

Topic 06

University Medicine

What this course is, and how to use it

This is the sixth course in University Medicine: **medical genetics**. MED01 explained the molecule; this course explains its inheritance – how variants travel through families and populations, and how the clinic reads them.

Scope limit, stated once: a study course, not a medical degree; every case below is fictional and nothing here licenses or guides treatment.

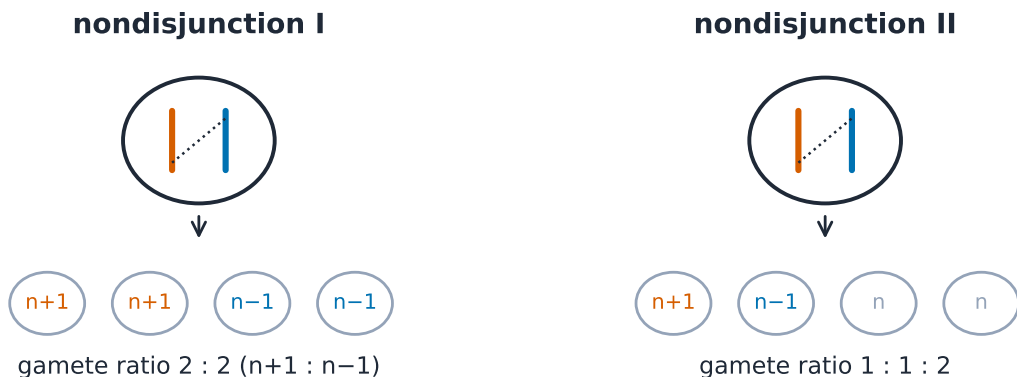
- Units 6.1–6.3 are the transmission rules: chromosomes, Mendel, and the exceptions.
- Units 6.4–6.5 are variation: mutation types and population frequencies.
- Units 6.6–6.7 are the clinic: testing, counselling, and the multifactorial majority.

The medicine habit: **every risk is a probability you compute** – segregation ratios, Hardy–Weinberg frequencies, Bayesian carrier updates – and every number below is something you recompute.

Chromosomes and karyotypes

Why it matters. The chromosome is the unit of transmission, and meiosis is the machine that moves it. When the machine misfires the consequence is a whole-chromosome dosage error – the most common survivable genetic conditions.

The idea, with a picture. The human **karyotype** : 46 chromosomes = 23 pairs (22 autosome pairs + XY/XX) ✓, counted at metaphase (MED04's mitosis). **Meiosis** : one duplication, two divisions → four haploid gametes. **Nondisjunction** – homologs (I) or sister chromatids (II) failing to separate – gives gametes with one too many or too few.



One mis-segregation, two windows (I vs II) – and different gamete ratios from each

The derivation (the 2:2 and the 1:1:2). Division-I nondisjunction: the homolog pair travels together $\rightarrow$ 2 gametes with $n+1$, 2 with $n-1$ – half and half ✓. Division-II: the homologs separate normally at I, then one sister pair sticks at II $\rightarrow$ 1 gamete $n+1$, 1 gamete $n-1$, 2 normal – a **1:1:2** ratio ✓. Down syndrome (trisomy 21, $\sim 47,XX/XY,+21$; incidence ≈ 1 in 700 births, rising with maternal age ✓) is the surviving example: about 95 % of cases are a free extra chromosome 21 from nondisjunction, about 90 % of those arise in the egg, and most of those at meiosis I.

Worked example 1 – writing a karyotype. $46,XX$ = female, standard ✓; $47,XY,+21$ = male, trisomy 21 ✓; $45,X$ = monosomy X (Turner, the only viable full monosomy ✓). The notation is a sentence: count, sex, change. Sex-chromosome aneuploidies ($47,XXY$; $47,XYY$; $47,XXX$) are milder than autosomal ones – X-inactivation and gene-poor Y buffer the dosage.

Worked example 2 – clinical link: the mosaic window. (Fictional case) mild features, two cell lines $46/47,+21$: nondisjunction occurred in an early mitotic division – a post-zygotic event. Mosaicism explains the milder picture (some tissue is euploid). It also warns the counsellor about the reverse case: a parent can carry trisomic cells only in the ovary or testis (**germline mosaicism**), so a condition can recur in a second child even when both parents' blood karyotypes are normal.

Common mistakes. Confusing meiosis-I and II windows (the gamete ratios differ: 2:2 vs 1:1:2). Calling Down syndrome “familial” (it is usually a de-novo meiotic error; recurrence risk is about 1 %, or the maternal-age risk if that is higher). Forgetting that $45,Y$ is never viable – X carries essential genes.

Summary. $46 = 23$ pairs; meiosis I segregates homologs, II sister chromatids; nondisjunction I $\rightarrow 2 \times (n+1)$ and $2 \times (n-1)$; II $\rightarrow 1:1:2$; trisomy 21 ($\sim 1/700$) is the surviving autosomal example; $45,X$ the only viable monosomy; mosaicism softens and complicates.

Mendelian inheritance and pedigrees

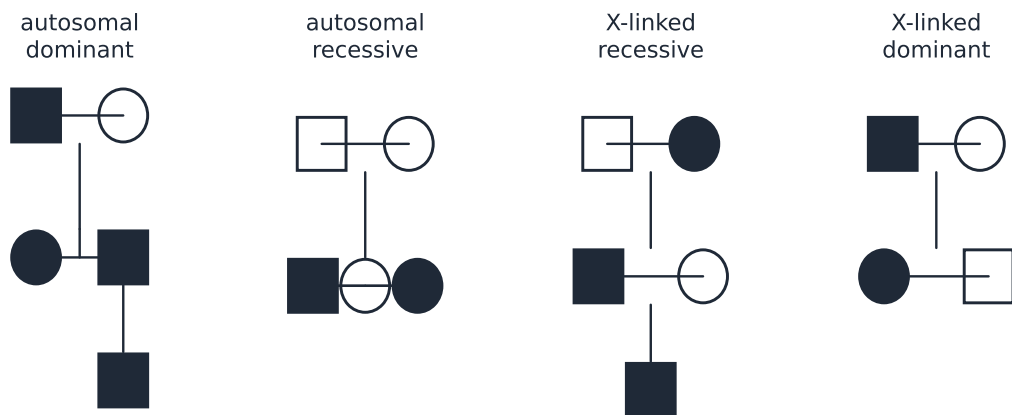
Why it matters. Mendel's ratios are the default reasoning engine of genetic counselling: given a family, compute who is at risk. The pedigree is the data structure; the ratios are the arithmetic.

The idea, with a picture. Pedigree conventions: squares male, circles female; filled = affected; horizontal line = mating; double line = consanguinity. Four single-gene patterns: **autosomal dominant** (every generation, M:F equal, father-to-son possible; onset often adult), **autosomal recessive**

(horizontal clustering, consanguinity, 1/4 of sibs), **X-linked recessive** X

(no male-to-male, affected males related through females), **X-linked dominant** X

(both sexes affected; an affected father passes it to ALL his daughters and to NONE of his sons ✓).



Four patterns, four signatures – read the squares and circles like a radiograph

The derivation (ratios from gametes). $Aa \times Aa$: gametes $A,a \times A,a \rightarrow AA, Aa, Aa, aa = 3:1$ affected:unaffected ✓ (dominant); recessive **carriers** $Aa \times Aa \rightarrow 1/4$ affected. X-linked recessive: carrier mother $X^A X^a \times$ normal father $\rightarrow$ sons $1/2$ affected, daughters $1/2$ carriers ✓ – a Punnett grid per pattern, and every risk quote in counselling is one of these grids plus penetrance.

Worked example 1 – risk down a pedigree. (Fictional) Huntington-like autosomal dominant: affected parent (Aa) $\times$ unaffected (aa) $\rightarrow$ each child $1/2$ at risk ✓. The child of an untested, still-healthy 25-year-old in that family: $1/2 \times 1/2 = 1/4$ ✓, because at 25 the parent's own risk is still about $1/2$. Age changes this by Bayes. Suppose (fictional figure) 20 % of carriers are still healthy at 60. For a healthy 60-year-old child of the affected parent: $P(\text{carrier} \mid \text{healthy at 60}) = \frac{\frac{1}{2} \times 0.2}{\frac{1}{2} \times 0.2 + \frac{1}{2} \times 1} = \frac{1}{6}$ ✓. “Unaffected so far” is evidence, and it moves the risk from $1/2$ to $1/6$.

Worked example 2 – clinical link: the de-novo dominant. (Fictional) achondroplasia in a child of average parents: $\sim 80\%$ of cases are new mutations (paternal age effect) ✓; sib recurrence is near population risk, but the affected child's own children are at $1/2$. Distinguishing inherited vs de-novo changes the whole counselling script.

Common mistakes. Equating “dominant” with “common” (dominant diseases are often rare and often de-novo). Forgetting new mutations break the classic pedigree (no affected parents). Assuming small families show ratios (probabilities, not guarantees: two carrier parents have three unaffected children $(3/4)^3 \approx 42\%$ of the time ✓, so a recessive condition can hide in a small family).

Summary. Four pedigree signatures; Punnett grids give $3:1$, $1/4$, $1/2$ -sons; age-of-onset and de-novo mutation modify raw ratios; risk = grid $\times$ pedigree evidence, updated by Bayes.

Non-Mendelian inheritance

Why it matters. The clinic's awkward families – maternal transmission, unequal expression, dosage surprises – are not Mendel failing; they are additional layers of transmission that every modern panel must interpret.

The idea, with a picture. **Mitochondrial inheritance** : mtDNA is maternally inherited only – all children of an affected mother may be affected, none of an affected father ✓; heteroplasmy (mixed mtDNA populations) makes severity a lottery. **Genomic imprinting** : expression depends on parental ORIGIN (Prader-Willi = paternal 15q deletion, Angelman = maternal 15q deletion – same region, opposite parental origin, opposite syndromes ✓). **Trinucleotide repeat expansion** : **anticipation** (earlier, more severe in successive generations) as repeats grow – Huntington CAG, fragile-X CGG.

three signatures Mendel never saw

mitochondrial

maternal line only — ALL children of an affected mother

imprinting (15q)

same deletion: paternal → Prader-Willi; maternal → Angelman

repeat expansion

anticipation: repeats grow — earlier and more severe

heteroplasmy · parent-of-origin · instability

Maternal lines, parent-of-origin, and expanding repeats – three signatures Mendel never saw

The derivation (why dosage origin matters). Imprinted genes are SILENCED by methylation (MED01's epigenetics) set in the germline and re-set each generation: only one parental copy works. Delete the WORKING copy → disease, so the same deletion on the paternal chromosome (no active copy, Prader-Willi) differs from the maternal (no active copy of a different gene, Angelman) ✓. Uniparental disomy (both copies from one parent) mimics a deletion: two silent copies.

Worked example 1 – the anticipation arithmetic. (Fictional) fragile-X family: premutation (55–200 CGG) mothers transmit expanded (>200, full mutation) with expansion risk rising with repeat length ✓. Huntington: paternal transmission of large CAG (>60) often gives juvenile onset – the repeat is unstable, growing meiosis to meiosis: anticipation is measurable, not folklore.

Worked example 2 – clinical link: the maternal-only line. (Fictional) a pedigree with affected mothers and children of both sexes, no male transmission over three generations: MELAS-pattern mitochondrial inheritance. Heteroplasmy explains the severity spread (the aunt deaf, the mother diabetic, the cousin encephalopathic) – one mutation, many phenotypes, because each child samples a different bottle-neck fraction of mutant mtDNA.

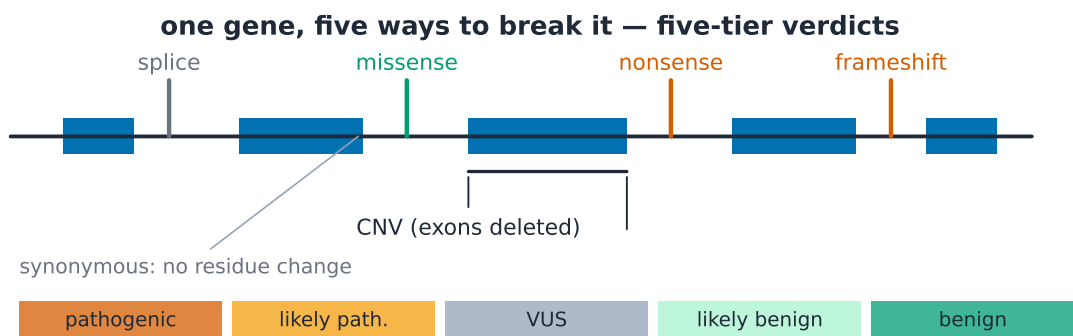
Common mistakes. Expecting mtDNA disease to affect every child of an affected mother equally (heteroplasmy). Confusing imprinting with dominant/recessive (both can be dominant-acting; the parent of origin is the clue). Treating anticipation as ascertainment bias (it is real meiotic instability).

Summary. mtDNA: maternal-only, heteroplasmy lottery; imprinting: same deletion, opposite parent, opposite syndrome (15q); repeat expansions: anticipation, premutation→full-mutation risk by length.

Mutation and variant interpretation

Why it matters. Sequencing found the variant; the clinic needs to know if it matters. Variant interpretation is the daily intellectual core of medical genetics – a graded evidence chain, not a yes/no.

The idea, with a picture. Variant types on a gene model: **synonymous** (no amino-acid change), **missense** (one residue), **nonsense** (stop; usually severe – truncation), **frameshift** (indel not a multiple of 3), **splice**, plus large **copy number variants** (CNVs: deletions/duplications of exons or whole genes). Grading: pathogenic, likely pathogenic, **variant of uncertain significance** (VUS), likely benign, benign – by population frequency, computational prediction, functional data, segregation, and the gene's established disease link ✓.



One gene, five ways to break it – and a five-tier verdict scale

The derivation (why frequency is the first filter). A variant common in healthy populations (e.g. >1 %) cannot cause a rare severe early disease: the arithmetic rules it out before any prediction algorithm runs. So allele frequency in population databases

(gnomAD) dominates the first pass; predicted-deleterious-but-common variants are usually benign background ✓. Take a dominant disease affecting 1 person in 10 000 and a variant carried by 1 person in 100. Even if this one variant caused every case, only $\frac{1/10\,000}{1/100} = \frac{1}{100}$ of its carriers could be affected ✓ – so it cannot be a fully penetrant cause.

Worked example 1 – the VUS lecture. (Fictional) a missense VUS in a breast-cancer gene found in an affected woman: the right answer is NOT to treat it as pathogenic. Cascade testing of relatives is not indicated on a VUS; the variant’s interpretation may be upgraded later by segregation (does it track disease?) and accumulation of case data ✓. Counselling language: “we found a spelling change; we do not yet know if it means anything.”

Worked example 2 – clinical link: the loss-of-function rule. (Fictional) a nonsense variant early in a gene whose established mechanism is **haploinsufficiency** (one working copy is not enough – e.g. PAX6 in aniridia): a truncating variant in such a gene is strong evidence of pathogenicity. The rule: gene mechanism (haploinsufficiency vs dominant-negative vs recessive) predicts which variant TYPES matter in that gene.

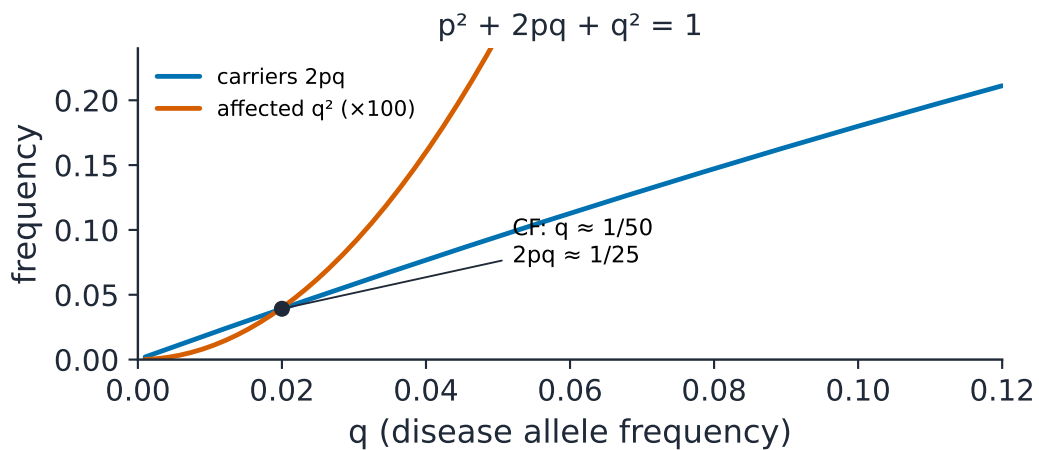
Common mistakes. Treating VUS as “probably pathogenic” (it is explicitly unknown – the commonest counselling failure). Applying dominant-negative logic to haploinsufficiency genes. Forgetting a variant can be pathogenic for one disease and benign for another (or recessive – a carrier without a second allele).

Summary. Five variant classes on a gene model; five-tier verdict scale; population frequency first (Bayes), then prediction, function, segregation; VUS stays VUS until evidence moves it; the gene’s mechanism selects which variant types count.

Population genetics

Why it matters. Allele frequencies make carrier risks predictable before any family history – the arithmetic behind newborn screening, carrier panels and ethnic-prevalence counselling. One equation does the work.

The idea, with a picture. Hardy–Weinberg equilibrium – : $p^2 + 2pq + q^2 = 1$ – genotype frequencies from allele frequencies, stable across generations IF mating is random, the population large, and no selection/migration/mutation ✓.



One equation: allele frequencies in, genotype frequencies out – carrier risks included

The derivation (why the binomial appears). Random union of gametes is a binomial draw: two alleles, frequencies p and q, so $P(AA) = p^2$, $P(Aa) = 2pq$, $P(aa) = q^2$ ✓ – the 2 is the two carrier orders. Cystic fibrosis: $q^2 \approx 1/2500$ (Northern European) → $q \approx 1/50$ → carriers $2pq \approx 1/25$ ✓ – the famous 4 % carrier rate from a disease rate. Sickle trait in West African populations ~1/4 carriers: q from 2pq, and heterozygote advantage (carriers resist malaria) explains why the allele stays common there although homozygotes are selected against.

Worked example 1 – carrier risk arithmetic. A woman with no CF family history: carrier risk $\approx 1/25$. Her partner screened negative (residual risk after a negative panel $\approx 1/300$: a panel that finds 92 % of carriers leaves $\frac{(1/25)(0.08)}{1-(1/25)(0.92)} \approx \frac{1}{300}$): affected-child risk = $1/25 \times 1/300 \times 1/4 \approx 1/30\,000$ ✓ – the whole carrier-screening industry is this one multiplication.

Worked example 2 – clinical link: the screened residual. (Fictional) a couple where one is a known carrier and the partner tests negative: risk $\approx 1 \times \text{residual}(1/300) \times 1/4 \approx 1/1200$ ✓. Why not zero? Detection is imperfect (CNVs, rare promoter variants); the residual is gene- and panel-specific – counselling quotes it, never “no risk”.

Common mistakes. Solving $q = \sqrt{\text{frequency}}$ when given a CARRIER rate (carriers are 2pq, not q²). Applying equilibrium where selection distorts (sickle regions, founder populations). Forgetting founder effects concentrate rare alleles (Tay–Sachs ~1/30 carriers in Ashkenazi Jews vs ~1/300 general ✓).

Summary. $p^2 + 2pq + q^2 = 1$; disease rate → $q = \sqrt{\text{disease}}$ → carrier = 2pq; residual risk after negative screens is quoted, not zero; selection and founder effects are the standard deviations from equilibrium.

Genetic testing and counselling

Why it matters. A test result is information about a family, not just a patient – and each method sees a different layer of the genome. Choosing the test and counselling the result are the clinical skills.

The idea, with a picture. Methods: **karyotyping** (metaphase spread; sees $\geq \sim 5\text{--}10\text{ Mb}$, balanced rearrangements), **microarray** (CMA: CNVs to $\sim 50\text{--}100\text{ kb}$; no balanced rearrangements ✓), **FISH** (targeted; rapid aneuploidy or microdeletion probe), **sequencing** (Sanger for one gene; NGS panels; exome/genome). Test choice by question: aneuploidy → karyotype/FISH/QF-PCR; developmental delay → CMA; known familial variant → targeted Sanger ✓.

the question chooses the window

karyotype	whole genome, $\geq 5\text{--}10\text{ Mb}$	balanced rearrangements seen
microarray (CMA)	genome-wide CNVs $\sim 50\text{--}100\text{ kb}$	balanced changes MISSED
FISH	targeted, fast	one probe, one question
sequencing	base-level, chosen scope	Sanger → panel → exome/genome

Four windows on the genome, four resolutions – the question chooses the window

The derivation (why resolution trades scope). A karyotype sees the whole genome at low resolution (large, balanced, structural); sequencing sees base-level detail in the regions it covers; CMA covers the genome at intermediate resolution but MISSES balanced changes (no net dosage). No single test sees everything – the clinical question maps to the method that can answer it ✓. That mapping is the counsellor’s first decision, before any consent form.

Worked example 1 – the cascade. (Fictional) a familial pathogenic BRCA1 variant: the proband’s positive result creates a TESTABLE risk ($1/2$ for each first-degree relative) – cascade testing finds carriers for screening and breaks the chain of uncertainty; relatives who test negative revert to population risk for that syndrome ✓. The pedigree multiplies the value of one result.

Worked example 2 – clinical link: the incidentalome. (Fictional) a genome sequenced for developmental delay finds an adult-onset predisposition variant incidentally: the clinic must decide what to return. Consent before testing sets the menu; a VUS-heavy report is counselled as uncertain, not alarming – and children’s results defer adult-onset disclosures where possible ✓.

Common mistakes. Ordering sequencing when a CNV is the likely mechanism (and

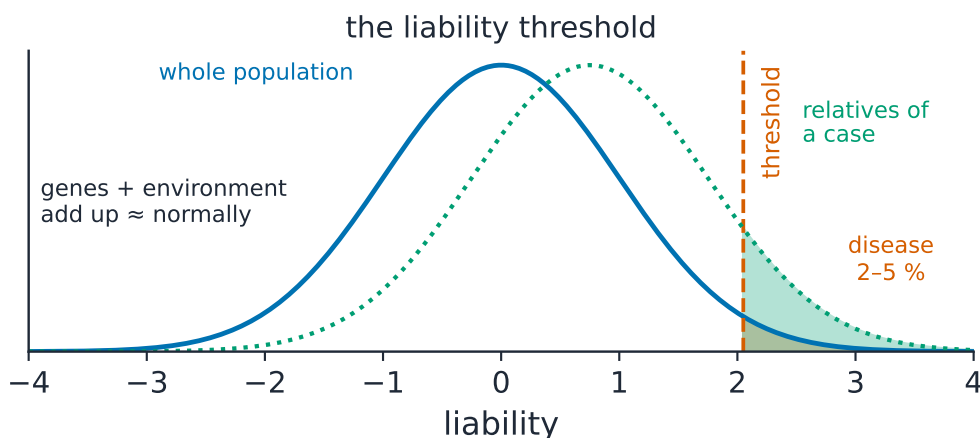
vice versa). Telling a relative who tests negative for the family variant they have “no risk” (they return to population risk, which is not zero). Forgetting pre-symptomatic testing of children is restricted to childhood-actionable conditions ✓.

Summary. Karyotype (large/balanced), CMA (CNV genome-wide), FISH (targeted fast), sequencing (base-level, chosen scope); the question picks the method; cascade testing multiplies one result; consent and the incidentalome are part of the test.

Multifactorial disease and pharmacogenomics

Why it matters. Most common disease – diabetes, hypertension, asthma, schizophrenia – and most drug responses are multifactorial: many genes of small effect plus environment. The clinic needs models that make “it runs in the family” quantitative.

The idea, with a picture. The **liability threshold model** : liability = genetic + environmental contributions (summing approximately normally); disease occurs when liability crosses a threshold ✓. Empiric recurrence risks: 2–5 % for most multifactorial malformations (vs 25 % recessive, 50 % dominant), RISING with (1) more affected relatives, (2) a more severe form in the affected person, and (3) an affected person of the LESS often affected sex ✓. That third rule is the **Carter effect** : pyloric stenosis is about four times commoner in boys, so an affected girl must carry more liability, and her relatives’ risk is higher.



A normal curve of inherited+environmental liability; the tail past the threshold is the disease

Pharmacogenomics : genotype-guided prescribing – the best-established examples: CYP2C19 clopidogrel (poor metabolisers cannot activate the prodrug), TPMT/thiopurines (severe toxicity in deficient), HLA-B*57:01 abacavir hypersensitivity (screen before prescribing ✓).

The derivation (why risks rise with each case). If parents of an affected child sit above average liability, additional affected relatives push the FAMILY’s inferred liability

ity higher – the whole distribution shifts right, and more siblings cross the threshold: empiric 2–5 % for one affected rises toward 5–10 % with two ✓. This is why multifactorial counselling quotes empiric tables (population studies), not Mendel’s ratios: many loci of small effect don’t segregate 1:2:1.

Worked example 1 – the recurrence quote. (Fictional) one child with neural-tube defect: empiric recurrence ~2–4 % (folate cuts it); two affected children: ~10 % ✓. The quote is from population tables, not a Punnett grid – and the folate advice (4 mg pre-conception) applies to EVERY subsequent pregnancy regardless of computed risk.

Worked example 2 – clinical link: the screened prescription. (Fictional) a patient starting clopidogrel after a coronary stent: CYP2C19 poor-metaboliser genotype → an alternative antiplatelet drug from day one, since the prodrug is barely activated. About 15 % of East Asians are poor metabolisers (two loss-of-function alleles), against about 2 % of Europeans ✓. HLA-B*57:01 before abacavir: the test PREVENTS the hypersensitivity.

Common mistakes. Quoting 50 %/25 % to multifactorial families (those are Mendel’s numbers; multifactorial is empiric 2–5 %). Adding “genetic” and “environmental” risk as percentages instead of liabilities. Treating a pharmacogenomic result as a disease diagnosis (it is a dosing instruction).

Summary. Liability ($\approx$ normal) $\times$ threshold = multifactorial disease; empiric recurrence 2–5 %, rising with count and severity; folate regardless of risk; pharmacogenomics (CYP2C19, TPMT, HLA-B*57:01) turns genotype into prescriptions.