Variable responses to medications complicate perioperative care. As a potential solution, we evaluated and synthesized pharmacogenomic evidence that may inform anesthesia and pain prescribing to identify clinically actionable drug/gene pairs. Clinical decision-support (CDS) summaries were developed and evaluated using Appraisal of Guidelines for Research and Evaluation (AGREE) II. We found that 93/180 (51%) of commonly-used perioperative medications had some published pharmacogenomic information, with 18 having actionable evidence: celecoxib/diclofenac/flurbiprofen/piroxicam/CYP2C9, codeine/oxycodone/tramadol CYP2D6, desflurane/enflurane/halothane/isoflurane/sevoflurane/succinylcholine/RYR1/CACNA1S, diazepam/CYP2C19, phenytoin/CYP2C9, succinylcholine/mivacurium/BCHE, and morphine/OPRM1. Novel CDS summaries were developed for these 18 medications. AGREE II mean ± standard deviation scores were high for Scope and Purpose (95.0 ± 2.8), Rigor of Development (93.2 ± 2.8), Clarity of Presentation (87.3 ± 3.0), and Applicability (86.5 ± 3.7) (maximum score = 100). Overall mean guideline quality score was 6.7 ± 0.2 (maximum score = 7). All summaries were recommended for clinical implementation. A critical mass of pharmacogenomic evidence exists for select medications commonly used in the perioperative setting, warranting prospective examination for clinical utility.

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medications will be considerable and will comprise an evidence base that justifies future prospective clinical examination of pharmacogenomics in this field.

METHODS
Data acquisition
A comprehensive list of commonly prescribed perioperative medications was first compiled using publicly available Anesthesia, Critical Care, and Acute Pain Medicine clinical practice guidelines and texts (Supplementary File 1). The goal was to assemble an expansive list, including not only medications that might be used for primary anesthesia, critical care, or pain treatment, but also supportive medications that are used in these contexts (e.g., antibiotics, gastrointestinal agents). Medications listed as common treatment options by any of the source texts were included. Two individuals (EHJ and PHO) reviewed and approved the resulting list. In total, 183 medications were included for appraisal.

Pharmacogenomic articles related to these medications were identified through a custom PubMed search query which has been previously successfully tested and utilized to comprehensively identify clinically relevant published pharmacogenomic evidence: “([Polymorphism, Genetic] OR "Genotype" Mesh) AND "Humans" Mesh) AND ("drug exposure" OR "Pharmacologic Actions" [Mesh]) OR (polymorphism AND drug)” [20]. All abstracts from articles assessing the association between a germline genetic variant and a pharmacogenomic outcome (i.e., toxicity, response) resulting from this search were manually reviewed by at least two independent reviewers for relevance and subsequently cataloged in the University of Chicago pharmacogenomic research and implementation database. Inclusion and exclusion criteria have been previously published [17, 18]. Briefly, disease risk genetic markers were excluded to focus exclusively on pharmacogenomics. Studies examining animal models and in vitro experiments, review articles, case studies, and those not written in English were also excluded. For articles deemed to assess the relationship between a pharmacogenomic marker and clinical outcome(s), the following study characteristics were entered into the database: PubMed ID, medication(s), genetic variant(s) (as denoted by dbSNP rs number), and common gene name. For each article, a preliminary designation (based on abstract review) of whether the article reported a “positive” or “negative” genetic association was also assigned. Each article for which the full paper was subsequently reviewed was critically assessed to confirm this designation, and the “positive” vs. “negative” associations reported by the authors were not simply accepted at face value but instead were evaluated and ultimately denoted by the review team.

Distinct from the above, a separate literature search was conducted to identify any additional articles, using drug-annotated references listed in PharmGKB (www.pharmgkb.org), reference lists within relevant CPIC guidelines (when available; www.cpicpgx.org), and reference lists assembled for medications with pharmacogenomic recommendations by the Dutch Pharmacogenetics Working Group (DPWG) (www.pharmgkb.org/page/dpwg).

Finally, for each medication we conducted a final PubMed search using the terms “[medication name]” and “polymorphism” to ensure that no remaining critical articles were missed (see Supplementary File 2, tab 2 for articles obtained through this search). Data were collected through January 31, 2018. All articles captured by these three various search methods were included. Notably, newly published guidance from CPIC and DPWG was periodically reviewed and incorporated into our analyses through January 2021.

Pharmacogenomic assessment
Publications identified via the above searches were assembled into an MS Excel spreadsheet arranged by medication. Sub-groupings for each medication were created to organize all studies together that evaluated the same drug/variant or drug/gene pair. All drug/variant or drug/gene pair groupings for each medication were then evaluated first at the group level, with all articles in each group assessed first at the abstract level (by EHJ). Each was assessed for eligibility to be taken forward for full article review, with the eligibility assessment performed based on study design, quality, sample size, and the presence of replication (including within the group). Importantly, this included manual inspection of both as-reported “positive” and as-reported “negative” studies within a group. The last author also independently triaged articles for eligibility at the abstract level using similar criteria, with any disagreement between the two assessors automatically triggering a given article to be taken forward for full review.

Finally, all articles within a given drug/gene or drug/variant pair group with an existing published clinical pharmacogenomic guideline (CPIC, DPWG) or with pharmacogenomic information in the FDA label were automatically eligible and taken forward for full review.

Assessment for clinical actionability
Articles selected for full review were then rigorously evaluated for scientific, genetic, statistical, and clinical methodological rigor using a formal framework for pharmacogenomic studies that follows state-of-the-art consensus guidelines (see Table 1) [21, 22]. Methodology from the assessed articles were required to meet multiple criteria described in Table 1, all at least at the “Lower Level of Support Evidence” designation or higher, in order to qualify as “potentially clinically actionable” and thus be further considered. Large cohort sizes, high-quality phenotype measurements (well-defined, prospectively measured, rigorously assessed, and objectively reproducible), assessment for genetic Hardy–Weinberg equilibrium, large magnitude of effect size, high clinical relevance (i.e., medications that carry serious risk of harm to the patient, and not having genetic information could greatly increase risk), inclusion of key alleles [23], and appropriate statistical analyses (including correction for multiple testing) increased support for clinical actionability. Detailed information for each of the publications supporting replicated, consistent and strong evidence was used to assess pairs with the following criteria collected from each study: year of publication, first author, medication(s) studied, diseases under study, genetic variants studied, sample sizes (cases/controls), dosing regimens, follow-up period, and outcomes measured.

Evidence synthesis for the resulting studies was conducted by at least two reviewers independently, with disagreement resolved through discussions until consensus. Drug/variant or drug/gene pairs identified as potentially clinically actionable through this process were taken forward for Clinical Decision-Support (CDS) summary development.

Clinical decision-support summary development
For medications that emerged from the above primary data assessment, CDS summaries were developed by two members of the evidence evaluation team (EHJ and PHO) using methods described previously [17, 18, 20]. Summaries included point-of-care guidance and specific prescribing recommendations, assignment of a “traffic signal” designation denoting genomic risk (high-risk = red light, caution = yellow light, and favorable = green light), references to available external pharmacogenomic guidelines where available (e.g., CPIC, FDA label), and individual annotations of the key supporting primary publications. Only for those ultimately deemed clinically actionable (ultimately deployed as CDS due to unanimous support after AGREE assessment, described below), a level of evidence was assigned and shown for the clinician using the following published criteria [24–26], which closely mirror criteria set forth by PharmGKB [13]: Level 1 indicates the evidence is supported by a well-performed, large study that either includes replication or has been externally replicated by other well-performed, large studies. Additionally, only those drug/variant or drug/ gene associations with existing published clinical guidelines or with pharmacogenomic information in the FDA label are eligible for a Level 1 designation. Level 2 indicates the evidence is based on at least one well-performed study of at least 100 patients with additional separate studies replicating the same result in the same direction. Level 3 evidence consists of a relatively smaller well-performed primary study (<100 patients) with biological relevance or an aggregate signal from several similarly-executed studies with which other contradictory studies with pharmacokinetic (PK) evidence can be supportive for assigning studies into Levels 2 or 3, but PK data alone are not adequate for solely supporting a CDS. Rather, all CDS are based on clinical studies having a primary clinical endpoint (e.g., toxicity or disease response) as the chief analyzed outcome. Light colors are assigned based on specific results (i.e., effect size of clinical outcome) combined with the potential risk to the patient (i.e., death, severe toxicity, and severe risk of non response).

Agree II scoring
After development of each proposed, potentially clinically actionable CDS summary, each CDS was subjected to formal evaluation using the Appraisal of Guidelines for Research and Evaluation (AGREE II) framework in order to assess its quality and to determine clinical use/appropriateness for prospective clinical evaluation or utilization. [18, 27] The AGREE II
Table 1. Scientific, methodologic, and clinical criteria used to critically evaluate pharmacogenomic articles via systematic review.

| Criterion                                      | High level of supporting evidence | Lower level of supporting evidence | Inappropriate supporting evidence |
|-----------------------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
| Cohort size                                   | Large                             | Medium or small studies           | Case reports*                    |
| Disease(s) being studied/clinical setting     | Homogeneous                       | Mixed, but with reasonable overlap | Heterogeneous                    |
| Subject age(s)                                | Present                           | Present                           | Absent                           |
| Race/ethnicity information                    | Present                           | Present                           | Absent                           |
| Sex/gender                                    | Present                           | Present                           | Absent                           |
| Possible population stratification            | Considered and excluded           | No consideration, but population homogenous | Heterogeneous population without appropriate analysis |
| Comedications and comorbidities               | Provided                          | Provided                          | Absent                           |
| Source of DNA                                 | Blood or buccal swab              | Peritumoral tissue                | Tumor                            |
| Genotyping methodology                        | Standard methods, with appropriate quality controls, and excellent coverage of all key (actionable) alleles | Standard methods, quality controls not explicitly stated, allele coverage represents the minimum acceptable alleles | Non-standard methods, failed quality controls, key allele(s) missing* |
| Haplotype definition (if haplotypes studied)  | Present                           | Present                           | Undefined                        |
| Hardy–Weinberg equilibrium                    | Present                           | Present                           | Deviation from HWE, or not tested |
| Variants where no effect was seen             | Included                          | Included                          | Not included                     |
|Phenotype measurement                          | Well-defined, prospectively measured, rigorously assessed, objectively reproducible | Well-defined, but potentially retrospectively collected | Adequate description of phenotype lacking |
| Data analysis                                 | Genetic effect tested alongside or after controlling for other clinical factors, and remains independently associated with the phenotype | Genetic effect rigorously tested against phenotype and is statistically associated, but other potential clinical factors not included/not tested in conjunction | Genetic association is lost after inclusion of other clinical or confounding factors |
| Gene/disease association testing              | Variant/gene(s) of interest do not confer disease susceptibility, and there is no association between the variant/gene(s) of interest and baseline disease factors nor disease prognostic classifiers/groups | Formal testing of variant/gene(s) of interest against disease/prognostic classifiers is not performed, but respective baseline characteristics are fully provided so that comparison of each diplotype groups can be performed, with no differences by diplotype group observed | Variant/gene(s) of interest confer disease susceptibility, and/or diplotype groups are imbalanced for key baseline disease characteristics/prognostic factors |
| Statistical analysis                           | Careful correction for multiple testing | Exploratory analysis            | No attention to multiple testing  |
| Clinical relevance of association             | Highly relevant (drug would be avoided, or dose would be changed, based on the result) | Potentially relevant (clinician may not avoid or dose-alter the drug, but might monitor the patient differently; or information might help inform prescribing in settings where there is otherwise equipoise about several treatment options) | Irrelevant (i.e., genetic variant is statistically associated but the information would not alter the clinical decision calculus; provides no additional information that would impact dosing, monitoring, or likelihood of response/toxicity) |
| Odds ratios with confidence intervals         | Present                           | Present                           | Absent                           |
| Effect size                                   | Large (OR > 5)                    | Moderate (OR 2–5)                 | Modest (OR < 2)                  |
| Direction of effect                           | Consistent                       | Consistent                       | Divergent                        |
| Supporting Pharmacokinetic Data               | Drug levels provide biologic explanation for observed clinical effect | Not applicable (e.g., for pharmacodynamic genes), or not obtained | Absent                           |
| Functional/biologic rationale                | Functional studies are performed and provide a credible explanation for the observed genetic relationship | Variant/gene has clear biologic relevance to the observed phenotype (alters known enzyme activity, is in relevant pathway, or affects drug target), but functional studies were not directly performed | Absent                           |

These criteria are applied at the article level, to each article being evaluated. These criteria follow formal, accepted standards in the field of pharmacogenomics. See also Ratan et al. [21] and Thorn et al. 2018 [21].

*OR Odds ratio of effect (carrier of actionable genotype vs. non-carrier).

*In pharmacogenomics, there is a history of case reports (especially those reporting drug-related deaths) being the provoking cause for more formal, larger investigations or for performing subsequent formal studies of a drug/gene relationship; in these instances, case reports might be considered supportive of an association, but case reports would generally not provide sufficient evidence in isolation.

*Key alleles were chosen based on a minimum set of variants that should be included in genotyping assays, as set forth by the Association for Molecular Pathology Clinical Practice Committee (Pratt et al. [23]). Studies of CYP2D6 where copy number assessment is not included, or studies of CYP2C19 lacking inclusion of *17, would be examples that fall into this category. For RYR1/CACNA1S, we utilized the list endorsed by the EMHG (https://www.emhg.org/diagnostic-mutations). For genes where no consensus allele list is yet published (e.g., CYP2D6), we used a proposed standard of requiring all alleles having known frequencies of at least 5% in the population being studied.

*Gene by treatment interaction analyses were not required to be performed, but were considered as a potential feature of high quality studies.

*Applies to studies where the primary phenotype of interest is a clinical endpoint (e.g., toxicity).
Table 1 criteria applied at the abstract level (n=93)  
- Did not meet Table 1 criteria (n=27)  
- CDS already implemented (n=15)

Table 1 criteria applied for full article review (n=51)  
- Did not meet Table 1 criteria (n=33)

Medications taken forward for CDS development and AGREE Scoring (n=18)  
- No medications removed at this stage

Medications recommended for implementation (n=18)  
- No published pharmacogenomic studies with positive associations (n=87)

Fig. 1 Article evaluation process. For the 180 included medications, over 1900 publications were initially identified and assessed. In total, 93 medications (51.1%) were found to have at least one published positive pharmacogenomic study. A total of 66 medications had associated drug/variant or drug/gene pair groups containing individual articles that were eligible for full article-level review. Pharmacogenomic evidence had been previously formally evaluated by our group (in prior studies) for 15 of these medications. The remaining 51 medications (encompassing 200 unique drug/variant or drug/gene pairs) were supported by 382 publications that were fully appraised at the publication level (sent for full review). After assessment of these publications, 18 medications were deemed potentially clinically actionable, and thus CDS were developed and subjected to AGREE II scoring. All CDS were unanimously recommended for clinical implementation.

RESULTS

Study demographics

For the 180 included medications, over 1900 publications were initially identified and assessed (Supplementary File 2, tab 1). The article evaluation process is depicted in Fig. 1. In total, 93 medications (51.1%) were found to have at least 1 published positive pharmacogenomic study. A total of 66 medications had associated drug/variant or drug/gene pair groups containing individual articles that were eligible for full article-level review (Supplementary File 3). Pharmacogenomic evidence had been previously formally evaluated by our group (in prior studies) for 15 of these medications (17, 18, 26). The remaining 51 medications (encompassing 200 unique drug/variant or drug/gene pairs) were supported by 382 publications that were fully appraised at the publication level (sent for full review). Of these 51 medications, 18 were deemed to have rigorous, replicated, high quality pharmacogenomic evidence in the literature.

Clinically actionable associations

Table 2 shows details for the 18 medications with high quality, replicated pharmaco genetic evidence supporting clinical actionability. Of note, the Table highlights only the positive studies for each gene–drug pair, though both negative and positive studies were considered when determining clinical actionability, and negative studies were cited in our CDS. Publication-level evidentiary information for the key studies supporting the replicated, consistent and strong-evidence drug/variant and drug/gene pairs are provided in Table 3. There did not appear to be any pattern based on year of FDA drug approval that predicted medication-specific clinical actionability (Fig. 2). Almost all of the 18 medications determined to be clinically actionable have similar CPIC, DPWG, and/or FDA label prescribing guidance. Original CDS summaries for each potential genotype associated with each potential clinical consequence were then developed for each of the 18 medications. Screen shots of genotype-specific CDS summaries for sevoflurane and succinylcholine, as examples, are shown in Fig. 3. The remaining CDS summaries are available in Supplementary File 4. One composite summary was written for all of the NSAIDs (celecoxib, diclofenac, flurbiprofen, ibuprofen, and piroxicam as associated with CYP2C9), and one composite summary was written for the six anesthetics (desflurane, enfurane, halothane, isoflurane, sevoflurane, and succinylcholine as associated with RVR1 and CACNA1S mutations).

Agree II results

Four domains were assessed for scoring the newly-developed proposed clinical summaries, with scores summed and scaled to a total percentage of the maximum possible score (100) (Table 4). For the 11 summaries encompassing the 18 potentially clinically actionable medications, the Scope & Purpose domain received an average score of 95.0 ± 2.8 (mean ± standard deviation) (range 90.0–100), and the Rigor of Development domain scored 93.2 ± 2.8 (range 90.0–96.7). The Clarity of Presentation domain scored an 87.3 ± 3.0 (range 83.3–93.3), and the Applicability domain an 86.5
| Medication | Gene     | Variant or phenotype | Implication                                                                 | CPIC/DPWG/FDA PGx Info | # of Positive studies | Top supporting publications | Total # of study subjects in supporting publications | Clinical effects                                                                                                           | Recommended clinical action                                                                                          | Actionable genotype/phenotype frequencies |
|------------|----------|----------------------|-----------------------------------------------------------------------------|------------------------|-----------------------|-------------------------|---------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------|

### Analgesia

**Codeine**<sup>a</sup>  
Gene: CYP2D6  
Variants: UM/NM/IM/PM  
Implication:  
- UM: risk of CNS depression and death;  
- IM: decreased analgesic effect with standard dosing;  
- PM: high risk of lack of analgesic effect  

- Y/Y/Y 27 1–11 362  
- Undetectable active metabolite in 36% of patients given codeine [4];  
- Undetectable active metabolite in all 12 PMs [6];  
- 50% higher plasma concentration of active metabolite w/more sedation in UMs than in NMs [9].  

- Avoid codeine in UM and PM individuals.  
- Monitor closely in IM individuals.  
- UM: 1–2%  
- IM: 2–11%  
- PM: 5–10%  

**Tramadol**  
Gene: CYP2D6  
Variants: UM/NM/IM/PM  
Implication:  
- UM: risk of serious adverse drug effects (respiratory depression) and toxicity (nausea/vomiting);  
- IM: decreased analgesic effect with standard dosing;  
- PM: high risk of inadequate analgesia  

- Y/Y/Y 28 1, 12–16 536  
- Response rate of 78.4% vs. 53.3% (NM vs. PM) [16];  
- 10 of 18 PMs required rescue medication, significantly more than other phenotypes [15].  

- Avoid tramadol in PM individuals.  
- Reduce initial dose by 30% in UM individuals.  
- Monitor closely in IM individuals.  
- UM: 1–2%  
- IM: 2–11%  
- PM: 5–10%  

**Oxycodone**  
Gene: CYP2D6  
Variants: UM/NM/IM/PM  
Implication:  
- UM: narcotic-related toxicity;  
- IM and PM: decreased analgesic effect with standard dosing  

- N/Y/Y 8 17–19 141  
- Cumulative postoperative doses higher for PMs and IMs, lower for UMs, compared to NMs (25 mg, 22 mg, 18 mg versus 20 mg) [17];  
- UMs experience more side effects than NMs [18].  

- Monitor closely in UM, IM, and PM individuals.  
- UM: 1–2%  
- IM: 2–11%  
- PM: 5–10%  

**Morphine**  
Gene: OPRM1  
Variants: *118G*  
Implication: Inadequate Analgesia  

- Y*/N/N 28 20–23 8462  
- Each additional copy of the G allele increases morphine intake by 1.87 mg and pain score by 0.51 units [20].  

- Monitor closely in individuals with A/G or G/G genotypes.  
- AG: 40–49%  
- GG: 14–15%  

**Celecoxib**<sup>b</sup>  
Gene: CYP2C9  
Variants: *2 allele***  
Implication: Gastrointestinal Bleeding  

- Y/N/Y<sup>3</sup> 10 24–30, 58 685  
- NSAID treatment associated with bleeding compared to aspirin OR = 15.7) [24];  
- 2 to eightfold higher plasma concentrations with the risk allele [27].  

- Reduce initial dose by at least 50% for *3/*3 individuals.  
- Reduce initial dose by 25–50% for *2/*3 and *2/*2 individuals.  
- Reduce initial dose by 25–40% for *1/*3 individuals.  
- Monitor closely in *1/*2 individuals.  
- *3 heterozygote: 2–7%  
- *3 homozygote: <1%  
- *2 heterozygote: <1%  
- *2 homozygote: <1%  
- *1 homozygote: <1%  

**Diclofenac**<sup>c</sup>  
Gene: CYP2C9  
Variants: *3 allele***  
Implication: Gastrointestinal Bleeding  

- Y/N/Y<sup>3</sup> 10 24–30, 58 685  
- NSAID treatment associated with bleeding compared to aspirin OR = 15.7) [24];  
- 2 to eightfold higher plasma concentrations with the risk allele [27].  

- Reduce initial dose by at least 50% for *3/*3 individuals.  
- Reduce initial dose by 25–50% for *2/*3 and *2/*2 individuals.  
- Reduce initial dose by 25–40% for *1/*3 individuals.  
- Monitor closely in *1/*2 individuals.  
- *3 heterozygote: 2–7%  
- *3 homozygote: <1%  
- *2 heterozygote: <1%  
- *2 homozygote: <1%  
- *1 homozygote: <1%  

### Anesthesia

**Mivacurium**  
Gene: BCHE  
Variants: K-variant  
Implication: Prolonged apnea  

- N/N/Y 5 31–35 114  
- Patients have been seen to have paralysis for up to 12 h after standard doses of mivacurium.  

- Avoid mivacurium in those with the A/A, AK/A, and AK/AK genotypes.  
- Use with caution in those with the A/U, AK/U, A/K, and AK/K genotypes.  
- Monitor closely in those with the K/K and K/U genotypes.  
- A/U: 4%  
- AK/U: 10%  
- A/K: 22%  
- AK/K: 4%  
- K/K: 8%  
- K/U: 18%
| Medication      | Gene       | Variant or phenotype | Implication                        | CPIC/DPWG/FDA PGx Info<sup>a</sup> | # of Positive studies | Top supporting publications<sup>b</sup> | Total # of study subjects in supporting publications | Clinical effects                                                                 | Recommended clinical action                                                                 | Actionable genotype/phenotype frequencies<sup>c</sup> |
|-----------------|------------|----------------------|------------------------------------|-------------------------------------|-----------------------|------------------------------------------|------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Desflurane     | RYR1       | 40 RYR1 mutations, 2 CACNA1S mutations | Malignant hyperthermia            | Y/N/Y                               | 41                    | 36–40, 57                                | 200                                               | 101 of 196 of malignant hyperthermia patients carry a risk allele [41]. | Avoid succinylcholine and volatile anesthetic use in individuals carrying any risk alleles. | RYR1 variants: <1%                                                                 |
| Enflurane      | CACNA1S    |                      |                                    |                                     |                       |                                          |                                                   |                                                                 |                                                                                                                                  |                                                   |
| Halothane      |            |                      |                                    |                                     |                       |                                          |                                                   |                                                                 |                                                                                                                                  |                                                   |
| Isoflurane     | RYR1       | mutations, 2 CACNA1S mutations |                                    |                                     |                       |                                          |                                                   |                                                                 |                                                                                                                                  |                                                   |
| Sevoflurane    |            |                      |                                    |                                     |                       |                                          |                                                   |                                                                 |                                                                                                                                  |                                                   |
| Succinylcholine| BCHE       | A-variant            | Prolonged apnea                    | N/N/Y                              | 14                    | 31, 32, 35, 41, 42                      | 1312                                              | Prolonged apnea of 1–6 h in homozygous genotypes, and 6–20 min. in heterozygous carriers (normal 4–6 min) [41]. | Avoid succinylcholine in homozygous carriers of the A-variant. Administer cautiously in heterozygous carriers. | A allele frequency: <4%                                                                 |
| Antiepilepsy   | CYP2C9     | NM/IM/PM             | IM and PM: neurotoxicity or severe cutaneous adverse reactions (SCAR) | Y/Y/Y                              | 40                    | 2, 43–53                                | 5704                                              | OR = 11 for SCAR [43]; OR = 15.3 for neurotoxicity [44] | Reduce initial maintenance dose by 50% in PM individuals and 25% in IM individuals. | IM: 8% PM: 1%                                                                 |
| Phenytoin      |            |                      |                                    |                                     |                       |                                          |                                                   |                                                                 |                                                                                                                                  |                                                   |
| Antianxiety    | CYP2C19    | NM/IM/PM             | IM and PM: increased emergence time from anesthesia | N/N/Y                              | 5                     | 54–56                                   | 102                                               | General anesthesia median emergence time of 18, 13, 10 min in PM, IM, and NMs, respectively [54]. | Monitor closely in PM and IM individuals. | IM: 18–45% PM: 2–15%                                                                 |
| Diazepam       |            |                      |                                    |                                     |                       |                                          |                                                   |                                                                 |                                                                                                                                  |                                                   |

CPIC Clinical Pharmacogenetics Implementation Consortium, DPWG Dutch Pharmacogenomics Working Group, FDA Food and Drug Administration; PGx information from CPIC and DPWG is indicated as “yes” if clinical guidelines are available. UM Ultrarapid metabolizer, NM normal metabolizer, IM intermediate metabolizer, PM poor metabolizer.

<sup>a</sup>Y yes, N no, CPIC and DPWG both provide actionable recommendations, whereas FDA may provide general information about genetic alleles without specific prescribing guidance.

<sup>b</sup>Details of supporting publications are reported in Table 3. Complete references available in Supplementary File 5.

<sup>c</sup>As reported in supporting publications or CPIC guidelines.

<sup>d</sup>Also addresses tramadol and oxycodone in guideline.

<sup>e</sup>See Discussion for specific details about CPIC evaluation of this drug/gene pair.

<sup>f</sup>Only the NSAIDs that were specifically included in pharmacogenomic clinical outcome studies and/or pharmacogenomic-pharmacokinetic studies that demonstrated the genetic association were specifically developed into Clinical Decision-Support summaries.

<sup>g</sup>Dosing and/or caution information provided for celecoxib, piroxicam, and flurbiprofen.
Table 3. Publication-level evidentiary information for the key studies supporting the replicated, consistent, and strong-evidence drug/variant and drug/gene pairs.

| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|--------------|--------------|-------------------------|-----------|-------------------------------------|-------------------------------|-----------------------------|
| Lotsch et al. 2009 | Open randomized crossover design in which CYP2D6 activity score was tested in comparison to genotype-based classification and plasma dextromethorphan metabolic ratio | 57 healthy Caucasian subjects genotyped for CYP2D6 receiving either dextromethorphan or codeine | Codeine, codeine metabolites, morphine, and morphine metabolites were measured after extraction of plasma samples. | CYP2D6 activity score; plasma concentration | 50 mg oral codeine or 30 mg dextromethorphan | Most subjects at the lower 15% of morphine formation from codeine were correctly identified by CYP2D6 genotype- or phenotype-based systems, while CYP2D6 genotyping predicted only the 50% who carried gene duplications in subjects at the upper 15% of morphine formation. Dextromethorphan-based phenotyping identified 67.5% of subjects with high morphine formation. |
| Williams et al. 2002 | Randomized double-blind study | 96 children undergoing adenotonsillectomy | Blood was drawn 1 h after induction for the measurement of plasma morphine and morphine metabolites. | CYP2D6 PM, IM/PM, IM, NM; plasma concentration | Codeine 1.5 mg/kg or morphine 0.15 mg/kg | Plasma morphine concentrations were related to phenotype (p < 0.02). Plasma morphine metabolite concentrations, as measured by the M3G:M6G ratio, were not significant (EM group: 4.5, IM group: 3.4, IM/PM group: 2.95) p > 0.05. |
| Eckhardt et al. 1998 | Randomized placebo-controlled double-blind trial | Pain tolerance was assessed in 18 adults undergoing the cold pressor test. | Codeine and morphine metabolites were measured in serum and urine. | CYP2D6 EM, PM; response and adverse events | Codeine 170 mg or morphine 20 mg | Following administration of codeine, analgesia was observed in EM but not PM-EM: 54.9 ± 42.2 vs. 1.7 ± 4.2 p < 0.01; PM: 9.6 ± 10.9 vs. 3.3 ± 23.7 p > 0.05; No differences in adverse effects among phenotype groups were observed; Morphine concentrations after codeine administration comparable to after administration of morphine were only observed in EM; Percentage of codeine dose converted to morphine and metabolites was 3.9% in EM compared to 0.17% in PM. |
| Sindrup et al. 1990 | Double-blind, placebo-controlled crossover study | Pain tolerance to laser stimuli was assessed in 24 adults. | Pain threshold measurements and medication level in plasma was measured before ingestion of codeine or placebo and then 90, 150, and 210 min after ingestion. | CYP2D6 EM, PM; efficacy | Codeine 75 mg; placebo | In EM, there was a statistically significant increase in pain thresholds 90 and 150 min after codeine with no difference after placebo. In PM, neither codeine nor placebo resulted in significant changes in pain threshold. Codeine concentrations were significantly higher in EM than in PM but did not differ 150 and 210 min after codeine administration. In EM, there was a significant correlation between the plasma concentration of morphine and pain threshold difference after codeine and after placebo after 90 min. |
| Poulsen et al. 1996 | Randomized, double-blind, three-way, crossover study | Pain tolerance was assessed via the cold pressor test in addition to heat and pressure stimulation in 28 adults. | Pain tests were performed before and 1, 2, 3, and 4 h after medication administration. | CYP2D6 EM, PM; adverse effects | Codeine 75 mg or 100 mg; Morphine 20 mg or 30 mg; placebo | After codeine administration, neither morphine nor morphine-6-glucoronide could be detected in 13 of the 14 PMs, whereas at least one of the compounds could be detected in all EM. Codeine only reduced pain measures significantly in EM. In PMs, adverse effects were more pronounced on morphine as opposed to codeine, and a slight difference was observed between codeine and placebo. In EM, there was no difference between codeine and morphine and more pronounced adverse effects on both drugs as compared to placebo. |
Table 3 continued

| Author, Ref.          | Study design                        | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|-----------------------|-------------------------------------|-------------------------|-----------|--------------------------------------|-------------------------------|-----------------------------|
| Sistonen et al. 2012  | Telephone interviews for self-reported adverse effects | 111 mothers who used codeine during pregnancy were assessed for potential genetic association with adverse effects, specifically CNS depression. | Mothers were initially called after giving birth. A second follow-up call was conducted within one year of the original call. | CYP2D6 PM, EM, UM; ABCB1 rs11280503; ABCB1 rs2032582; ABCB1 rs1045642; UGT2B7 rs62298861; OPRM1 rs1799971; OPRM1 rs563649; COMT rs4633; COMT rs4818; COMT rs4680; toxicities | Codeine use during pregnancy | Genetic model combining the maternal risk genotypes in CYP2D6 and ABCB1 was significantly associated with adverse outcomes in infants (OR: 2.68; 95% CI 1.61–4.48, p = 0.0002) and their mothers (OR: 2.74; 95% CI 1.53–4.84, p = 0.0005). |
| Kirchheiner et al. 2007 | Pharmacokinetic/pharmacodynamic study | 26 healthy Caucasian volunteers | Blood samples were obtained before codeine was administered and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after administration. Pupil diameter measured as a pharmacodynamic parameter. | CYP2D6 EM, PM, UM; plasma metabolite levels | Single dose of 30 mg codeine | Median morphine and M3G AUCs were significantly different among EM, PM, and UM (p = 0.02 and p < 0.02, respectively). Higher O-demethylated codeine metabolites with increasing CYP2D6 activity was detected (p < 0.001). 50% higher plasma concentration of active metabolite in UM compared to NM. Influence of genotype on pupil diameter not significant. |
| Kirchheiner et al. 2008 | Pharmacokinetic/pharmacodynamic study | 22 healthy volunteers | Pharmacokinetic parameters measured were total clearance, renal clearance and maximum concentration. Pharmacodynamics were measured using cold pressor test, pupillometry, and standardized adverse event recording. | CYP2D6 EM, UM; drug plasma concentrations and adverse events | Single dose of 100 mg tramadol | Maximum plasma concentrations of the active metabolite were significantly higher in the UM group than the EM group (p = 0.005). Median tramadol AUC was 786 and 587 mug.h.L in EM and UM, respectively, and the corresponding median metabolite AUC was 416 and 448 mug.h.L (p = 0.005). UM experienced increased pain threshold and tolerance and a stronger miosis after tramadol. Nearly half of the UM group experienced nausea compared to only 9% of the EM group. |
| Pedersen et al. 2006 | Open-label crossover trial with different formulations | 16 healthy volunteers | Urine and plasma concentrations of tramadol and metabolite (M1) were measured 48 h after administration. | CYP2D6 EM, PM; drug plasma concentration | 150 mg single-dose oral racemic tramadol, 50 mg single oral racemic tramadol every 8 h for 48 h, 100 mg intravenous racemic tramadol | In all three phases, significant differences existed between EM and PM in AUC and half-life of (+)-tramadol (p < 0.0015), (-)-tramadol (p = 0.0062), (+)--M1 (p < 0.0001) and (-)--M1 (p < 0.0370). EM and PM also showed significant differences for Cmax of (+)-M1 (p < 0.0001) and (-)--M1 (p < 0.001). No significant differences between absolute bioavailability of tramadol in EM and PM. Urinary recoveries of (+)-tramadol and (-)-tramadol, in addition to (+)--M1 and (-)--M1 were significantly different in EM and PM (p < 0.05). |
| Garcia-Quetglas et al. 2007 | Pharmacokinetic study | 24 healthy volunteers | Blood samples were collected at 30, 60, 90, 120, 150, 180, and 210 min and 4, 5, 6, 8, 10, 12, 24, 36, and 48 h after oral administration of tramadol. Tramadol and metabolites (M1 and M2) were measured. | CYP2D6 EM, PM; drug plasma concentration | 100 mg racemic tramadol | Plasma concentrations of tramadol enantiomers were consistently higher in PM than in EM, with 1.98 and 1.74-fold differences in mean AUC, respectively. Oral clearance of (+)- and (-)- tramadol were 1.91- and 1.71-fold greater in PM. The mean AUC values of (+)--M1 and (-)--M1 were 4.33 and 0.89-fold greater in EM. Differences in AUC for M2 enantiomers were 7.40 and 8.69-fold greater in PM. |
| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|-------------|--------------|-------------------------|-----------|-------------------------------------|-------------------------------|----------------------------|
| Stamer et al. 2007 | Pharmacokinetic study | 174 patients receiving intravenous tramadol for postoperative analgesia | Blood samples were drawn 30, 90, and 180 min after administration and were analyzed for plasma concentrations of (+) and (−) tramadol and (+) and (−) O-desmethyltramadol. Efficacy was also measured. | CYP2D6 PM, IM, EM, UM; drug plasma concentrations and efficacy | Intravenous tramadol 3 mg/kg | Median AUC-time curves for (+)-O-desmethyltramadol were 0, 38.6, 66.5, and 149.7 ng × h/ml for PM, IM, EM, and UM (p < 0.001). In PM, nonresponse rates to tramadol increased fourfold compared to other genotypes (p < 0.001). |
| Stamer et al. 2003 | Prospective cohort study | 271 patients recovering from abdominal surgery | Pain scores, analgesic consumption, and need for rescue medication was collected. | CYP2D6 EM, PM; response and dose | After titration of individual loading dose, patients could self-administer 1 ml bolus doses of the drug combination tramadol 20 mg/ml, dipyrone 200 mg/ml and metoclopramide 0.4 mg/ml via patient-controlled analgesia. | Percentage of non-responders was significantly higher in the PM group (46.7%) compared with the EM group (21.6%, p = 0.005). Tramadol loading dose differed between EM and PM (108.2 ± 56.9 and 144.7 ± 22.6 mg, p < 0.001). More PM patients needed rescue medication in the recovery room and during PCA period (21.6 vs. 43.3%, p = 0.02). |
| Stamer et al. 2010 | Pharmacokinetic study | 121 patients receiving oxycodone before emerging from anesthesia and patient-controlled anesthesia for 48 h postoperatively. | Blood samples were drawn at 30, 90, and 180 min after initial oxycodone dose. Plasma concentrations of oxycodone, oxymorphone, noroxycodone and noroxymorphone were analyzed. Pain scores were also obtained. | CYP2D6 PM, IM, EM, UM; drug plasma concentrations | Oxycodone 0.05 mg/kg before emerging from anesthesia and for use as patient-controlled analgesia. | Mean oxymorphone/oxycodone ratios were 0.10, 0.13, 0.18, and 0.28 in PM, IM, EM, and UM respectively (p<0.005). Oxycodone consumption within the first 12 h postoperatively was highest in PM (p = 0.005). Pain scores did not differ between genotypes. |
| Samer et al. 2010 | Randomized crossover (five arms) double-blind placebo-controlled study | 10 healthy volunteers | Experimental pain (cold pressor test, electrical stimulation, thermode), pupil size, psychomotor effects and toxicity were assessed after oral oxycodone administration. | CYP2D6 UM, PM, EM, IM; toxicities and response | On five occasions, patients randomly received oxycodone (0.2 mg/kg) and placebo; oxycodone and quinidine; oxycodone and ketoconazole; oxycodone and quinidine + ketoconazole; placebo | UM experienced increased pharmacodynamic effects compared to EM. This effect was not seen in PM. Side effects were observed after CYP2D6 and/or CYP3A4 blockade in UM. |
| Samer et al. 2010 | Randomized crossover (five arms) double-blind placebo-controlled study | 10 healthy volunteers | Blood samples for plasma concentrations of oxycodone and metabolites oxymorphone, noroxycodone, and noroxymorphone were collected for 24 h after dosing. | CYP2D6 UM, PM, EM; drug plasma concentration | On five occasions, patients randomly received oxycodone (0.2 mg/kg) and placebo; oxycodone and quinidine; oxycodone and ketoconazole; oxycodone and quinidine + ketoconazole; placebo | Oxymorphone C(max) was 62% and 75% lower in PM than EM and UM. Noroxymorphone C(max) was reduced by 90% in PM. In UM, oxymorphone and noroxymorphone concentrations increased and noroxycodone exposure was halved. |
| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/outcome measure | Medication and dosing regimens | Results of reviewed markers |
|-------------|--------------|-------------------------|-----------|-----------------------------------|-------------------------------|----------------------------|
| Sia et al. 2008 | Pharmacodynamic study | 586 women receiving morphine for postcesaerean analgesia | Pain scores, severity of nausea and vomiting, incidence of pruritis, and self-administered morphine were recorded for the first 24 h postoperative. | OPRM1 A118G; adverse events | Bolus dose of 1 mg morphone, lockout of 5 min, and total hourly dose of 10 mg for treatment of postoperative pain (patient-controlled analgesia). | The 24 h self-administered intravenous morphine consumption was lowest in the AA group (p = 0.001). Pain scores were lowest in the AA group and highest in the GG group (p = 0.049). The AA group had the highest incidence of nausea (p = 0.02). |
| Sia et al. 2013 | Prospective cohort study | 973 patients undergoing scheduled total hysterectomy under general anesthesia | The association of a common polymorphism in the OPRM1 gene with patient-rated pain scores and amount of morphine use. | mu-opioid receptor gene OPRM1; response and dose | The PCA was set to deliver 1 mg IV bolus of morphine per demand with a lockout time of 5 min, without continuous background infusion. The maximum amount of morphine allowed was 10 mg/h. For the next 24 h, the cumulative dose of morphine administered by each patient within every 4 h period was recorded. Patients were monitored and could also request for additional IV morphine in 1-mg boluses. | There was no statistically significant association with OPRM1 118A>G for either pain threshold or pain tolerance. There was a statistically significant association of genotype with total morphine and morphine self-administered through PCA, with the GG group using the most and the AA group the least (p = 0.006). |
| Hwang et al. 2014 | Systematic review and meta-analysis | 346 articles were retrieved from databases, and 18 studies involving 4607 participants were included in the final analyses. | The standardized mean difference (SMD) of required amounts of opioids between AA homozygotes and G-allele carriers was calculated. | OPRM1 A118G polymorphism; opioid dose | postoperative opioid response | In a random-effect meta-analysis, G-allele carriers required a higher mean opioid dose than AA homozygotes (SMD, −0.18; P = 0.003). Although there was no evidence of publication bias, heterogeneity was present among studies (I² = 66.8%). In the subgroup meta-analyses, significance remained robust in Asian patients (SMD, −0.21; P = 0.001), morphine users (SMD, −0.29; P < 0.001), and patients who received surgery for a viscus (SMD, −0.20; P = 0.008). |
| Klepstad et al. 2011 | Cohort study including a development and validation analysis | A total of 2294 cancer pain patients from 17 centers located in 11 countries were recruited to the study. Participants were adult patients (>18 years of age) with a malignant disease who were using an opioid for moderate to severe pain. | The dose and routes of opioids, both scheduled and rescue doses, for the last 24 h, the duration of opioid treatment and previous number of unsuccessful trials with other opioids were recorded. Oral opioid equivalent morphine doses were calculated using standard tables. | 112 SNPs in the 25 candidate genes OPRM1, OPRD1, OPRK1, ARRB2, GNAZ, HINT1, Stat6, ABCB1, COMT, HRH1, ADRA2A, MCT1, TACR1, GC1H, DRD2, DRD3, HTR3A, HTR3B, HTR2A, HTR3C, HTR3D, HTR3E, HTR1, or CNR1; opioid efficacy and dose | Morphine (n = 830), oxycodone (n = 440), fentanyl (n = 699), or other opioids (n = 234). | None of 112 SNPs in the 25 candidate genes showed significant associations with opioid dose in both the development and the validation analyses. |
| Author, Ref.        | Study design                          | Population and diseases                                                                 | Follow-up                                                                 | Genotype/phenotypes/outcome measure | Medication and dosing regimens | Results of reviewed markers                                                                 |
|-------------------|---------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------|---------------------------------|------------------------------------------------------------------------------------------|
| Carbonell et al. 2010 | Prospective, multicenter, case-case study | Patients hospitalized for acute upper gastrointestinal bleeding (AUGIB) related to the use of NSAIDs. A total of 131 patients had been treated with aspirin and 57 patients had been treated with an NSAID other than aspirin. | Any hospitalization for AUGIB related to NSAIDs. | CYP2C9 359Leu (CYP2C9*3) loss-of-function allele | 131 patients were treated with aspirin and 57 were treated with other types of NSAIDs. Aspirin had been given as an antiaggregant treatment (<325 mg/day) in 78 patients, including in 2 patients who were on a chronic regimen of low-dose aspirin in addition to a short course of high-dose aspirin (1 g twice a day). In the group taking non-ASP NSAIDs, 18 were on ketoprofen, 12 were on diclofenac, 11 were on ibuprofen, 10 were on piroxicam, 4 were on naproxen, 4 were on celecoxib, 1 was on flurbiprofen, 1 was on meloxicam, 1 was on tenoxicam, and 1 was on rofecoxib; 6 of these patients were taking 2 non-ASP NSAIDs concomitantly. | In the aspirin group, 12 patients (9.2%) had the CYP2C9 359Leu allele as compared with 19 (33.3%) in the non-ASP group (odds ratio (OR) = 5.0; 95% confidence interval (CI) 2.2–11.1, P < 0.0001). In a multivariate analysis, CYP2C9 359Leu remained associated with the non-ASP group (OR = 7.2 (2.6–20.3), P = 0.0002) even though 40% of these patients were under treatment with antulcer drugs at the time of admission. |
| Garcia-Martin et al. 2004 | Cohort pharmacokinetic study | 130 healthy volunteers                                                                 | Plasma samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after administration and immediately frozen until analysis. | CYP2C8 and CYP2C9 ibuprofen clearance | All participants received a single oral dose of a solution of 400 mg racemic ibuprofen. | Ibuprofen clearance values were 4.04 L/h (95% confidence interval (CI) 3.61–4.47 L/h), 2.79 L/h (95% CI, 2.07–3.52 L/h), and 0.40 L/h (95% CI, 0.37–0.43 L/h) for carriers of CYP2C8 genotypes *1/*1, *1/*3, and *3/*3, respectively, and 4.43 L/h (95% CI, 3.94–4.92 L/h), 3.26 L/h (95% CI, 2.53–3.99 L/h), 2.91 L/h (95% CI, 1.52–4.30 L/h), 2.05 L/h (95% CI, 0.63–3.74 L/h), 1.83 L/h (95% CI, 1.24–2.41 L/h), and 1.13 L/h (95% CI, 0.58–1.66 L/h) for carriers of the CYP2C9 genotypes *1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3, and *3/*3, respectively. The P values for comparison across nonmutated, heterozygous, and homozygous genotypes were as follows: P < 0.001 for CYP2C8*3, P < 0.005 for CYP2C9*2, and P < 0.001 for CYP2C9*3. |
| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|-------------|--------------|------------------------|-----------|-----------------------------------|--------------------------------|----------------------------|
| Vogl et al. 2015 | Cohort pharmacokinetic study | 283 healthy young adults | The urinary metabolic ratio MR (concentration of CYP2C9-dependent metabolite divided by concentration of flurbiprofen determined two h after flurbiprofen administration served as phenotyping metric. | CYP2C9*1, *2, *3; metabolic ratios | 8.75 mg of flurbiprofen | Linear statistical models correlating genotype and phenotype provided highly significant allele-specific MR estimates of 0.596 for the wild-type allele CYP2C9*1, 0.405 for CYP2C9*2 (68% of wild type), and 0.113 for CYP2C9*3 (19% of wild type). If these estimates were used for flurbiprofen dose adjustment, taking 100% for genotype *1/*1, an average reduction to 84%, 60%, 68%, 43%, and 19% would result for genotype *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3, respectively. |
| Prieto-Pérez et al. 2013 | Crossover pharmacokinetic trial | 24 healthy volunteers | Blood samples were collected at the following times: baseline (before receiving the drug), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 24, 48, and 72 h after administration. The maximum plasma concentration (Cmax) and the time to reach Cmax (Tmax) were the actual observed values. | CYP2C9*2, CYP2C9*3, CYP2C8*4, CYP2C9*2, and CYP2C9*3; clearance values | 200 mg single-dose celecoxib with 240 mL of water | Subjects carrying CYP2C9 *1/*3 and CYP2C9 *3/*3 had a higher AUC (2- and 7.7-fold, respectively) and Cmax (1.5- and 1.8-fold, respectively) and lower clearance (2.3- and 10-fold, respectively) than those carrying CYP2C9 *1/*1. Half-life was 2.7-fold higher in subjects with CYP2C9 *3/*3 than in those with the wild type but not in those with CYP2C9 *1/*3. |
| Lundblad et al. 2006 | Open-label pharmacokinetic study | 13 healthy volunteers | On days 1 and 7, blood samples were collected before and up to 24 h after celecoxib intake. | CYP2C9*1/*1, CYP2C9*1/*3, and CYP2C9*3/*3; drug and metabolite accumulation | Daily dose of celecoxib, 200 mg, was administered orally each morning for 7 days | A marked drug accumulation over the 7-day period was noticed in subjects genotyped as CYP2C9 *3/*3, with median trough values of 5.1 μmol/L, as compared with 0.2 and 0.3 μmol/L in subjects genotyped as CYP2C9 *1/*1 and CYP2C9*1/*3, respectively. Significantly lower levels of both metabolites were found in subjects genotyped as CYP2C9*3/*3. |
| Pilotto et al. 2007 | Non-randomized, case–control study | 26 patients with endoscopically documented NSAID-related gastrointestinal bleeding lesions and 52 age-, sex- and NSAID use-matched controls with no lesions at endoscopy | N/A | CYP2C9*2 and *3; adverse events | Treatment with an NSAID that undergoes CYP2C9 metabolism | Setting the CYP2C9 *1/*1 wild type as reference, significantly higher frequencies of CYP2C9 *1/*3 (34.6% vs. 5.8%; P < 0.001; odds ratio [OR], 12.9; 95% confidence interval [CI], 2.917–57.922) and CYP2C9*1/*2 (26.9% vs. 15.4%; P = 0.036; OR, 3.8; 95% CI, 1.090–13.190) were identified in bleeding versus control patients, whereas no differences between bleeding and controls were observed in the distribution of CYP2C9 *2/*3 heterozygotes. |
| Kircheiner et al. 2002 | Pharmacokinetic, genetic association study | 21 healthy volunteers | Plasma samples were taken at 0.05, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 24, 28, 34, and 48 h after administration. | CYP2C9*1/*1, CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*2, CYP2C9*2/*3, and CYP2C9*3/*3; drug clearance | Oral dose of 600 mg racemic ibuprofen | The pharmacokinetics of racemic and of S-ibuprofen depended on the CYP2C9 Leu559 polymorphism: population mean S-ibuprofen clearances were 3.25 L/h (95% confidence interval [CI], 2.84 to 3.71), 2.38 L/h (95% CI, 2.09 to 2.73), and 1.52 L/h (95% CI, 1.33 to 1.74) in carriers of the CYP2C9 genotypes *1/*1, *1/*3, *1/*3, and *3/*3, respectively. The CYP2C9 variant*2 exhibited no significant effect. |
| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|-------------|--------------|-------------------------|-----------|------------------------------------|-------------------------------|-------------------------------|
| Gätke et al. 2005 | Prospective, multicenter study | 58 adult patients who had previously been issued with warning cards by the Danish Cholinesterase Research Unit, requesting them and the anesthesiologist to contact the Research Unit if they were to undergo surgery | After induction of anesthesia, the ulnar nerve was stimulated supramaximally every 12 s using train-of-four (TOF) nerve stimulation. The evoked response from the adductor pollicis muscle was measured using mechanomyography. | A, U, and K variants of the BCHE gene; response | Patients who were homozygous for the A variant, whether linked with the K variant or not (A/A, AK/A, and AK/AK), were given 0.03 mg/kg intravenous mivacurium. Patients carrying the wild type (U/U) and patients with heterozygous occurrence of the A variant or with heterozygous or homozygous occurrence of the K variant (U/K, K/K, U/A, U/AK, and K/AK) received 0.2 mg/kg intravenous mivacurium. | Heterozygosity of the K variant prolonged the time to train-of-four 0.70 from 26.6 to 34.5 min (30%; not significant) as compared with the wild type. Heterozygosity of the K variant linked to the A variant prolonged the corresponding time from 32 to 42.7 min (33%; P 0.03) as compared with patients who were heterozygous for solely an A allele. For eight patients who were homozygous for both the A and K variants, the time to 25% recovery was 78-89 min as compared with 44-57 min in patients who were homozygous for the A variant or had only one linked K variant. |
| Cerf et al. 2002 | Prospective, multicenter cohort study | 36 patients from different institutions in France exhibiting a prolonged response to mivacurium or succinylcholine | Blood samples were withdrawn within 72 h after the event except in one patient, in whom a blood sample was obtained 5 days after anesthesia. | A and U variants of the BCHE gene; response | The mivacurium or succinylcholine dose varied per each patient in the study | Thirty-two patients had a BCHE deficiency of genetic origin: 20 were homozygous (AA), 10 were heterozygous (UA) for the A variant, and 2 did not have the A mutation (UU). One heterozygous UA patient had normal BCHE activity. Nine among the heterozygous UA and the two homozygous UU patients probably carried a not-screened variant. |
| Klinger et al. 2015 | Multicenter, genetic association study | 200 patient cases of malignant hyperthermia were included | N/A | RYR1 mutations of all 106 RYR1 exons and additionally for known mutations of CACNA1S; adverse events | Halothane, isoflurane and enflurane (varied per patient). | Crises triggered by enflurane had a significantly higher clinical grading scale (CGS) compared to halothane, isoflurane and sevoflurane. Of the 200 patients, 103 carried RyR1 variants, of which 14 were novel. CGS varied depending on the location of the mutation within the RYR1 gene. |
| Jensen and Viby-Mogensen 1995 | Prospective familial cohort study with purposeful sampling of individuals with abnormal clinical responses | A total of 6688 individuals from 2081 families were investigated. 1247 were referred because of a suspected abnormal response to succinylcholine. | Monitoring post-succinylcholine administration | J, A, F, S, K, J, and H variant of BCHE; response | Succinylcholine 1.0-1.5 mg/kg | The time to sufficient recovery of neuromuscular function following succinylcholine 1.0-1.5 mg/kg was 15-30 min in patients heterozygous for one abnormal gene, 35-45 min in patients heterozygous for two abnormal genes and 90-180 min in patients homozygous for the atypical gene. Patients with two newly discovered genotypes (AK 5 patients) and AH (1 patient) showed slightly prolonged (20 min) and markedly prolonged (90 min) duration of action of succinylcholine, respectively. |
| Author, Ref.   | Study design                                                                 | Population and diseases                                                                 | Follow-up                                                                 | Genotype/phenotypes/ outcome measure                                                                 | Medication and dosing regimens | Results of reviewed markers |
|---------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------|----------------------------|
| Levano et al. 2005 | Abnormal responder study                                                      | Nine patients with a neuromuscular block of 14 min to 5 h                              | Patients were contacted 24–48 h after administration of succinylcholine. | A, F, S, H, J, K variants of BCHE; response                                                        | Succinylcholine                | Seven of nine patients were mutation carriers. Five of these had more than one mutation. The A and K variants were the most frequent variations. Three of four patients who were homozygous for the A variant were also carriers of the K allele. The authors identified one novel mutation (G1294T) introducing a stop codon at amino acid position 432. The duration of neuromuscular block was substantially different between patients with identical BCHE genotypes. |
| Chung et al. 2014 | Case-control, genome-wide association study with a validation cohort           | 105 cases with phenytoin-related severe cutaneous adverse reactions, 78 cases with maculopapular exanthema, 130 phenytoin-tolerant control participants, and 3655 population controls from Taiwan, Japan, and Malaysia | Plasma samples of controls who received the maintenance dosage were collected within 24 h after the last dose of phenytoin. Available samples from phenytoin-tolerant controls and patients with severe cutaneous adverse reactions were obtained before or after withdrawal of phenytoin. | GWAS was performed which is composed of 909,622 single-nucleotide polymorphisms (SNPs). phenytoin | Direct sequencing of CYP2C19 identified missense variant rs1057910 (CYP2C9*3) that showed significant association with phenytoin-related severe cutaneous adverse reactions (odds ratio, 12; 95% CI, 6.6–20; \( P = 1.1 \times 10^{-17} \)). A meta-analysis using the data from the 3 populations showed an overall odds ratio of 11 (95% CI, 6.2–18; \( z = 8.58; P < 0.00001 \)) for CYP2C9*3 association with phenytoin-related severe cutaneous adverse reactions. |
| Kesavan et al. 2010 | Case-control, pharmacogenomic association study                              | 292 Tamilian patients who were taking phenytoin for the treatment of various epileptic seizures; 58 with PHT toxicity and 234 controls without toxicity | Blood samples (6 ml) for measurement of phenytoin level were obtained from all subjects within 4–14 h after the last dose of phenytoin. | CYP2C9*1, CYP2C9*2, CYP2C9*3, CYP2C19*1, CYP2C19*2, and CYP2C19*3 alleles; adverse effects | These patients had been receiving oral phenytoin for more than 2 months and were on a stable drug regimen at the time of the clinical and drug level assessments. | When risk ratios were calculated for each mutant CYP2C9 genotype separately, the adjusted odds ratio for CYP2C9*1/*3 was found to be 13.3 (95% confidence interval 5.8–40.3, \( P < 0.0001 \)) for the cases compared to controls. When the four single-nucleotide polymorphisms of CYP2C9 and CYP2C19 were analyzed using a haplotype approach, significant difference in the distribution of the C-C-G-G haplotype was observed between the cases and controls. |
| Depondt et al. 2011 | Retrospective, candidate gene study with replication cohort                   | 495 patients with epilepsy                                                             | Clinical data were extracted from medical records and entered in a web-based clinical database. For each patient, the following clinical data were recorded: (i) presence or absence of any adverse drug reaction (ADR) attributed by the clinician to CBZ, sodium valproate (VPA) and phenytoin (PHT) therapy, (ii) efficacy of VPA and (iii) overall efficacy of AEDs with a major action on sodium channels. | EPMX1 and CBZ adverse drug reactions; G53, G59, GSTA3, GSTA4, GSTA5, GSTA7, GSTM3, GSTM4, UGT1A6, UGT2B7, CYP2A6, CYP2C9 and VPA adverse drug reactions and efficacy; SCN1A, SCN2A, SCN3A, SCN8A and overall AED efficacy; CYP2C9 and PHT adverse drug reactions; GSTM1 and GBZ adverse drug reactions | phenytoin, carbamazepine, valproic acid (drug and dose varied among patients) | After correction for multiple comparisons, two associations remained significant: CYP2C9*2 and *3 alleles and PHT ADRs (\( P = 0.008 \)); and GSTM1 CNV and CBZ ADRs (\( P = 0.009 \)). Replication of the association of GSTM1 CNV with CBZ ADRs in the second patient cohort failed to show a significant association. |
Table 3 continued

| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|-------------|--------------|-------------------------|-----------|------------------------------------|-------------------------------|---------------------------|
| Hung et al. 2012 | Case-control, candidate gene study examining pharmacokinetics and pharmacodynamics | 269 epileptic patients under maintenance phenytoin monotherapy and 190 healthy volunteer controls | Compliance was monitored over the course of the study period. | CYP2C9*3 | Patients reached a maintenance dose for at least 1 year (phenytoin concentration: 15.13 ± 6.62 mg/l) | Results of a bivariate analysis demonstrated that among tested polymorphisms, carriers of the variant CYP2C9*3 tended to require significantly lower maintenance phenytoin dosages than wild-type carriers (p < 0.0001); on the other hand, carriers of the variants CYP2C9*3 or CYP2C19*3 revealed significantly higher concentration-dose ratio (CDR) than wild-type carriers (p < 0.004). In a further multivariate analysis, variants in SCN1A, CYP2C9, CYP2C19 and ABCB1 genes were significantly associated with CDRs of phenytoin under adjustment of age, gender and epilepsy classifications. |
| Aynacioglu et al. 1999 | Mixed pharmacokinetic cohort study including healthy volunteers | 499 unrelated Turkish subjects; 280 outpatients with various trivial diagnoses and 218 healthy volunteers | Blood sample was drawn and trough levels taken 12 h after phenytoin was administered. | Cysteine144 (CYP2C9) and leucine359 (CYP2C9*3); drug plasma concentration | After at least 4 h of fasting, each subject took a 300 mg phenytoin tablet with tap water at around 23.00 h | Mean phenytoin serum concentrations at 12 h after dosage were 4.16 mg (95% CI 3.86–4.46) in carriers of the genotype CYP2C9*1/1, 5.52 mg (4.66–6.39) in CYP2C9*1/2, and 5.65 mg (4.86–6.43) in CYP2C9*1/3. These differences were significant and accounted for 31% of total variability in phenytoin trough levels. |
| Mamiya et al. 1998 | Retrospective, population-defined pharmacokinetic study | 134 Japanese adult patients with epilepsy | Serum phenytoin concentration data at steady state | CYP2C9 Arg144/Cys; Ile359/Leu and CYP2C19 (1*, 2* or 3*); EM and PM; elimination rates | Routine treatment with oral administration of the tablet or granule of phenytoin | The mean maximal elimination rate (V-max) was 42% lower in the heterozygote for Leu359 allele in CYP2C9, and the mean Michaelis-Menten constants (Km) in the heterozygous extensive metabolizers and the poor metabolizers of CYP2C19 were 22 and 54%, respectively, higher than those without the mutations in CYP2C9/19 genes. |
| Odani et al. 1997 | Retrospective pharmacokinetic study | 44 Japanese patients with epilepsy | Most serum samples had been obtained for measurement of approximate peak levels 2 to 5 h after dosing. | CYP2C9 Arg144 → Cys and Ile359 → Leu and CYP2C19 (m1 and m2); elimination rates | Phenytoin had been administered at 12 h intervals to most patients, and the mean daily dose was 5.18 mg/kg/day phenytoin. | The maximal elimination rate (V-max) of phenytoin among patients with the heterozygous wild type/Leu359 in CYP2C9 was 33% lower than that among patients with normal CYP2C9. The V-max values of phenytoin were slightly decreased (up to 14%) among patients with CYP2C19 mutations compared with patients with normal CYP2C19. |
| Inomato et al. 2005 | Prospective, correlative pharmacokinetic study | 63 native Japanese patients who were scheduled for either a mastectomy or leg surgery | Blood was drawn from the indwelling arterial catheter before and at 15 and 30 min and 1, 2, 3, and 24 h after administration of diazepam. | CYP2C9; EM, IM, and PM; drug plasma concentration | Received 0.1 mg/kg diazepam intravenously on entering the operating room | The PM subjects showed a larger area under the curve representing the concentration of diazepam over a 24 h period (P = 0.0259), lower clearance of diazepam (P = 0.0287), and longer emergence time (median, 18 min; 25–75th percentile range, 13–21 min; P < 0.001) in comparison with subjects in the EM group. The IM group also showed a longer emergence time (median, 13 min; 25–75th percentile range, 9–20 min; P < 0.001) and a larger variation in this parameter in comparison with the EM group. |
### Table 3 continued

| Author, Ref. | Study design | Population and diseases | Follow-up | Genotype/phenotypes/ outcome measure | Medication and dosing regimens | Results of reviewed markers |
|--------------|--------------|-------------------------|-----------|-------------------------------------|-------------------------------|---------------------------|
| Wan et al. 1996 | Pharmacokinetic study | 21 healthy male Chinese subjects | 10 mL venous blood samples were collected at 0, 1, 2, 4, 8, 12, and 24 h and 2, 3, 6, 12, 18, and 24 days after dosing. | CYP2C19, PM and EM; drug plasma concentration | A single oral dose of 5 mg diazepam. | The plasma elimination half-lives of diazepam (100.8 ± 32.3 h) and desmethyldiazepam (219.9 ± 62.7 h) in PMs were significantly longer than those (34.7 ± 23.0 h for diazepam, 103.1 ± 25.9 h for desmethyldiazepam) of the 17 phenotyped extensive metabolizers (EM), and those (30.8 ± 24.9 h for diazepam, 103.1 ± 27.5 h for desmethyldiazepam) of the five genotyped EMs. |
| Qin et al. 1999 | Pharmacokinetic study | 18 unrelated healthy Chinese men | 10 mL venous blood samples were collected at 1, 2, 4, 8, 12, and 24 h and then 2, 3, 6, and 12 days after administration. | CYP2C19 wild type (wt) and ml; elimination rates | A single oral dose of 5 mg diazepam with 100 mL water was given to the subjects in the morning after overnight fasting | The plasma elimination half-life values of diazepam (84.0 ± 13.7 h) and desmethyldiazepam (176.0 ± 28.9 h) in subjects of ml/ml were significantly longer than those in wt/ml subjects (62.9 ± 9.8 h for diazepam; 132.1 ± 24.9 h for desmethyldiazepam; both \( P < 0.01 \)) or those in wt/wt subjects (20.0 ± 10.8 h for diazepam; 99.2 ± 21.7 h for desmethyldiazepam; both \( P < 0.01 \)). A significant difference in the corresponding half-life values existed between the wt/ml and wt/wt subjects (\( P < 0.01 \). As expected, the slowest mean clearance of diazepam was observed in the ml/ml subjects (2.8 ± 0.9 mL/min) and the fastest in the wt/wt subjects (19.5 ± 9.8 mL/min), with the wt/ml heterozygotes having an intermediate value (7.2 ± 2.6 mL/min). |

**UM** Ultrarapid metabolizer, **NM** normal metabolizer, **EM** extensive metabolizer, **IM** intermediate metabolizer, **PM** poor metabolizer.
Our study comprehensively identified high-quality replicated pharmacogenomic evidence supporting clinical actionability for 18 medications commonly-used in the perioperative setting, and we proposed and appraised for these medications CDS summaries with actionable prescribing recommendations. We thus observed a critical mass of medications for which clinically actionable pharmacogenomic associations exist. Given the large number of these medications that a patient may be exposed to when undergoing anesthesia and postoperative care, and the high stakes of perioperative drug-related morbidities [2], our findings argue that these 18 medications deserve formal consideration for clinical implementation in developing pharmacogenomic programs, or for prospective testing in clinical utility evaluations/clinical trials. One such immediate evaluation—at our institution—is their deployment in our electronic medical record-linked pharmacogenomic software tool to support our recently-launched prospective clinical pharmacogenomic study which will examine clinical utility (clinicaltrials.gov #NCT03729180) [32] among research subjects consenting to preemptive pharmacogenomic testing in advance of their surgery. This randomized study will evaluate the actual impact of the presence of preemptively-known pharmacogenomic results prior to anesthesia and perioperative care, and will allow examination of whether knowledge of clinically ‘actionable’ patient-specific results alters clinical outcomes like adverse events and/or non response. As such, this current work lays the important foundation for future prospective testing of the potential clinical impact of pharmacogenomic genotyping and CDS delivery during perioperative care.

Until now, pharmacogenomic results have been infrequently utilized in anesthesia and critical care clinical settings [33, 34]. Barriers to clinical use not only included prior skepticism about the readiness of evidence for clinical utility examinations, but also lack of available genetic testing and reimbursement, concerns about test turnaround times, lack of integration into clinical workflows/electronic medical records, and inadequate decision-support for providers unfamiliar with genomics [15, 16, 35, 36]. This latter point—including confusion around recommendations for many pharmacogenomic drug/gene pairs—has likely slowed the adoption of pharmacogenomic testing in anesthesia, as it has in other areas. For example, preemptive RYR1 screening is not endorsed by the Malignant Hyperthermia Association of the U.S. (MHAUS) for the general population, yet it is endorsed if there is a pretest probability for MH-susceptibility [37]. Separately, CPIC guidelines clearly recommend against using triggering medications if an implicated genetic alteration in RYR1 or CACNA1S is known. Indeed, it would be difficult to find a clinician who would proceed with use of a trigger medication without at least confirmatory (e.g., contracture) testing, if a genetic alteration were known.

Recent prospective studies are beginning to address and overcome these evidence/guideline uncertainties, especially in other areas of medicine [26, 38–40]. Of particular relevance to postoperative pain management, Smith et al. recently showed that pain scores could be improved by the use of CYP2D6-informed analgesic drug guidance in intermediate and poor metabolizer chronic pain patients [41]. While it is not known whether these findings would also extend to patients receiving analgesia in the postoperative setting, these data as well as those of other emerging studies [32, 42] may begin to assert a mandate for genomic medicine/precision medicine considerations. Our study thus creates an evidence-driven decision-support
framework to enable prospective evaluation of pharmacogenomic testing in the perioperative setting (i.e., to examine the potential clinical utility of having pharmacogenomic results for key perioperative medications in advance of a patient’s surgery date).

This study took an approach to evidence appraisal that included a recognized rubric (AGREE) for considering clinical guidelines because the ultimate goal was to synthesize current pharmacogenomic evidence into CDS summaries that could be clinically deployed, embedded within EMR clinical workflows, and applied—especially to support prospective clinical utility evaluation contexts. We importantly wanted to harmonize the ultimate CDS drug/gene recommendations (when possible) with those of other available bodies, most importantly including FDA and CPIC (the latter being the world’s best-recognized pharmacogenomic guidance body). Consistently, our guidance does harmonize, reflecting the fact that like conclusions are reached by our process as those of other consensus bodies like FDA and CPIC which reflects collective agreement about the available current evidence. Small differences, such as the list of individual NSAIDs being implicated as actionable related to CYP2C9 [43], likely reflect our process’ more stringent requirement for existence of studies showing clinical outcomes differences, not just pharmacokinetic phenotypes. In other instances (e.g., BCHE/mivacurium and BCHE/ succinylcholine as actionable in our rubric and included in the FDA labels [44, 45], but without a current CPIC guideline), there is not necessarily disagreement (in fact CPIC grades this pair as “B/C”) [46] but rather that this pair has not yet risen to the level of a published guideline by CPIC. It should also be noted that CPIC recently evaluated morphine/OPRM1 and acknowledged the presence of evidence for a small increase in postoperative morphine dose requirements based on genotype, but concluded that the alteration in morphine dose was “so modest as to not be clinically actionable [47].” Our process and our AGREE reviewers instead chose to call this morphine dose difference—which has been repeatedly statistically associated with rs1799971 within this gene—as “actionable,” because clinical knowledge of pharmacogenomic information for morphine/OPRM1 at worst would be non-inferior to blinded prescribing [48] and at best could benefit prescribers especially in the critical postoperative period where pain control is so essential. Finally, within the same recent CPIC guideline [47], CYP2D6 and both hydrocodone and oxycodone were assessed. Similar to morphine and OPRM1, CYP2D6 and oxycodone rose to the level of clinical actionability in our rigorous analysis, though CPIC did not publish guidance for this gene–drug pair. Specifically, CPIC stated that it was “difficult to conclude” whether CYP2D6 affects analgesia or risk of toxicity for oxycodone. Despite a surface level difference in our recommendations, our CDS summaries for oxycodone, indeed, echo what has been suggested by CPIC. The oxycodone CDS (available in Supplemental File 4) states that there is a “potential” association between CYP2D6 and oxycodone analgesic effect, and the recommendation

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**Fig. 3  Clinical decision-support summaries for sevoflurane and succinylcholine.** These are examples of the clinical decision-support (CDS) summaries written for sevoflurane with CACNA1S/RYR1 variants, and for succinylcholine with BCHE.

| PGx Signal | Drug | Level of Evidence |
|------------|------|-------------------|
|            | Sevoflurane | Level 1 |

Your patient’s genotype is strongly associated with malignant hyperthermia (MH) susceptibility. Your patient should not be administered succinylcholine or volatile anesthetics. An alternative anesthetic plan using medications that are not known to trigger MH (such as nitrous oxide, propofol, ketamine, and nondepolarizing neuromuscular blockers) should be developed. Appropriate preparation of anesthesia workstations should also be undertaken.

Both the Malignant Hyperthermia Association of the United States (MHAUS) and the European Malignant Hyperthermia Group (EMHG) have identified distinct causative mutations in the ryanodine receptor (RYR1) gene and dihydropyridine receptor (CACNA1S) gene which are accepted as diagnostic mutations for MH susceptibility. Your patient carries one of these mutations. You may or may not wish to pursue confirmatory testing (e.g., caffeine-halothane contracture test) however, in the absence of or while awaiting such testing, your patient should be considered MH susceptible.

This guideline is consistent with MHAUS and EMHG recommendations, recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC), and FDA labeling. Genetic counseling should also be offered to your patient and his/her family members as MH susceptibility is inherited in an autosomal dominant pattern.

References: Br J Anaesth (2015) Br J Anaesth (2001) Onchuan J Rare Dis (2014) Pharmacogenet Genomics (2015) Pharmacogenet Genomics (2016)

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| PGx Signal | Drug | Level of Evidence |
|------------|------|-------------------|
|            | Succinylcholine | Level 1 |

Your patient’s genotype in the butyrylcholinesterase (BChE) gene is associated with a normal neuromuscular response to succinylcholine. Standard initial succinylcholine dosing is recommended.

It should be noted, however, that genotyping for other rare variants in the BChE gene has not been performed. Patient susceptibility to prolonged apnea due to these variants cannot be ruled out.

References: Anesthesia (1996) Anaesthesiological Journal (2015) Proc Natl Acad Sci U S A (1999) Anesthesiology (2000) Anesth Analg (2002)

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**IMPORTANT NOTE:** This information displays medications according to their pharmacogenomic likelihood of various clinical outcomes for this specific patient. Other clinical factors, including but not limited to drug-drug interactions, organ dysfunctions, and comorbidities, should be considered when determining overall appropriateness of these medications for this patient.
to providers is to “closely monitor”. In our synthesis, we particularly valued the evidence from a well-performed positive prospective study that was focused on postoperative analgesia with oxycodone [49], along with several other smaller positive supporting studies [50–52]. Notably, our CDS also cites the same negative studies cited by CPIC [53, 54]. Hence, the evidence for hydrocodone for CYP2D6 intermediate and poor metabolizers is ultimately-included, clinically actionable findings. We acknowledge, however, that candidate gene studies, most of what we uncovered in our comprehensive analysis, may bias research towards certain parts of the genome [55]. As more genome-wide association studies surrounding pharmacogenomic markers are published, we will ensure necessary updates to our CDS occur. Separately, our CDS were written with guidance to consider deviation from a “standard dose”, however, it is acknowledged that in anesthesia and perioperative analgesia many medications are typically titrated to effect. This fact will be important to keep in mind during clinical applications. An additional important consideration is that many phenotypes studied in the perioperative setting have a complex background, where both genetic and non-genetic factors interact, potentially limiting clinical utility of pharmacogenomic results. The heritability of some of these genetic factors is largely unknown, and we acknowledge the fact that patients’ genetic backgrounds may differ from the population in which pharmacogenomic studies were conducted.

### Table 4. Pharmacogenomic decision-support guideline AGREE II scores and recommendations for implementation in the perioperative setting.

| Medication | Gene | Variants | Domainsa | Scope and purpose | Rigor of development | Clarity of presentation | Applicability | Overall quality | Recommended for implementation |
|------------|------|----------|-----------|------------------|----------------------|-----------------------|--------------|----------------|--------------------------------|
| **Analgesia** | | | | | | | | | |
| Codeine | CYP2D6 | UM/NM/IM/PM | 92.2 | 93.3 | 84.4 | 80.0 | 6.5 | YES |
| Tramadol | CYP2D6 | UM/NM/IM/PM | 96.7 | 92.2 | 85.6 | 86.7 | 6.8 | YES |
| Oxycodone | CYP2D6 | UM/NM/IM/PM | 96.7 | 94.4 | 86.7 | 85.0 | 7.0 | YES |
| Morphine | OPRM1 | A118G | 90.0 | 91.1 | 83.3 | 85.0 | 6.5 | YES |
| Celecoxib | CYP2C9 | *3 allele | 100.0 | 96.7 | 93.3 | 91.7 | 7.0 | YES |
| **Anesthesia** | | | | | | | | | |
| Mivacurium | BCHE | K-variant | 93.3 | 90.0 | 87.8 | 88.3 | 6.5 | YES |
| Desflurane | RYR1 | A-variant | 93.3 | 90.0 | 90.0 | 90.0 | 6.8 | YES |
| Enflurane | CACNA1S | 40 RYR1 | 93.3 | 90.0 | 90.0 | 90.0 | 6.8 | YES |
| Halothane | RYR1 | A-variant | 93.3 | 90.0 | 90.0 | 90.0 | 6.8 | YES |
| Isoflurane | CACNA1S | 40 CACNA1S | 93.3 | 90.0 | 90.0 | 90.0 | 6.8 | YES |
| Sevoflurane | CACNA1S | 40 CACNA1S | 93.3 | 90.0 | 90.0 | 90.0 | 6.8 | YES |
| Succinylcholine | BCHE | A-variant | 94.4 | 91.1 | 85.6 | 86.7 | 6.8 | YES |
| **Antiepilepsy** | | | | | | | | | |
| Phenytoin | CYP2C9 | NM/IM/PM | 96.7 | 96.7 | 90.0 | 90.0 | 7.0 | YES |
| **Antianxiety** | | | | | | | | | |
| Diazepam | CYP2C19 | NM/IM/PM | 96.7 | 96.7 | 86.7 | 81.7 | 6.8 | YES |

*Scores in this table represent the average of the individual scores from five independent expert appraisers. The exception is the overall quality scores, which were calculated as the averages of the individual scores from four of the five appraisers, as one appraiser did not submit Overall Quality scores.

For each of the four Domains, the maximum score = 100.0. For Overall Quality, the maximum score = 7.0. UM = Ultrarapid metabolizer, NM = normal metabolizer, IM = intermediate metabolizer, PM = poor metabolizer. SD = standard deviation.
conducted. In the future, even more complex decision supports will likely be required to integrate multiple genetic loci, in addition to non-genetic factors. Finally, we acknowledge that the clinical guidance for some medications in our CDS is to closely monitor the patient, which should be done in the absence of genomic results as well. This calls into question the definition and use of the word “actionable”, which may be context-specific [56]. The idea, however, is that an “actionable” result may not require immediate action on the part of the provider. Rather, the provider may ultimately and eventually act sooner than he or she otherwise would without pharmacogenomic results.

In summary, we found that actionable pharmacogenomic evidence for perioperative medications is considerable, justifying development of evidence-integrating CDS-based implementation tools to enable future prospective investigations of the utility of pharmacogenomic information in the perioperative setting. Such subsequent work will ultimately determine the potential impact on clinical decision making and patient outcomes.

REFERENCES

1. Zheng SL, Sun J, Wiklund F, Gao Z, Wiklund F, Gao Z, Stattin P, Purcell LD, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen. Clin Cancer Res. 2009;15:1105–11.

2. Nanji KC, Patel A, Shaikh S, Seger DL, Bates DW. Evaluation of perioperative medication errors and adverse drug events. Anesthesiology. 2016;124:25–34.

3. Weiss AJ, Elixhauser A, Bae J, Encinosa W. Origin of adverse drug events in U.S. Hospitals, 2011: Statistical Brief #158. Rockville (MD): Healthcare Cost and Utilization Project (HCUP) Statistical Briefs; 2006.

4. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011;377:2215–25.

5. Mavridou P, Dimitriou V, Manataki A, Arnaoutoglou E, Papadopoulos G. Patient’s anxiety and fear of anesthesia: effect of gender, age, education, and previous experience of anesthesia. A survey of 400 patients. J Anesth. 2013;7:104–8.

6. Denborough MA. Malignant hyperthermia. 1962. Anesthesiology. 2008;108:156–66. doi:10.1097/01.anes.0000303868.38525.8c

7. Sangkuhl K, Dirksen RT, Alvarellos ML, Altman RB, Klein TE. PharmGKB summary: the Pharmacogenomics Knowledge Base (PharmGKB) and the Pharmacogenetics Research Network. Clin Pharmacol Ther. 2011;89:464–73. doi:10.1038/clpt.2010.271

8. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526:433–50.

9. Kalow W. Pharmacogenetics and anesthesia. J Am Soc Anesthesiol. 1964;25:377–87.

10. Hopkins PM, Ruffert H, Snoek MM, Girard T, Glahn KP, Ellis FR, et al. European malignant hyperthermia group guidelines for investigation of malignant hyperthermia susceptibility. Br J Anaesth. 2015;115:531–9.

11. Relling MV, Klein TE. CPLIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clin Pharmacol Ther. 2011;89:464–7.

12. van der Wouden CH, Cambon-Thomsen A, Cecchin E, Cheung KC, Davila-Fajardo CL, Deneer VH, et al. Implementing pharmacogenomics in Europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. Clin Pharmacol Ther. 2017;101:341–58.

13. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sanghvi K, Thorn CF, et al. Pharmacogenomic knowledge for personalized medicine. Clin Pharmacol Ther. 2012;92:414–7.

14. Swen JJ, Wilting I, de Goede AL, Grandia LM, Mulder H, Touw DJ, et al. Pharmacogenetics: from bench to bed. Clin Pharmacol Ther. 2008;83:781–9.

15. Borden BA, Galecki P, Wellmann R, Danahey K, Lee SM, Patrick-Miller L, et al. Assessment of provider-perceived barriers to clinical use of pharmacogenomics during participation in an institutional implementation study. Pharmacogenom. 2019;29:31–8.

16. McKinnon RA, Ward MB, Sorich MJ. A critical analysis of barriers to the clinical implementation of pharmacogenomics. Ther Clin Risk Manag. 2007;3:751–9.

17. Wellmann R, Borden BA, Danahey K, Nanda R, Polite BN, Stadler WM, et al. Analyzing the clinical actionability of germline pharmacogenomic findings in oncology. Cancer. 2018;124:3052–65.

18. Kaufman AL, Spitz J, Jacobs M, Sorrentino M, Yuen S, Danahey K, et al. Evidence for clinical implementation of pharmacogenomics in cardiac drugs. Mayo Clin Proc. 2015;90:716–29.

19. Hussain S, Kengisberg BB, Danahey K, Lee YM, Galecki PM, Ratan MJ, et al. Disease-drug database for pharmacogenomic-based prescribing. Clin Pharmacol Ther. 2016;100:179–90.
AUTHOR CONTRIBUTIONS
BAB: data acquisition, data analysis, and drafting of paper. EUH: study conception and design, data acquisition, data analysis, and drafting of paper. KD: data acquisition, data analysis. ES: data acquisition, data analysis. JLA: data analysis. MA: data analysis. RK: data analysis. SS: data analysis. TMT: data analysis. MJR: study conception and design. PHO: study conception and design, data acquisition, data analysis, and drafting of paper.

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COMPETING INTERESTS
EHJ is currently an employee of OneOme. MJR is a co-inventor holding patents related to pharmacogenetic diagnostics and receives royalties related to UGT1A1 genotyping outside of this work. All other authors declared no competing interests.

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