Predictive Biomarkers and Personalized Medicine

**ERCC1 and ERCC2 Polymorphisms Predict Clinical Outcomes of Oxaliplatin-Based Chemotherapies in Gastric and Colorectal Cancer: A Systemic Review and Meta-analysis**

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**Abstract**

**Purpose:** Nucleotide excision repair (NER) modulates platinum-based chemotherapeutic efficacy by removing drug-produced DNA damage. To summarize published data on the association between polymorphisms of NER genes (**ERCC1** and **ERCC2**) and responses to oxaliplatin-based chemotherapies, we carried out a meta-analysis of gastric and colorectal cancer for commonly studied polymorphisms **ERCC1** rs11615C>T and **ERCC2** rs13181T>G.

**Patients and Methods:** In 17 previously published studies, 1,787 cancer patients were treated with the oxaliplatin-based regimen. Primary outcomes included therapeutic response (TR; i.e., complete response + partial response vs. stable disease + progressive disease), progression-free survival (PFS), and overall survival (OS). We calculated OR or HR with 95% CIs to estimate the risk or hazard.

**Results:** We found consistent and clinically substantial risk or hazard for TR, PFS, and OS in the oxaliplatin-treated gastric and colorectal cancer patients with an ethnic discrepancy. For **ERCC1** rs11615C>T, the T allele was associated with reduced response and poor PFS and OS in Asians (TR: OR = 0.53 and 95% CI = 0.35–0.81; PFS: HR = 1.69 and 95% CI = 1.05–2.70; and OS: HR = 2.03 and 95% CI = 1.60–2.59). For **ERCC2** rs13181T>G, the G allele was associated with reduced response and poor PFS and OS in Caucasians (TR: OR = 0.56 and 95% CI = 0.35–0.88; PFS: HR = 1.41 and 95% CI = 1.02–1.95; and OS: HR = 1.42 and 95% CI = 1.11–1.81).

**Conclusions:** NER **ERCC1** rs11615C>T and **ERCC2** rs13181T>G polymorphisms are useful prognostic factors in oxaliplatin-based treatment of gastric and colorectal cancer. Larger studies and further clinical trials are warranted to confirm these findings. *Clin Cancer Res; 17(6): 1632–40. ©2011 AACR.*

**Introduction**

Fluoropyrimidines are essential in the treatment of gastric and colorectal cancer in advanced stages and have shown survival benefit compared with the best supportive care (1, 2). Oxaliplatin is the new generation of platinum drugs that improve response rate and survival after adding to the 5-fluorouracil (5-Fu)/leucovorin (LV) regimen. Combination treatment with 5-Fu/LV plus oxaliplatin (FOLFOX) is now considered the standard treatment of gastric and colorectal cancer, with a response rate of more than 40% for the first-line treatment (3, 4). Despite the efficacy of combined chemotherapies, a large proportion of patients display varying levels of resistance, indicating that the therapeutic efficacy has a remarkable interindividual variability. Since DNA kinking is the major feature of platinum–DNA adducts that block DNA replication and lead to cancer cell death (5, 6), which is recognized and repaired by the nucleotide excision repair (NER) pathway, it is conceivable that the interindividual difference in the NER capacity may influence the efficacy of oxaliplatin-based chemotherapy and clinical outcomes of the treated cancer patients. **ERCC1** and **ERCC2** proteins are major components of the NER complex, acting as the rate-limiting enzymes in the NER pathway. Therefore, SNPs in these loci can affect the efficiency of NER.

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suboptimal DNA repair capacity (8, 9). Previous studies have suggested that ERCC1 is a promising predictive marker for response to the platinum-based chemotherapy because of its low expression associated with increased chemotherapeutic sensitivity (10). Therefore, these ERCC1 and ERCC2 SNPs may be useful prognostic markers for treatment with platinum agents.

We identified 65 related publications by initial screening (as of June 1, 2010), of which 21 publications seemed to meet the inclusion criteria. We excluded 1 study, in which data were inestimable and authors were unreachable (16), 2 studies that used other chemotherapeutic agents (i.e., irinotecan and cetuximab) in addition to FOLFOX or XELOX (17, 18), and 1 study with study sample size less than 45 (ref. 19; Fig. 1). As a result, the final data pool consisted of 17 studies, including 1,787 cancer patients (Table 1).

**Results**

We estimated the OR for objective response versus no response after platinum-based chemotherapy [CR (complete response) + PR (partial response) vs. PD (progressive disease) + SD (stable disease), using the WHO criteria, ref. 11, or RECIST (Response Evaluation Criteria in Solid Tumors) criteria, ref. 12]. Progression-free survival (PFS) and overall survival (OS) were evaluated by pooled Cox proportional HRs and 95% CIs by published methods (13), because a meta-analysis of summary results is statistically as efficient as a joint analysis of individual participant data (14). We assessed the between-study heterogeneity by the Cochran Q test with a significance level of P<0.05. We carried out initial analyses with a fixed-effect model and confirmatory analyses with a random-effect model, if there was significant heterogeneity. We used inverted funnel plots and the Egger test to examine the effect of publication bias. We compared the difference in the effect estimates between subgroups as described previously (15). All P values were 2-sided, and all analyses were carried out using the Stata software (Stata Corporation) and Review Manager (v5.0).

**Translational Relevance**

Combination treatment with oxaliplatin and fluoropyrimidines is the standard treatment of gastric and colorectal cancer which improves patient response and overall survival. The nucleotide excision repair (NER) pathway is responsible for the removal of DNA adducts caused by oxaliplatin and thus may influence chemotherapeutic efficacy. Our meta-analysis provided evidence of an association between NER ERCC1 rs11615C>T and ERCC2 rs13181T>G single nucleotide polymorphisms and clinical outcomes in gastric and colorectal cancer patients, both Asians and Caucasians, receiving oxaliplatin-based chemotherapy. Our results suggest that it is feasible to use a pharmacogenomic approach to predict clinical outcomes of oxaliplatin-treated gastric and colorectal cancer patients.

**Patients and Methods**

**Study selection**

We searched for relevant publications before June 1, 2010, in English literature by using electronic MEDLINE and EMBASE databases with the following terms: "ERCC1," "ERCC2 or XPD," or "ERCC," "gastric or stomach cancer," "colon or colorectal cancer," "polymorphism or variant," and "treatment or chemotherapy." References of the retrieved articles were further screened for earlier original studies. The inclusion criteria were as follows: advanced, recurrent, or metastatic gastric or colorectal cancer; treated purely by regimens of FOLFOX (oxaliplatin plus 5-Fu/leucovorin) or XELOX (oxaliplatin plus capecitabine, a drug which converts to 5-Fu in vivo), excluding neoadjuvant chemotherapy; cancer histologically or pathologically confirmed; East Asian (China, Korea, and Japan) or Caucasian (European descendents) ethnicity; and ERCC1 rs11615C>T and or ERCC2 rs13181T>G genotyped. The corresponding contacts were contacted to obtain missing information, and some studies were excluded if critical missing information was not obtained by our repeated requests. Abstracts, unpublished reports, and articles with sample size less than 45 or written in non-English language were also excluded.

**Statistical methods**

We estimated the OR for objective response versus no response after platinum-based chemotherapy [CR (complete response) + PR (partial response) vs. PD (progressive disease) + SD (stable disease), using the WHO criteria, ref. 11, or RECIST (Response Evaluation Criteria in Solid Tumors) criteria, ref. 12]. Progression-free survival (PFS) and overall survival (OS) were evaluated by pooled Cox proportional HRs and 95% CIs by published methods (13), because a meta-analysis of summary results is statistically as efficient as a joint analysis of individual participant data (14). We assessed the between-study heterogeneity by the Cochran Q test with a significance level of P<0.05. We carried out initial analyses with a fixed-effect model and confirmatory analyses with a random-effect model, if there was significant heterogeneity. We used inverted funnel plots and the Egger test to examine the effect of publication bias. We compared the difference in the effect estimates between subgroups as described previously (15). All P values were 2-sided, and all analyses were carried out using the Stata software (Stata Corporation) and Review Manager (v5.0).

**ERCC1 rs11615C>T**

**Objective response.** Nine studies including 855 patients were eligible for the final analysis. In the dominant model, the minor variant T allele was not associated with objective response in all patients (T/T + C/T vs. C/C: OR = 0.89; 95% CI = 0.50–1.57; Fig. 2A) and no single study altered the result substantially by the sensitivity test. However, stratified analysis by ethnicity showed a significant difference in the estimates of effect between Asians and Caucasians (P = 0.002) and the T allele was associated with a significantly lower objective response rate in Asians (OR = 0.53; 95% CI = 0.35–0.81). When only colorectal cancer was included, the OR was similar to that of the overall patients (OR = 0.88; 95% CI = 0.42–1.87; Table 2). No publication bias was detected by either the funnel plot or the Egger test (data not shown).

**Progression-free survival.** Eleven studies including 1,230 patients were eligible for the final analysis. The T allele was associated with a nonsignificant increase of hazard for PFS in all patients (T/T + C/T vs. C/C: HR =
65 relevant studies identified and screened

44 studies excluded by title or abstract examination

1 study with data inestimable and author unreachable

2 studies used other agents

1 study with sample size < 45

21 reports retrieved for further evaluation

17 reports finally included

14 reports of ERCC1 C118T
9 reports of ERCC2/XPD Lys751Gln

Table 1. Studies on oxaliplatin-based chemotherapy and ERCC1 (rs11615 C>T) and ERCC2 (rs13181 T>G) polymorphisms included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Tumor</th>
<th>Drug</th>
<th>n</th>
<th>Biomarkers</th>
<th>SNPs</th>
<th>Allele frequencya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asians</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al. (21)</td>
<td>Taiwan</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>168</td>
<td>TR, OS, PFS</td>
<td>rs11615</td>
<td>T: 0.254</td>
</tr>
<tr>
<td>Lai et al. (34)</td>
<td>Taiwan</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>188</td>
<td>TR, OS, PFS</td>
<td>rs13181</td>
<td>G: 0.080</td>
</tr>
<tr>
<td>Keam et al. (22)</td>
<td>Korea</td>
<td>Gastric</td>
<td>FOLFOX</td>
<td>73</td>
<td>TR, OS, PFS</td>
<td>rs11615</td>
<td>T: 0.260</td>
</tr>
<tr>
<td>Liang et al. (35)</td>
<td>China</td>
<td>Colorectal</td>
<td>FOLFOX or XELOX</td>
<td>99</td>
<td>TR, PFS</td>
<td>rs11615</td>
<td>T: 0.288</td>
</tr>
<tr>
<td>Seo et al. (36)</td>
<td>Korea</td>
<td>Gastric</td>
<td>FOLFOX</td>
<td>75</td>
<td>TR, OS, PFS</td>
<td>rs11615</td>
<td>T: 0.240</td>
</tr>
<tr>
<td>Huang et al. (37)</td>
<td>China</td>
<td>Gastric</td>
<td>FOLFOX</td>
<td>89</td>
<td>OS, PFS</td>
<td>rs11615</td>
<td>T: 0.281</td>
</tr>
<tr>
<td>Liang et al. (38)</td>
<td>China</td>
<td>Colorectal</td>
<td>FOLFOX or XELOX</td>
<td>113</td>
<td>OS</td>
<td>rs11615</td>
<td>T: 0.323</td>
</tr>
<tr>
<td>Caucasians</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le Morvan et al. (39)</td>
<td>France</td>
<td>Colorectal</td>
<td>FOLFOX or XELOX</td>
<td>59</td>
<td>TR, OS, PFS</td>
<td>rs13181</td>
<td>G: 0.381</td>
</tr>
<tr>
<td>Paré et al. (20)</td>
<td>Spain</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>126</td>
<td>TR, OS, PFS</td>
<td>rs11615</td>
<td>T: 0.586</td>
</tr>
<tr>
<td>Park et al. (40)</td>
<td>USA</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>70</td>
<td>TR</td>
<td>rs13181</td>
<td>G: 0.421</td>
</tr>
<tr>
<td>Chua et al. (41)</td>
<td>Australia</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>115</td>
<td>TR, OS, PFS</td>
<td>rs11615</td>
<td>T: 0.635</td>
</tr>
<tr>
<td>Spindler et al. (42)</td>
<td>Denmark</td>
<td>Colorectal</td>
<td>XELOX</td>
<td>66</td>
<td>TR, PFS</td>
<td>rs13181</td>
<td>T: 0.652</td>
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<tr>
<td>Viguier et al. (43)</td>
<td>France</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>61</td>
<td>TR</td>
<td>rs11615</td>
<td>T: 0.557</td>
</tr>
<tr>
<td>Ruzzo et al. (44)</td>
<td>Italy</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>166</td>
<td>PFS</td>
<td>rs11615</td>
<td>T: 0.557</td>
</tr>
<tr>
<td>Stoehlmacher et al. (45)</td>
<td>USA</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>106</td>
<td>OS, PFS</td>
<td>rs11615</td>
<td>T: 0.505</td>
</tr>
<tr>
<td>Martinez-Balibrea et al. (46)</td>
<td>Spain</td>
<td>Colorectal</td>
<td>FOLFOX or XELOX</td>
<td>96</td>
<td>PFS</td>
<td>rs11615</td>
<td>T: 0.615</td>
</tr>
<tr>
<td>Etienne-Grimaldi et al. (47)</td>
<td>France</td>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>117</td>
<td>TR, OS, PFS</td>
<td>rs13181</td>
<td>G: 0.354</td>
</tr>
<tr>
<td>HapMapc</td>
<td>China (normal)</td>
<td></td>
<td></td>
<td>137</td>
<td></td>
<td>rs13181</td>
<td>T: 0.243</td>
</tr>
<tr>
<td></td>
<td>Europe (normal)</td>
<td></td>
<td></td>
<td>136</td>
<td></td>
<td>rs13181</td>
<td>G: 0.095</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>113</td>
<td></td>
<td>rs13181</td>
<td>T: 0.642</td>
</tr>
</tbody>
</table>

Abbreviation: TR, therapeutic response.
aAllele frequencies are shown as the T allele of ERCC1 rs11615 and the G allele of ERCC2 rs13181.
bPFS data were not available.
1.33; 95% CI = 0.94–1.87; Fig. 2B), and the single study by Parè and colleagues (20) showed substantial influence over the pooled result, the exclusion of which elevated the HR significantly (HR = 1.46; 95% CI = 1.07–1.99). Although stratified analysis by ethnicity showed a clinically substantial and statistically significant increase in the hazard of progression in Asian patients (HR = 1.69; 95% CI = 1.05–2.70), further comparison did not show significant
Table 2. Analysis of the association between ERCC1 rs11615C>T and ERCC2 rs13181T>G polymorphisms and objective response, PFS, and OS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective response</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1 rs11615C&gt;T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (859)</td>
<td>0.81 (0.58-1.15)</td>
<td>0.58 (0.37-0.90)</td>
<td>0.005 11 (1,230) 1.38 (1.17-1.65)</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (378)</td>
<td>0.53 (0.35-0.81)</td>
<td>0.26 (0.13-0.52)</td>
<td>0.598 5 (504) 0.80 (0.55-1.16)</td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (471)</td>
<td>0.89 (0.80-0.99)</td>
<td>0.77 (0.68-0.86)</td>
<td>0.368 6 (672) 0.85 (0.76-0.94)</td>
</tr>
<tr>
<td>Colorectal only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (707)</td>
<td>0.77 (0.54-1.12)</td>
<td>0.88 (0.62-1.24)</td>
<td>0.002 8 (989) 0.93 (0.77-1.12)</td>
</tr>
</tbody>
</table>

| ERCC2 rs13181T>G | | | |
| All | | | |
| 6 (629) | 0.53 (0.37-0.78) | 0.588 (0.38-0.88) | 0.001 8 (931) 1.42 (1.17-1.77) |
| Asian | | | |
| 2 (261) | 0.56 (0.26-0.98) | 0.388 (0.19-0.79) | 0.022 4 (466) 0.72 (0.39-1.37) |
| Caucasian | | | |
| 4 (464) | 0.89 (0.80-0.99) | 0.77 (0.68-0.86) | 0.001 6 (672) 0.88 (0.76-1.02) |
| Colorectal only | | | |
| 5 (552) | 0.52 (0.35-0.77) | 0.427 (0.26-0.68) | 0.006 5 (596) 0.80 (0.58-1.12) |

| aStudy: the number of studies included in the analysis. | | |
| bPhet: P value of between-study heterogeneity. | | |
NER Gene Polymorphisms and Platinum Therapy

Discussion

In this meta-analysis, we provided evidence of an association between ERCC1 rs11615C>T and ERCC2 rs13181T>G SNPs and clinical outcomes of Asian and Caucasian patients with gastric and colorectal cancer, respectively, who were treated by oxaliplatin-based chemotherapy. Previous studies showed that clinical outcomes, measured as either tumor progression or survival, were better in patients susceptible to higher levels of platinum-induced DNA adducts (23, 24). Resistance to platinum may result from numerous mechanisms (25), among which NER is the predominant mechanism for moderate levels of platinum resistance seen clinically (26). There is evidence that cancer patients with congenital NER mutations are sensitive to platinum treatment and that hypersensitivity of testicular cancer to cisplatin is due to DNA repair deficiency (27, 28). ERCC1 and ERCC2 are two key rate-limiting enzymes in the multistep NER process. ERCC1, in collaboration with the XPF protein, is involved in DNA lesion recognition, whereas ERCC2 is a subunit of human transcripational initiation factor TFIIH with ATP-dependent helicase activity. Therefore, functional ERCC1 and ERCC2 SNPs may contribute directly to phenotypes of drug sensitivity by modifying functions of the related genes and reflect platinum sensitivity as an inborn trait.

Our meta-analysis used objective response, PFS, and OS as primary parameters to assess the influence of NER SNPs on clinical outcomes of oxaliplatin-based chemotherapy because these parameters are intrinsically correlated but not necessarily consistent with one another. Most often, a low objective response rate suggests tumor resistance to the chemotherapeutic regimen and a short PFS and OS is very likely the consequence. However, a high objective response rate may lead to an increased PFS and OS or no survival benefit at all (29), showing the necessity of including all 3 parameters to make a comprehensive assessment. In our meta-analysis, ERCC1 rs11615 T allele was a biomarker of low objective response, a short PFS, and OS in Asian patients, whereas ERCC2 rs13181 G allele showed significant or marginally significant association with low objective response, a short PFS, and OS in overall patients, Caucasians, and colorectal cancer subgroups. Although some single studies may have influenced the significance of the pooled results, the association tendency was obvious with or without these studies. The consistent changes of 3 parameters strongly suggested that ERCC1 rs11615C>T and ERCC2 rs13181T>G both had an effect on oxaliplatin-based chemotherapy and that objective response could be a useful surrogate of survival in oxaliplatin-treated gastric and colorectal cancer patients.

Our results could be reasonably explained by the biological significance of these 2 SNPs. The rs11615 T
An allele of ERCC1 polymorphism was found to be associated with high mRNA expression of the corresponding gene (30), whereas the rs13181 G allele of ERCC2 polymorphism was found to be associated with a low number of X-ray–induced chromatid aberrations (8). Functional studies confirmed a substantial influence of the ERCC1 rs11615 C>T and ERCC2 rs13181 T>G SNPs on the phenotype of NER capacity (7, 31, 32), and possessing the TT genotype of ERCC2 rs13181 T>G SNP was associated with the risk of suboptimal DNA repair up to 7-fold, compared with the GG/GT genotypes (8). Hence, patients carrying the ERCC1 rs11615 T or ERCC2 rs13181 G allele may have higher DNA repair capacity that could effectively reduce the anticancer effect of oxaliplatin, leading to poor prognosis of these patients.

Notably, there was an apparent ethnic discrepancy in the prognostic values between Asians and Caucasians and statistical test also confirmed the existence of ethnical difference in the estimates of effect for the ERCC1 rs11615 T...
allele. As shown in Table 1, there was a remarkably lower prevalence of ERCC2 rs13181 G allele in Asians than in Caucasians, which might explain the lack of effect of ERCC2 rs13181T>G SNP in Asian patients. However, it is interesting to find that there was no predictive value of ERCC1 rs11615C>T SNP in Caucasians, even though the rs11615 T allele was much more common in Caucasians than in Asians. Although the underlying mechanisms are not clear, numerous factors, such as gene–gene interaction from different genetic background and gene–environment interaction from different lifestyles, may have played a role. Additional large studies are warranted to investigate these possibilities.

Despite our efforts to make an accurate and comprehensive analysis, limitations of our meta-analysis need to be addressed. First, some data were excluded from our analysis because of loss of contact (16) or missing data in the original study (33), which could cause some bias in our estimates but was unlikely to change our major conclusions, because Spindler and colleagues showed no association between ERCC1 rs11615C>T polymorphism and PFS in Caucasians (33) and Liu and colleagues showed no association between ERCC2 rs13181T>G polymorphism and OS in Asians (16), which were consistent with our findings. Second, most of the included studies were retrospective and differed significantly in study designs. In addition, the frequencies of ERCC1 rs11615 T and ERCC2 rs13181 G alleles were also substantially different among patient populations with different ethnicity. All these may have caused wide and significant heterogeneity between studies. Third, our analysis largely used unadjusted estimates, because not all published studies presented adjusted estimates or when they did, the estimates were not adjusted by the same potential confounders. However, when only those studies with the available adjusted estimates were used, the conclusions were not significantly changed (data now shown). Fourth, we were unable to analyze the association between ERCC1 and ERCC2 SNPs and platinum toxicities, because few studies provided this information or used different toxicity profiles. Finally, oxaliplatin is not used as a single compound but in combination with 5-Fu in the regimen, and unfortunately, we were unable to investigate potential gene–gene interactions between NER variants and folate-metabolizing gene variants because of the limited publications available on this topic.

Overall, our meta-analysis showed that ERCC1 rs11615C>T and ERCC2 rs13181T>G SNPs might be useful prognostic factors for assessing clinical outcomes of oxaliplatin-based chemotherapies (FOLFOX or XELOX) in gastric and colorectal cancer. However, future prospective studies with large sample sizes and better study designs are required to confirm our findings.

Disclosure of Potential Conflicts of Interest

The authors have declared no conflicts of interest. The contents of the study are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Authors’ Contributions

M. Yin, J. Yan, Q. Wei conceived the ideas, conducted literature search, and data collection; E. Martinez-Balibrea, F. Graziano, H.J. Lenz, H.J. Kim, J. Robert, S-A. Im, W-S. Wang, and M-C. Etienne-Grimaldi provided the raw data of their original studies, and all authors contributed to the writing, revising, and approval for final submission.

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References


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