Pharmacogenomic data may help guide treatment options for opioid use in patients with cancer-related pain, but test results should be available at the point of care.

Clinical Implications of Opioid Pharmacogenomics in Patients With Cancer
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Background: Pain can be a significant burden for patients with cancer and may have negative effects on their quality of life. Opioids are potent analgesics and serve as a foundation for pain management. The variation in response to opioid analgesics is well characterized and is partly due to genetic variability.

Methods: We reviewed the results of clinical studies to evaluate the relationships between genetic variants and select genes involved in the pharmacokinetics and pharmacodynamics of opioids, with an emphasis on patients with cancer.

Results: In patients with cancer-related pain, genetic variation in OPRM1, COMT, and ABCB1 is associated with response to morphine, which is the most well-studied opioid. Although it has not been studied in patients with cancer-related pain, the effect of CYP2D6 variation is well characterized with codeine and tramadol. Evidence is limited for associating the genetic variation and pain response of oxycodone, hydrocodone, and fentanyl in patients with cancer.

Conclusion: The clinical availability of pharmacogenomic testing and research findings related to these polymorphic genes suggest that genotyping patients for these genetic variants may allow health care professionals to better predict patient response to pain and, thus, personalize pain treatment.

Introduction
Pain is one of the most burdensome symptoms associated with cancer and its treatment and is estimated to affect 49% to 57% of patients with curable cancer and 56% to 75% of patients with advanced disease. Uncontrolled pain can have significant adverse effects on function, mood, sleep, and quality of life, and studies suggest that pain is an independent prognostic factor for overall survival in cancer. A study of 2,761 patients with cancer reported that one-third of patients with initial pain had a significant reduction in pain at 1 month and one-fifth had an increase in pain scores. Opioids are the most potent analgesics available and remain the cornerstone of clinical pain management. The choice of opioid analgesic depends on a number of medical and nonmedical factors. Nonopioid and co-analgesics (eg, nonsteroidal anti-inflammatory drugs), as well as nonpharmacological measures, are often used to improve analgesic control, reduce opioid requirements, or both, as well as minimize adverse events related to opioid use.
regardless of the analgesic type, effective pain management depends on achieving a favorable balance between adequate analgesia and adverse events.

It is well documented that patients vary considerably in their response to pain therapies, including medication. Response in analgesia and to adverse events may vary between patients with similar pain levels or disease status and may vary among patients at different stages of the care trajectory. Increasingly, research has been aimed at identifying the hereditary basis for interindividual differences in drug effects to explain altered efficacy and adverse events. Currently, genetic factors may be responsible for 12% to 60% of response variability in opioid therapy. Using genetic variation to help guide drug therapy choices may be helpful in balancing the exclusion of low-yield therapy, avoiding adverse events, and achieving pain control.

Genes Modulating Opioid Response
Many genes have been studied to identify pharmacogenomic markers in opioid therapy, including genes implicated in the pharmacodynamics (OPRM1, COMT) and pharmacokinetics (CYP2D6, CYP3A4/5, ABCB1) of opioids.

Pharmacokinetics
Transporters
One of the most studied transporters in opioids is a member of the adenosine triphosphate–binding cassette, sub-family B, member 1 (ABCB1), also known as P-glycoprotein or multidrug resistance protein 1. ABCB1 transporters are present in numerous locations, including the gastrointestinal tract, liver, kidneys, and the blood–brain barrier, and they facilitate the absorption, distribution, and elimination of medications, including opioids such as morphine and fentanyl and their metabolites. Impairment of these transporters may result in increased bioavailability of oral medications, decreased renal excretion, and increased central nervous system concentrations. Specifically, the transport of opioids into the brain through the blood–brain barrier may be affected by variations in ABCB1 transporters at this site. ABCB1 is highly polymorphic, with more than 100 single nucleotide polymorphisms (SNPs) identified, but C3435T (rs1045642) is the most widely studied. The 3435T variant is associated with decreased mRNA expression, protein expression, or both in some tissues. Although the results have been mixed, several studies report a difference in pain relief and opioid doses between reference and variant genotypes.

Cytochrome P450 Enzymes
Cytochrome P450s are a gene superfamily of catalytic proteins that fill important roles across the spectrum of cellular biochemical reactions, including endogenous hormone production and xenobiotic metabolism. This includes the activation of many opioids from a relatively inert compound to a pharmacologically active molecule. The enzyme CYP3A4 plays a role in the metabolism of numerous medications, including many opioids (eg, methadone, oxycodone, hydrocodone, fentanyl), but few studies link genetic variations to opioid response. The cytochrome P450 enzyme 2D6 (CYP2D6) influences the metabolism of 25% of all drug therapies, including codeine, hydrocodone, oxycodone, and tramadol, as well as tricyclic antidepressants. Genetic variation in the CYP2D6 enzyme is one of the most studied and well-understood of all the drug-metabolizing enzymes. The effect of variation on phenotype is typically classified into 4 major groups: poor metabolizers (5%–10%), intermediate metabolizers (2%–11%), extensive metabolizers (77%–92%), and ultra-rapid metabolizers (1%–2%). These percentages are based on data for whites and will vary for other ethnicities. Reports of therapeutic failure (lack of pain control, opioid-related adverse events, or both) in patients with specific genotypes receiving select opioids (codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone) suggest a significant impact of CYP2D6 genetic variants on drug efficacy and adverse-event profile. In addition, CYP2D6 metabolizer status becomes particularly important when concomitant medications affecting other pharmacokinetic pathways are used. Serious or fatal, inadvertent codeine overdose can occur when a patient with cancer and CYP2D6 ultrarapid metabolizer status is also treated with CYP3A4 inhibitors, such as clarithromycin and voriconazole. The “double hit” of hyperactivation to morphine via CYP2D6 and the reduced inactivation due to blocked CYP3A4 leads to life-threatening respiratory depression.

Pharmacodynamics
OPRM1
The µ-opioid receptor gene encoded by the genetic locus OPRM1 is the primary binding site for endogenous opioid peptides and opioid analgesics. As such, OPRM1 is a biologically plausible candidate for evaluating the role of polymorphism in the clinical effects of opioids. More than 100 SNPs have been described for OPRM1. The most prevalent and widely studied SNP is a nonsynonymous nucleotide substitution at position 118 (A118G; rs1799971). The frequency of this SNP widely varies among different races and ethnicities: 4.7% in Africans, 15.4% in Europeans, 48.5% in Japanese, and 14% in Hispanics. To assess the possible functional effect of each allele of this gene, persons are identified by 1 of 3 genotypes: homozygous G/G, homozygous A/A, or heterozygous G/A.
This SNP has been associated with variation in opioid response in a number of settings, including cancer-related pain.37 Numerous studies have examined the relationship of OPRM1 genetic variants to pain control in the oncology setting with mixed results.17,28-31

COMT

COMT encodes an enzyme involved in the metabolism of catecholamines, including epinephrine, norepinephrine, and dopamine, which play a role in pain modulation.32 Impairment of the catechol-O-methyltransferase (COMT) enzyme, which results in increased concentrations of dopamine, can suppress the production of endogenous opioids (eg, enkephalin), which, in turn, cause subsequent opioid receptor expression upregulation.16 The COMT gene locus contains multiple SNPs; the most studied SNP is Val158Met, also known as rs4680.33 It has been postulated that this polymorphism leads to a 3- to 4-fold reduced activity of the COMT enzyme and has been associated in patients with cancer with increased sensitivity to painful stimuli (for the Val/Val genotype) and with lower doses of morphine required for satisfactory relief of pain (for the Met/Met genotype).28,33-35 Variation in COMT may also affect unwanted effects of opioid treatment such as sedation.36

A limited number of studies have examined the relationship of variants in these genes to pain control in cancer, and nearly all of these studies have involved the acute postoperative period with outcomes related to cancer recurrence and progression.12,27 Few studies have involved patients with cancer, and patient-reported pain outcomes in relation to these genetic variants and pain relief is sparingly used.15 Commonly used opioids in patients with cancer and the genetic variants reported to modulate response are reviewed in the Table.14,16,25-28,31,33,36

Pharmacogenomics

Morphine

Because the μ-opioid receptor is the main site of action for morphine, numerous studies have evaluated the OPRM1 A118G variant in relation to pain response, adverse events, or both in patients with cancer and have had mixed results.38 Other variants commonly studied include COMT Val158Met and ABCB1 C3435T.15

One study evaluated the relationship of 4 OPRM1 polymorphisms and pain control in 207 study patients with cancer pain.39 A total of 99 volunteers who completed the Brief Pain Inventory (BPI) survey and had adequate pain control were included in the final analysis.39 The A118G variant alone was related to morphine dose. Participants with G/G genotype (225 ± 143 mg/24 hours) required significantly higher doses of morphine when compared with participants with wild-type A/A (97 ± 89 mg/24 hours) and A/G (66 ± 50 mg/24 hours). In contrast, the Val158Met variant was associated with lower doses of morphine. Participants with Val/Val genotype (97 ± 89 mg/24 hours) required significantly higher doses of morphine when compared with participants with wild-type Met/Met (66 ± 50 mg/24 hours).

<table>
<thead>
<tr>
<th>Opioid Agent</th>
<th>Study</th>
<th>Genetic Variant</th>
<th>No. of Patients</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Reyes-Gibby28</td>
<td>OPRM1 A118G  COMT Val158Met  ABCB1 C3435T</td>
<td>695</td>
<td>No difference in dose requirements for all variants</td>
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<tr>
<td>Morphine</td>
<td>Ross35</td>
<td>CYP3A5*3  ABCB1 C1236T</td>
<td>60</td>
<td>Greater central adverse events with *3/*3 genotype</td>
</tr>
<tr>
<td></td>
<td>Belfer33</td>
<td>COMT Val158Met  ABCB1 C3435T</td>
<td>221</td>
<td>No difference in central adverse events (confusion, drowsiness, hallucination) Other COMT and ABCB1 variants associated with central adverse events</td>
</tr>
<tr>
<td></td>
<td>Branford37</td>
<td>OPRM1 A118G</td>
<td>156</td>
<td>No difference in response</td>
</tr>
<tr>
<td></td>
<td>Kasai and Ikeda26</td>
<td>OPRM1 A118G</td>
<td>99</td>
<td>Patients with G/G genotype required higher doses of morphine when compared with A/G and A/A genotypes</td>
</tr>
<tr>
<td></td>
<td>Lotsch16</td>
<td>OPRM1 A118G  ABCB1 C3435T</td>
<td>137</td>
<td>Patients with OPRM1 A/A identified as having good responses indicated by decrease in numerical rating scale Presence of ≥ 1 OPRM1 G allele were found have worst response regardless of ABCB1 genotype Patients with OPRM1 A/A and ABCB1 T/T best responders with greatest decrease in scores</td>
</tr>
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<td></td>
<td>Ravindra-nathan25</td>
<td>OPRM1 A118G  COMT Val158Met</td>
<td>207</td>
<td>Patients with OPRM1 A/A and COMT Met/Met combined required lowest morphine dose when compared with other combinations of genotypes</td>
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<tr>
<td></td>
<td>Reyes-Gibby28</td>
<td>OPRM1 A118G  COMT Val158Met  ABCB1 C3435T</td>
<td>827</td>
<td>No difference in dose requirements for all variants</td>
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<tr>
<td></td>
<td>Ross35</td>
<td>COMT Val158Met</td>
<td>207</td>
<td>Patients with Val/Val genotype required higher dose of morphine compared with Val/Met and Met/Met</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Haji14</td>
<td>CYP2D6</td>
<td>450</td>
<td>No difference in pain intensity or adverse events (nausea, sedation, cognition) between metabolizer status</td>
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<tr>
<td></td>
<td>Reyes-Gibby28</td>
<td>OPRM1 A118G  COMT Val158Met  ABCB1 C3435T</td>
<td>445</td>
<td>No difference in dose requirements for all variants</td>
</tr>
</tbody>
</table>
Those with the A/G genotype also had the highest average BPI scores, a finding pointing to the possible undertreatment of pain, which might explain the lower doses administered to those with that genotype. In addition, the authors found no differences in adverse-event intensity between the groups.

A subsequent study reanalyzed the same 207 volunteers to look for a relationship between the COMT variant Val158Met polymorphism and morphine requirements. In this study, all participants were included in the analysis. Those with the Val/Val genotype received the highest dose of morphine (155 ± 160 mg/24 hours) followed by those with the Val/Met genotype (117 ± 100 mg/24 hours) and the Met/Met genotype (95 ± 99 mg/24 hour; P = .025).

Reyes-Gibby et al conducted a secondary analysis combining the results of the above-mentioned studies in the same patients to explore the joint effects of COMT Val158Met and OPRM1 A118G variants on the efficacy of morphine for cancer pain. Carriers of both wild-type OPRM1 A/A and COMT Met/Met genotypes had the lowest morphine dose (87 mg/24 hours; 95% confidence interval [CI]: 57–116), which significantly differed from study participants with neither Met/Met nor A/A who had the highest dose (147 mg/24 hours; 95% CI: 100–180). After controlling for demographic and clinical variables, such as age, sex, time from cancer diagnosis, and months using morphine, the joint-effect results remained.

Camp et al evaluated the relationship of OPRM1 A118G and ABCB1 C3435T variants to pain response in 137 study patients with cancer receiving treatment with morphine. Pain response was measured using an 11-point numerical rating scale (NRS) and the main end point was a change in NRS at the end of the first 7 days. At the end of the first 7 days, study patients with wild-type OPRM1 A/A genotype had a significantly greater change in NRS score (3.73; standard deviation [SD] ± 1.73) when compared with homozygous-variant study patients (3.73; SD ± 1.72). Multivariate analysis assessed the joint effects of variation in the 2 genes. Study patients with at least 1 OPRM1 variant were the worst responders regardless of ABCB1 genotype; conversely, study patients with wild-type OPRM1 A/A genotype had a good response. Study patients with wild-type OPRM1 A/A and homozygous-variant ABCB1 T/T genotype were the best responders, with an NRS score of 4.8 ± 1.62.

Some studies report lack of association with numerous genetic variants. An observational, single time point trial with 156 study patients with cancer found no association with the OPRM1 A118G variant and response to morphine. This study evaluated numerous genetic variants in 4 genes (OPRM1, ARRB2, STAT6, and UGT2B7) and consisted of morphine responders (controlled on morphine for ≥ 1 month) and nonresponders (switched alternative agents due to inadequate analgesia with titrated doses or intolerable adverse events). No association was found with variants in OPRM1 and UGT2B7, but numerous variants in the other 2 genes were associated with response. One of the largest trials to date evaluated the influence of 112 genetic variants of 23 candidate genes on the efficacy of numerous opioids in 2,201 study patients with cancer: morphine (n = 827), oxycodone (n = 445), fentanyl (n = 695), and other opioids (n = 234). All drug doses were converted to equivalent morphine doses and pain intensity was measured using the BPI. Klepstad et al noted that all SNPs, including OPRM1 A118G, ABCB1 C3435T, and COMT Val158Met, failed to show a relationship with opioid dose. A case-control study of 221 participants with cancer treated with morphine reported no association with COMT Val158Met or ABCB1 C3435T variants and the central adverse events of confusion, drowsiness, and hallucination. Of note, other variants in COMT and ABCB1 were associated with central adverse events. Because of these conflicting data, concluding whether these variants predict morphine analgesia or adverse events is difficult. The most benefit will likely be derived from combining these markers to identify patients with a poor-response profile for which an alternative therapy may be preferred.

**Codeine**

The analgesic properties of codeine are derived from its conversion to morphine and morphine-6-glucoronide by CYP2D6 (Fig). Persons who are CYP2D6 poor metabolizers have little or no CYP2D6 enzyme activity and will not attain a meaningful degree of pain control. An important safety concern is that persons with extra copies of CYP2D6 convert codeine to morphine to a greater extent and may be at risk for adverse events such as sedation and even respiratory depression. The results of numerous studies (mainly in patients without cancer) suggest a difference in analgesia and adverse effects across CYP2D6 metabolizer statuses and these differences have been highlighted in a peer-reviewed guideline by the Clinical Pharmacogenetics Implementation Consortium. Therefore, CYP2D6 testing is useful in determining which patients will derive the most benefit from codeine use as well as patients who may be at increased risk for toxicity.

**Tramadol**

Similar to codeine, CYP2D6 is responsible for the conversion of tramadol to O-desmethyltramadol, which has a 200-fold greater affinity for the µ-opioid.
receptor target (see Fig). Several studies have reported that CYP2D6 poor metabolizers display decreased analgesic response with tramadol than those who are extensive metabolizers. No studies have focused on the pharmacogenomics of tramadol specifically in a cancer population; however, given the evidence in other pain populations, tramadol is likely to have reduced clinical benefit in patients who poorly metabolize CYP2D6.

**Oxycodone**
The majority of oxycodone is metabolized to noroxycodone by CYP3A4 (see Fig). A smaller percentage (11%) is converted by CYP2D6 to the active metabolite oxymorphone, which has a 40-fold higher affinity and 8-fold higher potency for μ-opioid receptors than oxycodone. Studies evaluating CYP3A4 variation to oxycodone response are scarce, whereas studies in healthy volunteers and postoperative patients have reported mixed results on CYP2D6 polymorphisms and response to oxycodone. In a cross-sectional study of 450 study patients with cancer treated with oxycodone, Andreassen et al reported no difference in pain intensity using the BPI or the incidence of adverse events (nausea, sedation, cognitive) between CYP2D6 metabolizer statuses.

In the large study of 2,201 study patients with cancer being treated with various opioids, including 445 of whom were treated with oxycodone, Klepstad et al could not determine an association with OPRM1, ABCB1, and COMT variants (as well as numerous other genes) and opioid requirements. Based on this evidence, little basis exists for the use of pharmacogenomics to personalize the use of oxycodone therapy in patients with cancer.

**Hydrocodone**
Hydrocodone is metabolized by CYP2D6 to the active metabolite hydromorphone, which has a 10- to 33-fold greater affinity for μ-opioid receptors than hydrocodone (see Fig). Additional metabolism includes the formation of norhydrocodone by CYP3A4, and 40% of clearance is attributed to non-CYP pathways. No studies have focused on the pharmacogenomics of hydrocodone specifically in a cancer population. Thus, little basis exists for the use of pharmacogenomics to personalize the use of hydrocodone therapy in patients with cancer.
Fentanyl
Fentanyl is primarily metabolized by CYP3A4/5 to the inactive metabolite norfentanyl (see Fig). Most of the current literature assessing the effect of CYP3A4/5 on pain outcomes involves the postoperative patient population, and a robust association has not yet been discovered. Klepstad et al studied 2,201 volunteers with cancer being treated with various opioids, including 695 of whom were treated with fentanyl, and found no association with OPRM1, ABCB1, and COMT variants (as well as numerous other genes) and opioid requirements. A small trial of 60 Asian study patients with cancer who were treated with transdermal fentanyl reported more and greater-intensity central adverse events with patients homozygous for CYP3A5*3 when compared with patients with *1/*1 and *1/*3 genotypes. The authors also studied 3 ABCB1 variants (C1236T, G2677A/T, and C3435T), and C1236T alone was associated with response with the homozygous T/T variant. To date, the utility of CYP3A4/5 and ABCB1 testing to personalize fentanyl dosing is uncertain.

Implementation in Clinical Practice
The clinical availability of pharmacogenomics testing and the research findings related to these polymorphic genes suggest that genotyping patients for some of these genetic variants may help predict response to pain treatment with good rates of sensitivity and specificity and with greater benefits for patients and decreased health care utilization. One key element of using pharmacogenomics for the treatment of cancer pain is employing a preemptive testing strategy so the results will be available at the point of care. It is crucial to have information on individual patient pharmacogenomics at the time of a care decision so that the data can be used to guide therapeutic decision-making. As part of this preemptive strategy, these results must be readily retrievable. In addition, use of clinical-decision support alerts has been shown to inform clinicians of important genetic results and guide treatment at the point of care.

Conclusions
Opioids are heavily used in the treatment of patients with cancer-related pain, and individual genetic variation affects the pharmacokinetics and pharmacodynamics of opioids. The evidence linking commonly used opioids has been reviewed for patients with cancer and the genetic variants reported to modulate response and results. Although the results seem promising, prospective studies randomizing patients to genotype-guided pain management compared with standard practice are needed. In addition, further evaluation of complex interactions (drug–gene–gene and drug–drug–gene) must be explored. If pharmacogenomics data are used to guide treatment decisions, then a preemptive testing strategy is a key element that must be included and test results must be available at the point of care.

References