

Exercise walk-through

6.6

Genetic testing and counselling

University Medicine

Genetic testing: the question chooses the window

- 1 **Windows Karyotype** (≥ 5 –10 Mb, balanced seen); CMA (CNVs 50–100 kb, balanced MISSED); FISH (targeted fast); sequencing (base-level, chosen scope).
- 2 **Mapping** Aneuploidy $\rightarrow$ karyotype/FISH; developmental delay $\rightarrow$ CMA first; known familial variant $\rightarrow$ targeted Sanger.
- 3 **Cascade** One positive familial result $\rightarrow$ 1/2 for each first-degree relative; negatives return to population risk.

Genetic testing - the figure

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 $\rightarrow$ panel $\rightarrow$ exome/genome

Four methods, four resolutions, one comparison.

Exercises 2.1-2.3

2.1 Which method detects balanced translocations? [3]

2.2 First-line test for unexplained developmental delay? [3]

2.3 What does a negative familial-variant test return a relative to? [3]

Exercises 2.1-2.3

2.1 Which method detects balanced translocations? [3]

2.1

- Karyotype (microscopy of metaphase spreads).
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2.2 First-line test for unexplained developmental delay? [3]

2.2

- Chromosomal microarray.
-

2.3 What does a negative familial-variant test return a relative to? [3]

2.3

- Population risk for that syndrome.

Exercise 3.1

3.1 A familial pathogenic variant is found in a proband (fictional).

State each first-degree relative's a-priori risk ($1/2$). Explain how cascade testing converts uncertainty into binary results. State two considerations before testing a healthy 19-year-old relative (autonomy; insurance/psychological). [7]

Exercise 3.1

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3.1

- Each sibling and each parent: $1/2$ a priori.
- Cascade testing: relatives tested for THE familial variant → positives enter screening, negatives return to population risk – uncertainty becomes binary.
- Considerations: autonomy (the 19-year-old decides); implications for insurability and psychological burden; timing.

Exercise 3.2

3.2 A genome sequencing test for a child's developmental delay finds an incidental adult-onset predisposition (fictional).

State the general policy (defer adult-onset results in children). Explain why consent before testing matters here. State what changes if the finding is childhood-actionable. [7]

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3.2 A genome sequencing test for a child's developmental delay finds an incidental adult-onset predisposition (fictional).

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3.2

- Defer the adult-onset result until the child can consent.
- Consent before testing sets the return-of-results menu (opt in/out); after the fact, the choice is already gone.
- If childhood-actionable (treatable/preventable now), return it - the child's health benefit overrides deferral.