

20-35% of patient's treated<sup>4</sup>. Irinotecan related mortality rates have been reported as high as 5.3%<sup>5</sup>. 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)<sup>6</sup>.

## References

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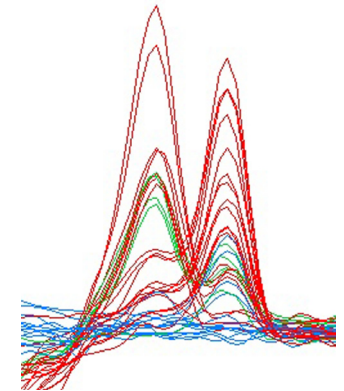
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# Genetic Screening for Gilbert's Syndrome Detection of UGT1A1\*28 Mutation



*Vitamins and  
Gastroenterology Laboratory*

*Clinical Biochemistry  
City Hospital*



## 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 Gilberts 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 disease<sup>1</sup>. 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 acid<sup>2</sup>. It is most often detected during routine blood tests taken during periods

of fasting, infection, intense exercise and after surgery. The frequency of Gilberts 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)<sub>6</sub>TAA element<sup>2</sup>. The insertion of two extra nucleotides (TA) within this TATA box results in a A(TA)<sub>7</sub>TAA 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 Gilberts 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 –Gilberts 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 world wide for the treatment of metastatic colorectal cancer<sup>3</sup>. Its use is limited by toxic side effects including myelosuppression, which occurs in about