UNIVERSITY MEDICINE • EXERCISE SHEET

6.7 Multifactorial disease and pharmacogenomics

Name: _____ Class: _____ Date: _____ **Total: 23 marks**

KEY WORDS liability threshold model

Objective

Quote multifactorial recurrence risks and apply pharmacogenomic screens.

1 Key knowledge and worked examples

■ **The bell and its threshold**

Liability (genes + environment) ≈ normal; disease past the threshold. Empiric 2–5 % after one affected; rising with more affected relatives, severity, and the more-affected sex ✓.

■ **Worked example: the NT defect quote**

One affected child: 2–4 % (folate cuts it); two: ~10 % ✓ – tables not grids, and folate regardless.

2 Practice

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]

3 Exam-style questions

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

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

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]

Solutions

2.1

- 2–5 % ✓.

2.2

- CYP2C19 poor metaboliser (no prodrug activation).

2.3

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

3.1

- 2–4 % after one; ~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.

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.