Question 25 – Respiratory
The carrier frequency for cystic fibrosis (CF) in the Caucasian population in Australia is approximately 4%. The ΔF508 mutation accounts for 75% of all mutations among carriers in this population.

A girl is diagnosed with CF. DNA studies identify one ΔF508 mutation but fail to identify a mutation in the other allele. DNA studies of her unaffected brother are normal.

What is the risk of her brother being a carrier?

A. <1%  
B. 4%  
C. 25%  
D. 50%  
E. 66%

Answer: D

To answer this question you need to know:
- CF genetics
  - One can have CF with either 2 copies of the same mutation OR 1 copy of 2 different mutations

CF genetics
- Commonest fatal inherited disease among Caucasians
- **Autosomal recessive**
- Mutation in single large gene on **chromosome 7** that encodes the CFTR (cystic fibrosis transmembrane conductance regulator protein)
- **Carrier frequency 1:25** (1 in 25 people carry the CF gene ie are heterozygotes)
- Prevalence 1:2700
- 1:2000-3000 live births
- To have CF, the affected person must have 2 defective genes and must have inherited an affected gene from each parent
- This can be **2 copies of the same CF mutation, or 1 copy of one mutation and 1 copy of another mutation**
- Very small numbers of patients with phenotypic evidence of CF (symptoms and +ve sweat test) in the absence of CFTR mutations

Diagnosis of CF
1) Sweat test (Gold standard)
   - Collection of >50mg sweat in 45 minutes
   - ↑ sweat chloride levels > 60 meq
   - False negatives in hypoproteinaemic oedema + steroids
   - Those with unusual genotypes tend to have normal sweat tests (<1%)

2) Molecular/ DNA testing
   - Picks up < 90% mutations (only tests for 20-30 most common mutations)

3) Nasal potential difference measurement
   - Measure nasal transepithelial potential difference at basal state, after amiloride nasal spray and chloride-free nasal spray
   - Abnormal Cl secretion more associated with pancreatic insufficiency
   - Na hyper-absorption more associated with lung disease
   - False negatives in nasal polyps/ inflammation

4) Infancy screening (Immunoreactive trypsin IRT)
   - Levels fall rapidly with infancy
   - Negative test after 8 weeks unreliable
- Rationale for screening: early intervention and better outcome (early referrals, nutritional support leads to better outcome, trials)

5) Others eg sperm count/ duodenal fluid testing

- Prevalence
  - Number of people having a disease at a particular time with no regard to when they first got the disease (ie a "cross section")
  - Indicates neither when someone got the disease nor if previously diseased persons recover or die, it is not a good indicator of overall rate, or risk of getting a disease

- Incidence
  - Rate
  - How many new cases in a fixed population over a fixed time period