Genetics and Genomics in Precision Medicine

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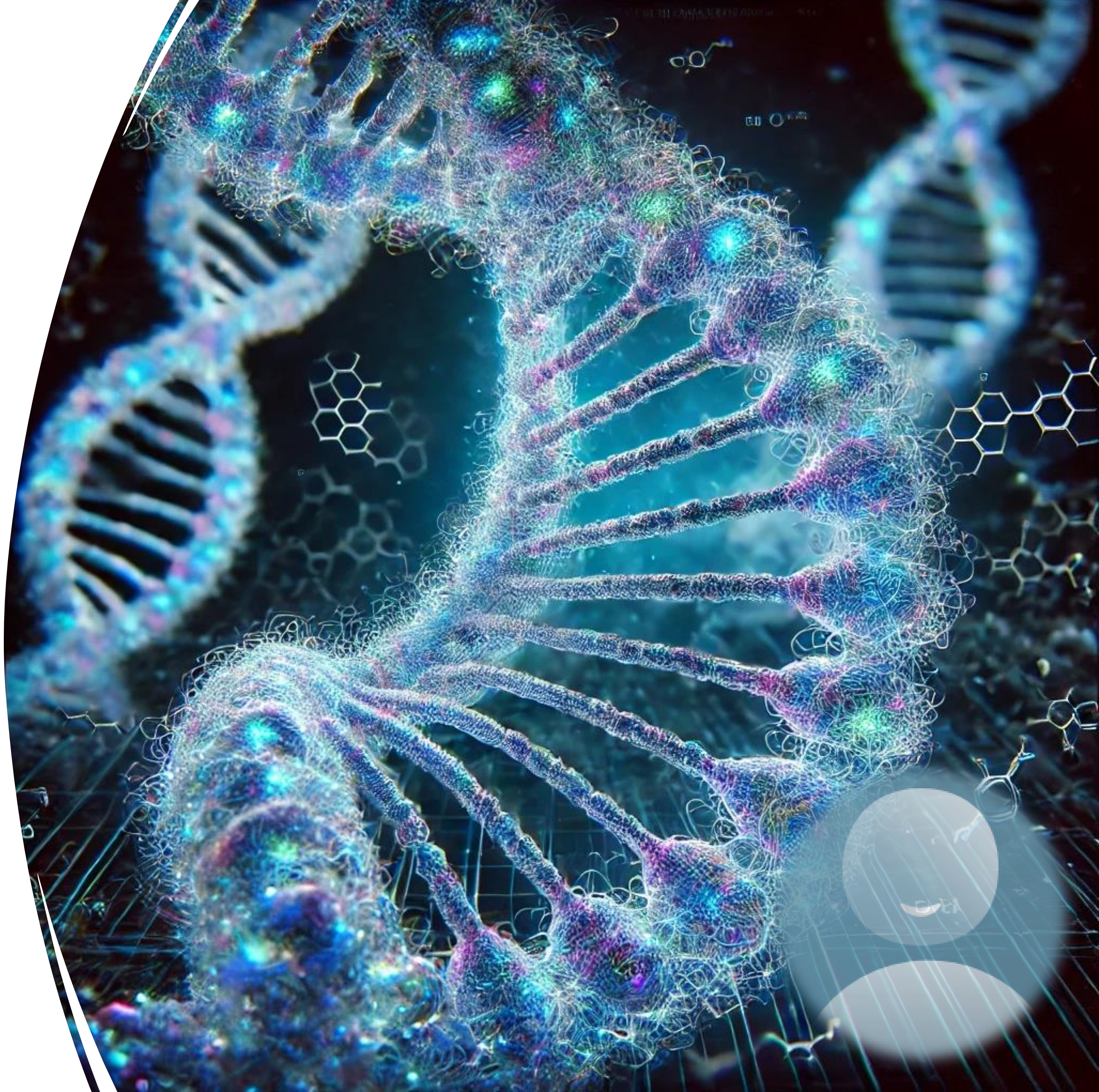


Learning Objectives

- Understand the principles of Molecular Genetics and Genomics
- Gain insights into the role of genomics and its applications in healthcare
- Delineate the challenges associated with genomic testing

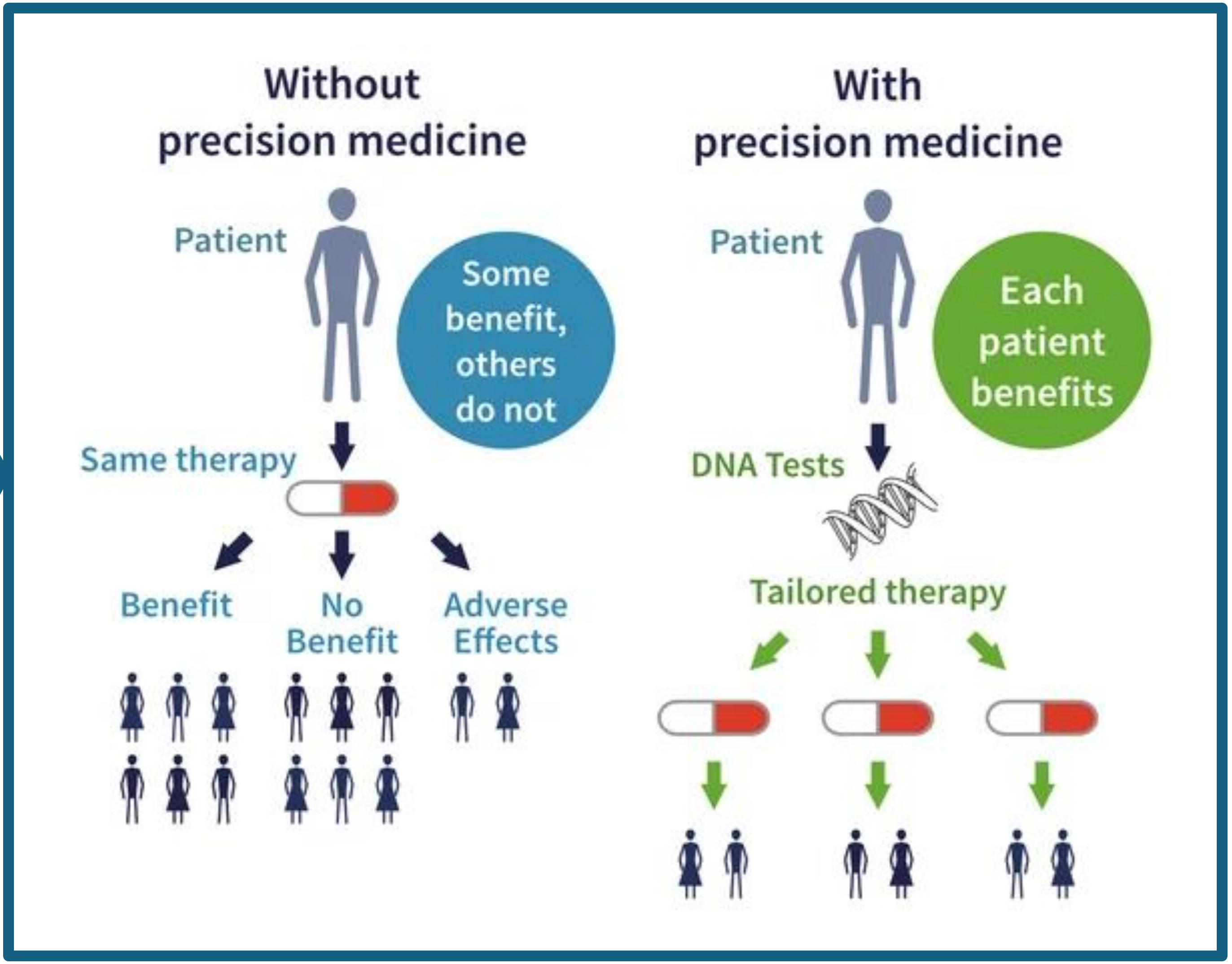
Why Genetics and Genomics Matter in PM?

NIH National Human Genome Research Institute

- Precision medicine (generally considered analogous to personalized medicine or individualized medicine) is an innovative approach that uses information about an individual's **genomic**, environmental and lifestyle information to guide decisions related to their medical management. The goal of precision medicine is to provide more a precise approach for the prevention, diagnosis and treatment of disease.
- Precision medicine or precision healthcare is medical care that takes advantage of large data sets of individuals such as their **genome** or their entire electronic health record to tailor their healthcare to their unique attributes. It is common sense that no two individuals are the same, and so they should not get the same healthcare. Precision healthcare embodies that simple idea.

Why Genetics and Genomics Matter in PM?

An individual's DNA is a cornerstone of PM



Genetics and Genomics Foundations

Genetics

- The study of individual genes, their inheritance, and how they influence traits and diseases.
- **Focus**: Single gene mutations or variations (e.g., **sickle cell disease**, **cystic fibrosis**).

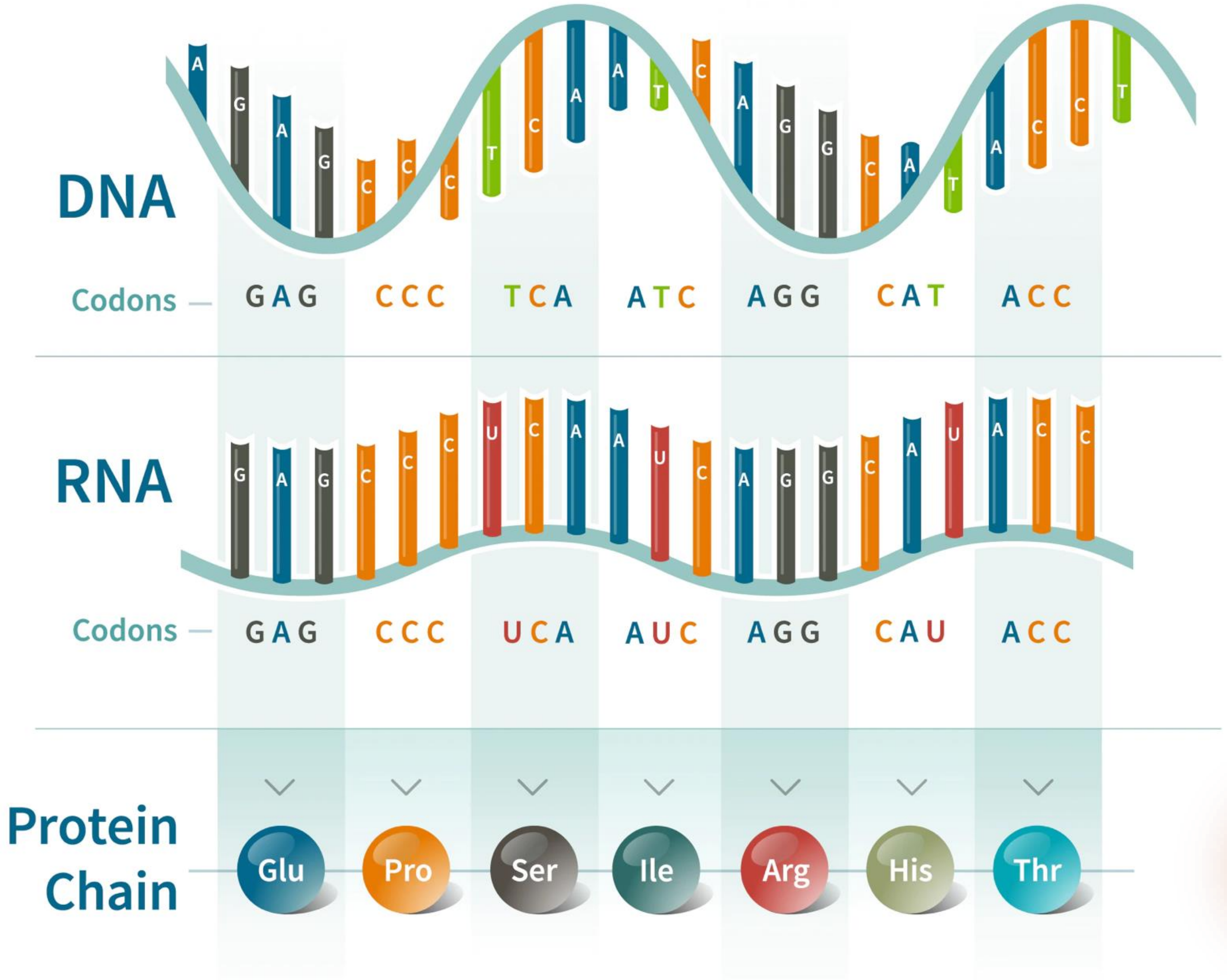
Genomics

- The study of the entire genome, including all genes and non-coding regions, and their interactions.
- **Focus**: Large-scale genetic analysis and the interplay of multiple genes (e.g., **cancer genomics**, **multi-omics**).

Molecular Genetics

- A branch of biology that studies the structure, function, and regulation of genes at the molecular level.
- **Focus:** How genetic information is encoded in DNA, how genes are expressed and regulated, and how mutations can affect biological processes.
- Molecular genetics integrates techniques from biochemistry, molecular biology, and genomics to understand gene function, inheritance patterns, and their implications in health and disease.

How does DNA instruct for proteins?



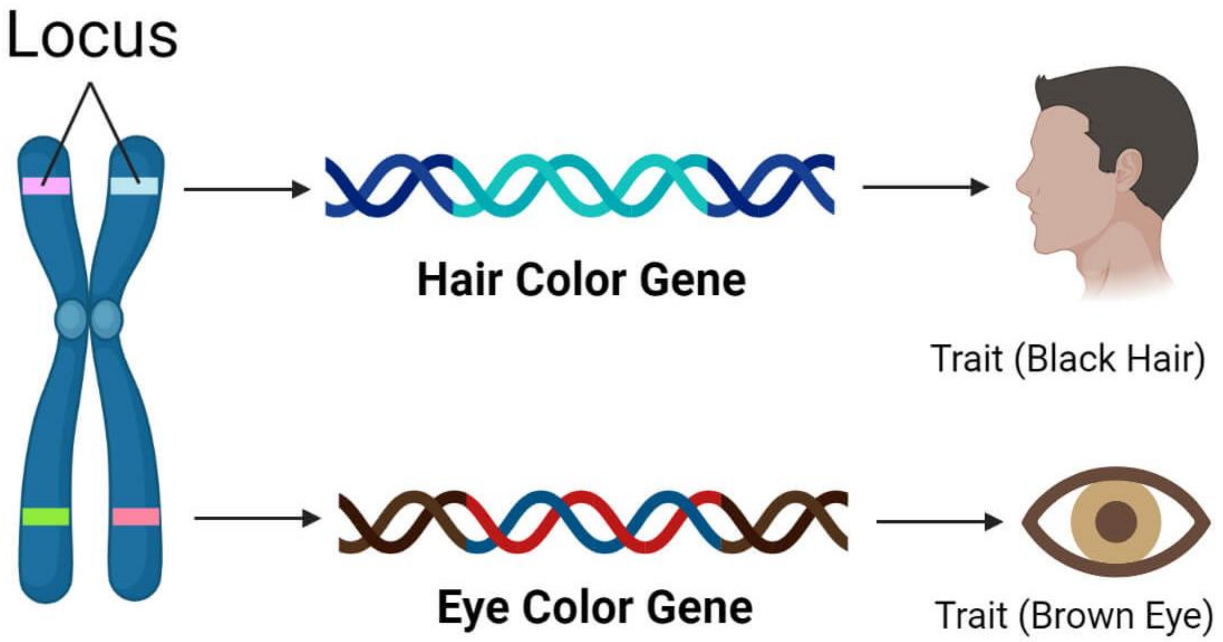
Proteins do much of the work inside the cell, so they contribute to determine how cells behave (phenotype).

What happens when the instructions (DNA) are altered?

Genotype vs. Phenotype

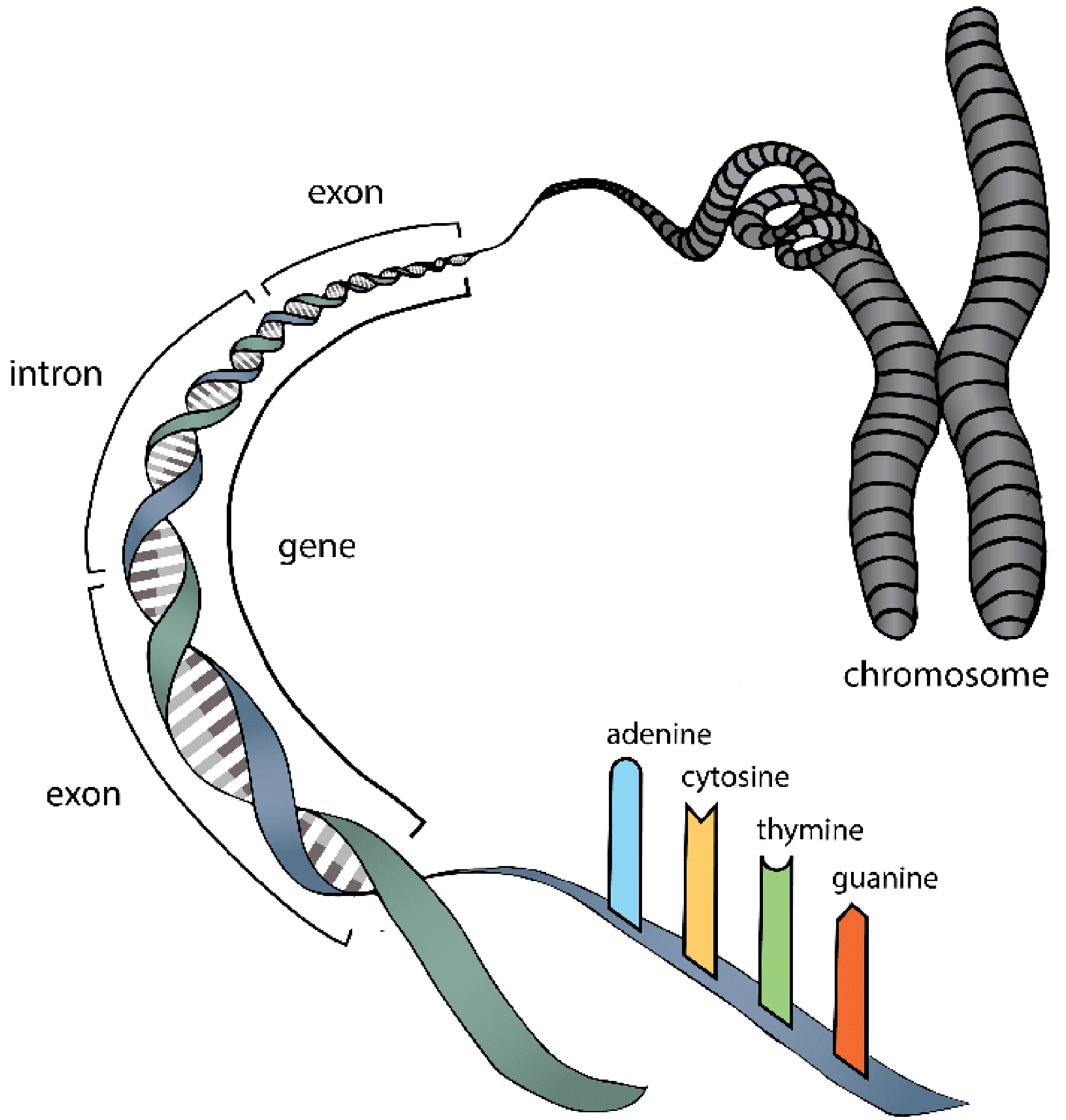
Genotype – Individual’s genetic makeup, including mutations, polymorphisms, and gene variations.

Phenotype - Observable traits and characteristics, including clinical symptoms, physical traits, and disease manifestations.



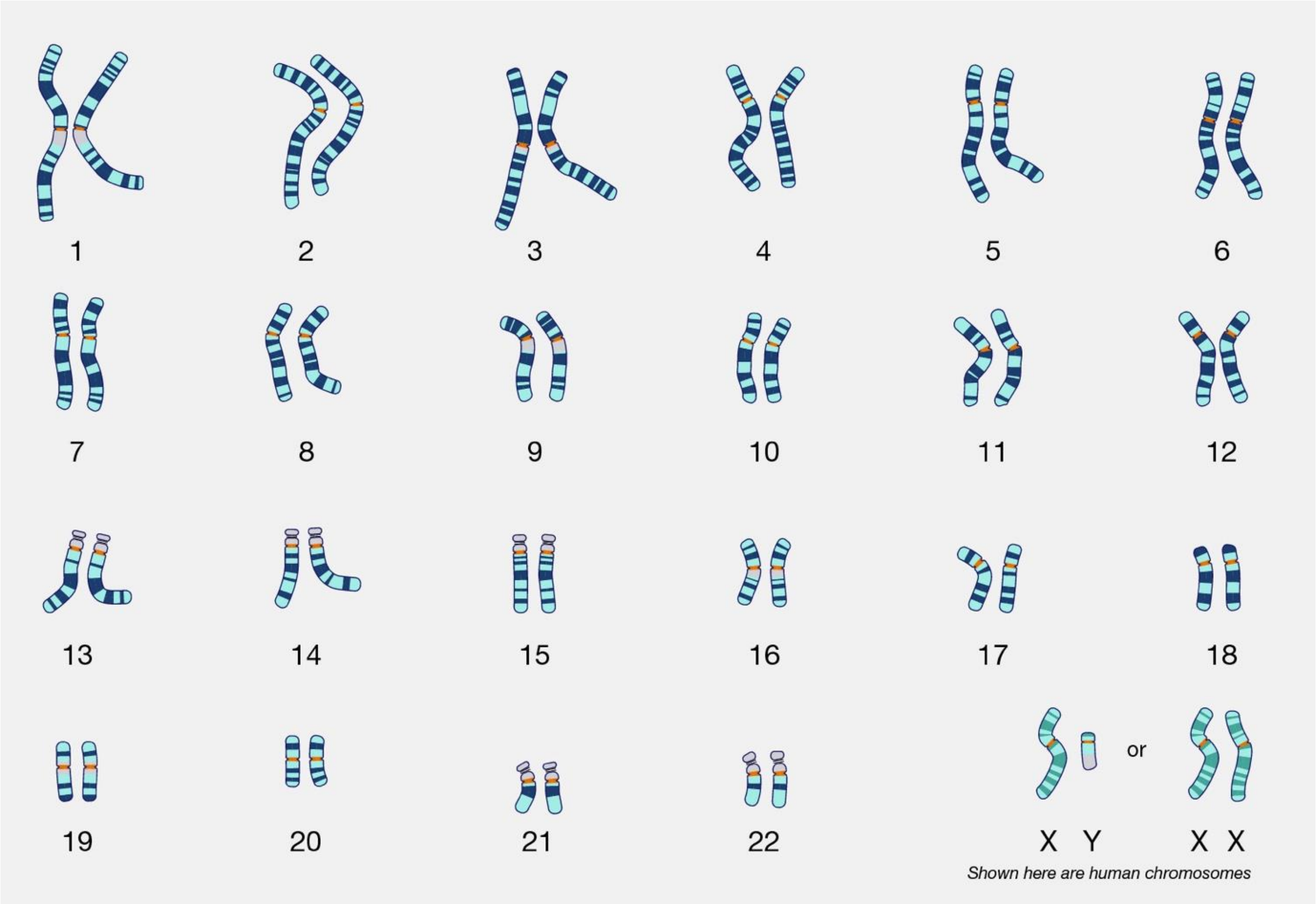
Genetic Alterations

- Genetic alterations can occur at the level of the chromosome or nucleotide



Cytogenetics and Karyotyping: Analyzing Chromosomes

Cytogenetics is a field of study that deals with chromosomes and related abnormalities. Chromosome analysis is also known as karyotyping and involves the pairing of homologous chromosomes.

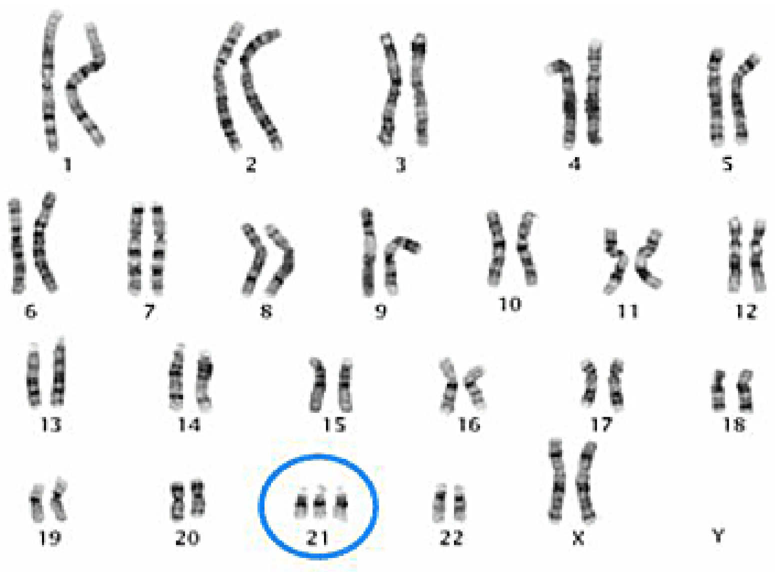


https://www.genome.gov/genetics-glossary/Karyotype

Chromosomal Abnormalities: Types and Implications

- **Types of Abnormalities:**
  - **Numerical :** Changes in chromosome number, such as trisomy (e.g., Down syndrome) or monosomy (e.g., Turner syndrome).
  - **Structural :** Alterations in chromosome structure, including deletions, duplications, translocations, insertions, and inversions.

- Changes in the number or structure of chromosomes can lead to developmental disorders, congenital conditions, infertility, miscarriages, or predispositions to diseases such as cancer.



Karyogram of Down syndrome

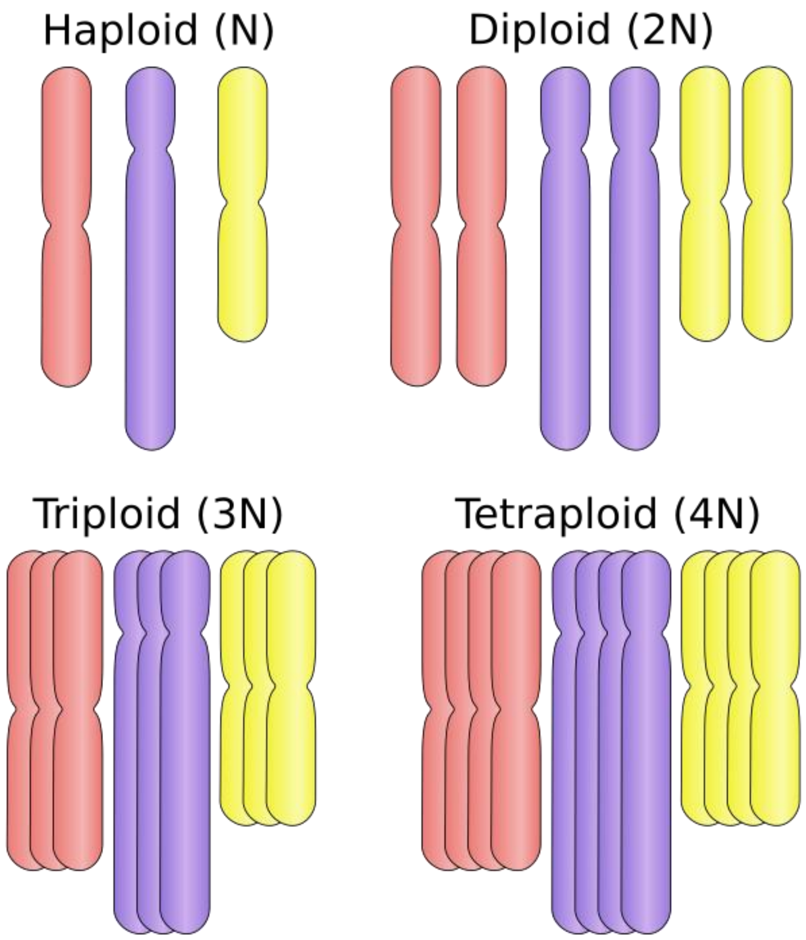
Copy Number Variations (CNVs): Change in Ploidy

EUPLOIDY

- **Definition**: The presence of a normal, complete set(s) of chromosomes.
- **Examples**:
  - Haploid (n): Single set of chromosomes, e.g., gametes (sperm and egg).
  - Diploid (2n): Two sets of chromosomes, e.g., most human somatic cells.

POLYPLOIDY

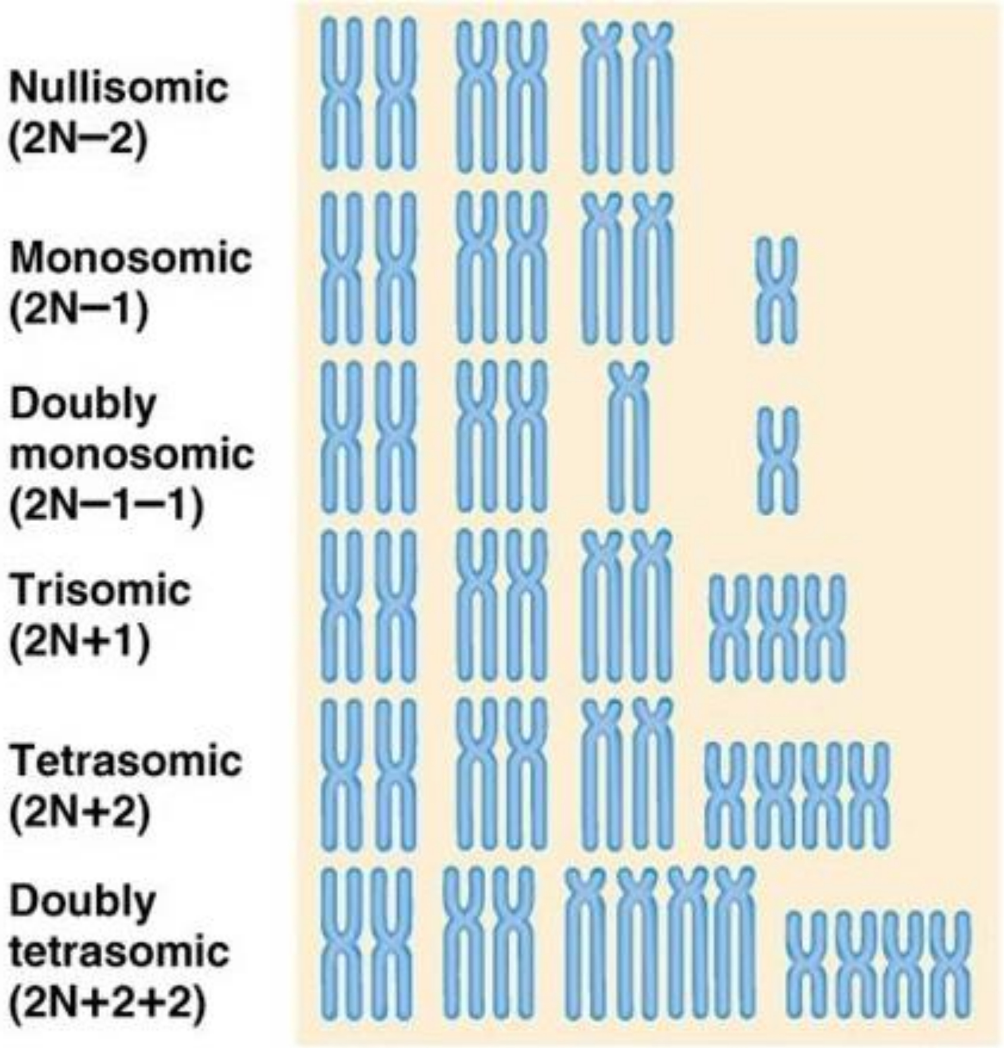
- **Definition**: More than two complete sets of chromosomes.
- **Examples**:
  - Triploidy (3n): Rare in humans, often incompatible with life.
  - Tetraploidy (4n): Seen in certain plants and rarely in human tumors.
- **Clinical Relevance**: Common in cancer cells and certain plants for agricultural purposes.



Copy Number Variations (CNVs): Change in Ploidy

ANEUPLOIDY

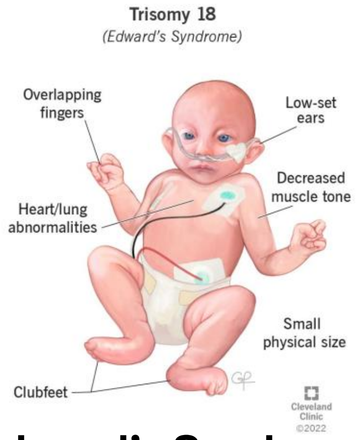
- **Definition**: An abnormal number of chromosomes, not in complete sets.
- **Examples**:
  - Trisomy: One extra chromosome (e.g., Trisomy 21 in Down syndrome).
  - Monosomy: One missing chromosome (e.g., Monosomy X in Turner syndrome).
- **Clinical Relevance**: A hallmark of many cancers and developmental disorders.



Common Chromosomal Syndromes

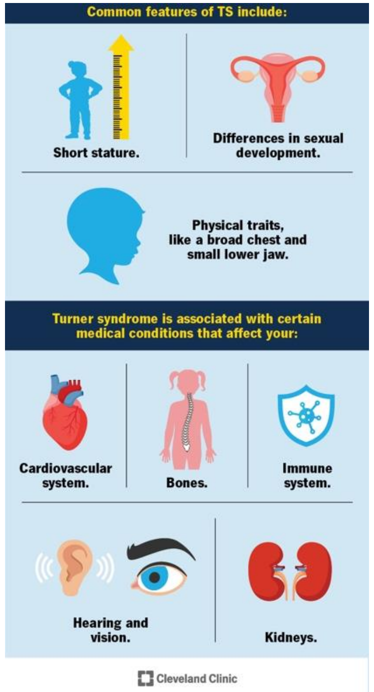
Disorder	Description
Down's syndrome (Trisomy 21)	Extra chromosome 21
Edward's syndrome (Trisomy 18)	Extra chromosome 18
Patau's syndrome (Trisomy 13)	Extra chromosome 13
Turner's syndrome (Monosomy X)	Single X chromosome in females
Klinefelter's syndrome	Two X chromosomes in males (XXY)
Triple X syndrome (super females)	Three X chromosomes in females
XYY syndrome	Two Y chromosomes in males

Down Syndrome

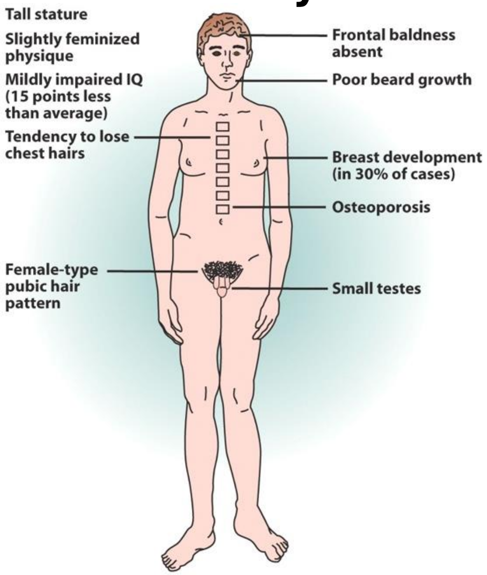


Edward's Syndrome

Turner's Syndrome



Klinefelter's Syndrome



Patau's Syndrome

Common Structural Chromosomal Abnormalities

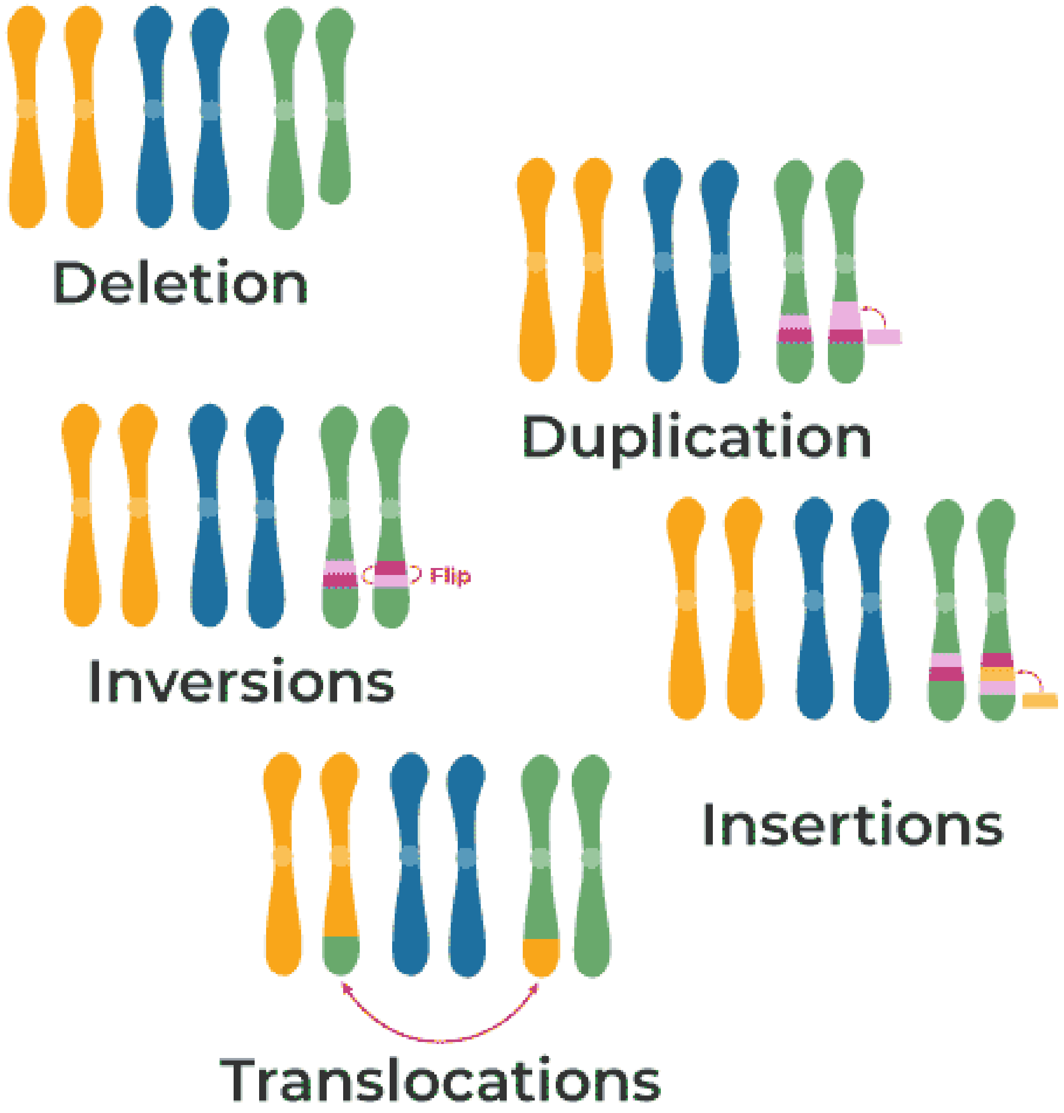
Deletions: A segment of the chromosome is missing, resulting in the loss of genetic material.

Duplications: A segment of the chromosome is repeated, leading to extra genetic material.

Inversions: A segment of a chromosome is reversed within the same chromosome, potentially altering gene function.

Insertions: A segment of DNA is inserted into a chromosome, which may disrupt normal gene sequences.

Translocations: A segment of one chromosome is transferred to another chromosome, which can disrupt gene regulation.



Structural Chromosomal Abnormalities in Disease

Deletions

Cri-du-chat Syndrome: Deletion on chromosome 5 (5p-), causing developmental delay and distinctive cry.

DiGeorge Syndrome: Deletion on chromosome 22 (22q11.2), leading to immune deficiency and heart defects.

Duplications

Charcot-Marie-Tooth Disease: Duplication on chromosome 17, causing peripheral nerve issues.

Patau Syndrome: Partial duplication of chromosome 13, leading to developmental issues and brain abnormalities.

Translocations

Chronic Myelogenous Leukemia (CML): t(9;22) translocation (Philadelphia chromosome), causing leukemia.

Burkitt Lymphoma: t(8;14) translocation, disrupting MYC gene regulation and causing lymphoma.

Inversions

Hemophilia A: Inversion on X chromosome, leading to blood clotting deficiency.

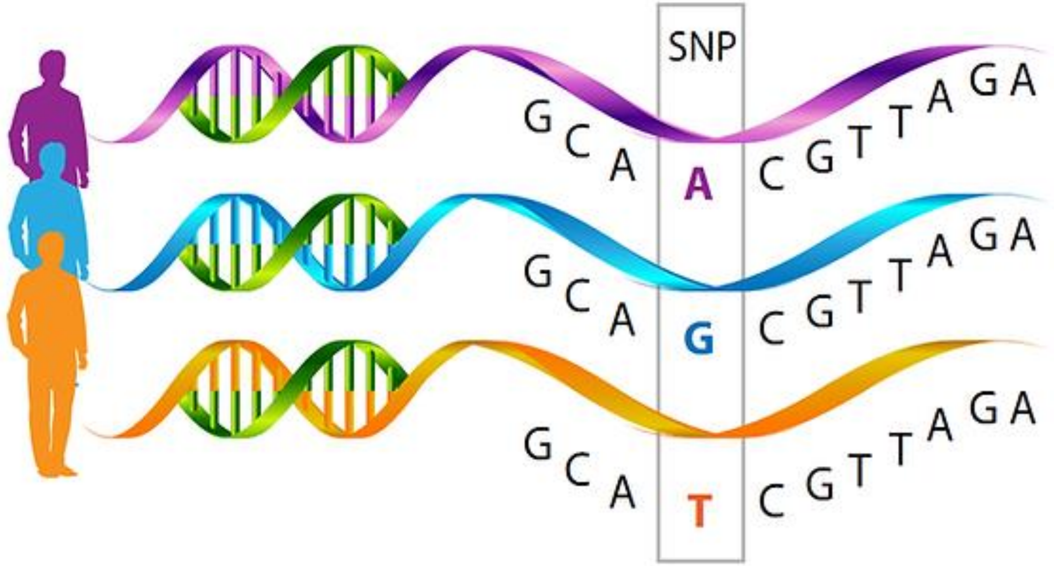
Insertions

Familial Adenomatous Polyposis (FAP): Insertion in the APC gene on chromosome 5, leading to the development of numerous colorectal polyps and increased cancer risk.

Single Nucleotide Polymorphism (SNP)

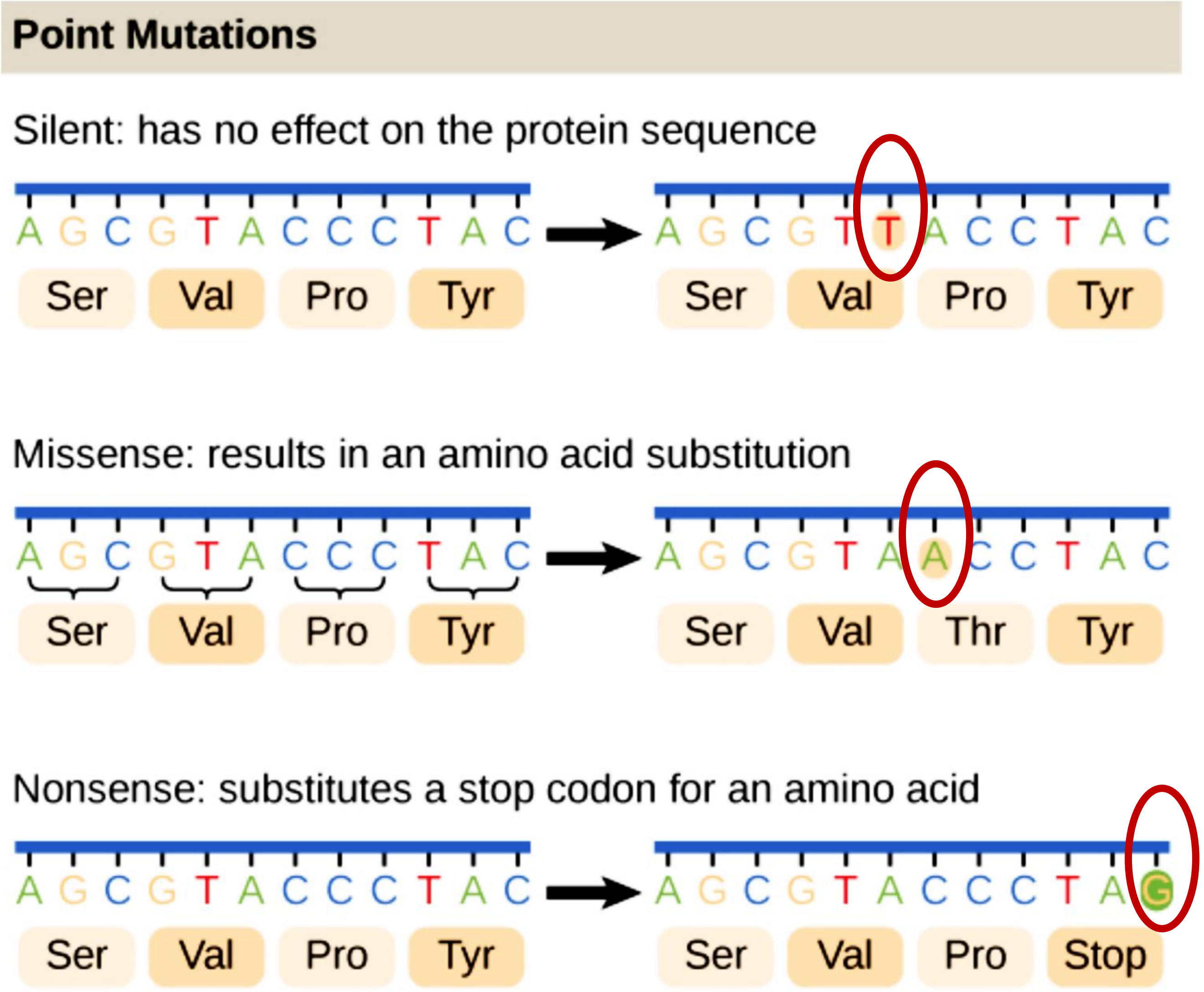
A variation in a single nucleotide at a specific position in the genome that occurs in at least 1% of the population.

•Over 10 million SNPs exist in the human genome.
•May alter gene function or regulation if located in coding or regulatory regions.
•Used as genetic markers for studying diseases and traits.
•**Types**:
- •**Synonymous SNPs**: Do not change encoded protein.
- •**Non-Synonymous SNPs**: Change protein structure or function.



Applications:
- •**Disease Risk**: SNPs associated with conditions like cancer, diabetes, and heart disease.
- •**Pharmacogenomics**: Predicting individual responses to drugs.
- •**Population Studies**: Understanding genetic diversity and ancestry.

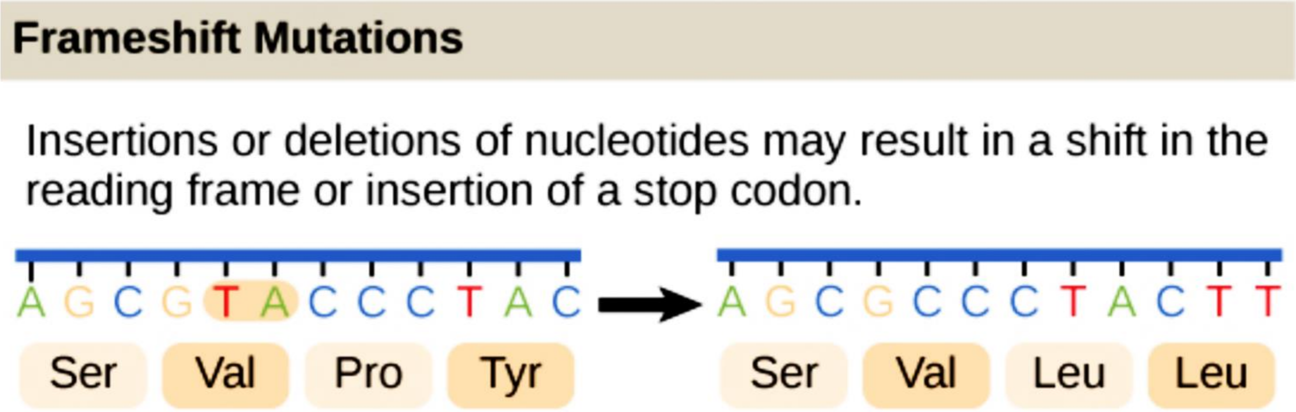
Nucleotide Alterations – Point Mutations



Point Mutations: Change in a single nucleotide base in the DNA sequence.

1) **Silent Mutation:** Does not alter the amino acid sequence of the protein.
2) **Missense Mutation:** A change in the nucleotide that results in a different amino acid being incorporated into the protein. This can affect protein function.
3) **Nonsense Mutation:** A change in the nucleotide that converts a codon into a stop codon, leading to premature termination of protein synthesis. This often produces a nonfunctional protein, particularly if it results in termination far upstream of the regular stop codon.

Nucleotide Alterations - Indels



Insertion and Deletion Mutations (Indels): These mutations involve the addition (insertion) or removal (deletion) of one or more nucleotides in the DNA sequence.

1) **Frameshift Mutation:** If the number of inserted or deleted nucleotides is not a multiple of three, it causes a shift in the reading frame, altering all downstream codons. This can result in a completely nonfunctional protein.
2) **In-frame Mutation:** If an insertion or deletion occurs in a multiple of three, the reading frame is not shifted, but an amino acid is added or lost, potentially affecting protein function.

Many Human Diseases Are Caused by Mutations in Single Genes

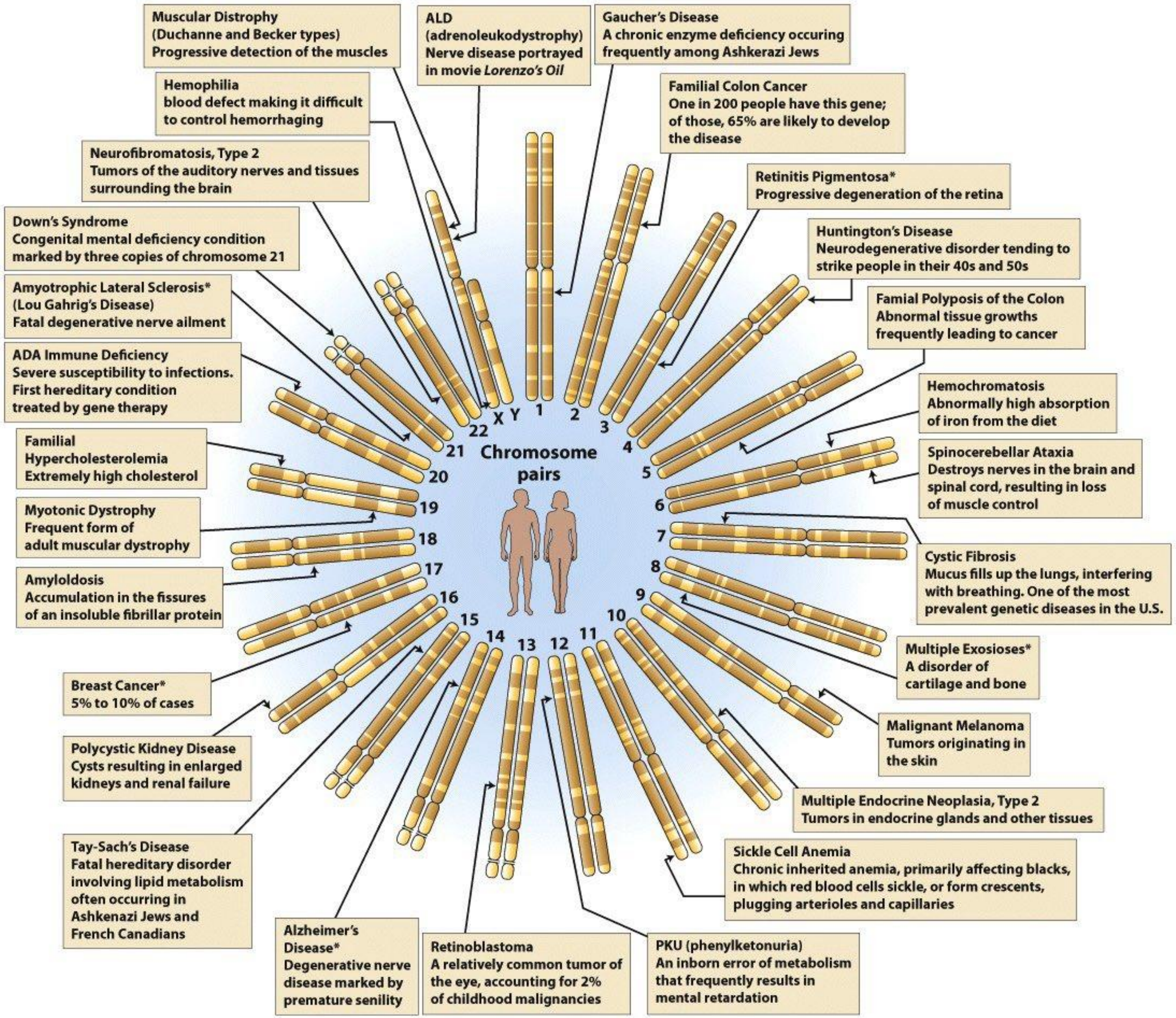
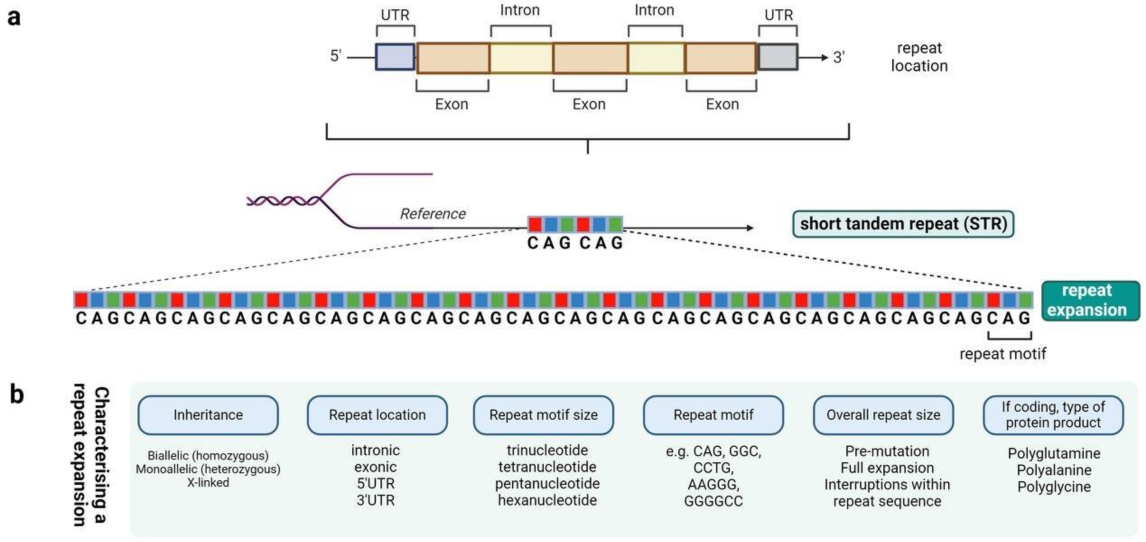


Figure 1-17
Introduction to Genetic Analysis, Tenth Edition

STRs and Repeat Expansion



Short Tandem Repeats (STRs) are short, repetitive DNA sequences, typically 2–6 base pairs long, that are repeated in tandem at specific genomic locations. These repeats are highly variable in length between individuals and are used in forensic and population genetics.

Pathological Threshold:

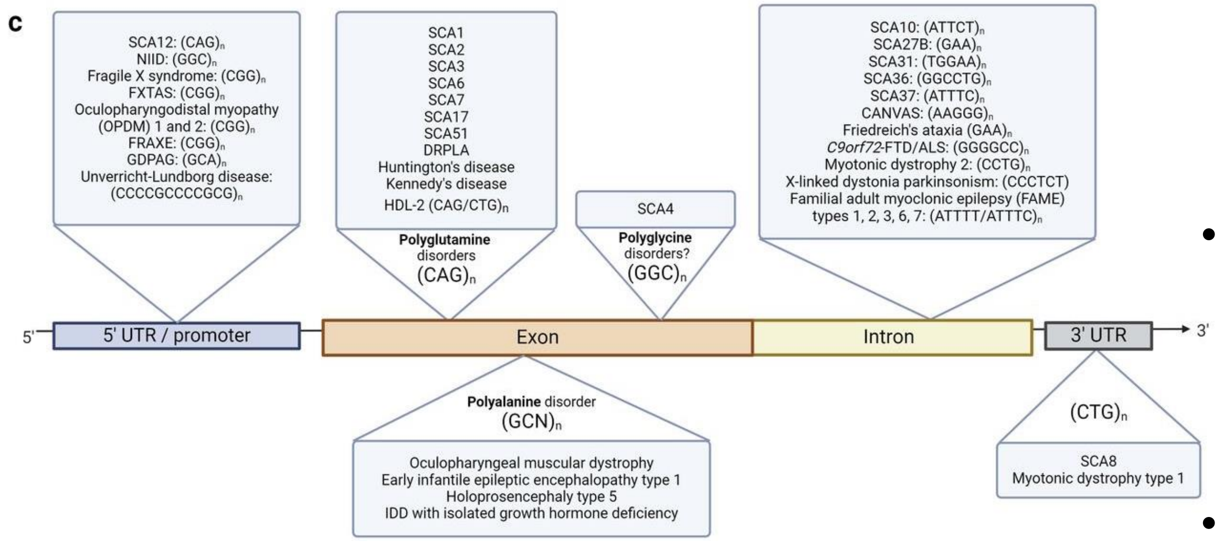
•In certain genes, expansions of STRs beyond a critical threshold disrupt normal gene function, leading to disease.

•The **normal range** of repeats is typically stable across generations, while expansions beyond the **premutation range** can increase repeat instability.

•The **pathogenic range** varies by disorder but often correlates with disease severity or earlier onset.

https://doi.org/10.1136/pn-2023-003938

Repeat Expansion Disorders



Examples of Repeat Thresholds in Disorders

- **Huntington's Disease**:
  - Normal: ≤26 CAG repeats
  - Premutation: 27–35 repeats (risk of expansion in offspring)
  - Pathogenic: ≥36 repeats
- **Fragile X Syndrome**:
  - Normal: ≤44 CGG repeats in the FMR1 gene
  - Premutation: 55–200 repeats
  - Pathogenic: >200 repeats, causing silencing of the FMR1 gene.
- **Myotonic Dystrophy Type 1**:
  - Normal: 5–34 CTG repeats in the DMPK gene
  - Premutation: 35–49 repeats
  - Pathogenic: ≥50 repeats

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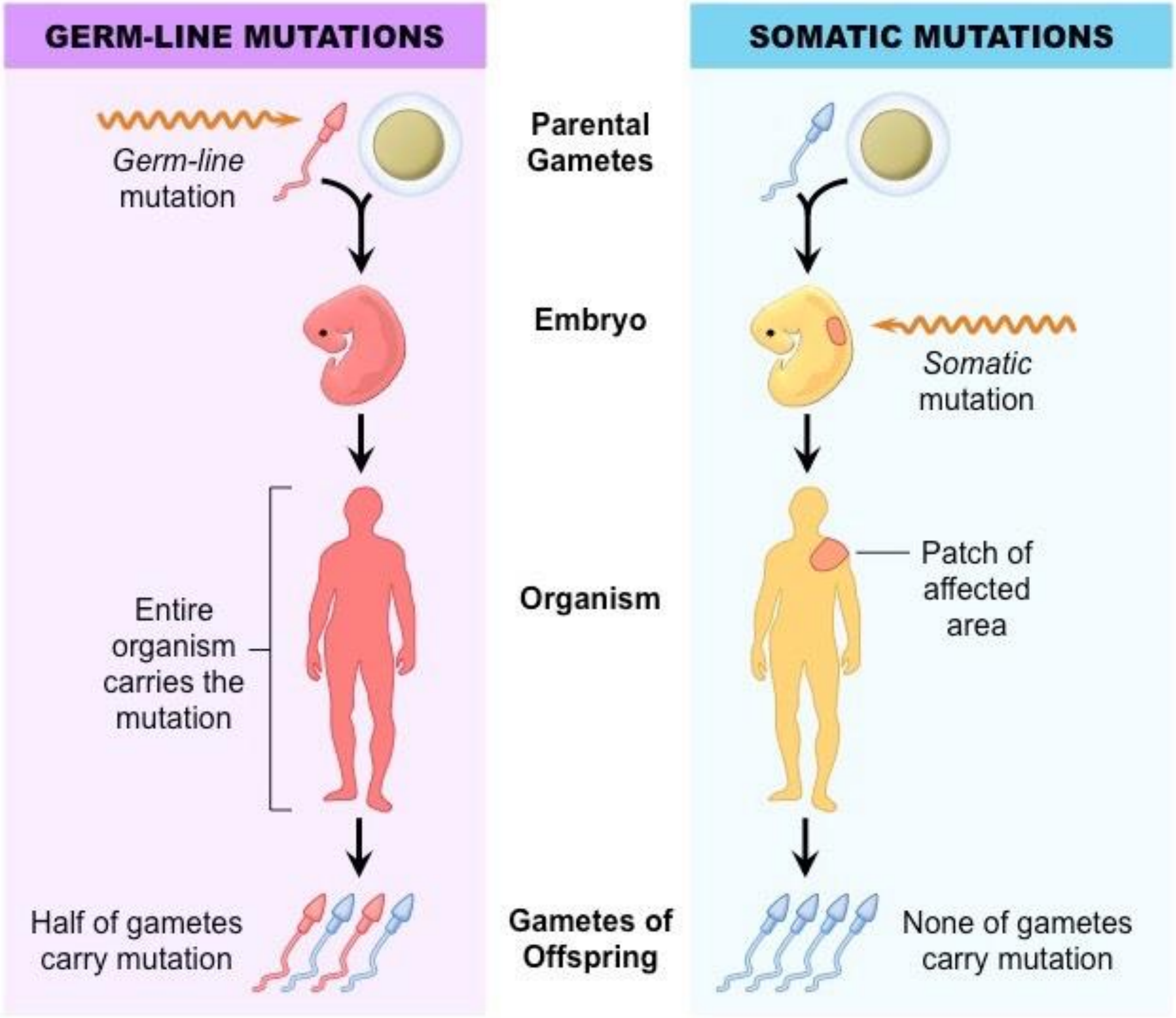
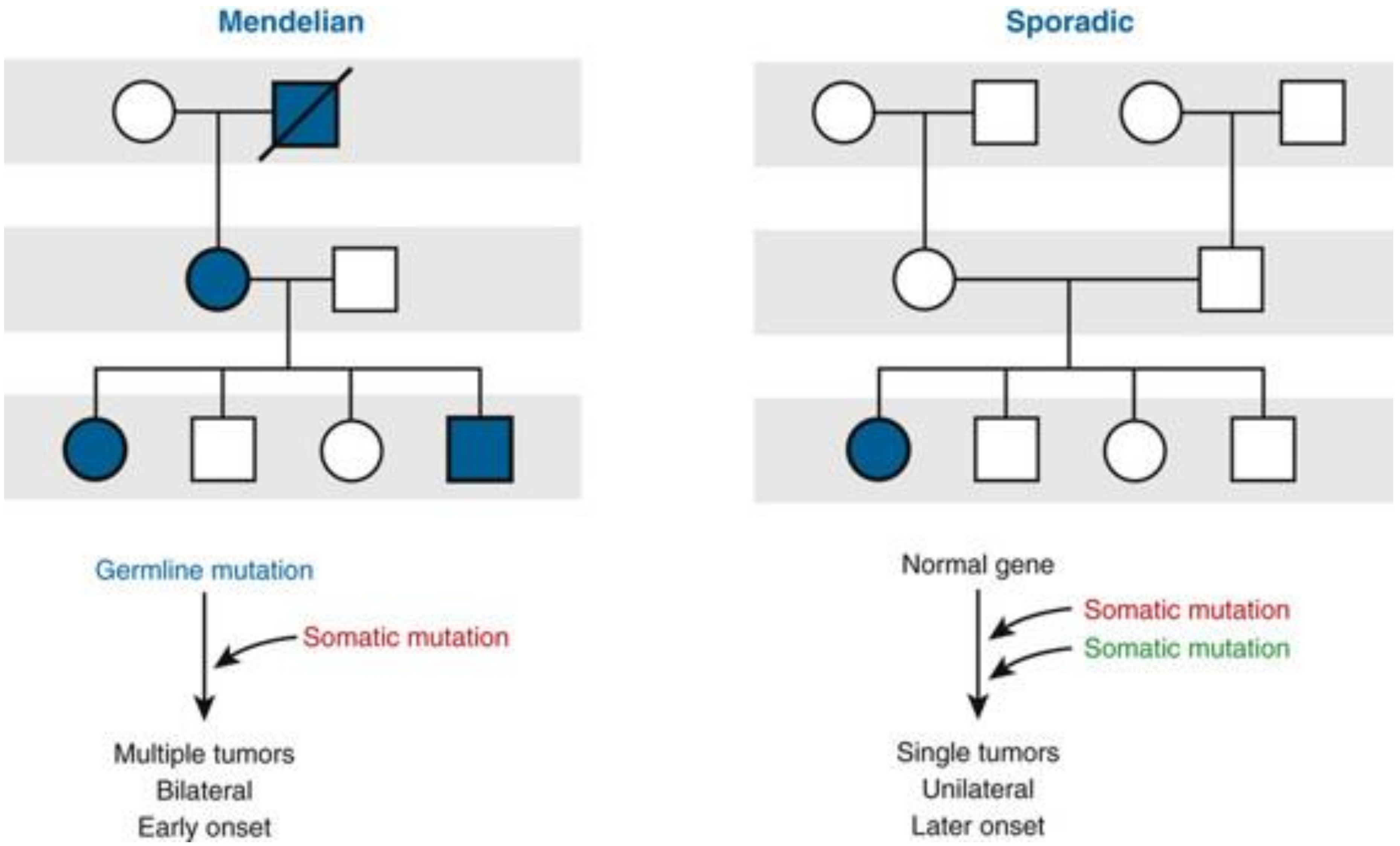
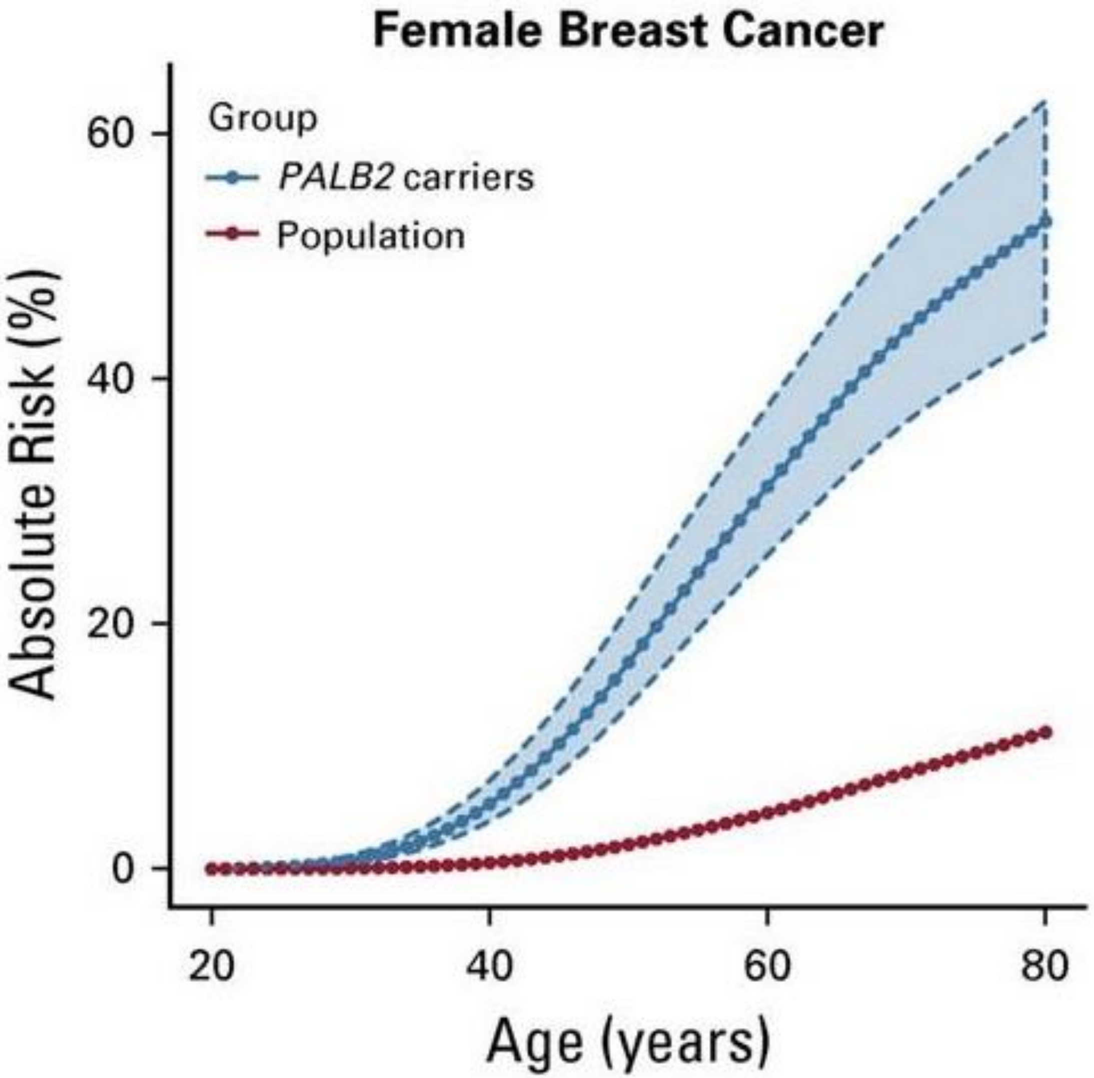
Germline vs. Somatic Mutations



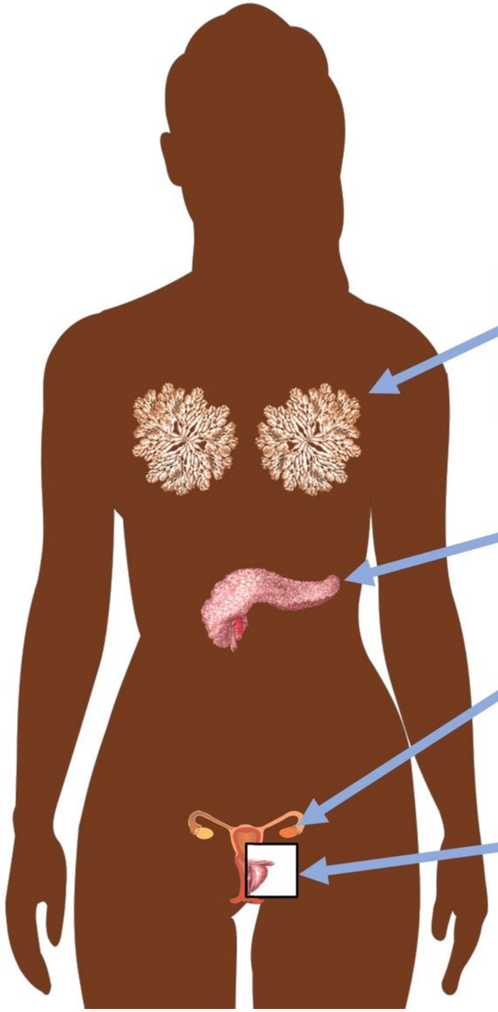
Germline vs. Somatic Mutations



PALB2 Germline Mutations: Breast Cancer Risk



BRCA Germline Mutations: Risk of Various Cancers



	BRCA1	BRCA2
Breast cancer:	**50% to 65%** Males: 1.2%	**40% to 55%** Males: Up to 9%
Pancreas cancer:	1-3%	2-7%
Ovarian cancer:	**40% to 65%**	**15% to 25%**
Prostate cancer:	9%	15%

Application of Genomics

Types of Genetic Testing

Molecular Genetic Tests

- Detect changes at the DNA, RNA, or protein level.
- Includes tests for **point mutations**, **insertions/deletions**, and **epigenetic changes**.
- Used to identify conditions caused by small-scale genetic changes (e.g., sickle cell anemia, cystic fibrosis).

Chromosomal Genetic Tests

- Identify larger-scale genetic changes, including alterations in chromosome structure or number.
- Includes **karyotyping**, **fluorescence in situ hybridization (FISH)**, and **copy number variations (CNVs)**.
- Used for detecting **aneuploidy**, **translocations**, and other chromosomal disorders (e.g., Down syndrome, certain cancers).

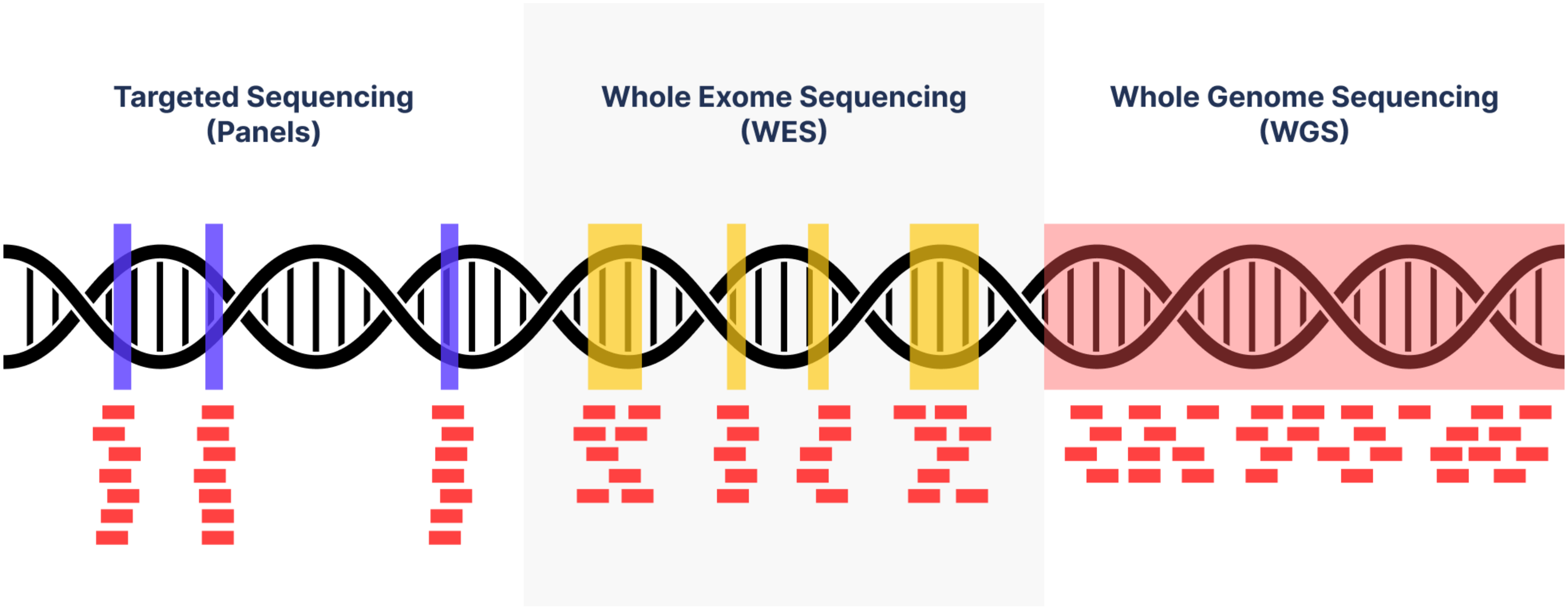
Biochemical Genetic Tests

- Assess the levels of proteins, enzymes, or metabolites.
- Used to evaluate the biochemical consequences of genetic mutations.
- Often used to diagnose **metabolic disorders** (e.g., phenylketonuria, enzyme deficiencies).

The Human Genome Project: From Blueprint to Completion

- **1990** – The Human Genome Project begins.
- **1995** – The first draft of small, individual sections of the human genome was completed.
- **2000** – A rough draft of the entire human genome was announced, providing the first public view of the sequencing.
- **2003** – Sequencing completed on 92% of 10 samples! The Genetic Information Non-Discrimination Act (GINA) is passed. The ENCODE project begins.
- **2006** – The largest human chromosome, 1, was fully sequenced.
- **2008** – The 1,000 Genomes Project is announced.
- **2022** – The full human genome sequence Telomere-to-Telomere is completed on the remaining 8%

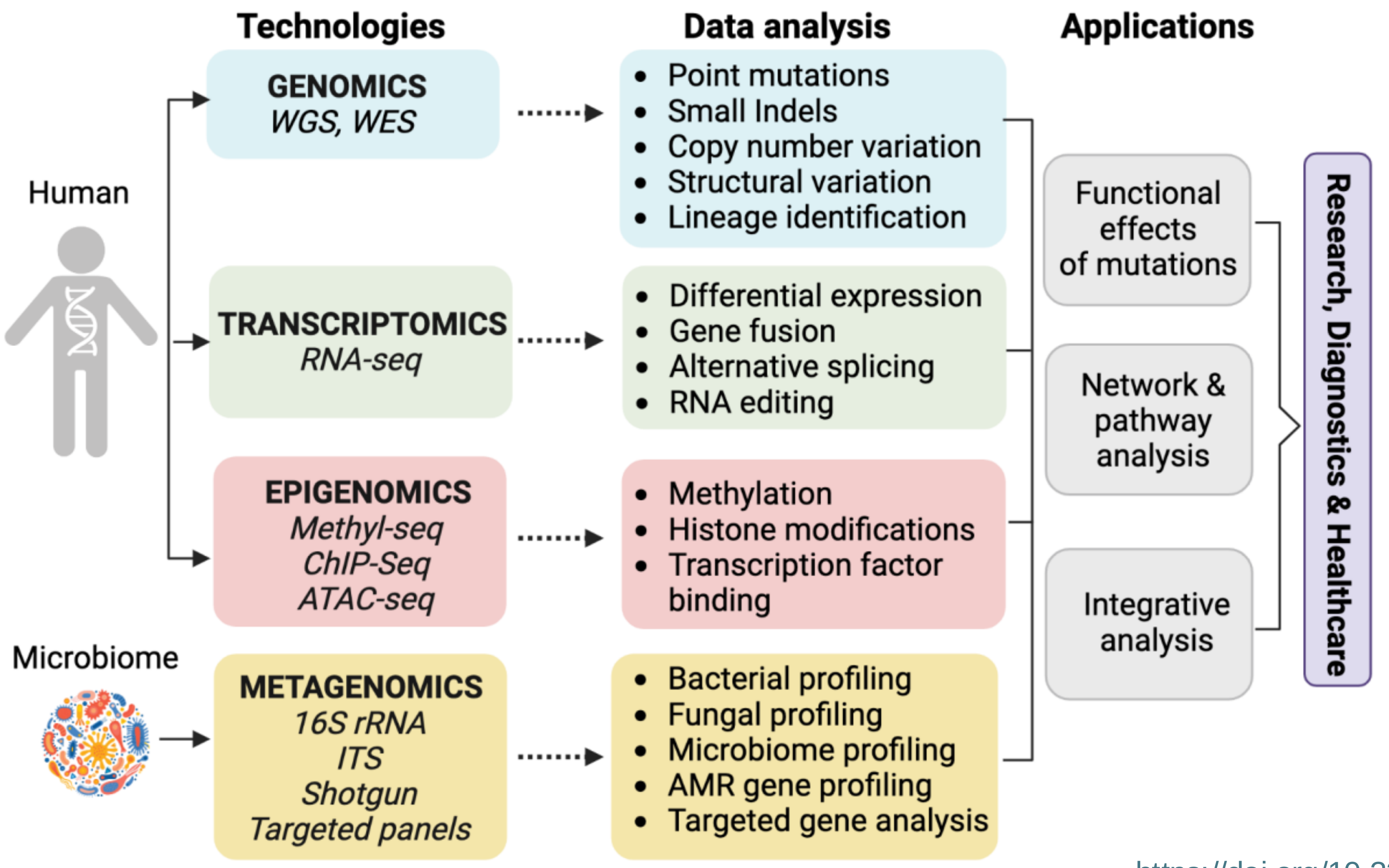
Comparing Sequencing Strategies for Genomic Insights



Approaches for Genomic Variant Detection

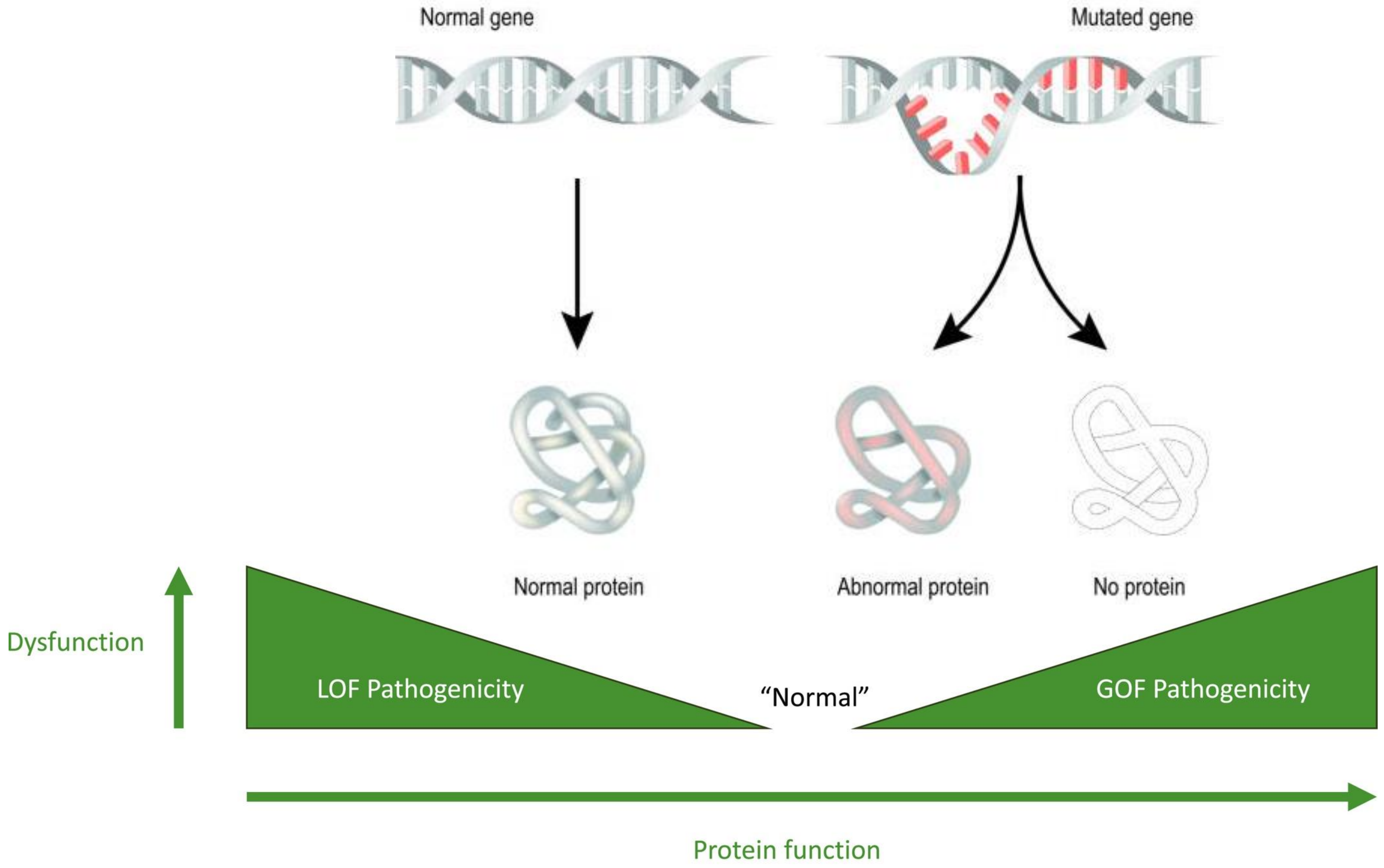
Single Nucleotide Variants (SNVs)	Single Gene Analysis	Multiple Gene Analysis	Copy Number Variants (CNVs)	Structural Variants
• Sanger Sequencing • PCR • Single Base Extension • SNP Arrays • Next-Generation Sequencing (NGS)	• PCR • Sanger Sequencing • MLPA (Multiplex Ligation-dependent Probe Amplification)	• Targeted NGS Panels (narrower scope) • NGS-based Gene Panels (multiple gene sets) • Whole Exome Sequencing (WES) • Whole Genome Sequencing (WGS) • RNA Sequencing (RNA-seq)	• SNP Arrays • MLPA • Microarray (aCGH) • NGS-based CNV Detection • FISH (Fluorescence In Situ Hybridization) • ddPCR (Digital Droplet PCR)	• Karyotyping • Microarray (aCGH) • FISH (Fluorescence In Situ Hybridization) • Long-Read Sequencing (e.g., PacBio, Oxford Nanopore)

Translating Genome Insights with NGS



https://doi.org/10.3390/biology12070997

Essential Concepts in Variant Classification



Pathogenic

Likely Pathogenic

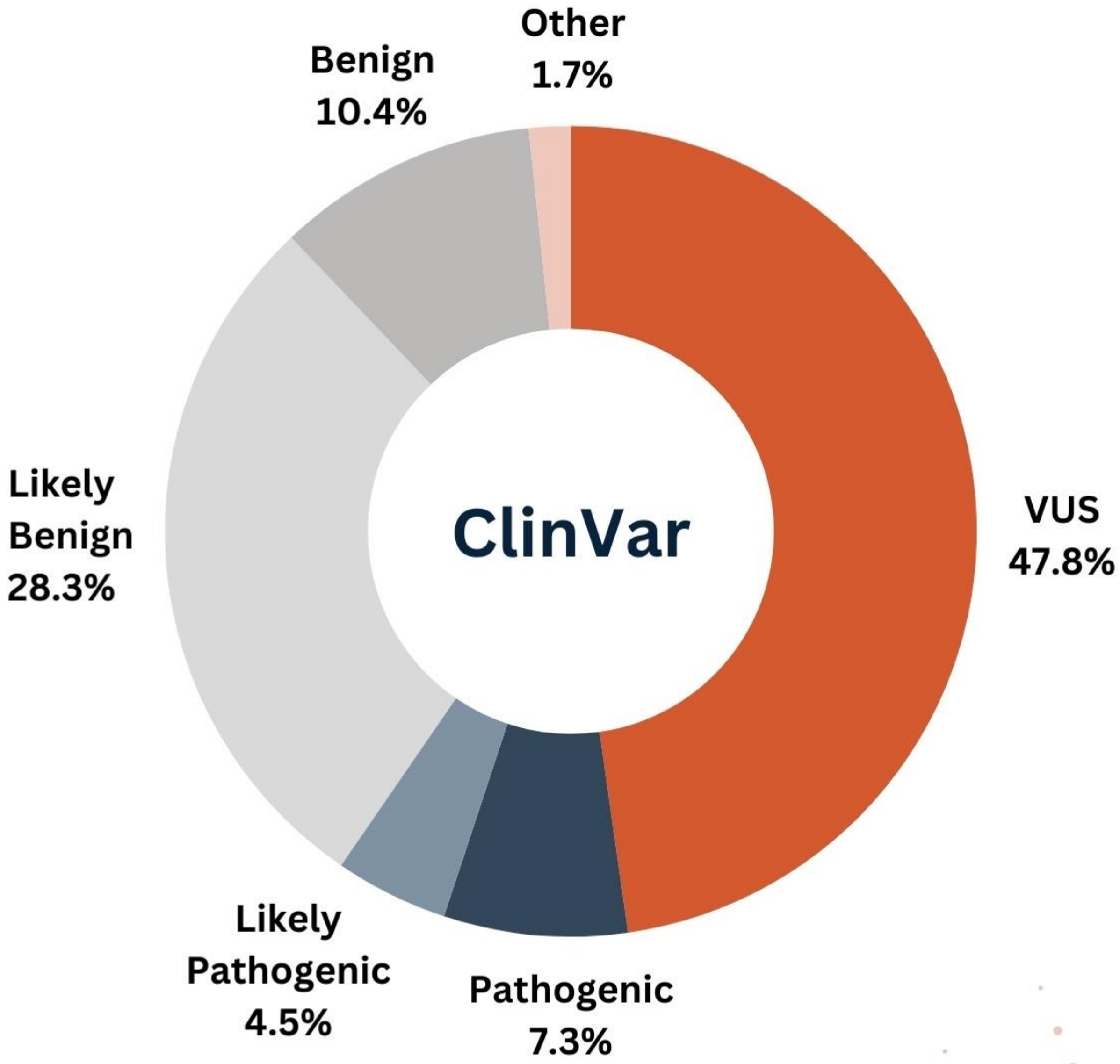
Variant of Uncertain Significance (VUS)

Likely Benign

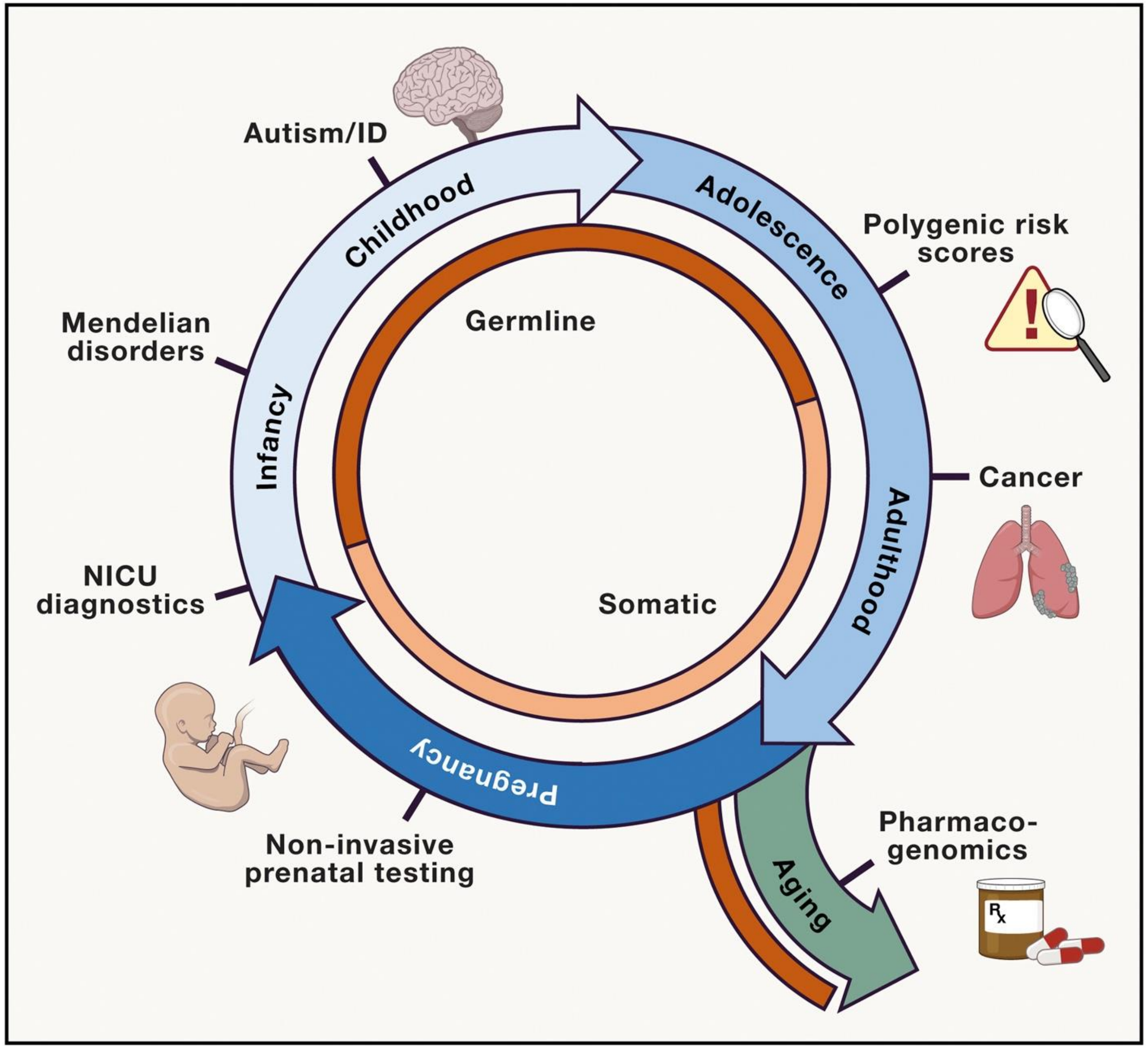
Benign

VUS: A Persistent Challenge

>1.2M variants are currently classified as “Uncertain Significance” in the ClinVar database

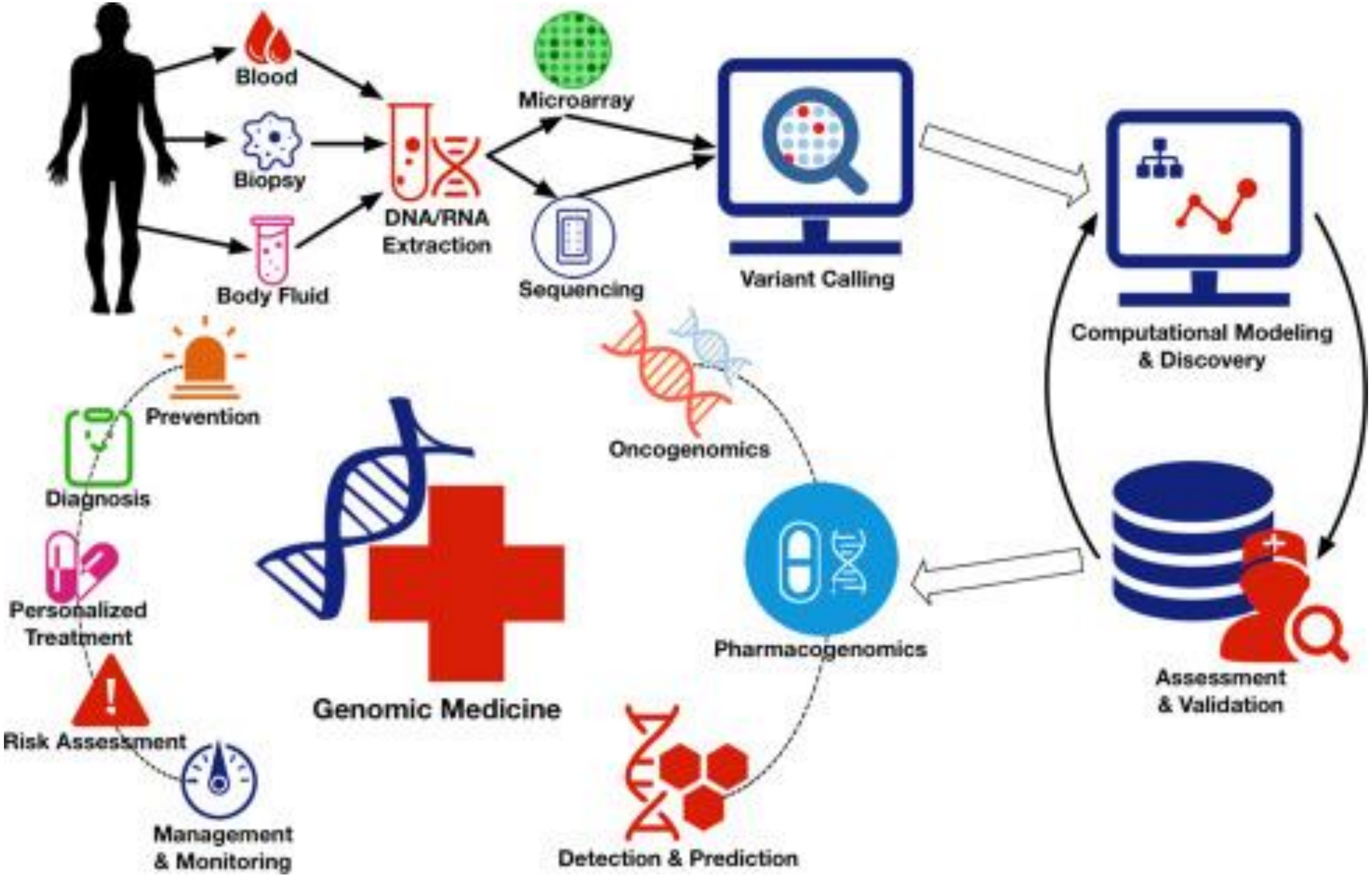


Genomic Medicine Throughout the Human Life Cycle

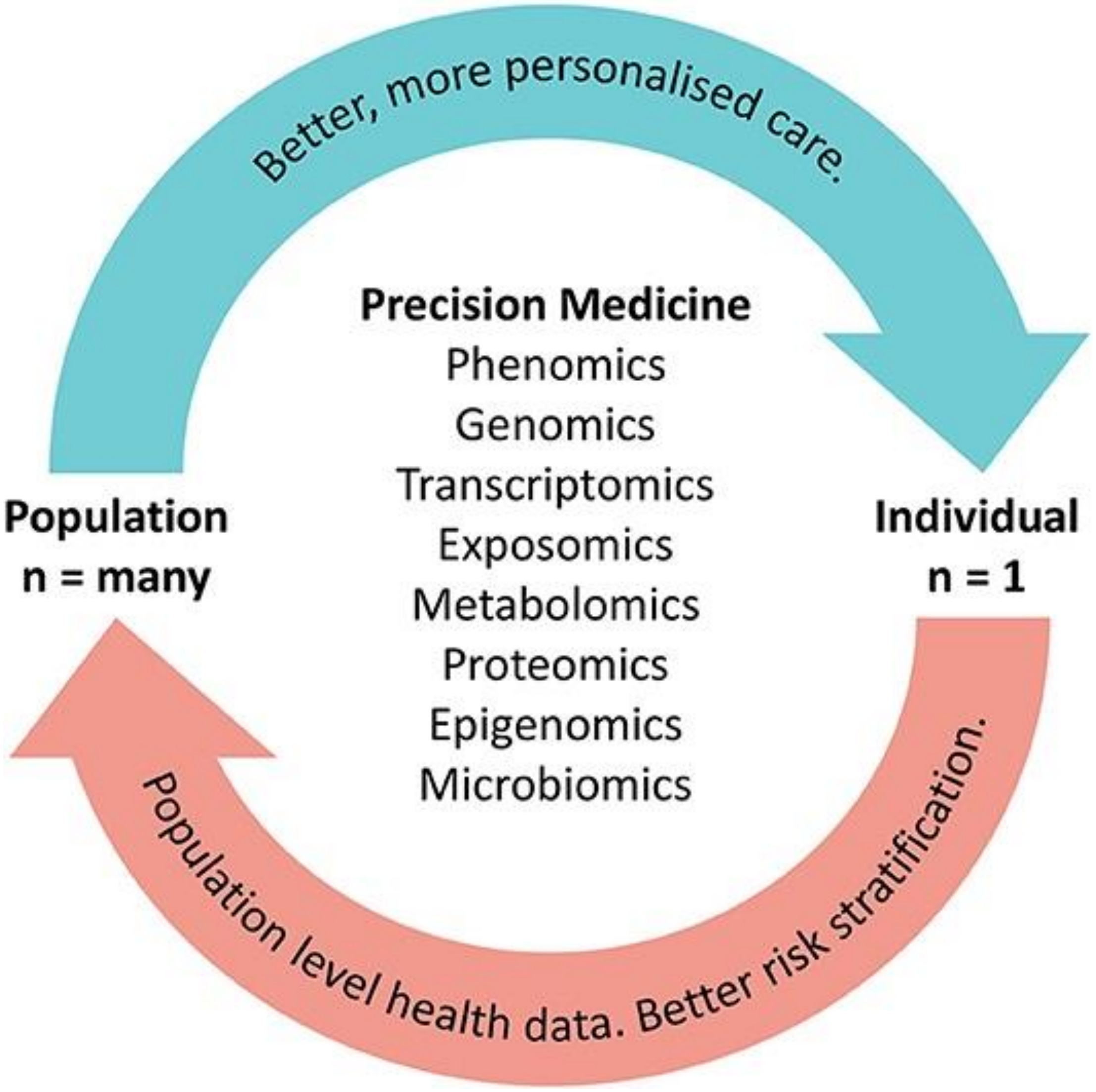


The Evolution of Medicine: Toward Precision Care

Harnessing Genomics for Precision Medicine



Practicing PM with integrative clinical and multi-omics data analysis



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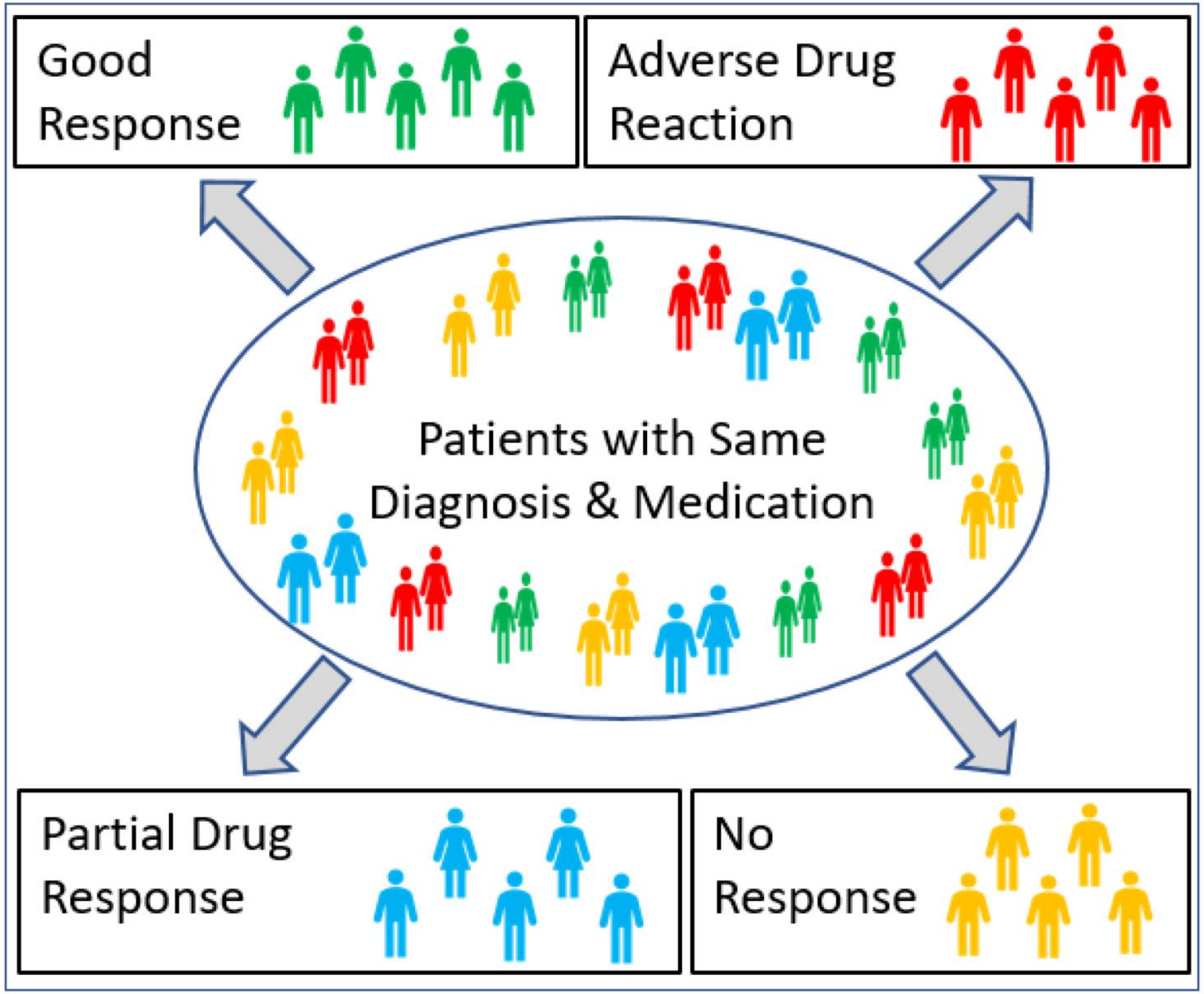
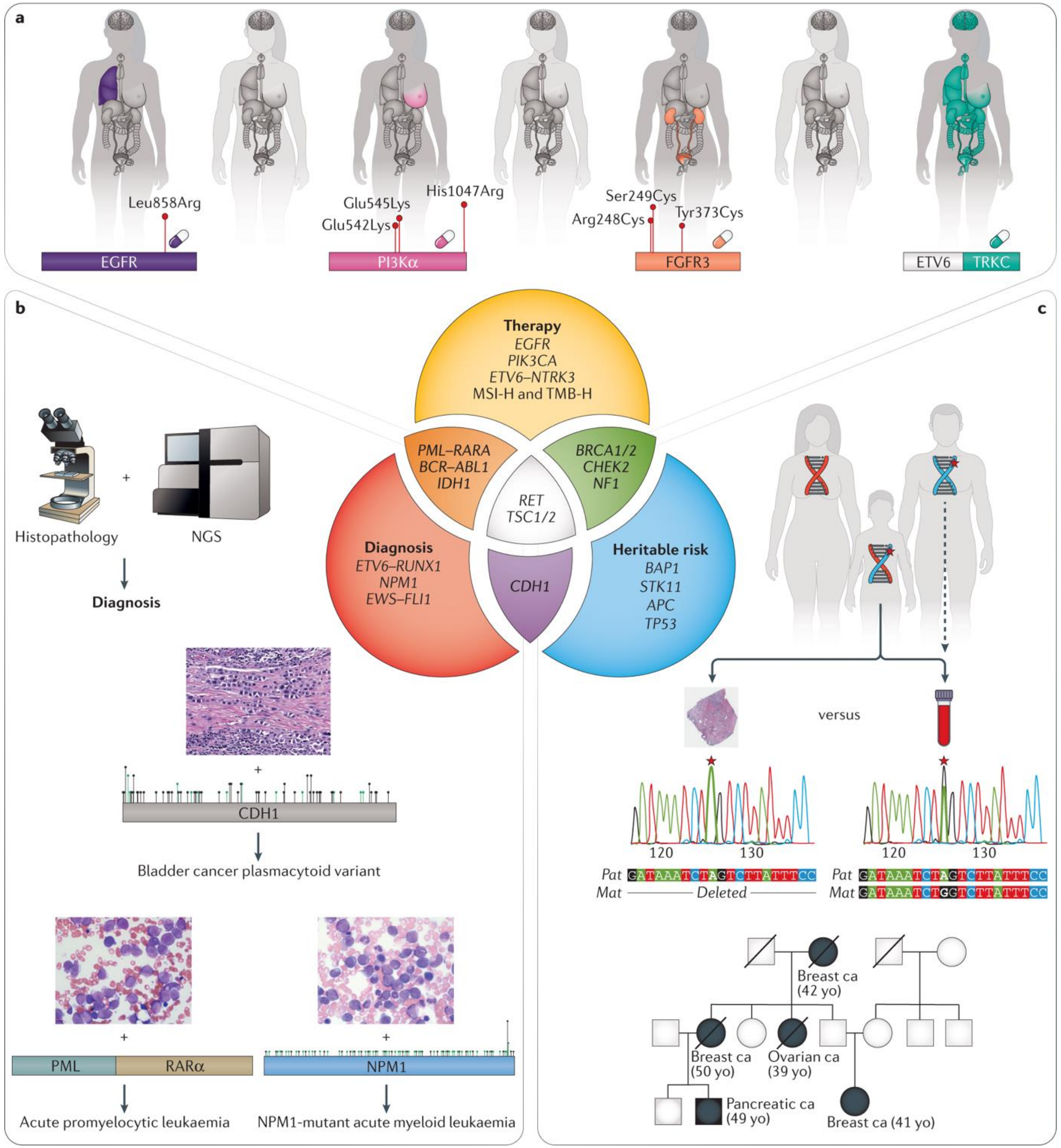
Pharmacogenomics and drug response in individuals with different genotypes.



Tumor genomic profiling in patient care



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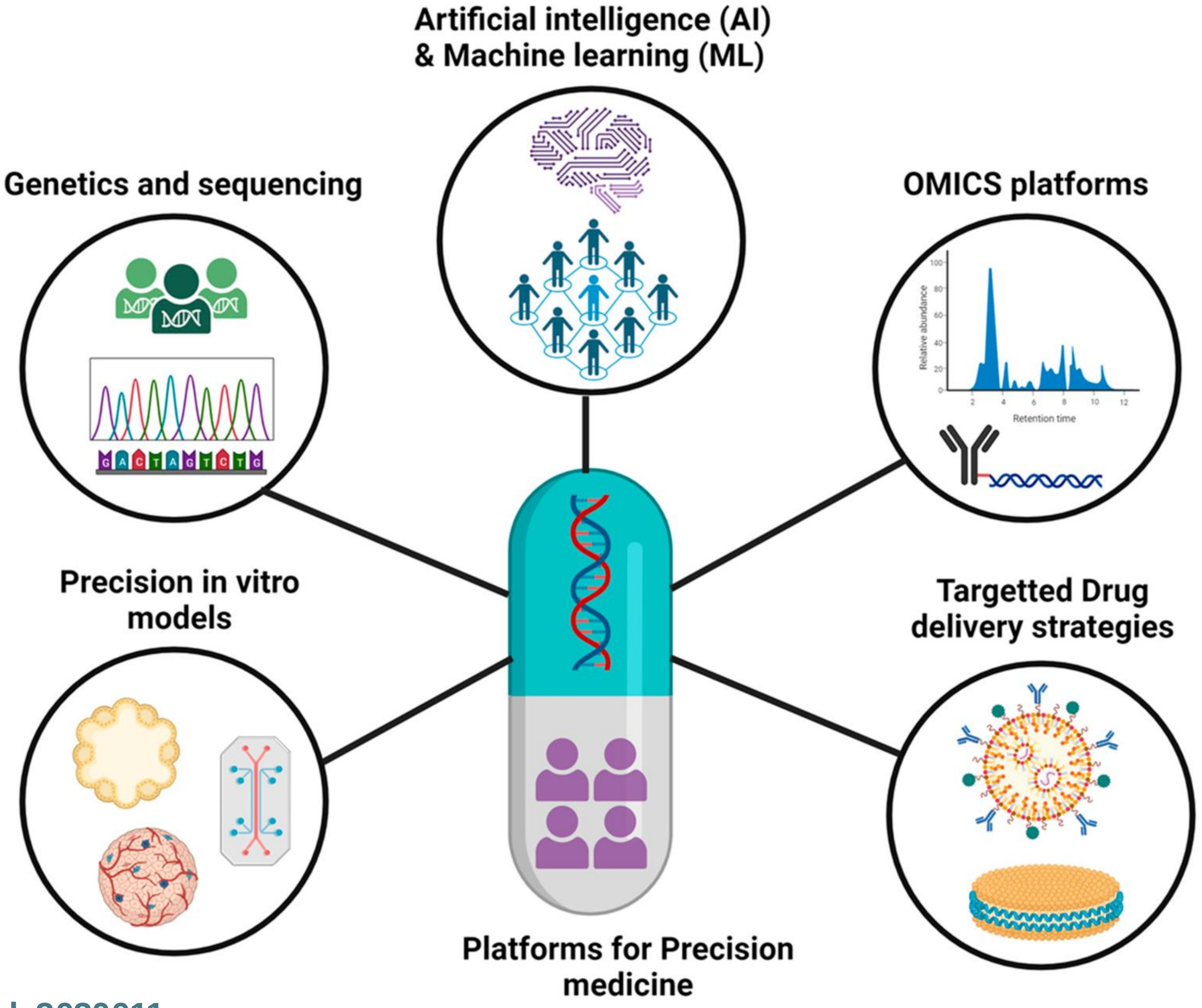
Platforms to Implement PM



https://doi.org/10.3390/organoids3030011

Clinical Challenges

Interpreting Complex Genomic Data

- Distinguishing clinically relevant mutations from benign variants is challenging.
- Integrating genomic data with patient history is key, but complex.

Ethical and Privacy Concerns

- Genomic data raises privacy, consent, and security issues, particularly in vulnerable populations.
- Ethical dilemmas also surround genetic testing in minors.

Limited Access to Testing and Data

- Disparities in access to genomic testing limit PM in underserved populations, and low-resource countries lack the necessary infrastructure.

Clinical Adoption and Implementation

- Barriers to routine clinical use include physician training, workflow integration, and reimbursement.
- Standardized protocols are needed for consistent application.

Ethical, Legal, and Social Issues (ELSI) in Genetic Testing

Ethical Considerations:

Ensuring informed consent is properly obtained, protecting patient privacy and confidentiality, addressing potential genetic discrimination, and navigating the implications of testing for family members. The ethical responsibility of disclosing incidental findings and respecting patient autonomy in decision-making are also key concerns.

Legal Considerations:

Compliance with regulations such as CLIA and FDA oversight for genetic testing, adherence to data protection laws like HIPAA and Genetic Information Nondiscrimination Act (GINA), and legal protections against genetic discrimination.

Social Considerations:

Addressing disparities in access to genetic testing, considering cultural perspectives on genetic information, and managing the psychological and societal impact of genetic findings.

The Future of Genomics in PM

Integrating Multi-Omics for Comprehensive Patient Profiles

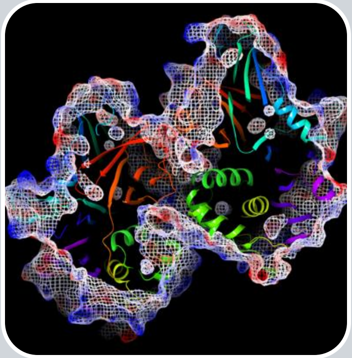
- Combining genomics, transcriptomics, proteomics, and metabolomics enables more accurate predictions and personalized treatments.

AI-Driven Tools for Genomic Analysis and Interpretation

- AI will enhance the analysis of large genomic datasets, improving variant interpretation, clinical decision-making, and identifying novel therapeutic targets.

Real-Time Genomic Monitoring for Treatment Response

- Real-time genomic monitoring may allow adjustments to therapies during treatment and track disease evolution, improving patient outcomes.



Improved Variant Interpretation and Databases

- More comprehensive genetic databases and refined tools will improve the classification of Variants of Uncertain Significance (VUS) and their clinical relevance.

Gene Editing and Therapeutic Applications

- Technologies like CRISPR-Cas9 offer potential for correcting genetic mutations and enhancing therapies, particularly in genetic disorders and cancer treatment.

Expanded Access to Genomic Testing

- Reducing the cost and increasing access to genomic testing will make PM more widely available, especially in underserved populations.

Summary - Genomics as a Pillar of PM

- **Foundation of Individualized Care** – Genomic insights drive tailored approaches to diagnosis, treatment, and disease prevention.
- **Understanding Genetic Variability** – Identifies mutations, structural variations, and inherited risks that influence health and therapeutic response.
- **Advancing Targeted Therapies** – Supports the development of precision treatments based on a patient's genetic profile.
- **Integrating into Clinical Practice** – Enables risk assessment, early detection, and personalized treatment strategies across diverse medical fields.
- **Challenges & Future Directions** – Ethical considerations, data privacy, equitable access, and the ongoing need for research and innovation.

Thank you!

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