UGT1A1 polymorphisms in cancer: impact on irinotecan treatment

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Abstract: Mutations in the UGT1A1 gene have been implicated in Gilbert syndrome, which shows mild hyperbilirubinemia, and a more aggressive childhood subtype, Crigler–Najjar syndrome. To date, more than 100 variants have been found in the UGT1A1 gene. Among them, UGT1A1*28 and UGT1A1*6 have been reported to be associated with severe toxicities in patients treated with irinotecan-based chemotherapy by increasing the dose of SN-38 (7-ethyl-10-hydroxy camptothecin), an active form of irinotecan. Many association studies and meta-analyses have demonstrated the contribution of UGT1A1*28 and UGT1A1*6 polymorphisms to the toxicities caused by irinotecan-based therapy. The aim of this review was to evaluate the impact of these variant upon the toxicities and the efficacy of irinotecan-based chemotherapy.

Keywords: UGT1A1, irinotecan, chemotherapy, toxicity, response, survival

Introduction
Irinotecan hydrochloride, inhibiting topoisomerase I, is one of the key anticancer drugs in chemotherapy for several cancers such as colorectal cancer, lung cancer, gastric cancer, and gynecologic cancers.1–4 The patients treated with irinotecan occasionally experience severe neutropenia and delayed diarrhea; however, the occurrence of these adverse reactions has been unpredictable and largely unexplained.5 An active metabolite of irinotecan, SN-38 (7-ethyl-10-hydroxy camptothecin), is glucuronidated by uridine diphosphate glucuronosyltransferase 1As (UGT1As), such as UGT1A1, and is inactivated by forming the SN-38 glucuronide (SN-38G). Among these UGT1A enzymes, UGT1A1 protein has the highest ability to glucuronidate SN-38.6 Various studies have demonstrated a relationship between UGT1A1 genotypes affecting SN-38 pharmacokinetics and the experienced toxicity.7 The transport pathway of irinotecan is shown in Figure 1. In addition to UGT1A1 polymorphism, polymorphisms of carboxylesterase (CES) and ATP-binding cassette (ABC) genes have been reported to affect the metabolism of irinotecan.8,9 In this review, the impact of UGT1A1 genotypes on irinotecan treatment will be discussed.

UGT1A1 polymorphisms and disease susceptibility
Mutations in the UGT1A1 gene have been implicated in Gilbert’s syndrome, which shows mild hyperbilirubinemia, and a more aggressive childhood subtype, Crigler–Najjar syndrome.10,11 A common cause of decreased UGT1A1 activity is the insertion of a TA in the TATA box at the promoter region of the UGT1A1 gene, which was named as UGT1A1*28.10 Individuals with homozygous UGT1A1*28 had higher levels of serum bilirubin compared with those with heterozygous UGT1A1*28 or the wild-type allele.10
Gilbert’s syndrome, also known as constitutional hepatic dysfunction or familial nonhemolytic jaundice, is an inherited disorder of the liver resulting in an overabundance of bilirubin. Most of the patients with Gilbert’s syndrome are asymptomatic; however, they sometimes present with episodes of mild intermittent jaundice due to predominantly unconjugated hyperbilirubinemia. Crigler–Najjar syndrome is a rare, but more severe, disorder of bilirubin metabolism and is divided into two distinct forms (types I and II) based upon the severity of the disease. Gilbert’s syndrome is part of a continuous spectrum of altered glucuronidation that extends to the fatal Crigler–Najjar disease.

Gilbert’s syndrome is primarily linked to UGT1A1*28 variants, but other variants in the promoter and coding regions are also involved in the predisposition of the disease. To date, more than 100 variants have been identified in the UGT1A1 gene. Among these polymorphisms, the clinically important variants are listed in Table 1.

Recently, a large population-based cohort study, the Rotterdam Study, investigated the association between UGT1A1 genotype and incidence of coronary heart disease (CHD). However, in this study, neither bilirubin nor UGT1A1*28 genotype was associated with development of CHD. Another large trial evaluating 1,780 unrelated individuals aged more than 24 years suggested that homozygous UGT1A1*28 alleles and higher serum level of bilirubin were related with lower risk of cardiovascular disease (CVD). Serum bilirubin has a protective effect on CVD and CVD-related disease. It seems that individuals with Gilbert syndrome and UGT1A1*28 allele and having moderate elevation of serum bilirubin could have a lower risk of CHD and CVD.

**UGT1A1*28 allele and efficacy of irinotecan-based therapy**

Emerging data on the role of genetic variants in the UGT1A1 gene confirm that the UGT1A1*28 allele is associated with severe toxicities in irinotecan-based chemotherapy. Additionally, it seems that patients with the allele were also associated with better outcome, despite severe toxicities. A study by Toffoli et al conducted in 238 patients with metastatic colorectal cancers, showed that...
are listed in Table 2.22,26–36 Representative studies evaluated in these meta-analyses with *28/*28 or *1/*28 alleles, due to severe toxicities. These results might reflect a lower dose intensity of irinotecan in patients with *28/*28 alleles.26,28,32–34 Some reports suggested significant associations between diarrhea and *28/*28 alleles27,31,33 Several meta-analyses have examined the impact of the *28 allele on the toxicities of irinotecan-based therapy. A study by Hoskins et al,37 evaluating 821 cases, revealed that severe hematological toxicities were more frequently observed in *28/*28 patients, when the irinotecan doses were high (>250 mg/m²) or intermediate (150–250 mg/m²). However, the risk was not elevated in patients treated with low doses of irinotecan (<150 mg/m²).37 Another study by Hu et al38 reported that the *28/*28 genotype was associated with an increased risk of neutropenia not only at medium (response rate [RR] = 2.0, 95% confidence interval [CI] = 1.6–2.5, p < 0.01) or high doses (RR = 7.2, 95% CI = 3.1–16.8, p < 0.01) of irinotecan but also at low doses (RR = 2.4, 95% CI = 1.3–4.4, p < 0.01) from the results of meta-analyses evaluating 1,998 patients. Additionally, a study by Liu et al39 confirmed that patients with *28/*28 genotype had higher incidence of neutropenia compared with *1/*1 or *1/*28 genotype cases, in addition to suggesting that patients with *1/*28 genotype had significantly higher rate of severe neutropenia compared with *1/*1 genotype cases (odds ratio [OR] = 1.84, 95% CI = 1.24–2.72, p < 0.01).

**UGT1A1*28 allele and the toxicities of irinotecan-based therapy**

Many studies have evaluated toxicities in patients treated with irinotecan-based therapy according to UGT1A1 genotypes.22,26–36 Table 2 summarizes representative studies evaluating the incidence of neutropenia and diarrhea. In terms of neutropenia, approximately half of these studies suggested a significant contribution of *28/*28 alleles to severe toxicities. A study by Kweekel et al40 analyzing high-dose irinotecan regimens (250 or 350 mg/m²) revealed that patients with *28 allele had a significantly higher rate of febrile neutropenia compared with *1/*1 cases.

Several studies evaluating 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) regimen also reported significantly higher incidence of severe neutropenia in cases with *28/*28 alleles.26,28,32–34 Some reports suggested significant association between diarrhea and *28/*28 alleles.27,31,33 Several meta-analyses have examined the impact of the *28 allele on the toxicities of irinotecan-based therapy. The most frequent and important variant in the Asian population is UGT1A1*6, which is rarely found among Caucasians. Representative studies evaluating UGT1A1*6 and clinical outcomes in patients treated with irinotecan-based therapy are listed in Table 3.40–50 Most of these studies were mainly focused on the toxicities of the regimens,40,42,44–46,49,50 and quite a few studies reported the clinical outcomes such as response rate and survival.47,48 Some studies reported that there were no significant associations between *6 alleles and the efficacy,
including response rate and survival.\textsuperscript{40,44,45} Among the studies listed, almost all the studies reported significant relationship between \textit{UGT1A1}\textsuperscript{*6/*6} and severe neutropenia, compared with \textsuperscript{*1/*1} cases. Additionally, half of the studies suggested significantly higher incidence of severe neutropenia in patients with \textit{UGT1A1}\textsuperscript{*1/*6}.\textsuperscript{42,44,48-50} A study evaluating a combination therapy with irinotecan and cisplatin reported an increased risk of severe diarrhea in patients with \textsuperscript{*1/*6} alleles.\textsuperscript{99}

A meta-analysis evaluating mainly Asian studies reported that patients with \textsuperscript{*6/*6} alleles had increased incidences of severe neutropenia with both high/medium (OR = 3.95, 95\%CI = 2.05–7.64, \textit{p} < 0.01) and low doses (OR = 0.01) of irinotecan. This trend was lower in \textsuperscript{*28/*28} (OR = 1.55 for high/medium, OR = 1.55 for low dose, and OR = 0.97, 95\%CI = 0.37–2.79 for no difference) and low doses (OR = 9.64, 95\%CI = 2.01–45.28, \textit{p} < 0.01) and low doses (OR = 11.14, 95\%CI = 5.99–21.58 for no difference) and low doses (OR = 11.14, 95\%CI = 5.99–21.58 for no difference).

\begin{table}[h]
\centering
\small
\textbf{Table 2} Severe toxicities according to \textit{UGT1A1}\textsuperscript{*28} genotyping
\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
\textbf{Study} & \textbf{No of patients} & \textbf{Regimens} & \textbf{Irinotecan dose (mg/m}^2\textbf{)} & \textbf{Neutropenia G3–4, \%} & \textbf{Diarrhea G3–4, \%} & \textbf{Efficacy} \\
\hline
\multicolumn{7}{|c|}{\textbf{Odds ratio (95\%CI)}} \\
\hline
Rouits et al\textsuperscript{26} & 73 & FOLFIRI, mFOLFIRI & 85/1w, 180/2w & 23.33 (3.08–177.04) & 6.22 (1.58–24.47) & 2.70 (0.39–18.92) & 1.69 (0.44–6.43) & – \\
\hline
Marcuello et al\textsuperscript{27} & 95 & IRI-Tomudex, etc & 80/1, 180/2w, 350/3w & – & – & 11.00 (2.27–53.37) & 2.36 (0.85–6.57) & RR, no difference (NS) \\
\hline
Toffoli et al\textsuperscript{28} & 250 & FOLFIRI, mFOLFIRI & 180/2w & 2.08 (0.60–7.28) & 1.99 (0.91–4.38) & 0.86 (0.10–7.49) & 2.52 (0.93–6.81) & RR 40\% (\textsuperscript{*1/*1}), 42\% (\textsuperscript{*1/*28}), 67\% (\textsuperscript{*28/*28} (\textit{p} = 0.03) \\
\hline
Côté et al\textsuperscript{29} & 89 & FOLFIRI & 180/2w & 6.40 (1.20–34.20) & 1.88 (0.58–6.11) & – & – & – \\
\hline
Kweekel et al\textsuperscript{30} & 218 & IRI, IRI-Cape & 250 or 350/3w & – & – & IRI 11.14 (0.89–140.12) & IRI-Cape 2.08 (0.53–8.14) & – \\
\hline
Braun et al\textsuperscript{31} & 326 & IRI, IRI-SFU & 300–350/3w, 180/2w & IRI 1.73 (0.16–18.40) & IRI 1.28 (0.52–3.13) & IRI 1.20 (0.12–11.91) & IRI-SFU 2.75 (0.49–15.38) & – \\
\hline
Ferraldeschi et al\textsuperscript{32} & 92 & FOLFIRI, IRI-Cape, etc & 180/2w, 250 or 350/3w & 2.53 (0.40–16.15) & 2.14 (0.66–7.03) & 14.00 (1.09–179.00) & IRI 0.48 (0.08–2.74) & IRI-Cape 1.06 (0.46–2.46) \\
\hline
McLeod et al\textsuperscript{33} & 212 & IFL, IROX & 100–125/1w, 200/3w, IFL 3.04 (0.44–20.91) & IFL 1.71 (0.40–7.26) & IFL 1.94 (0.47–8.01) & IFL 1.24 (0.32–4.77) & – & – \\
\hline
Martinez-Balibre et al\textsuperscript{34} & 149 & FOLFIRI, FUJIRI & 80/1w, 180/2w & 4.00 (1.12–14.32) & 1.67 (0.67–4.20) & 4.96 (1.49–16.55) & IFL 0.97 (0.37–2.52) & RR of IROX, lower in \textsuperscript{*28/*28} (\textit{p} = 0.02) \\
\hline
Gilmelius et al\textsuperscript{35} & 136 & FLIRI, Lv-SFU-IRI & 180/2w & 6.88 (1.70–27.75) & 1.75 (0.55–5.56) & 1.42 (0.15–13.79) & 1.85 (0.47–7.25) & RR, no difference (NS) \\
\hline
Shulman et al\textsuperscript{36} & 214 & TEGAFIRI, XELIRI, etc & 80/w, 180/2w, IFL 5.43 (1.50–19.67) & IFL 1.53 (0.48–4.85) & 1.53 (0.48–4.85) & 1.38 (0.63–3.04) & – & – \\
\hline
Lamas et al\textsuperscript{37} & 100 & IRI-Cape, mFOLFIRI & 100 or 125/w, 180/2w, IRL 4.00 (0.09–7.25) & IRL 2.49 (0.85–7.29) & IRL 2.49 (0.85–7.29) & IRL 2.49 (0.85–7.29) & – & – \\
\hline
\multicolumn{7}{|c|}{Abbreviations: CI, confidence interval; RR, response rate; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; NS, not significant; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; mFOLFIRI, modified FOLFIRI; IRI-Tomudex, irinotecan plus tomudex; IRL, irinotecan; IRI-Cape, irinotecan plus capetitabine; IRI-SFU, irinotecan plus 5-fluorouracil; IFL, irinotecan plus 5-fluorouracil; IROX, irinotecan plus oxaliplatin; FUJIRI, irinotecan plus high-dose 5-fluorouracil; FLIRI, irinotecan plus bolus 5-fluorouracil/leucovorin; Lv-SFU-IRI, irinotecan, bolus infused 5-fluorouracil/leucovorin; TEGAFIRI, uracil, florafur, leucovorin, and irinotecan; XELIRI, capetibatine plus irinotecan.} \\
\end{tabular}
\end{table}
Genotype-based dose modification studies
Accumulated evidence suggests that optimal doses of irinotecan according to UGT1A1 genotype are needed. Several dose-finding studies have been published; however, most of the studies were dose modifications of the FOLFIRI regimen (Table 4).52–56 Three studies evaluating irinotecan doses in FOLFIRI showed that the maximal tolerated dose (MTD) in patients with *1/*1, *1/*28, and *1/*6 alleles was higher than the standard doses of the FOLFIRI regimen.52–54 The MTD in the *1/*1 patients was also higher than that of patients with *1/*28 and *1/*6 alleles, and the MTD in patients with *28/*28, *6/*6, and *28/*6 alleles was lower than the current standard doses of the FOLFIRI regimen.53,54 In the Asian population, incorporation of UGT1A1*6 in addition to UGT1A1*28 would be needed for the safety

Table 3 Severe toxicities according to UGT1A1*6 genotyping

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Regimens</th>
<th>Irinotecan dose</th>
<th>Neutropenia G3–4 (%) Odds ratio (95% CI)</th>
<th>Diarrhea G3–4 (%) Odds ratio (95% CI)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jada et al40</td>
<td>45</td>
<td>IRI</td>
<td>375/3w</td>
<td>–</td>
<td>7.75 (0.40–149.70)</td>
<td>1.11 (0.11–11.49)</td>
</tr>
<tr>
<td>Sai et al41</td>
<td>49</td>
<td>IRI</td>
<td>60/1w, 100, 125, 150/2w</td>
<td>28.00 (0.92–851.54)</td>
<td>8.00 (0.82–78.47)</td>
<td>–</td>
</tr>
<tr>
<td>Takano et al42</td>
<td>30</td>
<td>IRI-cisplatin</td>
<td>60/1w</td>
<td>–</td>
<td>11.20 (1.73–72.30)</td>
<td>–</td>
</tr>
<tr>
<td>Seo et al43</td>
<td>39</td>
<td>FOLFIRI</td>
<td>150/2w</td>
<td>0.97 (0.24–3.90)</td>
<td>–</td>
<td>0.56 (0.10–3.08) RR, OS, no difference (NS)</td>
</tr>
<tr>
<td>Onoue et al44</td>
<td>133</td>
<td>IRI-platinum, FOLFIRI</td>
<td>&lt;60, &gt;100</td>
<td>7.78 (1.36–44.50)</td>
<td>4.27 (1.71–10.62)</td>
<td>–</td>
</tr>
<tr>
<td>Satoh et al45</td>
<td>73</td>
<td>IRI</td>
<td>150/2w</td>
<td>9.33 (1.96–44.49)</td>
<td>0.85 (0.16–4.51)</td>
<td>18.18 (0.68–483.94)</td>
</tr>
<tr>
<td>Okuyama et al46</td>
<td>39</td>
<td>FOLFIRI</td>
<td>150/2w</td>
<td>4.04 (0.15–108.57)</td>
<td>1.93 (0.44–8.42)</td>
<td>–</td>
</tr>
<tr>
<td>Wang et al47</td>
<td>130</td>
<td>FOLFIRI, IFL</td>
<td>180/2w</td>
<td>0.59 (0.06–5.54)</td>
<td>0.97 (0.44–2.13)</td>
<td>4.47 (0.16–30.12) 1.99 (0.77–5.13) PFS, OS, no difference (NS)</td>
</tr>
<tr>
<td>Gao et al48</td>
<td>276</td>
<td>FOLFIRI, XELIRI</td>
<td>180/2w</td>
<td>4.07 (1.50–11.04)</td>
<td>2.02 (1.06–3.86)</td>
<td>1.98 (0.40–9.77) 0.90 (0.27–2.95) RR, no difference (NS)</td>
</tr>
<tr>
<td>Gao et al49</td>
<td>133</td>
<td>IRI-cisplatin, FOLFIRI, etc</td>
<td>180/2w</td>
<td>6.40 (1.30–31.60)</td>
<td>3.34 (1.43–7.79)</td>
<td>2.25 (0.23–21.86) 1.13 (0.27–4.75) –</td>
</tr>
<tr>
<td>Ichikawa et al50</td>
<td>1,376</td>
<td>FOLFIRI, IRIS, etc</td>
<td>150/2w</td>
<td>3.34 (2.19–5.10)</td>
<td>1.64 (1.21–2.17)</td>
<td>1.91 (NS) 0.84 (NS) –</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, response rate; PFS, progression-free survival; OS, overall survival; NS, not significant; IRI, irinotecan; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; IFL, irinotecan plus 5-fluorouracil; XELIRI, capecitabine plus irinotecan; IRIS, irinotecan plus S-1.

Table 4 Genotype-based dose-finding studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>Genotype</th>
<th>Starting dose, mg/m²</th>
<th>Results, mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toffoli et al52</td>
<td>FOLFIRI</td>
<td>*1/*1</td>
<td>215</td>
<td>MTD = 370</td>
</tr>
<tr>
<td></td>
<td>*1/*28</td>
<td>215</td>
<td>MTD = 310</td>
<td></td>
</tr>
<tr>
<td>Marcuello et al53</td>
<td>FOLFIRI</td>
<td>*1/*1</td>
<td>180</td>
<td>MTD = 390</td>
</tr>
<tr>
<td></td>
<td>*1/*28</td>
<td>110</td>
<td>MTD = 340</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*28/*28</td>
<td>90</td>
<td>MTD = 310</td>
<td></td>
</tr>
<tr>
<td>Kim et al54</td>
<td>FOLFIRI</td>
<td>*1/*1</td>
<td>240</td>
<td>MTD = 330</td>
</tr>
<tr>
<td></td>
<td>*1/*28, *1/*6</td>
<td>240</td>
<td>MTD = 300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*28/*28, *6/*6, *6/*28</td>
<td>240</td>
<td>MTD = 150</td>
<td></td>
</tr>
<tr>
<td>Hazama et al55</td>
<td>Irinotecan (every 2w)+ doxifluridine</td>
<td>*1/*1</td>
<td>70</td>
<td>MTD &gt; 150; RD = 150</td>
</tr>
<tr>
<td></td>
<td>*1/*28</td>
<td>70</td>
<td>MTD = 100; RD = 70</td>
<td></td>
</tr>
<tr>
<td>Lu et al56</td>
<td>FOLFIRI + bevacizumab</td>
<td>*1/*1</td>
<td>180</td>
<td>MTD = 260</td>
</tr>
<tr>
<td></td>
<td>*1/*28</td>
<td>180</td>
<td>MTD = 240</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*28/*28</td>
<td>120</td>
<td>MTD = 210</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MTD, maximal tolerated dose; RD, recommended dose; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan.
of irinotecan-based chemotherapy. All these results suggested that patients with heterozygous UGT1A1 variants, in addition to those with homozygous UGT1A1 variants, had lower MTD of irinotecan compared with those with wild-type alleles.

**Current recommendation for UGT1A1 genotyping in daily practice**

The US Food and Drug Administration recommends on the irinotecan drug label that patients with the *28/*28 genotype should receive a lower starting dose of irinotecan. Additionally the recommendation also noted that “the precise dose reduction in this patient population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment”.57

According to European Society for Medical Oncology (ESMO) guidelines, testing for UGT1A1 polymorphisms should be considered only if severe toxicity potentially related to treatment with irinotecan occurs. The ESMO guideline noted that testing for UGT1A1 is particularly important when irinotecan is used at high doses (300–350 mg/m²) but of less importance when it is administered at lower doses (125–180 mg/m²).58

According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines, it is especially desirable to test for a UGT1A1 genetic polymorphism before administering irinotecan to patients with a high serum bilirubin level, elderly patients, patients whose general condition is poor (eg, performance status 2 [PS2]), and patients in whom severe toxicity (especially neutropenia) developed after the previous administration of irinotecan.59 The guidelines also noted that “irinotecan toxicity cannot be predicted with certainty on the basis of the presence of a UGT1A1 genetic polymorphism alone”, and that “it is essential to monitor patients’ general condition during treatment and to manage adverse drug reactions carefully, irrespective of whether a genetic polymorphism is detected”.

In the USA, single agent irinotecan (350 mg/m², triweekly, monotherapy) is usually used as one of the “irinotecan-based therapies”, so the doses of irinotecan are usually higher than in Europe (180 mg/m², biweekly, combination) or Japan (150 mg/m², biweekly, combination). Although the recommendations for UGT1A1 genotyping are different according to the doses of irinotecan which are clinically often used in daily practice, clinical usefulness should be always considered in all patients who receive irinotecan-based therapy.

**Conclusion**

Emerging data confirmed an increased risk of severe toxicities, such as neutropenia, in patients with UGT1A1*28 and/or UGT1A1*6 genotype when the patients received irinotecan-based chemotherapy. Homozygous variants and double heterozygous variants showed a higher risk of severe toxicities compared with single heterozygous variants. However, genotype-based studies suggest that MTD is clearly lower in patients with heterozygous UGT1A1 variants compared with those with wild-type alleles. Further clinical studies that include heterozygous UGT1A1 variants, in addition to homozygous variants, are needed to evaluate the clinical utility of UGT1A1 genotyping in patients treated with irinotecan-based therapy. On the other hand, although severe toxicities were clearly evident when the dose of irinotecan was high or intermediate, the incidence of these toxicities was significantly higher even when the dose of irinotecan was lower. Furthermore, clinical significance in terms of tumor response or survival was not found according to UGT1A1 genotypes. Further investigations, such as genotype-based therapy, are needed for increasing the efficacy and decreasing the toxicities for patients receiving irinotecan-based therapy.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


