joint practice guideline. *J Genet Couns* 21:484-493.

### **Tumor genome analysis**

Vogelstein B, Papadopoulos N, Velculescu VE et al. 2013. Cancer genome landscapes. *Science* 339:1546-1558.

MacConaill LE. 2013. Existing and emerging technologies for tumor genomic profiling. *J Clin Oncol* 31:1815-1824.

# Array

Technology that allows the simultaneous analysis of many pieces of DNA on a single chip.

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## Related Glossary Terms

Drag related terms here

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## Index

[Chapter 5 - Multi-Gene Panels](#)

[Chapter 6 - Whole Exome/Genome Sequencing](#)

[Chapter 8 - Chromosomal Microarray](#)

## BAC array

A type of chromosome microarray in which bacterial artificial chromosomes (BACs) are created, and applied in the array, to target multiple DNA sequences of interest.

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### Related Glossary Terms

Drag related terms here

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Find Term

**Chapter 8 - Chromosomal Microarray**

# Bases

A base is the variable component of a nucleic acid. DNA contains the four bases thymine (T), cytosine (C), adenine (A) and guanine (G). These bases form base pairs along the length of the DNA helix. A pairs with T, while G pairs with C. The order of these bases (ATCG) comprise the DNA sequence. [Genome British Columbia]

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## Related Glossary Terms

Drag related terms here

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**Chapter 1 - Testing Landscape**

Chapter 2 - Single Gene Sequencing-1

Chapter 6 - Whole Exome/Genome Sequencing

# Codon

Consists of three adjacent DNA nucleotides, or base pairs, that code for a single amino acid.

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## Related Glossary Terms

Drag related terms here

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## Copy number

When the number of copies of a particular gene or a part of the gene varies from one individual to the next.

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### Related Glossary Terms

Copy number variant

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**Chapter 3 - Deletion Duplication Analysis**

Chapter 3 - Deletion Duplication Analysis

# Copy number variant

When the number of copies of a particular gene or a part of the gene varies from one individual to the next.

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## Related Glossary Terms

Copy number

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### Chapter 3 - Deletion Duplication Analysis

Chapter 3 - Deletion Duplication Analysis

Chapter 3 - Deletion Duplication Analysis

Chapter 5 - Multi-Gene Panels

Chapter 6 - Whole Exome/Genome Sequencing

Chapter 8 - Chromosomal Microarray

Chapter 8 - Chromosomal Microarray

Chapter 9 - Fluorescent In Situ Hybridization

# Cystic fibrosis

An inherited disease characterized by the buildup of thick, sticky mucus that can damage many of the body's organs. The disorder's most common signs and symptoms include progressive damage to the respiratory system and chronic digestive system problems. The disease is caused by variants, or mutations, in the CFTR gene. [Genetics Home Reference]

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## Related Glossary Terms

Drag related terms here

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Chapter 7 - Chromosome Analysis

**Chapter 8 - Chromosomal Microarray**

## Driver mutation

In a tumor cell, a variant in a gene that gives the cell a selective growth advantage. This is often an initiating event for tumor growth and expansion.

---

### Related Glossary Terms

Drag related terms here

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### Index

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Chapter 11 - Tumor Genome Analysis-1

Chapter 11 - Tumor Genome Analysis-1

# Exon

The portion of a gene that codes for protein.

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## Related Glossary Terms

Drag related terms here

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Find Term

## Family trios

An affected individual, or proband, and his or her parents. Parental studies are useful to evaluate the clinical significance of a novel variant identified in the affected individual. In whole exome and whole genome sequencing, the lab often requests DNA samples on the family triad when the test is initially ordered.

---

### Related Glossary Terms

Drag related terms here

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**Index**

Find Term

**Chapter 6 - Whole Exome/Genome Sequencing**

## Fragile X syndrome

Fragile X syndrome is a genetic condition that causes a range of developmental problems including learning disabilities and cognitive impairment. Usually, males are more severely affected by this disorder than females. Variants, or mutations, in the FMR1 gene cause fragile X syndrome. [Genetics Home Reference]

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### Related Glossary Terms

Drag related terms here

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**Chapter 8 - Chromosomal Microarray**

Chapter 9 - Fluorescent In Situ Hybridization

## Genes

The fundamental unit of inheritance. Genes encode messages for the synthesis of proteins and functional RNAs. Genes help determine an organism's appearance, its metabolism and may interact with the environment to influence its behavior. [Genome British Columbia]

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### Related Glossary Terms

Drag related terms here

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# Genome

A genome is an organism's complete set of DNA – basically a blueprint for an organism's structure and function. [Genome British Columbia]

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# Germline

The group or line of cells that gives rise to reproductive cells (sperm or eggs). Mutations in the germ line are passed on to future generations. Cells that are not part of the germline are called somatic cells. [Genome British Columbia]

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## Hereditary breast and ovarian cancer

An adult-onset, cancer predisposition syndrome characterized by a high risk of breast and ovarian cancers, and an increased risk of other cancers such as prostate, pancreatic, and melanoma. HBOC is most often caused by a pathogenic variant, or mutation, in the BRCA1 or BRCA2 genes.

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# Intron

The portion of a gene that does not code for protein.

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# Lynch syndrome

An adult-onset, cancer predisposition syndrome. It is caused by a mutation in one of the genes involved in the mismatch repair pathway. Individuals with Lynch are at increased risk for colon and other cancers, including gastric, urinary tract, brain, small bowel, pancreatic, hepatobiliary and sebaceous carcinoma. Women with Lynch are at increased risk for endometrial and ovarian cancer.

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## Marker chromosomes

An extra, structurally abnormal chromosome of unidentified origin. The clinical significance of a marker chromosome depends on its specific genetic material.

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## Metaphase chromosomes

Metaphase is a stage during the process of cell division (mitosis or meiosis). Usually, individual chromosomes cannot be observed in the cell nucleus. However, during metaphase of mitosis or meiosis the chromosomes condense and become distinguishable as they align in the center of the dividing cell. Metaphase chromosomes are used during the karyotyping procedure that is used to look for chromosomal abnormalities. [NHGRI Glossary]

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# Microarray

Technology that allows the simultaneous analysis of many pieces of DNA on a single chip.

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## Microsatellite

Microsatellite sequences are repetitive DNA sequences usually several base pairs in length. Microsatellite sequences are composed of non-coding DNA and are not parts of genes. Microsatellite instability (MSI) is a change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell.  
[NHGRI Glossary] [NCI Dictionary]

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# Monosomy X

A chromosomal condition that affects development in females. The most common feature of Turner syndrome is short stature, which becomes evident by about age 5. An early loss of ovarian function (ovarian hypofunction or premature ovarian failure) is also very common. Turner syndrome results when only one normal X chromosome is present in a female's cells, rather than two sex chromosomes. [Genetics Home Reference]

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## Next generation sequencing (NGS)

High-throughput DNA sequencing technologies. Millions of DNA strands can be sequenced in parallel with significantly more throughput than other methods, including Sanger sequencing.

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# Nucleotide

Organic compound made up of a purine or pyrimidine (base) joined to a sugar and a phosphate group. Nucleic acids (DNA & RNA) contain nucleotides linked together in long chains. [Genome British Columbia]

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# Oligoarray

A type of chromosome microarray in which short DNA sequences are created and applied to the array, to target multiple DNA sequences of interest.

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# Probe

A probe is a single-stranded sequence of DNA or RNA used to search for its complementary sequence in a sample genome. The probe is placed into contact with the sample under conditions that allow the probe sequence to hybridize with its complementary sequence. The probe is labeled with a radioactive or chemical tag that allows its binding to be visualized. In a similar way, labeled antibodies are used to probe a sample for the presence of a specific protein. [NHGRI Glossary]

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## Promoter methylation

An epigenetic modification to the portion of DNA responsible for starting transcription of a gene that affects the expression of the gene.

**Promoter:** A region of DNA contains sequences important in gene transcription. Mutations in the promoter region may cause incorrect expression of the gene and can lead to disease. [Genome British Columbia]

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## Reference sequence

The “normal” DNA sequence that laboratories use for comparison with an individual’s DNA. The reference sequence represents an aggregate from multiple donors.

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## Regulatory regions

A DNA region that effects the expression of a proximal gene.

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# Sanger sequencing

A “first generation” method for determining the sequence of a DNA strand.

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## Sickle cell disease

A group of disorders that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. Characteristic features of this disorder include a low number of red blood cells (anemia), repeated infections, and periodic episodes of pain. Variants, or mutations, in the HBB gene cause sickle cell disease. [Genetics Home Reference]

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## SNP array

A type of chromosome microarray that can detect single base variants (single nucleotide polymorphisms; SNPs).

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# Somatic

Variants in the genes that form in the body cells only. Unlike in germ cells, variants or manipulations in these cells are not passed on to the next generation. [Genome British Columbia]

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## Spinal Muscular Atrophy

An inherited disease that affects the central nervous system. It is characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells (i.e., lower motor neurons). Other features may include poor weight gain, sleep disordered breathing, scoliosis, and joint contractures. SMA is caused by copy number variants in the SMN1 or SMN2 genes.

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# Structural rearrangement

A change in the structure of the chromosome(s), such as a translocation.

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# Syndrome

The word syndrome refers to a group of symptoms, sometimes in different body systems, that consistently occur together due to a common underlying cause.

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## Trisomy 18 (Edward syndrome)

A chromosomal condition associated with abnormalities in many parts of the body. Individuals with trisomy 18 often have slow growth before birth (intrauterine growth retardation) and a low birth weight. Affected individuals may have heart defects and abnormalities of other organs that develop before birth. Due to the presence of several life-threatening medical problems, many individuals with trisomy 18 die before birth or within their first month. Most cases of trisomy 18 result from having three copies of chromosome 18 in each cell in the body instead of the usual two copies. [Genetics Home Reference]

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## Trisomy 21 (Down syndrome)

A chromosomal condition that is associated with intellectual disability, a characteristic facial appearance, and weak muscle tone (hypotonia) in infancy. All affected individuals experience cognitive delays, but the intellectual disability is usually mild to moderate. People with Down syndrome may have a variety of birth defects. Most cases of Down syndrome result from trisomy 21, which means each cell in the body has three copies of chromosome 21 instead of the usual two copies. [Genetics Home Reference]

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# Variant

A variant is DNA alteration that is different from the general population or reference sequence. Variants have varying impacts on disease risk, some having no effect and others significantly increasing risk (pathogenic mutation).

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## Variants of uncertain significance

A genetic variant for which the pathogenicity can neither be confirmed nor ruled out.

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