Common Diseases and Cancer Genetics

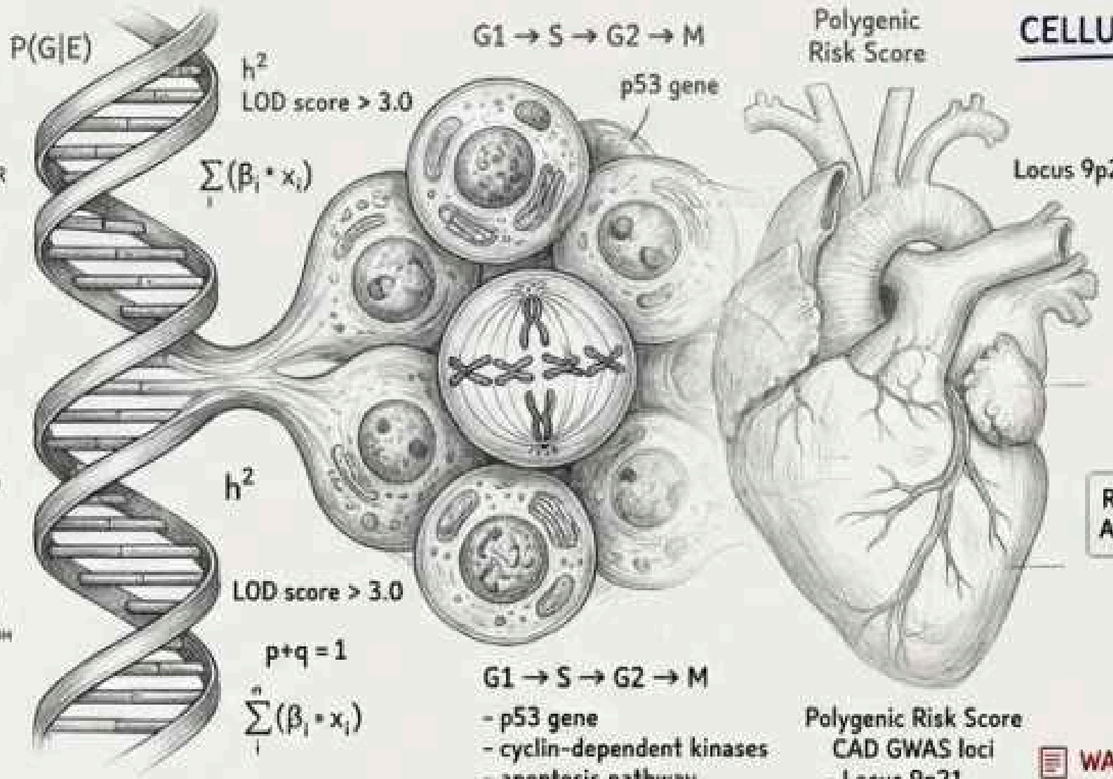
A Visual Synthesis of Heritability, GWAS, and Cellular Control

HERITABILITY & GWAS MATRIX

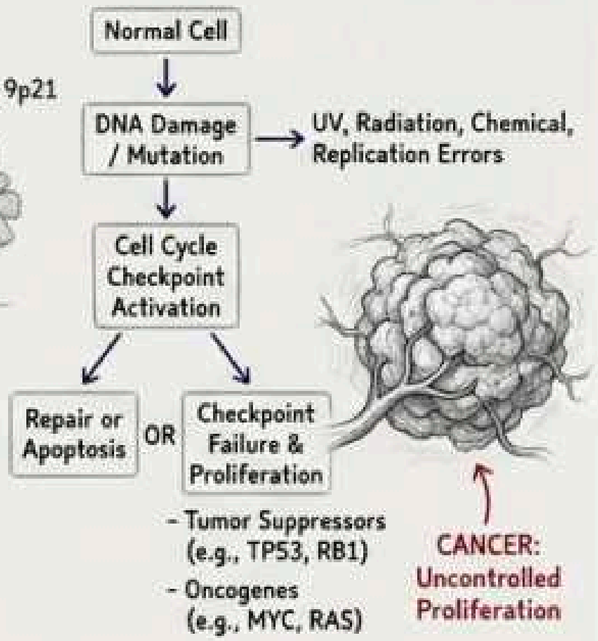
Trait Type	Heritability (h^2)	GWAS Discovery	Clinical Example (Dark Green)
Monogenic	High ($h^2 > 0.8$)	Single Locus, Large Effect	Cystic Fibrosis (CFTR)
Oligogenic	Moderate ($h^2 \sim 0.4$–0.8)	Few Loci, Moderate Effect	Hirschsprung Disease (RET)
Polygenic	Low/Moderate ($h^2 < 0.5$)	Many Loci, Small Effect	Coronary Artery Disease (CAD)
Complex (GxE)	Variable	Gene–Environment Interaction	Type 2 Diabetes (TCF7L2 + Diet)

CFTR

⚠ CRUCIAL DATA: Most common diseases are polygenic and require large-scale GWAS for discovery.



CELLULAR CONTROL & CANCER BASIS

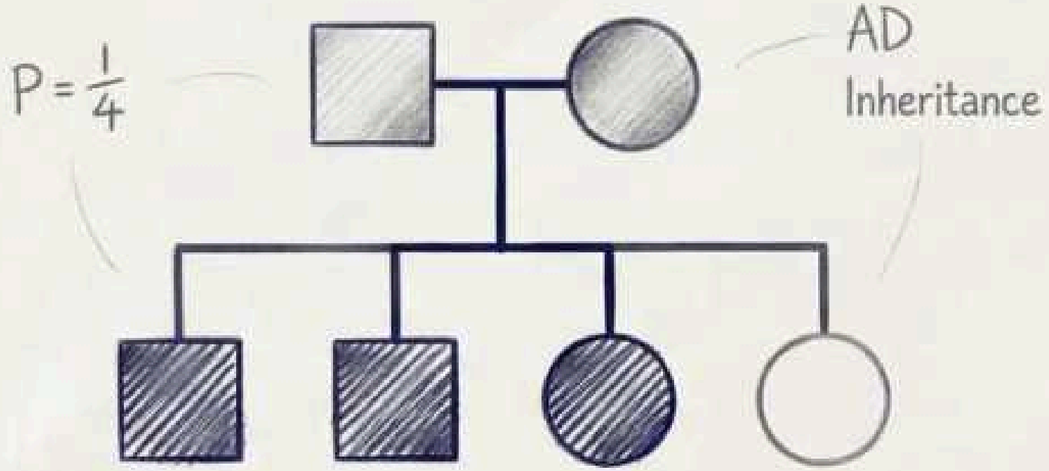


WARNING: Accumulation of driver mutations leads to malignant transformation and metastasis.

Exploring multifactorial traits, polygenic risk, gene-environment interaction, and the genetic basis of cancer cells.

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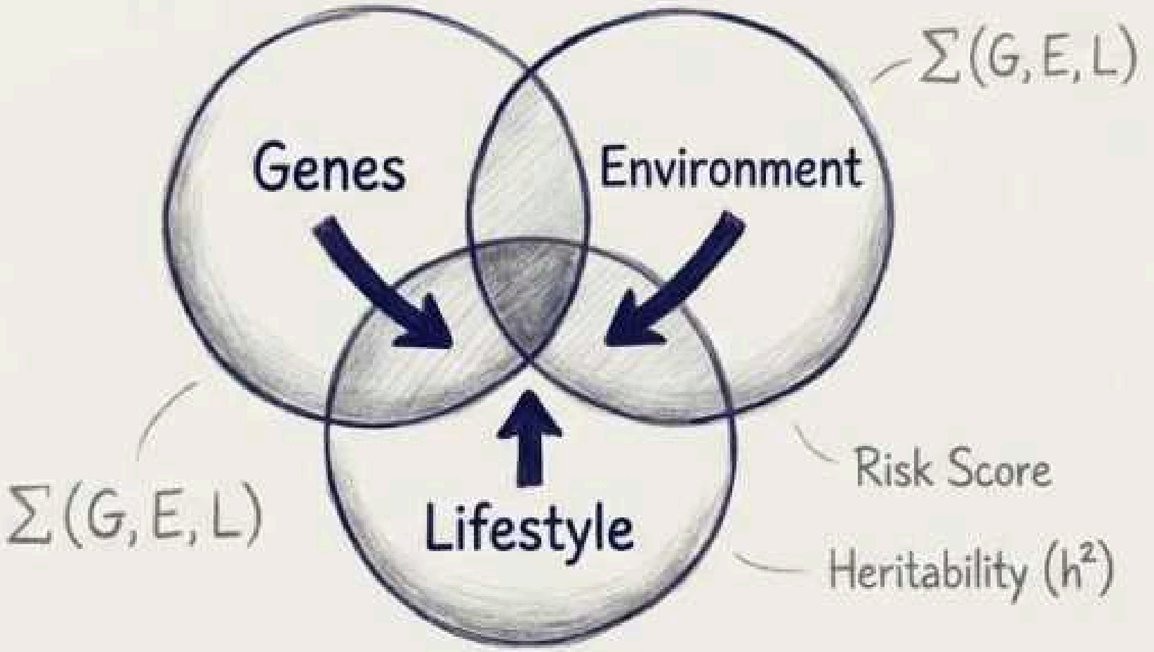
Mendelian / Rare



Individually rare

Strict inheritance patterns

Multifactorial / Complex

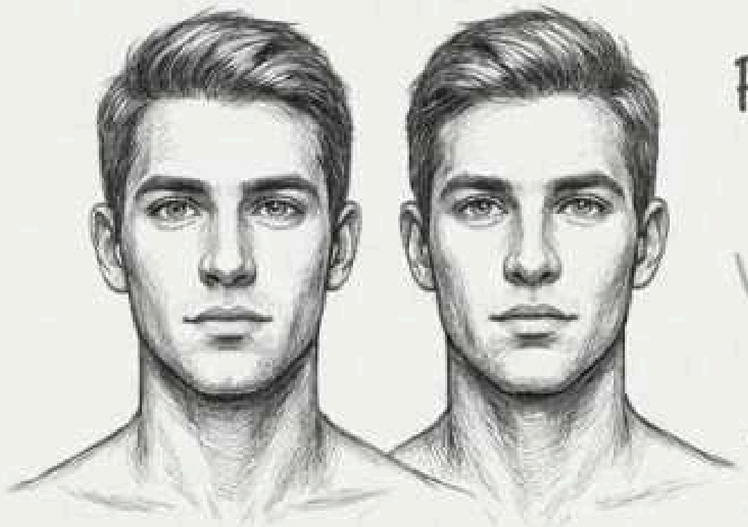


These fill clinics. Run in families without neat patterns.

Driven by combined effects of many small-effect genetic variants + environment.

Heart disease, Type 2 diabetes, Asthma, High blood pressure, Mental health conditions.

¶ 5.2



≈100% DNA Shared

P(MZ)

$$H^2 = \frac{V_G}{V_P}$$

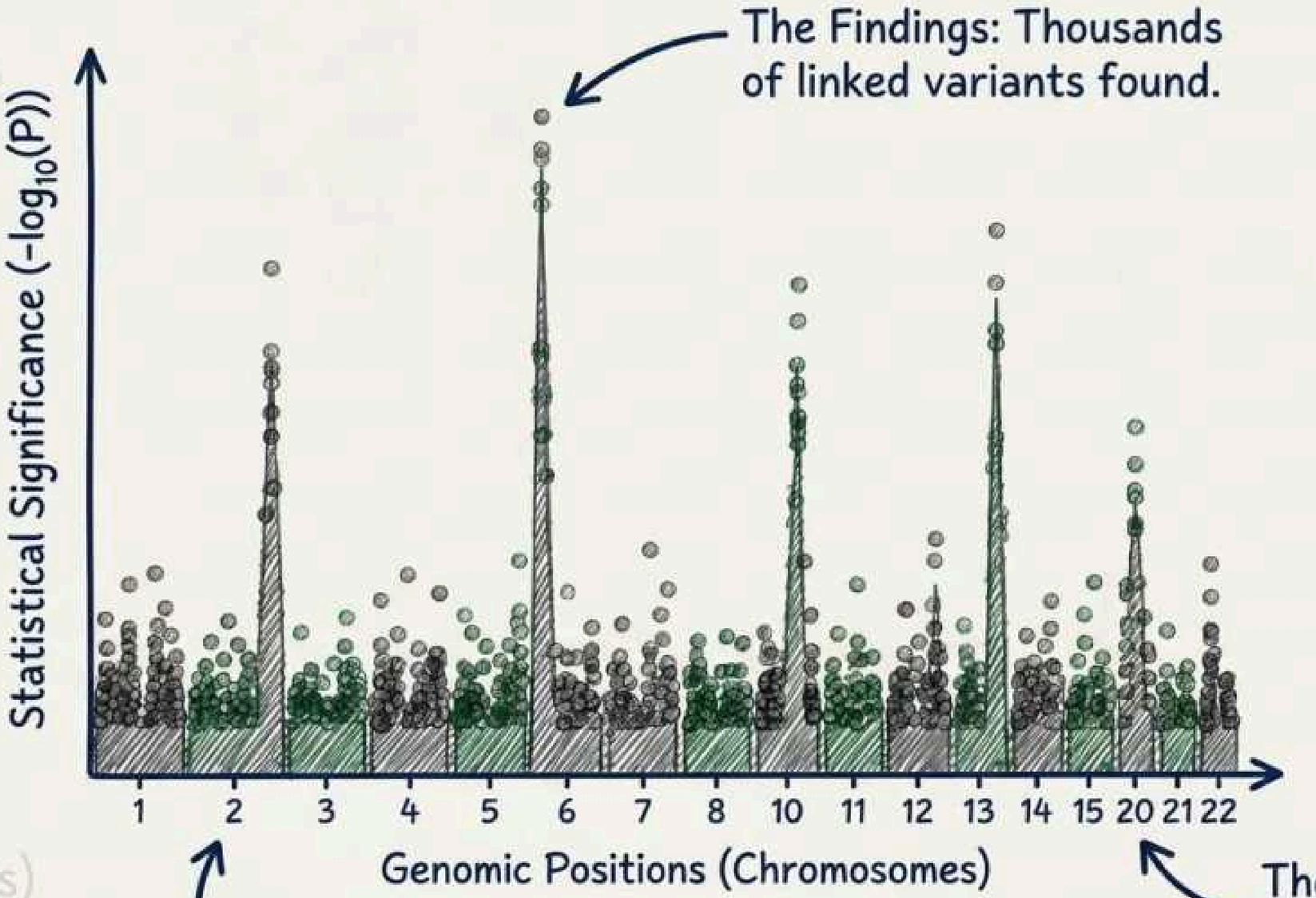
P(DZ)



≈50% DNA Shared

Comparing identical vs. non-identical twins reveals the genetic contribution to a condition in a population.

Crucial Caveat: Heritability describes variation in a population, NOT how much of one person's disease is caused by genes. Highly heritable conditions can still be heavily influenced by the environment.

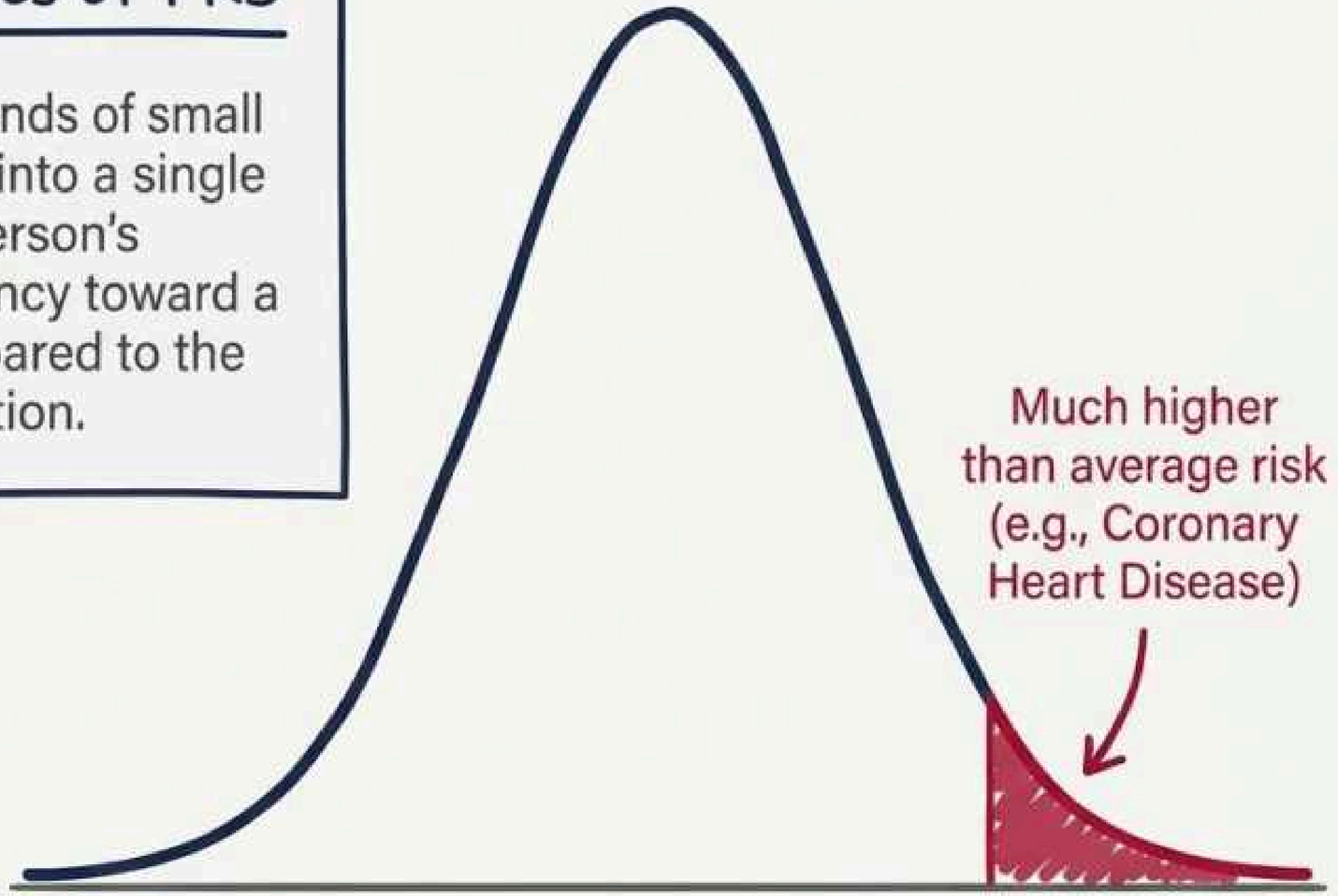


Crucial Detail:
Many of these variants lie in regulatory regions (controlling genes) rather than in the coding genes themselves.

¶5.4

The Mechanics of PRS

Adds up thousands of small genetic effects into a single estimate of a person's inherited tendency toward a condition compared to the general population.



Limitations:

- PRS are probabilities, not destiny.
- Work less well in populations underrepresented in original research.
- Role in routine clinical care is still evolving.

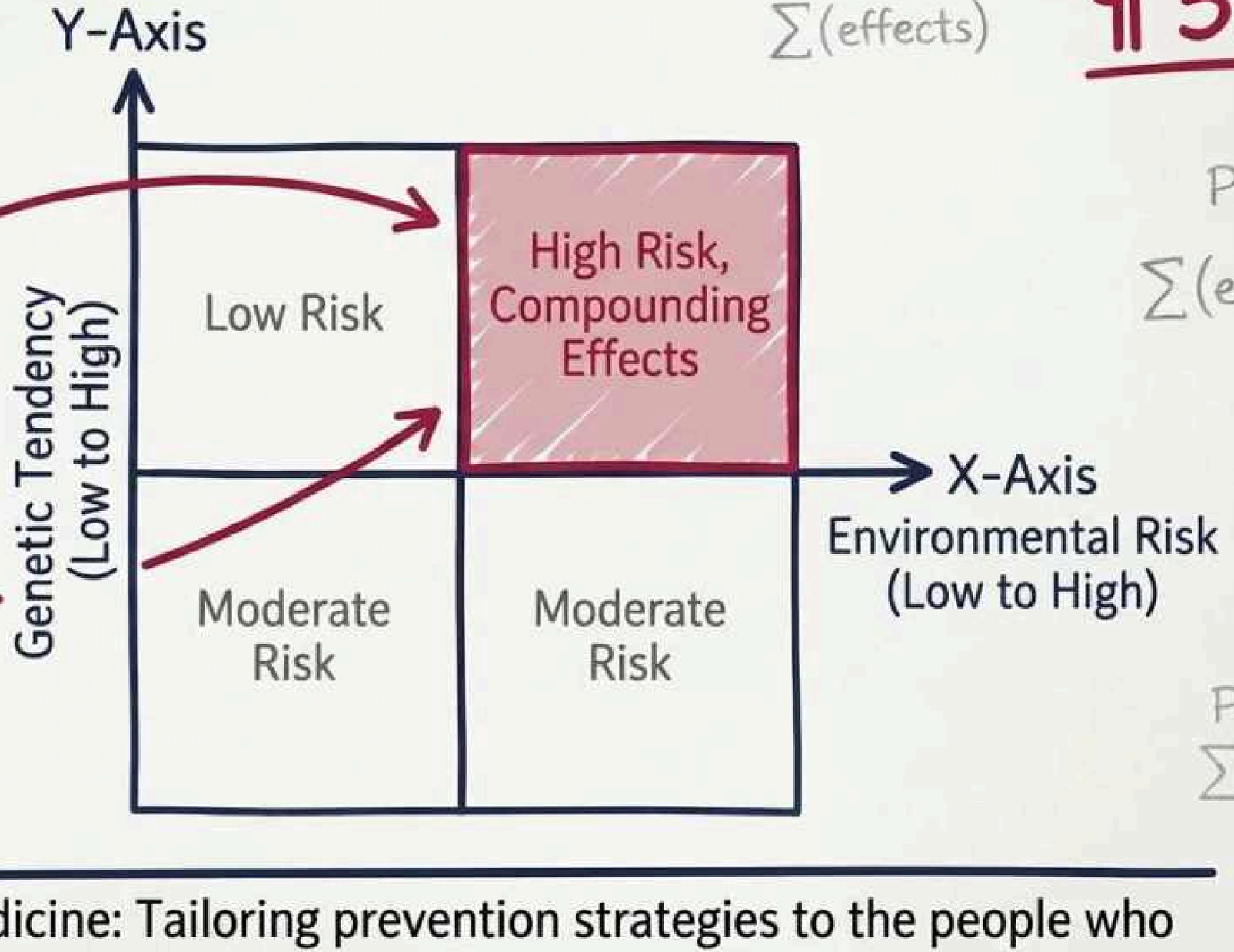
GxE

P(var)
∑(effects)

¶ 5.5

Metabolic Example:
A genetic tendency toward Type 2 diabetes matters most in an environment of plentiful food and little exercise.

Respiratory Example:
Smoking raises lung disease risk for everyone, but genetically vulnerable individuals face severe compounding risk.



P(var)
∑(effects)

P(var)
∑(effec

LOC4*

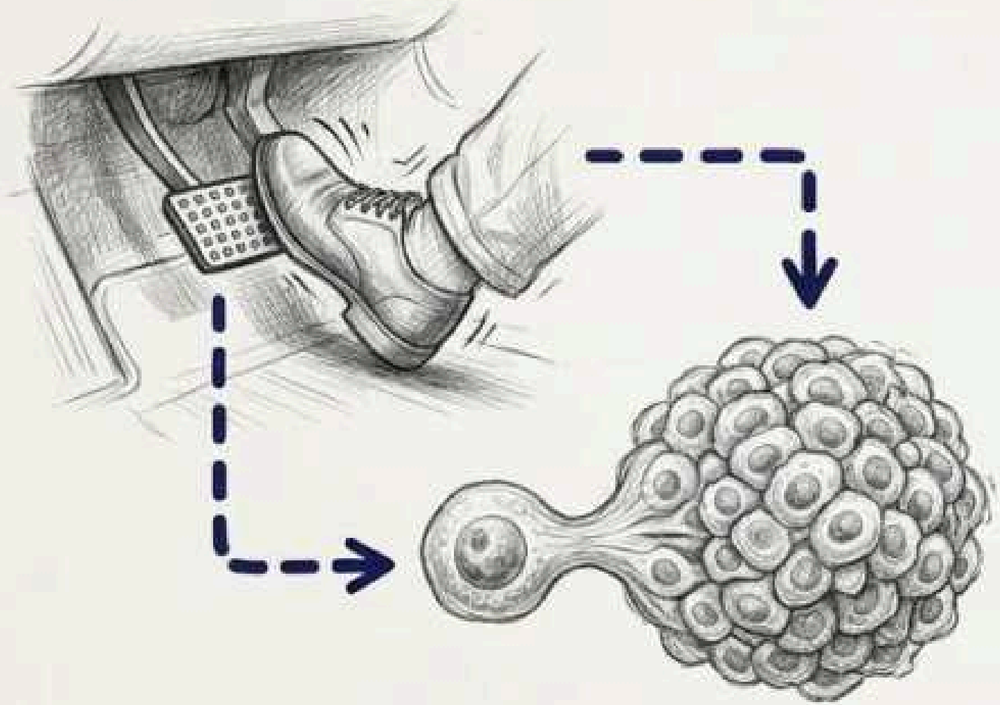
Personalised Medicine: Tailoring prevention strategies to the people who will benefit the most by understanding these specific interactions.

P(var)
Σ(effects)
P(mut)

Cancer is a genetic disease of cells: driven by accumulated somatic changes in growth/division genes.

¶ 5.6

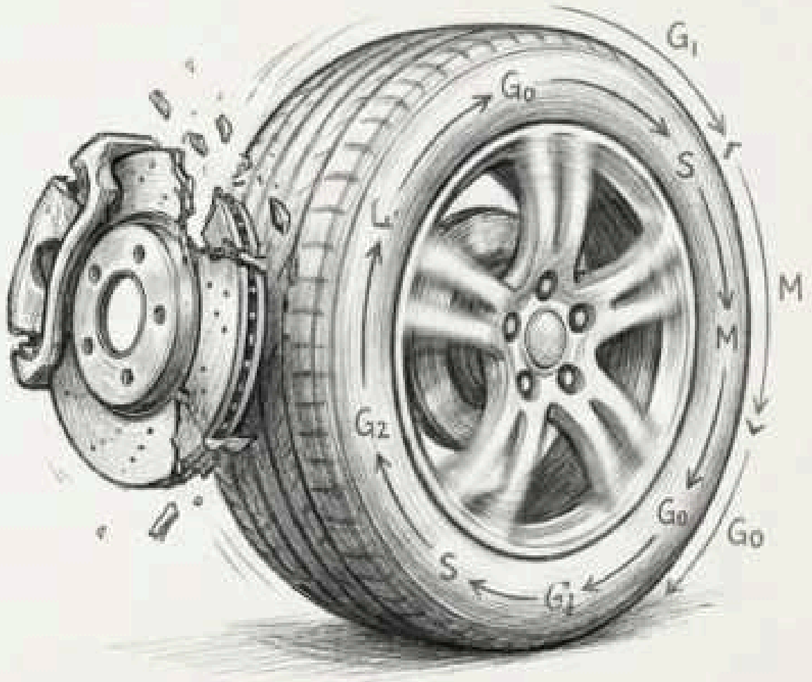
Oncogenes



Promote cell growth.

A permanent ‘on’ switch acts like a jammed accelerator.

Tumour Suppressor Genes



Normally restrain growth or repair DNA.

Losing them is like losing the brakes entirely.

genetic →

genetic ←

Σ(effects)

P(mut)

genetic locus markers

premium academic whiteboard slide

The Two-Hit Idea (Alfred Knudson, 1970s - Retinoblastoma)

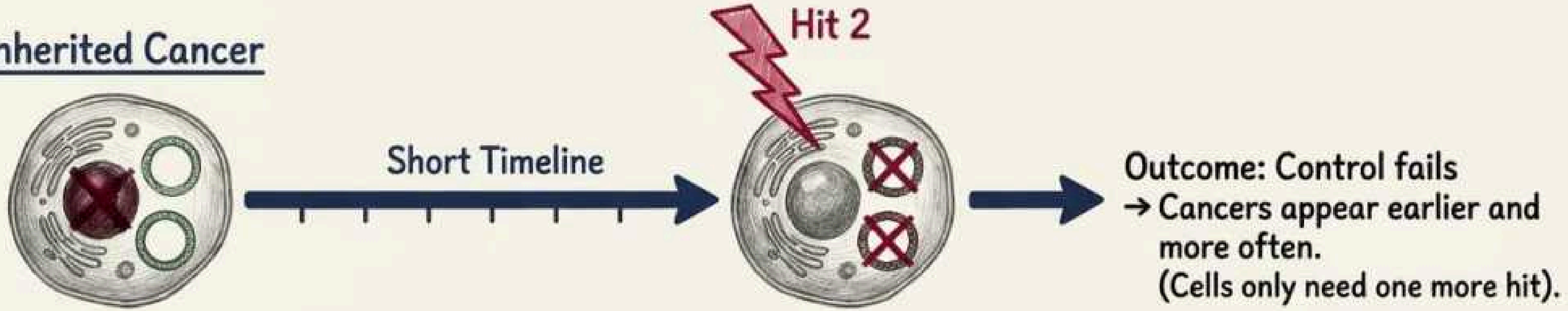
¶ 5.7

Sporadic Cancer



Healthy Cell
(Two Intact Copies)

Inherited Cancer



Cell Born with One Faulty Copy
(Inherited Mutation)

P(var)

P(mut)

¶ 5.8

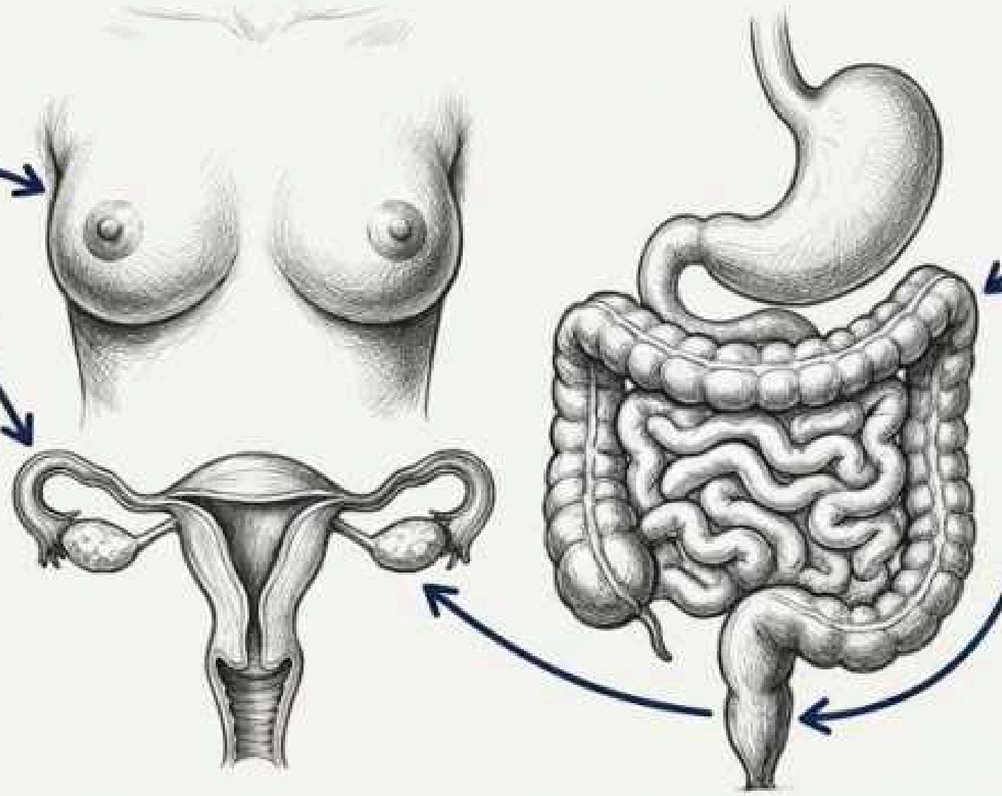
genetic locus markers

∑(effects)

LOC4*

BRCA1 / BRCA2

Inheriting a harmful variant substantially raises lifetime risk of breast, ovarian, and other cancers.



Lynch Syndrome

Caused by faulty DNA repair genes. Raises risk of bowel, womb, and other cancers.

genetic locus markers

LOC4*

- Clinical Application: Knowing variant status allows for extra screening, preventive options, and specific treatments.
- Important Context: Only a minority of cancers arise from a strongly inherited variant.

P(success)

LOC4*

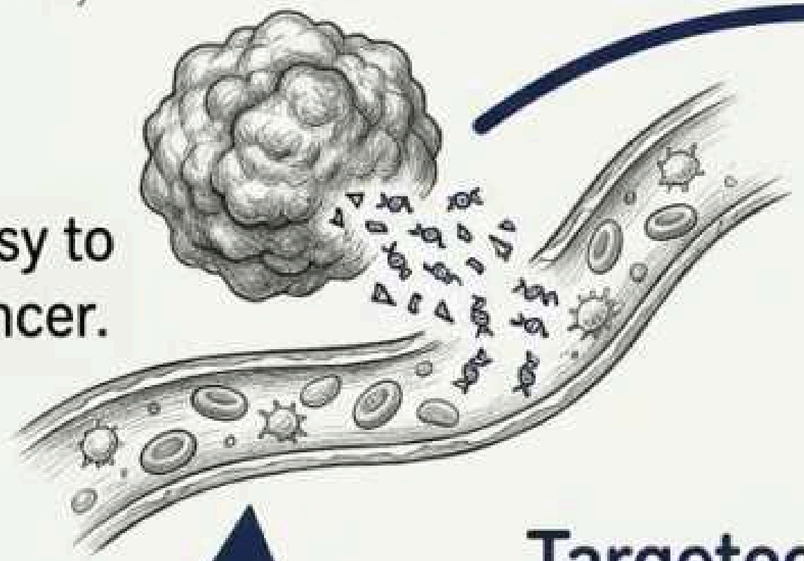
¶ 5.9

∑(outcomes)

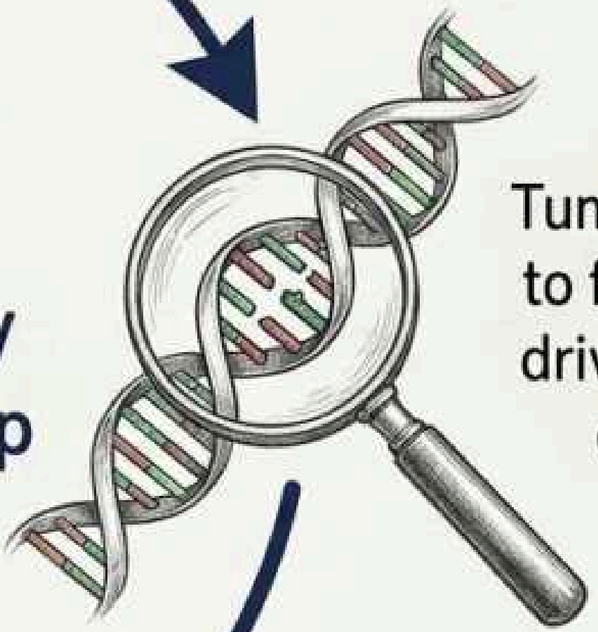
genetic markers

LOC4*

Liquid Biopsy to monitor cancer.



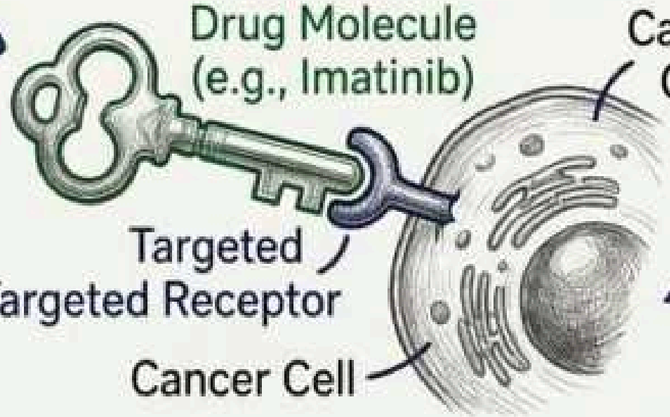
Targeted Therapy & Monitoring Loop



Tumours tested to find specific driving genetic changes.

P(drug efficacy)

Treatments chosen to target those changes, e.g., leukaemia drug from Lecture 4.



LOC4*

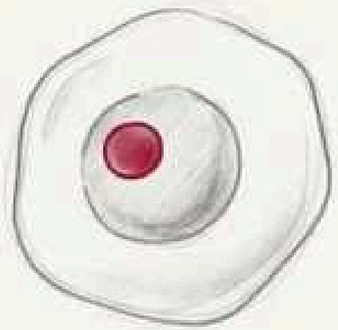
genetic markers

See Pathology (MED 505 B) and Pharmacology (MED 511 B) for deeper clinical mechanics.

¶ 5.10

Lecture 5 Synthesis Question

Using the **two-hit idea**, explain why people who inherit a faulty copy of a tumour suppressor gene tend to develop cancer earlier than other people.



Looking Ahead: The Final Lecture

- Genetic Testing Applications
- New Genetic Treatments
- The Ethical Questions They Raise

