

Exercise walk-through

6.7

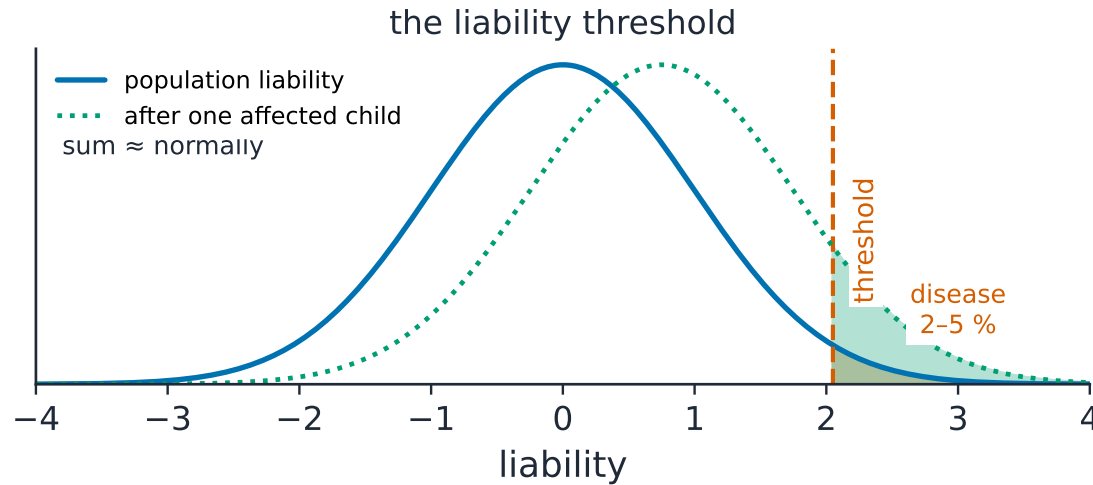
Multifactorial disease and pharmacogenomics

University Medicine

Multifactorial disease: the bell and its threshold

- 1 **Model** Liability (genes + environment) $\approx$ normal; disease past a threshold.
- 2 **Risks** Empiric 2–5% after one affected; rising with more affected relatives, severity, and the more-affected sex (toward 10% with two).
- 3 **PGx** CYP2C19/clopidogrel (poor metabolisers, ~20% East-Asian carriers); TPMT/thiopurines; HLA-B*57:01/abacavir - screen before prescribing.

Multifactorial disease - the figure



The liability bell with its threshold and the shifted family curve.

Check yourself

- **Nondisjunction** II gamete ratio? (1:1:2.)
- CF carriers from 1/2500? ($\approx 1/25$.)
- Affected-child risk, **carrier** + screened partner? ($\approx 1/1200$.)
- Multifactorial recurrence after one child? (2–5 %.)

Exercises 2.1-2.3

2.1 State the typical empiric recurrence for a multifactorial condition after ONE affected child. [3]

2.2 Which CYP variant status makes clopidogrel ineffective? [3]

2.3 Which HLA allele requires screening before abacavir? [3]

Exercises 2.1-2.3

2.1 State the typical empiric recurrence for a multifactorial condition after ONE affected child. [3]

2.1

- 2–5 % ✓.

2.2 Which CYP variant status makes clopidogrel ineffective? [3]

2.2

- CYP2C19 poor metaboliser (no prodrug activation).

2.3 Which HLA allele requires screening before abacavir? [3]

2.3

- HLA-B*57:01 (hypersensitivity).

Exercise 3.1

3.1 A couple has one child with a neural-tube defect (fictional).

Quote the recurrence risk and its modifiers (two affected $\rightarrow \sim 10\%$). Explain the liability-threshold basis of the rise. State the folate prescription and why it applies regardless of risk.

Exercise 3.1

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Quote the recurrence risk and its modifiers (two affected $\rightarrow$ $\sim 10\%$). Explain the liability-threshold basis of the rise. State the folate prescription and why it applies regardless of risk. [7]

3.1

- 2–4 % after one; $\sim 10\%$ after two.
- Additional affected relatives shift the family's liability distribution right: more siblings cross the threshold.
- Folic acid 4 mg/day pre-conception and first trimester for every subsequent pregnancy – cheap, safe, and risk-independent.

Exercise 3.2

3.2 A psychiatric service considers routine pharmacogenomic screening (fictional).

Discuss CYP2C19/clopidogrel (~20 % of East-Asian allele carriers are poor metabolisers), TPMT/thiopurines, and HLA-B*57:01/abacavir: what does each screen prevent? State the general principle (genotype as dosing instruction, not diagnosis). [7]

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3.2

- CYP2C19: prevents ineffective antiplatelet therapy (stent thrombosis); TPMT: prevents severe myelosuppression; HLA-B*57:01: prevents abacavir hypersensitivity.
- Each is a screening test with a prescription attached.
- Principle: the result guides the drug and dose – a dosing instruction, not a disease diagnosis.