20-35% of patient’s treated. Irinotecan related mortality rates have been reported as high as 5.3%. UGT1A1 is mainly responsible for the detoxification of irinotecan. In November 2004 the US FDA advisory committee on pharmaceutical sciences advised Pfizer Pharmaceuticals to amend the product information for Irinotecan (Camptosar) to include recommendations to reduce dosage for patients homozygous for UGT1A1*28 (7/7 genotype).

References
1. Arias IM. Chronic unconjugated hyperbilirubinemia without signs of overt haemolysis in adolescents and adults. J Clin Invest. 1962; 41:2233-2245
Sending Specimens for Analysis
Sample requirement: 4 ml EDTA whole blood sample.

- The sample must not have been frozen. If you have to store samples prior to dispatch please keep at 4°C.
- Please send samples by first class post at ambient temperature to the address on the back of this leaflet.
  We receive samples on a Saturday.

Note: Lithium heparin/serum samples cannot be used

What is Gilbert’s Syndrome?
Gilbert’s Syndrome is an inherited form of unconjugated hyperbilirubinaemia resulting in mild jaundice occurring in the absence of haemolysis or other underlying liver disease¹. Typically, total serum bilirubin concentration is between 20 and 50 μmol/L and may be noticeable within the sclera, skin and mucous membranes. The hyperbilirubinaemia is caused by reduced activity of the hepatic 1A1 isoform of the uridine diphosphoglucose glucuronosyltransferase enzyme (UGT1A1), which is responsible for conjugating water insoluble unconjugated bilirubin to glucuronic acid². It is most often detected during routine blood tests taken during periods of fasting, infection, intense exercise and after surgery. The frequency of Gilbert’s Syndrome in the UK population is approximately 10%.

Genetics of Gilbert’s Syndrome
The majority of cases of Gilbert’s Syndrome are caused by a polymorphism in the promoter region of the UGT1A1 gene, the A(TA)6TAA element². The insertion of two extra nucleotides (TA) within this TATA box results in a A(TA)7TAA mutant allele, designated UGT1A1*28. The UGT1A1*28 homozygous genotype is expressed as 7/7, a heterozygous genotype 6/7 and wildtype 6/6. Since Gilbert’s Syndrome is autosomal recessive, carriers (6/7 genotype) are not affected. Other rare mutations will also be reported when detected along with an appropriate explanation.

City Hospital UGT1A1*28 Genotyping Assay
We use the Roche LightCycler480 and specific Hybprobes to the UGT1A1 TATA promoter sequence. This FRET (fluorescence, resonance energy transfer) method yields distinct melting curves for the different UGT1A1 genotypes.

Results
UGT1A1*28 genotype = 6/6 (normal)
UGT1A1*28 genotype = 6/7 (carrier)
UGT1A1*28 genotype = 7/7 (positive – Gilbert’s Syndrome)

Patient Information
Patients should be informed about this genetic test prior to taking the sample.

Clinical use of UGT1A1*28 Genotyping

Confirming Gilbert’s Syndrome: A key reason to establish the diagnosis is to prevent further unnecessary investigations/procedures, which could include highly evasive liver biopsy.

Pharmacogenetics: UGT1A1 is involved in the metabolism of many drugs, for example: Irinotecan, atazanavir, thyroxine and paracetamol. Mutations that affect UGT1A1 levels of expression or enzyme function can affect response to these drugs and may result in serious side effects.

Irinogenetics: Irinotecan (CPT-11, brand name Camptosar) is approved worldwide for the treatment of metastatic colorectal cancer³. Its use is limited by toxic side effects including myelosuppression, which occurs in about