GENETICS · STUDY GUIDE

Exam 7 Study Guide

This guide covers the last two chapters. Chapter 13 follows the genes that build a body and the same genes, broken in one cell lineage, that drive cancer. Chapter 14 brings the whole course into the clinic: inheritance patterns in families, common disease, testing and the arithmetic and ethics of counseling. Work one chapter at a time. Read what to know, copy the tables by hand, and try each worked example with the steps covered. Then take the ten item self-test. The cram sheet at the end puts every rule and formula on one page.

WHAT THIS GUIDE COVERS

- Chapter 13 · genomic equivalence, potency, model organisms, maternal effect genes, the segmentation cascade, Hox genes and the ABC model, cyclins and CDKs, Rb, E2F and p53, oncogenes, tumor suppressors and two hits, and the multistep model.
- Chapter 14 · single gene patterns, penetrance, anticipation and imprinting, carrier frequencies, liability and twins, GWAS and odds ratios, kinds of tests, sensitivity, specificity and predictive value, Bayesian risk, and ethical, legal and social issues.

CHAPTER 13

Developmental and Cancer Genetics

What to know

Almost every cell carries the same genome, so development is **differential gene expression**. Nuclear transfer and induced pluripotent stem cells (made with Oct4, Sox2, Klf4 and c-Myc) prove **genomic equivalence**. Potency narrows from **totipotent** (zygote, can make placenta) to **pluripotent** (inner cell mass) to multipotent adult stem cells. **Determination** is commitment, shown by transplantation. **Differentiation** is the later, visible specialization.

Model organisms make development studiable: yeast for the cell cycle, flies for segmentation and Hox genes, worms for lineage, apoptosis and microRNAs, zebrafish for organs, mice for knockouts and *Arabidopsis* for flowers. **Forward genetics** goes from phenotype to gene through mutagen screens. **Reverse genetics** goes from gene to phenotype by knockout or knockdown. In worms, *egl-1*, *ced-9*, *ced-4* and *ced-3* match human BH3 only proteins, Bcl-2, Apaf-1 and caspases.

For a **maternal effect gene** such as *bicoid*, the embryo's phenotype follows its mother's genotype. A *bcd/bcd* female makes headless embryos even if they get a normal allele from the father.

Fly segmentation is a cascade. Maternal gradients (Bicoid in front, Nanos behind, nuclear Dorsal on the belly) set the axes. **Gap genes** make broad bands, **pair rule genes** make 7 stripes and **segment polarity genes** make 14. **Hox genes** then give each segment its identity. They sit in order along the chromosome, matching the body order (colinearity), and share the 180 bp **homeobox** encoding a 60 amino acid homeodomain. Losing a Hox gene usually makes a segment look more anterior. Mammals have 39 Hox genes in four clusters.

Flowers use the **ABC model**: A in whorls 1 and 2, B in 2 and 3, C in 3 and 4. A alone makes sepals, A + B petals, B + C stamens, C alone carpels. A and C repress each other, so losing one lets the other spread.

The cycle runs G1, S, G2 and M. **CDKs** are active only with **cyclins**, whose levels rise and fall. CAK activates, Wee1 inhibits and Cdc25 releases CDK1. p16 blocks CDK4/6, and p21 and p27 block CDK2. At the **restriction point**, cyclin D and then cyclin E complexes phosphorylate **Rb**, releasing **E2F**, which turns on more cyclin E in a positive loop. Checkpoints at G1/S, G2/M and the spindle halt the cycle. **p53**, held low by MDM2, rises after damage and induces p21 for arrest, repair genes, or apoptosis.

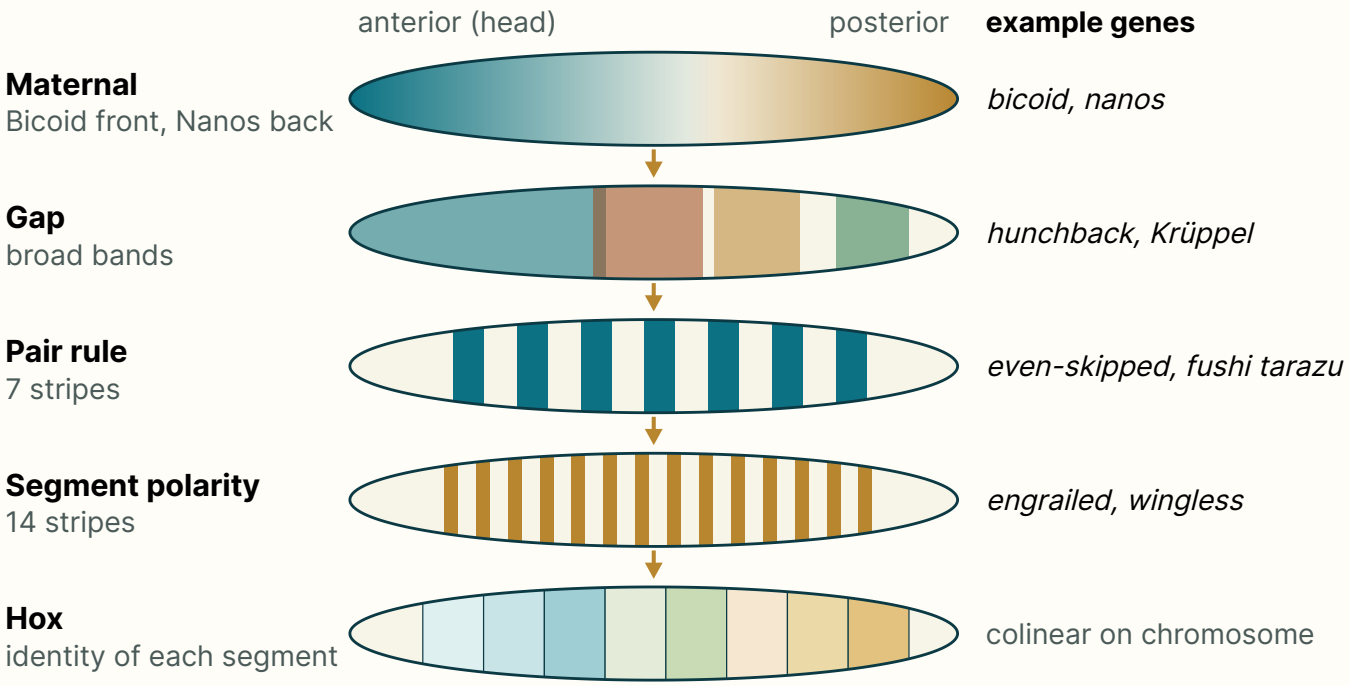
Proto-oncogenes become **oncogenes** by gain of function: point mutation (*KRAS* codon 12), amplification (*ERBB2*), a fusion gene (BCR-ABL1) or a move next to a strong enhancer (MYC in Burkitt lymphoma). One activated allele is enough. **Tumor suppressors** lose function and usually need two hits in the cell. Knudson's retinoblastoma work showed this: an inherited first hit makes tumors bilateral and early, so the predisposition is inherited as an autosomal dominant trait even

though the gene acts recessively in the cell. The second hit is often **loss of heterozygosity** or promoter methylation. Gatekeepers (RB1, APC, TP53) control growth. Caretakers (mismatch repair genes, BRCA1, BRCA2) guard the genome.

Cancer is **multistep** and clonal. If incidence rises as age^{k-1}, a log plot slope of about 6 suggests about 7 steps. The colorectal sequence runs *APC*, *KRAS*, 18q (*SMAD4*) and *TP53*. Genomic instability speeds things up. The hallmarks include sustained signaling, evading suppressors, resisting death, immortality through telomerase, angiogenesis, invasion, altered metabolism and immune evasion. Mutagens (screened by the Ames test) and viruses such as HPV, whose E6 and E7 disable p53 and Rb, supply hits. **Synthetic lethality** lets PARP inhibitors kill BRCA deficient tumors.

LOCK THESE IN

- Totipotent makes placenta too. Pluripotent makes every body cell, not the trophoblast.
- Maternal effect: the mother's genotype decides the embryo's phenotype.
- Gap bands, then 7 pair rule stripes, then 14 segment polarity stripes, then Hox identity.
- ABC: A sepal; A + B petal; B + C stamen; C carpel. A and C repress each other.
- Rb holds E2F. Cyclin D and E with their CDKs phosphorylate Rb and free E2F.
- Checkpoints stop the cycle. They do not repair. p21 blocks CDKs; Chk1 blocks Cdc25; Mad2 blocks Cdc20.
- Oncogene: one hit, gain of function. Tumor suppressor: two hits, loss of function.
- Incidence $\propto$ age^{k-1}. Doubling age multiplies incidence by 2^{k-1}.



Each tier reads the one above. Gradients become bands, bands become 7 stripes, 7 become 14, and Hox genes tell each segment what to be.

Rules and formulas for development and cancer

Item	Rule or formula	Note
Maternal effect broods	fraction of defective embryos = fraction of mothers homozygous mutant	father irrelevant
Phase length from a snapshot	time in phase ≈ (fraction of cells in phase) × cycle time	2C: G1; between: S; 4C: G2 + M
Human cycle (cultured)	G1 about 11 h; S 8 h; G2 4 h; M 1 h	about 24 h
Cyclin and CDK pairs	D-CDK4/6 (G1); E-CDK2 (G1/S); A-CDK2 (S); B-CDK1 (G2/M)	B-CDK1 = MPF
Two hit expected tumors, hereditary	cells at risk × rate per allele	one more hit needed
Two hit expected tumors, sporadic	cells × (2 × rate) × rate	two hits in one cell
Chance an eye is spared	$e^{-\text{expected tumors}}$	Poisson zero class
Age incidence	incidence $\propto t^{k-1}$; slope of log plot = k − 1	k = rate limiting steps
Ames result	positive if revertants ≥ 2 × control	with and without S9
ABC model	whorl 1 A; 2 A + B; 3 B + C; 4 C	A and C antagonistic
Retinoblastoma	about 40% hereditary (bilateral, early); 60% sporadic	penetrance about 90%

Worked examples

WORKED EXAMPLE 1 · A MATERNAL EFFECT CROSS

bcd^{+}*/bcd* females are crossed with *bcd/bcd* males. (a) What fraction of F_1 embryos are normal? (b) The F_1 mate at random. What fraction of F_2 embryos are defective?

STEP 1 · F_1 EMBRYOS

Their mother has one working allele, so every egg gets Bicoid mRNA. **All F_1 embryos are normal**, even the *bcd/bcd* ones.

STEP 2 · F_1 GENOTYPES

1/2 bcd^+/bcd and 1/2 *bcd/bcd*.

STEP 3 · F_2 EMBRYOS

An embryo is defective only if its mother is *bcd/bcd*. Half the F_1 females are, so **1/2 of F_2 embryos** are defective, and they come in whole broods.

WORKED EXAMPLE 2 · PHASE LENGTHS FROM DNA CONTENT

A culture doubles every 24 hours. Of 1,000 cells, 500 have 2C DNA, 300 are between 2C and 4C, and 200 have 4C DNA. Estimate each phase.

STEP 1 · ASSIGN PHASES

2C is G1. Between 2C and 4C is S. 4C is G2 or M.

STEP 2 · G1

$0.50 \times 24 =$ **12 h**.

STEP 3 · S

$0.30 \times 24 =$ **7.2 h**.

STEP 4 · G2 + M

$0.20 \times 24 =$ **4.8 h**. Check: 12 + 7.2 + 4.8 = 24.

WORKED EXAMPLE 3 · TWO HITS BY THE NUMBERS

A retina has about 4×10^6 cells at risk. Each *RB1* allele is lost in a given cell with chance 5×10^{-7}. Estimate tumors per eye for (a) a child with an inherited mutant allele and (b) a child without one.

STEP 1 · HEREDITARY

One hit needed per cell: $4 \times 10^6 \times 5 \times 10^{-7} =$ **2 tumors per eye**.

STEP 2 · CHANCE AN EYE IS SPARED

$e^{-2} = 0.135$, about 13.5 percent. Most children get tumors in both eyes.

STEP 3 · SPORADIC

Per cell: $2 \times 5 \times 10^{-7} \times 5 \times 10^{-7} = 5 \times 10^{-13}$. Per eye: $4 \times 10^6 \times 5 \times 10^{-13} =$ **2×10^{-6}**.

STEP 4 · COMPARE

About a million fold difference, which is why one inherited hit makes tumors nearly certain.

WORKED EXAMPLE 4 · COUNTING STEPS FROM AGE DATA

A cancer occurs at 8 per 100,000 per year at age 40 and 256 per 100,000 per year at age 80. If incidence rises as age^{k-1}, estimate k.

STEP 1 · RATIO

256 ÷ 8 = 32.

STEP 2 · AGE RATIO

80 ÷ 40 = 2, so $2^{k-1} = 32$.

STEP 3 · SOLVE

$2^5 = 32$, so k − 1 = 5 and **k = 6** rate limiting steps.

HEREDITARY CASES

A person who inherits one step needs one fewer somatic event, so the line is shallower and cases appear earlier.

TRAPS PEOPLE FALL INTO

- **Confusing determination with differentiation.** Determination is commitment, tested by transplant. Differentiation is what you see later.
- **Using the embryo's genotype for a maternal effect gene.** Use the mother's genotype.
- **Expecting a lost Hox gene to make a segment more posterior.** It usually becomes more anterior.
- **Forgetting A and C antagonism in the ABC model.** Losing one lets the other spread into its whorls.
- **Saying checkpoints repair DNA.** They stop the cycle and buy time. Repair is a separate job.
- **Calling tumor suppressor inheritance recessive.** It acts recessively in the cell, but the predisposition is inherited as dominant.
- **Thinking one oncogene is enough for cancer.** Cancer needs several driver mutations in one lineage.
- **Calling every second hit a new point mutation.** Loss of heterozygosity and methylation are common second hits.

Chapter 13 self-test · ten items

1. Which experiment best shows that a differentiated cell still has a complete genome?

- **A** Reprogramming skin cells into iPSCs with four factors
- **B** Measuring the telomere length in an adult neuron
- **C** Staining a karyotype of a differentiated liver cell
- **D** Counting the Barr bodies in a female skin cell

A. Reprogramming skin cells into iPSCs with four factors. iPSC reprogramming (and nuclear transfer) shows that cell identity can be reset, so no genes were lost. That is genomic equivalence.

2. A cell transplanted to a new site still develops into its original fate, though it looks like its neighbors. What does this show?

- **A** It had already lost genes from its genome
- **B** It was a multipotent adult stem cell
- **C** It was determined before it differentiated
- **D** It was totipotent at the time of transplant

C. It was determined before it differentiated. Determination is commitment that shows only when the cell is moved. Differentiation is the later visible change.

3. A *bcd/bcd* female mates with a bcd^{+}/bcd^{+} male. What are her embryos like?

- **A** Half lack head and thorax
- **B** All are normal
- **C** One quarter are defective
- **D** All lack head and thorax

D. All lack head and thorax. Bicoid is a maternal effect gene. Her eggs carry no Bicoid mRNA, so every embryo is defective even though each got a normal paternal allele.

4. A fly mutant loses every other segment. Which gene class is most likely affected?

- **A** A segment polarity gene
- **B** A pair rule gene
- **C** A gap gene
- **D** A maternal effect gene

B. A pair rule gene. Pair rule genes are expressed in 7 stripes, each two segments wide. Losing one removes alternate segments. Gap mutants lose blocks of adjacent segments.

5. In *Arabidopsis*, a mutant lacks B function. What does its flower look like, from outside in?

- **A** Sepal, petal, petal, sepal
- **B** Carpel, stamen, stamen, carpel
- **C** Petal, petal, stamen, stamen
- **D** Sepal, sepal, carpel, carpel

D. Sepal, sepal, carpel, carpel. Without B, whorl 2 has A alone (sepal) and whorl 3 has C alone (carpel).

6. What releases E2F at the restriction point?

- **A** Removal of Wee1 phosphates by the Cdc25 enzyme
- **B** Binding of p21 to the cyclin E and CDK2 pair
- **C** Phosphorylation of Rb by G1 cyclin and CDK complexes
- **D** Destruction of cyclin B by the APC/C at anaphase

C. Phosphorylation of Rb by G1 cyclin and CDK complexes. Cyclin D with CDK4/6, then cyclin E with CDK2, phosphorylate Rb so it lets go of E2F. p21 would block this, and cyclin B and Cdc25 act at mitosis.

7. After DNA damage, how does p53 most directly stop the cycle at G1/S?

A. It cleaves cohesin between sister chromatids

B. It induces p21, which inhibits cyclin E with CDK2

C. It degrades cyclin D through the proteasome directly

D. It binds DNA polymerase and halts replication

B. It induces p21, which inhibits cyclin E with CDK2. p53 is a transcription factor. Its target p21 is a CDK inhibitor. Checkpoints work by switching a driver of the cycle off.

8. Which change is a classic way a proto-oncogene becomes an oncogene?

A. Amplification of *ERBB2* to many copies

B. Promoter methylation silencing *MLH1*

C. Loss of both copies of *RB1* by deletion

D. A nonsense mutation in one *APC* allele

A. Amplification of *ERBB2* to many copies. Amplification is a gain of function. The others are losses of function in tumor suppressor genes.

9. Why is hereditary retinoblastoma usually bilateral and early?

A. Every retinal cell already has the first hit

B. The tumor cells travel from one eye to the other

C. Both eyes are exposed to the same mutagen early

D. The *RB1* mutation acts dominantly in each cell

A. Every retinal cell already has the first hit. With one mutant allele in every cell, a single somatic hit in any cell gives a tumor, and millions of cells are at risk.

10. In an Ames test, a compound gives 1.1 times the control count alone, but 9 times with S9 liver extract. What is it?

A. A direct mutagen with no need for liver enzymes

B. A mutagen that liver enzymes inactivate

C. A promutagen needing metabolic activation

D. A compound that is safe in every respect

C. A promutagen needing metabolic activation. It becomes mutagenic only after liver enzymes act on it, like benzo[a]pyrene from tobacco smoke.

Read the full chapter: Chapter 13 · Developmental and Cancer Genetics

CHAPTER 14

Human Inheritance, Genetic Testing and Counseling

What to know

Human genetics works backward from families. The **proband** brings the family to attention, and the **consultand** is the person seeking advice. **Autosomal dominant** conditions show vertical transmission, male to male transmission and a 1/2 risk to each child. Mechanisms include haploinsufficiency (familial hypercholesterolemia), dominant negative effects (Marfan syndrome) and gain of function (achondroplasia, Huntington disease). Incomplete penetrance, variable expressivity, new mutations (about 80 percent of achondroplasia, rising with paternal age) and germline mosaicism complicate pedigrees.

Autosomal recessive conditions show carrier parents, a horizontal pattern, a 1/4 risk each pregnancy and more cases after consanguinity. **X linked recessive** conditions mostly affect males, with no male to male transmission, and all daughters of an affected man are carriers. Mitochondrial conditions pass from mothers only, with heteroplasmy. Repeat expansions cause **anticipation**: Huntington disease expands mainly through fathers, fragile X through mothers.

Imprinting explains why the same 15q deletion gives Prader-Willi syndrome when paternal and Angelman syndrome when maternal.

Hardy Weinberg turns incidence into carrier frequency. Cystic fibrosis at 1 in 2,500 gives q = 1/50 and carriers about 1/25. For an X linked recessive, affected males equal q, carrier females are about 2q and affected females q^2.

Common diseases are **multifactorial**. In the **liability threshold model**, risk is modest (2 to 5 percent for first degree relatives), falls fast with distance, and rises with more affected relatives, with severity and in relatives of the less often affected sex (the **Carter effect**). Twin **concordance** compares MZ and DZ pairs, and $h^2 = 2(r_{MZ} - r_{DZ})$. Edwards' rule estimates first degree risk as the square root of population incidence.

GWAS compares SNP frequencies in cases and controls, with a threshold of 5×10^{-8}. Effects are reported as **odds ratios**, mostly 1.1 to 1.5. APOE ε4 is a large exception. Polygenic risk scores work best in the ancestry of the GWAS sample. Folic acid (0.4 mg daily, more after an affected pregnancy) shows how the environment shifts liability.

Tests answer different questions: diagnostic, predictive, carrier, prenatal screening and diagnosis, preimplantation, newborn and pharmacogenetic. Match the method to the variant: karyotype, FISH, microarray (misses balanced changes), targeted testing, panels, exome or genome, plus special tests for repeats and methylation. Variants run from pathogenic to benign, and a VUS should not guide care.

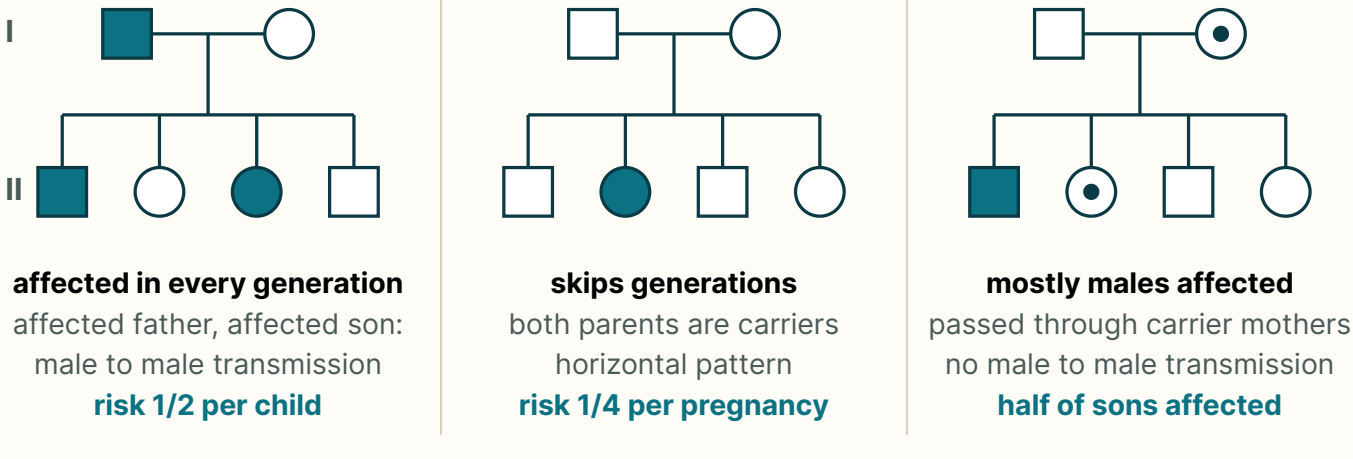
Sensitivity and **specificity** belong to the test. **Predictive values** depend on prevalence, so even a fine screen has a modest PPV for a rare condition. Prenatal screening uses cell free DNA, first trimester combined screening or the quad screen. CVS and amniocentesis are diagnostic. Newborn screening uses a heel stick at 24 to 48 hours to catch treatable conditions such as PKU.

Genetic counseling assesses risk, educates and supports, usually without directing reproductive choices. Use all known information: an unaffected sibling of a person with a recessive condition has a 2/3 carrier chance. **Bayesian** analysis runs prior, conditional, joint and posterior. Ethics rest on autonomy, beneficence, nonmaleficence and justice: informed consent, the right not to know, testing children only for childhood benefit, cascade testing, GINA's limits (no life, disability or

long term care coverage), secondary findings, equity in databases and caution about germline editing.

LOCK THESE IN

- AD: 1/2 to each child; male to male transmission possible.
- AR: 1/4 affected; an unaffected sibling is a carrier with chance 2/3.
- X linked recessive: half of a carrier's sons affected; daughters of affected men all carriers.
- q = √(incidence); carriers ≈ 2q.
- $h^2 = 2(r_{MZ} - r_{DZ})$; first degree multifactorial risk ≈ √(incidence).
- OR = (a × d) ÷ (b × c). OR of 1 means no association.
- PPV = TP ÷ (TP + FP). It falls as prevalence falls.
- Bayes: prior × conditional = joint; joint ÷ sum = posterior.



Reading a pedigree. Ask three questions: does it skip generations, does it pass father to son, and are mostly males affected?

Risk and test formulas

Quantity	Formula	Note
Carrier frequency (AR)	q = √(incidence); 2pq ≈ 2q	CF: 1/2,500 gives about 1/25
X linked recessive	males q; carrier females ≈ 2q; affected females q^2	hemophilia A: q = 1/5,000
Couple risk (AR)	P(carrier 1) × P(carrier 2) × 1/4	unaffected sibling 2/3
Falconer	$h^2 = 2(r_{MZ} - r_{DZ})$; $c^2 = r_{MZ} - h^2$; $e^2 = 1 - r_{MZ}$	assumes equal shared environments
Edwards' rule	first degree risk ≈ √(population incidence)	multifactorial only
Odds ratio	(cases with ÷ cases without) ÷ (controls with ÷ controls without)	cross product (ad)/(bc)
Sensitivity	TP ÷ all affected	property of the test
Specificity	TN ÷ all unaffected	property of the test
PPV and NPV	TP ÷ (TP + FP); TN ÷ (TN + FN)	depend on prevalence
Bayes	posterior = joint ÷ sum of joints	prior × conditional = joint
Residual carrier risk	prior × miss rate ÷ (prior × miss rate + noncarrier prior)	after a negative screen
Coefficient of relationship	1/2 first degree; 1/4 second; 1/8 first cousins	child of first cousins F = 1/16
Background risk	about 3 to 4% per pregnancy; first cousins add about 2 to 3 points	

Worked examples

WORKED EXAMPLE 1 · PREDICTIVE VALUE OF A SCREEN

A screen has 99 percent sensitivity and 99.5 percent specificity. It is used where the condition affects 1 in 1,000 pregnancies. What is the PPV?

STEP 1 · PICTURE 100,000 TESTS

Affected = 100. Unaffected = 99,900.

STEP 2 · TRUE POSITIVES

0.99 × 100 = 99.

STEP 3 · FALSE POSITIVES

0.005 × 99,900 = 499.5, about 500.

STEP 4 · PPV

99 ÷ (99 + 499.5) = **0.165, about 17 percent**.

MEANING

Most positive screens are false here. That is why a positive screen is confirmed by a diagnostic test before any decision, and the choice of what to do stays with the family.

WORKED EXAMPLE 2 · BAYES AND UNAFFECTED SONS

A woman's mother is an obligate carrier of Duchenne muscular dystrophy. The woman has two unaffected sons. What is her carrier risk, and what is the risk her next son is affected?

STEP 1 · PRIOR

Carrier 1/2; noncarrier 1/2.

STEP 2 · CONDITIONAL

Two unaffected sons: $(1/2)^2 = 1/4$ if a carrier, 1 if not.

STEP 3 · JOINT

Carrier 1/2 × 1/4 = 1/8. Noncarrier 1/2 × 1 = 4/8.

STEP 4 · POSTERIOR

(1/8) ÷ (1/8 + 4/8) = **1/5**.

STEP 5 · NEXT SON

1/5 × 1/2 = **1/10**.

WITHOUT BAYES

Ignoring the healthy sons would give 1/2 × 1/2 = 1/4, which overstates the risk.

WORKED EXAMPLE 3 · AN ODDS RATIO

300 of 1,000 cases and 200 of 1,000 controls carry a risk allele. Find the odds ratio.

STEP 1 · ODDS IN CASES

300 ÷ 700 = 0.429.

STEP 2 · ODDS IN CONTROLS

200 ÷ 800 = 0.250.

STEP 3 · RATIO

0.429 ÷ 0.250 = **1.71**. Cross check: (300 × 800) ÷ (700 × 200) = 240,000 ÷ 140,000 = 1.71.

ODDS VERSUS PROBABILITY

300/1,000 = 0.30 is a probability. 300/700 = 0.43 is odds.

WORKED EXAMPLE 4 · A NEGATIVE CARRIER SCREEN

Mirella's brother has cystic fibrosis; Mirella does not. Her partner Theo has no family history, comes from a group with carrier frequency 1/30, and tests negative on a screen that detects 85 percent of carriers. Find Theo's residual risk and the couple's risk for a first child.

STEP 1 · MIRELLA

Unaffected sibling of an affected person: carrier chance 2/3.

STEP 2 · THEO, PRIOR

Carrier 1/30; noncarrier 29/30.

STEP 3 · THEO, JOINT

Carrier and missed: 1/30 × 0.15 = 0.005. Noncarrier and negative: 29/30 × 1 = 0.967.

STEP 4 · THEO, POSTERIOR

0.005 ÷ (0.005 + 0.967) = 0.0051, about **1 in 194**.

STEP 5 · COUPLE

2/3 × 1/194 × 1/4 = **about 1 in 1,170**, down from 1 in 180 before his test.

TRAPS PEOPLE FALL INTO

- **Answering 1/2 for an unaffected sibling's carrier risk.** Use 2/3. The affected outcome is ruled out.
- **Treating sensitivity as PPV.** Sensitivity is fixed for a test. PPV moves with prevalence.
- **Mixing odds and probability.** Odds = with ÷ without.
- **Multiplying risk without using evidence.** Healthy sons or a negative test change the prior. Use Bayes.
- **Treating a VUS as pathogenic.** A VUS should not drive care. Many are later called benign.
- **Reading heritability as personal risk.** It describes variation in a population.
- **Thinking GINA covers life insurance.** It covers health insurance and employment only.

- **Testing children for adult onset conditions by default.** Test in childhood only when there is a childhood benefit.

Chapter 14 self-test · ten items

1. Which finding in a family most strongly argues against X linked inheritance?

A. The trait skips a generation once

B. An affected man has carrier daughters

C. Only males are affected in the family

D. An affected man has an affected son

D. An affected man has an affected son. A father gives his son a Y. Male to male transmission rules out X linkage.

2. Most people with achondroplasia have unaffected parents. Why?

A. The allele is recessive and both parents carry it

B. Most cases come from new mutations, often in sperm

C. The condition is mitochondrial and skips fathers

D. The allele has very low penetrance in parents

B. Most cases come from new mutations, often in sperm. About 80 percent are new FGFR3 variants, and their frequency rises with paternal age.

3. Hemophilia A affects about 1 in 5,000 males. About how many females are carriers?

A About 1 in 2,500

B About 1 in 50

C About 1 in 25 million

D About 1 in 5,000

A. About 1 in 2,500. q = 1/5,000. Carriers are about 2q = 1/2,500. Affected females would be q^2, about 1 in 25 million.

4. Pyloric stenosis is five times more common in boys. Whose relatives have the highest risk?

A Relatives through the father only

B Relatives of either, equally

C Relatives of an affected boy

D Relatives of an affected girl

D. Relatives of an affected girl. A girl must carry more liability to cross the higher threshold, so her relatives share more risk alleles. This is the Carter effect.

5. A multifactorial defect occurs in 1 in 400 births. Roughly what is the risk to a sibling of an affected child?

A About 25 percent

B About 50 percent

C About 5 percent

D About 0.25 percent

C. About 5 percent. Edwards' rule: √(1/400) = 1/20 = 0.05.

6. Which statement about a positive cell free DNA screen is correct?

A. It proves the fetus has the condition for certain

B. It should be confirmed by a diagnostic test

C. It is the same as an amniocentesis result

D. It cannot be caused by placental DNA

B. It should be confirmed by a diagnostic test. cfDNA is placental, and false positives occur, especially at low prevalence. CVS or amniocentesis confirms.

7. Which test is first line for a child with unexplained developmental delay?

A. Chromosomal microarray

B. A sweat chloride test

C. A routine G-band karyotype

D. A single gene test

A. Chromosomal microarray. Microarray detects gains and losses down to tens of kilobases. It cannot see balanced rearrangements.

8. Testing finds a variant of uncertain significance. What should happen?

A. Test every relative at once for it

B. It should not guide clinical decisions yet

C. Report it to the family as clearly benign

D. Treat it as a disease causing variant

B. It should not guide clinical decisions yet. A VUS lacks evidence either way. Many are later reclassified, usually as benign.

9. A woman carries a pathogenic *MLH1* variant. Her sister tests negative. What is the risk to the sister's daughter for this variant?

- A One quarter, through her mother
- B One half, as a first degree relative
- C Only the population background risk
- D Two thirds, as for a carrier sibling

C. Only the population background risk. The sister cannot pass a variant she does not carry. Each negative test also clears that person's descendants.

10. Which does GINA cover in the United States?

- A Every employer of any size
- B Life insurance and disability insurance
- C Long term care insurance only
- D Health insurance and employment

D. Health insurance and employment. GINA bars genetic discrimination in health insurance and by employers of 15 or more. It does not cover life, disability or long term care insurance.

Read the full chapter: Chapter 14 · Human Inheritance, Genetic Testing and Counseling

ONE PAGE

Cram sheet

Everything from chapters 13 and 14 in one place. Cover the right column and see if you can rebuild each row.

Chapter 13 at a glance

Topic	Key facts
Equivalence and potency	nuclear transfer, iPSC (Oct4, Sox2, Klf4, c-Myc); totipotent, pluripotent, multipotent
Genetic approaches	forward: phenotype to gene; reverse: gene to phenotype
Apoptosis genes	*egl-1* (BH3 only), *ced-9* (Bcl-2), *ced-4* (Apaf-1), *ced-3* (caspases)
Fly axes	Bicoid front, Nanos back; nuclear Dorsal ventral
Segmentation	gap bands; pair rule 7 stripes; segment polarity 14 stripes; Hox identity
Hox	colinear; 180 bp homeobox; 60 aa homeodomain; mammals 39 genes in 4 clusters
ABC model	A sepal; A + B petal; B + C stamen; C carpel; A and C repress each other
Cell cycle	cyclin D, E, A, B with CDKs; Wee1, Cdc25, CAK; p16, p21, p27; SCF and APC/C
Restriction point	Rb holds E2F; phosphorylation frees it; positive loop through cyclin E
Checkpoints	G1/S (p53, p21), G2/M (Chk1 blocks Cdc25), spindle (Mad2 blocks Cdc20)
Oncogenes	point mutation (*KRAS*), amplification (*ERBB2*), fusion (BCR-ABL1), enhancer move (MYC)
Tumor suppressors	two hits; LOH; methylation; gatekeepers and caretakers; TP53 in about half of cancers
Multistep	incidence $\propto$ age^{k-1}; APC, KRAS, SMAD4, TP53; hallmarks; HPV E6 (p53), E7 (Rb); PARP and BRCA

Chapter 14 at a glance

Topic	Key facts
AD	vertical; male to male; 1/2; haploinsufficiency, dominant negative, gain of function
AR	horizontal; carrier parents; 1/4; consanguinity; sibling carrier 2/3
X linked	mostly males; no male to male; daughters of affected men carriers; X linked dominant: father to all daughters
Mitochondrial	maternal only; heteroplasmy; bottleneck; threshold
Exceptions	penetrance; expressivity; new mutation; germline mosaicism; anticipation; imprinting
Hardy Weinberg	q = √incidence; carriers ≈ 2q; X linked: males q
Multifactorial	liability threshold; 2 to 5% first degree; Carter effect; Edwards √incidence
Twins	concordance; $h^2 = 2(r_{MZ} - r_{DZ})$
GWAS	5×10^{-8}; OR mostly 1.1 to 1.5; polygenic risk scores ancestry dependent
Tests	diagnostic, predictive, carrier, prenatal, PGT, newborn, pharmacogenetic
Performance	sensitivity, specificity; PPV and NPV depend on prevalence
Counseling	nondirective; Bayes: prior, conditional, joint, posterior
ELSI	consent, right not to know, minors, cascade testing, GINA limits, secondary findings, equity, germline editing

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