6.4 Mutation and variant interpretation

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

KEY WORDS variant of uncertain significance

Objective

Classify variants and grade them with the evidence chain.

1 Key knowledge and worked examples

■ **The classes**

Synonymous / missense / nonsense / frameshift / splice + CNVs; verdicts pathogenic → benign with VUS at the centre ✓.

■ **Worked example: the frequency kill**

A 1 %-population variant for a 1/10 000 dominant disease: posterior odds ≈ 1:100 AGAINST ✓ – Bayes before prediction algorithms.

2 Practice

2.1 Which variant type truncates the protein? [3]

2.2 What does VUS stand for and mean? [3]

2.3 Which variant class deletes whole exons? [3]

3 Exam-style questions

3.1 A nonsense variant early in a haploinsufficiency gene (fictional).

State the likely verdict with reasons (mechanism: one working copy insufficient). Contrast with a dominant-negative gene. State the phenotype-severity expectation. [7]

3.2 A missense VUS in a breast-cancer gene in an affected woman (fictional).

State the counselling (not pathogenic; no cascade on a VUS). List two evidence streams that could upgrade it (segregation in the family; accumulating case data). State one harm of treating it as pathogenic. [7]