**UGT1A1 (TA)n Polymorphisms**

**Indications for Ordering**
- Dosage planning for individuals
  - Who will receive high-dose irinotecan (>150 mg/m^2)
  - With a personal or family history of sensitivity to irinotecan
  - Who have experienced neutropenia while receiving irinotecan
- Confirm suspected diagnosis of Gilbert syndrome

**Test Description**
Polymerase chain reaction/fragment analysis
- Alleles tested
  - *36 (TA)5
  - *1 (TA)6
  - *28 (TA)7
  - *37 (TA)8

**Tests to Consider**
**UDP Glucuronosyltransferase 1A1 (UGT1A1) Genotyping 0051332**

**Disease Overview**
Pathophysiology
- Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzyme is responsible for the clearance of drugs (eg, irinotecan) and endogenous substances (eg, bilirubin)
- Irinotecan is a topoisomerase I inhibitor
  - Interrupts DNA replication in cancer cells, causing cell death
- Prodrug is metabolized to active metabolite SN-38
  - 100-1,000 times more cytotoxic than parent drug
  - Inactivated by UGT1A1
- Decreased UGT1A1 activity reduces ability to metabolize SN-38 to inactive form

Treatment issues
- Irinotecan (CPT-11, Camptosar)
  - Approved for treatment of metastatic colorectal cancer
  - May be used in metastatic lung, brain, and breast cancer
- Irinotecan is associated with severe diarrhea and neutropenia in 20-35% of individuals
  - Toxicity of irinotecan is associated with specific UGT1A1 genotype variants

**Genetics**
Gene – UGT1A1

**Variants**
- Polymorphic TA repeat in the TATA element of the 5’ promoter region of UGT1A1 may consist of
  - 5, 6, 7, or 8 repeats
    - 6 is common number of repeats – also known as UGT1A1*1 (TA)6
  - UGT1A1 variants are also associated with
    - Gilbert syndrome (benign familial hyperbilirubinemia)
    - Crigler-Najjar syndrome (rare form of nonhemolytic jaundice)

**Allele frequency**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasians</th>
<th>Asians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 (TA)6</td>
<td>0.61</td>
<td>0.84</td>
<td>0.47</td>
</tr>
<tr>
<td>*28 (TA)7</td>
<td>0.39</td>
<td>0.16</td>
<td>0.43</td>
</tr>
</tbody>
</table>

**Test Interpretation**
Sensitivity/specificity
- Analytical sensitivity – >99%
- Clinical sensitivity/specificity – risk of irinotecan toxicity by genotype (Marcuello, 2004)

<table>
<thead>
<tr>
<th>TA genotype</th>
<th>Diarrhea risk</th>
<th>Neutropenia risk</th>
<th>Irinotecan dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6 (*1/*1)</td>
<td>17%</td>
<td>15%</td>
<td>Standard</td>
</tr>
<tr>
<td>6/7 (*1/*28)</td>
<td>33%</td>
<td>27%</td>
<td>Based on clinical findings</td>
</tr>
<tr>
<td>7/7 (*28/*28)</td>
<td>70%</td>
<td>40%</td>
<td>Dose reduction recommended</td>
</tr>
</tbody>
</table>

**Results**
- *36 (TA)5 and *37 (TA)8 are reported
  - Dosing recommendations are less clear for these alleles
- No significant risk of irinotecan toxicity is associated with UGT1A1 genotype when using low-dose therapy (eg, 15-75 mg/m^2 for 5 days for 2 consecutive weeks)
- Homozygosity for the *28 (TA)7 allele is associated with Gilbert syndrome
Limitations

• Variants other than those targeted will not be detected
• Clinical significance of the rare *36 (TA)5 and *37 (TA)8 alleles in predicting irinotecan toxicities is not well established
• Genetic and nongenetic factors other than UGT1A1 may contribute to irinotecan toxicity and efficacy
• Diagnostic errors can occur due to rare sequence variations

Reference