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A systematic review and quality assessment of the clinical validity and utility of guideline recommendations for the use of germline genetic biomarkers to individualize drug selection or dosing

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List of Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation II
API	Application Programming Interface
ARR	Absolute Risk Reduction
CPG	Clinical Practice Guideline
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPNDS	Canadian Pharmacogenomics Network for Drug Safety
CSV	Comma Separated Values
CYP	Cytochrome P450
DPWG	Dutch Pharmacogenetics Working Group
E-utilities	Entrez Programming Utilities
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EM	Extensive Metabolizer
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GDPR	General Data Protection Regulation
HIV	Human Immunodeficiency Virus
HTML	Hypertext Markup Language
IM	Intermediate Metabolizer
JSON	JavaScript Object Notation
NNG	Number Needed to Genotype
PharmGKB	Pharmacogenomics Knowledge Base
PM	Poor Metabolizer
RCT	Randomized Controlled Trials
RD	Risk Difference
TPMT	Thiopurine S-Methyltransferase
UM	Ultrarapid Metabolizer

1. Introduction

“Adverse drug reactions cause a considerable amount of morbidity and mortality. It has been estimated that in Europe approximately 5% of all hospital admissions are caused by adverse drug reactions, that 5% of hospitalized patients will experience an adverse drug reaction during their hospital stay, and that adverse drug reactions cause 197,000 deaths annually throughout the European Union” [9]. The field of genomic medicine represents one potential solution to reduce health care costs associated with adverse drug reactions and poor response to pharmacotherapy. Specifically, the field of pharmacogenetics involves using the patient’s unique genetic makeup in combination with other clinical information to create a personalized medication regimen with greater efficacy and safety for the individual patient.

The patient’s pharmacogenetic information is becoming more readily available due to advances in genomic technologies enabling more accurate, faster, and less expensive tools for pharmacogenetic testing [38]. These tests are usually ordered by a treating physician. However, a growing number of companies are entering the market that are selling pharmacogenetic tests also straight to consumers. Thus, the question is not whether pharmacogenetics information will be available but how this information should be used to define the appropriate dose or to select the appropriate drug.

Pharmacogenomics research has uncovered an abundance of clinically relevant markers including both acquired (somatic) and inherited (germline) mutations. Somatic mutations are often attributed to treatment efficacy e.g., in cancer therapy, whereas germline mutations are used to identify patients at highest risk of developing serious adverse events. The U.S. Food and Drug Administration (FDA) currently lists 300 approved drugs with pharmacogenomic information in their labelling [56]. The pharmacogenomic information that is included in some, not all, of the product labels specifies dose adjustments or selection of appropriate drugs based on the genetic biomarker information. For example, the presence or absence of somatic mutations in the patient’s cancer cells determines whether specific targeted anticancer therapies are useful and therefore are indicated or not. The

required ‘companion diagnostic’ test will then become a form of gatekeeper for the treatment decision.

However, beyond companion diagnostics, the knowledge often lacks how the physician should deal with genotype data in terms of evidence-based stratification or individualization of drug therapy. Some pharmacogenetic dosing and drug selection recommendations are available in drug labels. Moreover, guidelines have been developed by consortia such as the Dutch Pharmacogenetics Working Group (DPWG), the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and by professional societies [58]. Routine adoption of pharmacogenetic tests requires evidence of their clinical effectiveness.

To develop evidence-based clinical practice guidelines for pharmacogenetic testing or to perform systematic reviews like this, it is necessary to screen databases with hundreds of publications in order to carefully extract the data relevant to a specific question. This time-consuming process impedes the implementation of new scientific findings in clinical practice. Therefore, a problem-solving strategy and the conception of a tool to promote and accelerate scientific work was developed and implemented during the course of this study. It enables scientists to automatically search databases and extract relevant information for short-term updates.

Aims of the study

This study had three main objectives.

– The first objective was to systematically assess the quality of the scientific evidence on which the guideline recommendations are based. We addressed the question of whether the scientific evidence is strong enough in terms of clinical validity and clinical utility to justify the guideline recommendations.
– The second objective was to systematically assess the methodological quality of pharmacogenetic guidelines. We examined the question of whether the overall quality of each pharmacogenetic guideline is sufficient and thus can be recommended for use in clinical practice by assessing its scope and purpose, stakeholder involvement, clarity of presentation, rigor of development, applicability, and editorial independence.
– With regard to the methodology, a third objective was to develop a software tool that supports the researchers in extracting relevant data from databases and thus accelerates the scientific work.

2. Methods

2.1. Data Search

A protocol on PROSPERO (registration CRD42016046258) was prepared and registered. Methods were based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Panic *et al.*, 2013). A search was conducted on MEDLINE (via PubMed), and EMBASE (via Ovid) for articles using strict inclusion and exclusion criteria. No language or date of publication constraints were applied. The primary search strategy was developed in PubMed using the following combination of key words: (dose OR dosing OR therapy) AND (recommendation OR guideline OR algorithm) AND (pharmacogenetic OR pharmacogenomic OR pharmacogenomics OR genotyping). The search was translated into EMBASE using database-specific controlled terms and key words in the appropriate search fields. Moreover, the Pharmacogenomics Knowledge Base (PharmGKB) database [58] and the International Guideline Library [24] for published pharmacogenetic drug dosing guidelines were searched.

2.2. Article Selection

Titles and abstracts were reviewed by two independent reviewers. Full text evaluations were done where the certainty of meeting the criteria was unclear.
The inclusion criteria were as follows:

- The article must be a guideline, i.e., it includes recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms.
- The selected article must contain guideline recommendation for a change in drug, drug dose, or drug monitoring based on at least one genetic variant (polymorphism) in the patient's germline genome.

Exclusion criteria consisted of articles that did not meet these inclusion criteria or did not report the guideline in full, e.g., conference abstracts. If there were several versions of a guideline then only the latest (valid) version was considered.

2.3. Assessment of the Level of Evidence and the Strength of Recommendation

Based on the research evidence used in the guidelines, the level of evidence as presented in Table 1 and the strength of recommendation (Table 3) for each genetic marker-drug pair were re-evaluated by applying predefined scales published by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative Working Group. This work focuses on two key questions, namely the clinical validity and the clinical utility [54]:

1. Clinical validity: How well do particular genetic markers predict pharmacokinetics (absorption, metabolism, excretion) or pharmacodynamics (efficacy) of a specific drug and do factors such as race/ethnicity affect these associations?
2. Clinical utility: Do the benefits (improved outcomes, i.e., better symptom relief, shorter time of response, increased survival, fewer adverse drug reactions) outweigh the harms when the pharmacogenetic test is used to influence patient management?

Further classification criteria for grading the quality of studies are listed in Table 2.

Table 1 provides a hierarchy of study designs for assessing quality of individual studies.

Level	Clinical validity	Clinical utility
1	Well-designed longitudinal cohort study	Meta-analysis of randomized controlled trials (RCT)
2	Well-designed case-control study	A single randomized controlled trial
3	Lower quality case-control and cross-sectional study	Controlled trial without randomization, cohort or case-control study
4	Case series, unpublished and/or non-peer reviewed research, clinical laboratory or manufacturer data, Consensus guidelines, expert opinion	Case series, unpublished and/or non-peer reviewed studies, clinical laboratory or manufacturer data, Consensus guidelines, expert opinion

Table 2 provides additional criteria adopted for grading the quality of studies, as defined by the EGAPP working group [54] and used in this analysis.

Clinical validity	Clinical utility
Clear description of the disorder/phenotype and outcomes of interest ▪ Status verified for all cases ▪ Appropriate verification of controls ▪ Verification does not rely on index test result ▪ Prevalence estimates are provided Adequate description of study design and test/methodology ▪ Adequate description of the study population ▪ Inclusion/exclusion criteria ▪ Sample size, demographics ▪ Study population defined and representative of the clinical population to be tested ▪ Allele/genotype frequencies or analyte distributions known in general and subpopulations Independent blind comparison with appropriate, credible reference standard(s) ▪ Independent of the test ▪ Used regardless of test results ▪ Description of handling of indeterminate ▪ Results and outliers ▪ Blinded testing and interpretation of results Analysis of data ▪ Possible biases are identified, and potential impact discussed ▪ Point estimates of clinical sensitivity and specificity with 95% confidence intervals ▪ Estimates of positive and negative predictive values	Clear description of the outcomes of interest ▪ What was the relative importance of outcomes measured; which were prespecified primary outcomes and which were secondary? Clear presentation of the study design ▪ Was there clear definition of the specific outcomes or decision options to be studied (clinical and other endpoints)? ▪ Was interpretation of outcomes/endpoints blinded? ▪ Were negative results verified? ▪ Was data collection prospective or retrospective? ▪ If an experimental study design was used, were subjects randomized? Were intervention and evaluation of outcomes blinded? ▪ Did the study include comparison with current practice/empirical treatment (value added)? Intervention ▪ What interventions were used? ▪ What were the criteria for the use of the interventions? Analysis of data ▪ Is the information provided sufficient to rate the quality of the studies? ▪ Are the data relevant to each outcome identified? ▪ Is the analysis or modeling explicit and understandable? ▪ Are analytic methods prespecified, adequately described, and appropriate for the study design? ▪ Were losses to the follow-up and resulting potential for bias accounted for? ▪ Is there assessment of other sources of bias and confounding? ▪ Are there point estimates of impact with 95% CI? ▪ Is the analysis adequate for the proposed use?

Table 3 shows the EGAPP criteria for assessing the body of evidence for the two components of evaluation (i.e., clinical utility and clinical validity) also used in our study [54].

Table 3 Grading the quality of evidence for the two components of evaluation.

Level	Clinical validity	Clinical utility
Convincing	Well-designed and conducted studies in representative population(s) that measure the strength of association between a genotype or biomarker and a specific and well-defined disease or phenotype. ▪ Systematic review/meta-analysis of Level 1 studies with homogeneity ▪ High quality Level 1 cohort study ▪ Several level 2 studies with homogeneity	Well-designed and conducted studies in representative population(s) that assess specified health outcomes ▪ Systematic review/meta-analysis of randomized controlled trials showing consistency in results ▪ At least one large randomized controlled trial (Level 2)
Adequate	▪ Systematic review of lower quality studies ▪ Review of Level 1 or 2 studies with heterogeneity ▪ Case-control study with good reference standards	▪ Systematic review with heterogeneity ▪ One or more controlled trials without randomization (Level 3) ▪ Systematic review of Level 3 cohort studies with consistent results
Inadequate	▪ Single case-control study (nonconsecutive cases or lacks consistently applied reference standards) ▪ Single Level 2 or 3 cohort/case-control study (reference standard defined by the test or not used systematically or study not blinded) ▪ Level 4 data	▪ Systematic review of Level 3 quality studies or studies with heterogeneity ▪ Single Level 3 cohort or case-control study ▪ Level 4 data

Finally, an overall assessment of the net benefit and the certainty of evidence was made based on the evidence report for clinical validity and clinical utility, according to Table 4.

Table 4 Recommendations based on certainty of evidence, magnitude of net benefit, and contextual issues [54].

Level of certainty	Recommendation
High or moderate	**Recommend for** . . . . . . if the magnitude of net benefit is substantial, moderate, or small, unless additional considerations warrant caution. Consider the importance of each relevant contextual factor and its magnitude or finding. **Recommend against** . . . . . . if the magnitude of net benefit is zero or there are net harms. Consider the importance of each relevant contextual factor and its magnitude or finding.
Low	**Insufficient evidence** . . . . . . if the evidence for clinical utility or clinical validity is insufficient in quantity or quality to support conclusions or make a recommendation. Consider the importance of each contextual factor and its magnitude or finding.

Each guideline was independently reviewed by two authors using predefined criteria summarized in Tables 1-4. If necessary, a third review author was consulted to resolve inconsistencies.

Table 5 lists genetic markers and their phenotypical characteristic as well as percentage distribution between the metabolizers, shown in the four columns.

Table 5 Classification metabolizer phenotype and frequencies in the Caucasian population.

	Poor metabolizer, PM:	**Intermediate metabolizer, IM:**	**Extensive metabolizer, EM:**	**Ultrafast metabolizer, UM:**
	No enzyme activity	**Decreased enzyme activity**	**Normal enzyme activity**	**Very high enzyme activity**
CYP2D6 **diplotype (Frequency)**	2 nonfunctional alleles (~5-10%)	1 reduced and 1 nonfunctional allele (~2-11%)	2 alleles encoding full or reduced function or 1 functional allele + 1 nonfunctional or reduced function allele (~77-92%)	More than two copies of functional alleles (~1-2%)
CYP2C9 **diplotype (Frequency)**	2 reduced function alleles (~1%)	1 functional allele + reduced function allele (~8%)	2 functional alleles (~ 91%)	
CYP2C19 **diplotype (Frequency)**	2 nonfunctional alleles (~4%)	1 functional allele + 1 nonfunctional allele or 1 increased activity allele + 1 nonfunctional allele (~18%)	2 functional alleles (~49%)	2 increased activity alleles or 1 increased activity allele + 1 functional allele (~26%)
CYP3A5 **diplotype (Frequency)**	2 nonfunctional alleles (~68%)	1 functional + 1 nonfunctional allele (~29%)	2 functional alleles (~3%)	
TPMT **diplotype (Frequency)**	2 nonfunctional alleles (~0,1-0,5%)	1 nonfunctional + 1 functional allele (~7-14%)	2 functional alleles (~86-93%)	
UGT1A1 **diplotype (Frequency)**	2 nonfunctional alleles (~11%)	1 normal functional or increased activity allele +1nonfunctional (~46%)	2 normal functional and / or increased activity allele (~43%)	
DPYD **diplotype (Frequency)**	2 nonfunctional alleles or 2 reduced function alleles or 1 nonfunctional + 1 reduced function allele (PM + IM ~3-5%)	1 functional + 1 nonfunctional or reduced function allele	2 functional alleles (~95-97%)	

2.4. Guideline Quality Assessment

The Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument was applied to assess the quality of the guidelines [10]. The AGREE II instrument consists of 23 items organized in six domains, followed by two items of global score (overall assessment). Each domain embraces a unique dimension in the clinical practice guideline (CPG) quality: scope and purpose, stakeholder(s) involvement, clarity of presentation, rigor of development, applicability, and editorial independence. The overall assessment includes a score for the general quality of the CPG and an assessment whether it is recommended for use in clinical practice. Each item was assessed using a 7-point scale (from 1 “strongly disagree” to 7 “strongly agree”).

Each guideline in this study was independently reviewed by three assessors.

2.5. Diagnostic Test Evaluation

Measures of Diagnostic Accuracy

The discriminative potential of a pharmacogenetic test can be quantified by the measures of diagnostic accuracy such as sensitivity and specificity, likelihood ratios, and the area under the ROC curve. The first step in the calculation of most of these variables is to make a 2x2 table with groups of subjects divided according to the outcome in columns, and categories according to the genetic test in rows (Table 6).

Table 6 Contingency table for the calculation of clinical validity measures.

		Event	***No event***
Pharmacogenetic Test	Carrier of risk allele	a (true positive)	c (false positive)
	Non-carrier of risk allele	b (false negative)	d (true negative)

Sensitivity	a / (a+b)
Specificity	d / (c+d)
Positive likelihood ratio	Sensitivity / (1-Specificity)
Negative likelihood ratio	(1-Sensitivity) / Specificity
Diagnostic odds ratio	= (a/b) / (c/d)

Number Needed to Genotype

Measures such as the number needed to genotype (NNG) are of high importance for health care decision makers. Epidemiological evaluations can be based on a 2x2 contingency table, listing the number of carriers and noncarriers of risk genotypes who show or do not show a certain health outcome (Table 7). The NNG defines the number of people that need to be genotyped to prevent one death or adverse event [27].

Table 7 Contingency table for the calculation of clinical utility measures.

		Event	***No event***
Intervention	Genotyping	a	b
	Control	c	d

Genotyping group event rate	a/(a+b)
Control group event rate	c/(c+d)
Absolute risk reduction (ARR)	control group event rate - genotyping group event rate
Number needed to genotype (NNG)	1/ARR

2.6. Implementing a Software Tool for Data Retrieval and Updating

The assessment of the different sources and papers for the large number of drugs related to this thesis is time consuming and repetitive. The clinical guidelines are updated continuously, therefore changes would require considerable effort. In order to automate recurring tasks and to reduce ongoing effort, methods based on the programming language Python have been developed that retrieve data from web interfaces, filter and structure them for the purposes of this thesis and export the data in suitable formats for further use.

The script language Python works on all common operating systems and uses an easy and efficient syntax. Thus, the developed methods are available to other scientists and can be used for similar purposes with little effort. The methods developed in this thesis consist of two parts:

- Sources
- Output

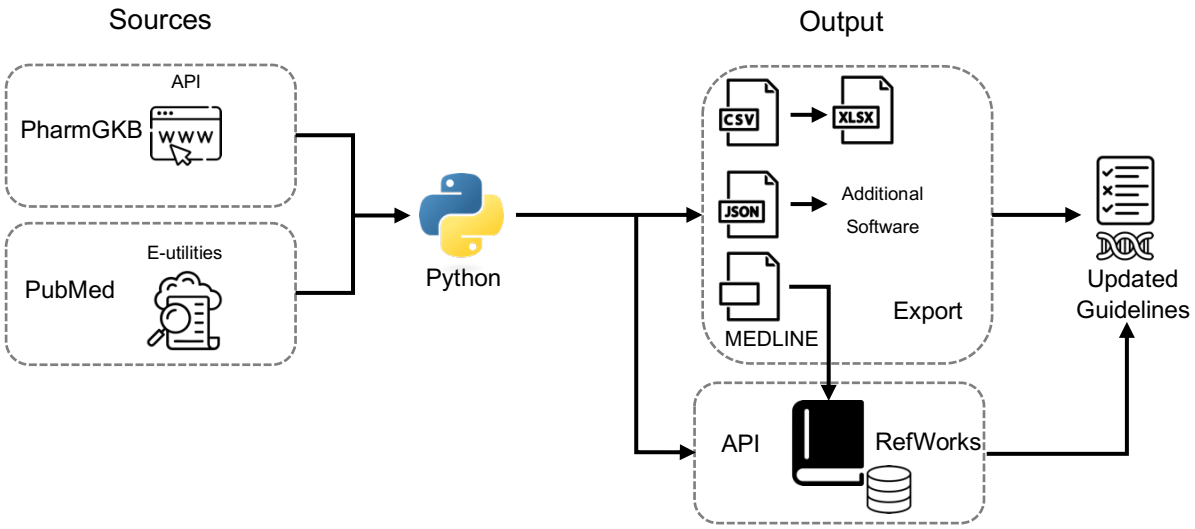

Figure 1 Python scripting supports the data retrieval, combination and extraction of relevant literature information and exports data to multiple file formats and into the reference management software RefWorks.

Sources

PubMed

According to the article selection method in section 2.2 the MEDLINE database is used via PubMed. The search string returns more than 1.200 references. To export PubMed data, the Entrez Programming Utilities (E-utilities) are available. The call of the standardized URL accepts parameters to refine the search and set the output format. For the purpose of this thesis, two of the nine utilities were used, ESearch and EFetch. Details about the utilities can be found at [49]. With ESearch full texts can be found based on title and year, which can be used to automatically export the reference list of CPIC guidelines from the MEDLINE database. EFetch accepts a list of PubMed IDs and provides the complete export of the metadata of references, e.g., in order to transfer them to the reference management system.

PharmGKB

The PharmGKB curates pharmacogenomic-based drug dosing guidelines and offers an extensive set of information and data published via the website, the public application programming interface (API) and JavaScript Object Notation (JSON) downloads. Clinical annotations, which include relationships between certain genetic variants and the medication, are the main focus. These annotations are filtered to include drug related recommendations only. This is used for the PubMed IDs of all references in the PharmGKB database to call EFetch and receive an

exportable list of the publications from the PubMed database that can be exported to a reference management system.

The API is available at api.pharmgkb.org, the following endpoints are used:

- */v1/site/publications/pharmgkb*
  Filtered by “type”: “guideline” for getting all PharmGKB publications related to clinical guideline annotations.
- */v1/site/guidelinesByDrugs*
  Filtered by “recommendation”: “true” for getting all guidelines annotations that include recommendations for drug dosing. Each annotation ID is used for the following endpoint.
- */v1/data/guideline/<AnnotationID>*
  The PharmGKB guidelines annotations propose dosing recommendation dependent on certain genotypes. The data is presented in a Hypertext Markup Language (HTML) formatted table which requires further steps to be extracted. The *pandas* library implements the functionality to convert HTML data into Python data structure. Three values are of interest: genotype, therapy recommendation, and rationale. These are mapped to the according table columns of the PharmGKB dosing recommendation.

Output

Automatic Table Data

The output of one of the Python scripts is a comma separated values file (CSV). Microsoft Excel is used for data visualization with tables. With Excel it is possible to create a table template and import the data dynamically from CSV files. With this approach, data can be easily imported into existing projects. This automatic process replaces the manual and tedious work to format tables and keeping data up to date. Changes to the template can be propagated at any time by recreating the table using the newest CSV file after running Python script. The data from PharmGKB is automatically extracted and combined to create the structure of Table 9 with the columns drug, gene, guideline, genotype, recommendation, rationale and level of evidence. CSV is a very common file format and is compatible with other software tools.

PRISMA

Another script supports the search strategy and evaluation of the values required for the flow diagram of the PRISMA systematic review. The references from the MEDLINE search are merged with the references from the PharmGKB publications list.

- Using the PubMed ID, a unique list is guaranteed since duplicates are automatically removed by the software tool. Although the current implementation uses PubMed and PharmGKB, the merge of the references from the electronic database search could be expanded to other sources such as EMBASE or the International Guideline library as well. If the databases do not provide the PubMed ID, the ESearch API can be used to find the ID based on title, digital object identifier, authors, and other metadata.
- The references are screened as part of this second step. This is especially effortful and requires sufficient data management. Therefore, the RefWorks reference management is used as a database. RefWorks allows to define up to 15 customized data fields per publication, e.g., for describing the clinical utility, clinical validity, hierarchies of data sources or major findings. Custom tags and folders can be used to classify each publication and structure or group the data. A big advantage of RefWorks lies in the availability of the API that can be used to further automate the literature management. Even without programming skills, MEDLINE references can be exported to a PubMed file that can be imported into RefWorks.

- Using the MEDLINE database, RefWorks and PharmGKB API would allow to programmatically extract the following values for the PRISMA flow diagram:
    - *n = {} records identified through PubMed database searching.*
      Count number of entries from ESearch result.
    - *n = {} records identified through PharmGKB database searching.*
      Count number of published recommendations via API.
    - *n = {} records after duplicates removed.*
      The Python script matches the records by PubMed ID and returns a list with unique entries.
    - *n = {} full-text assessed for eligibility.*
      Assessment of full-texts via RefWorks, therefore value is calculated by using the API and fetching the total number of records.
    - *n = {} publications with genotype-stratified prescribing recommendations for n = {} drugs included.*
      Publications with recommendations are labeled accordingly within RefWorks, such that the API call for records can be filtered by this attribute. In RefWorks, a folder is created for each drug. Counting the total number of folders via API returns the number of drugs.

3. Results

3.1. Results of the Systematic Literature Search

The systematic search, dated February 28, 2020 (Figure 2) revealed 32 guideline publications that met our inclusion criteria.

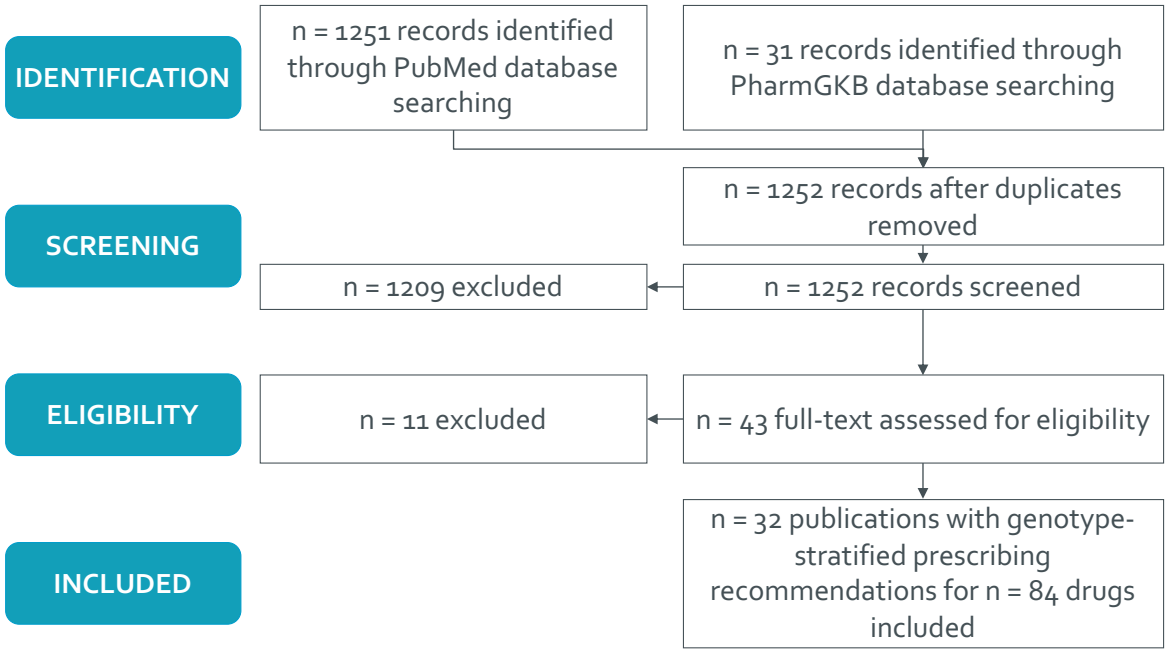

Figure 2 Search strategy, PRISMA flow diagram.

In the guidelines, 84 drugs with at least one recommendation for adjusting the dosage or choosing a different drug based on germline markers in a total of 21 genes were identified. The individual guideline statements extracted from the 32 publications are summarized in Table 9. This analysis overall assessed 106 individual genetic-marker drug pairs. By far the most frequently mentioned genes in the guidelines belong to the group of cytochrome P450 (CYP) encoding genes; 29% and 16% of the drugs were related to genetic markers in *CYP2D6* and *CYP2C19*, respectively. The network graph **(**Figure 3**)** shows the marker genes and the related drugs that were identified in the guideline publications.

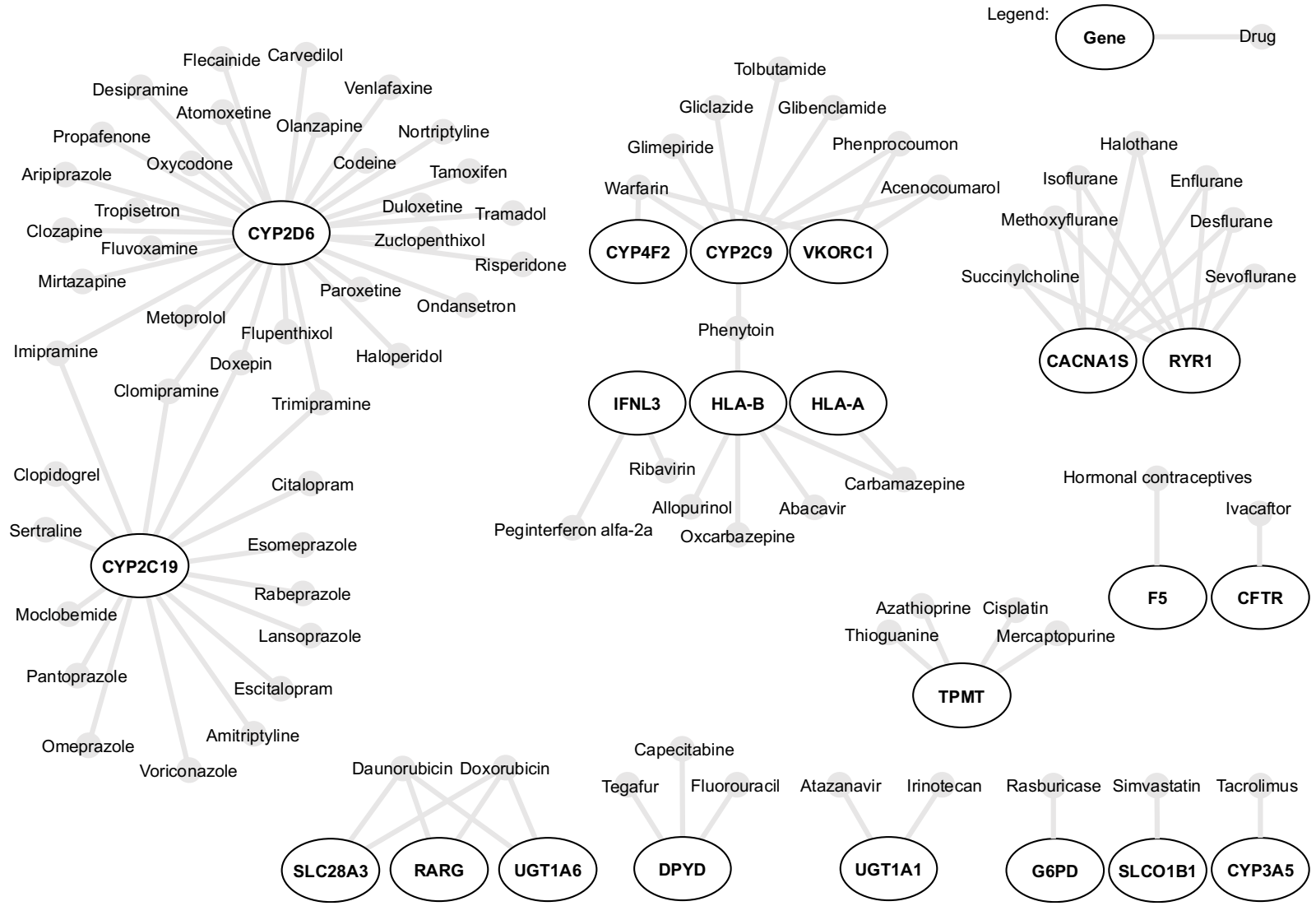

Figure 3 Marker genes with related drugs mentioned in the guideline publications.

3.2. Re-Evaluation of the Level of Evidence and the Strength of Recommendation using EGAPP Criteria

Almost all guidelines identified sufficient evidence for an association of germline genetic markers with kinetics, efficacy or adverse reactions of the respective drug, i.e., clinical validity. However, in terms of clinical utility, a significant gap between the recommendations and the evidence on which they are based was found. For only 15 drugs, the guideline developers identified clinical trials that compared health outcomes in patients using genetically versus clinically guided drug therapy. Table 8 lists the drugs mentioned in pharmacogenetic guidelines for which the guideline developers have identified evidence related to clinical utility.

Table 8 Drugs mentioned in following guidelines which considered clinical utility studies.

Drug	Genetic marker	Guideline	Clinical validity	Clinical utility
Abacavir	HLA-B*5701	DPWG 2019 Abacavir is contra-indicated for *HLA-B**5701-positive patients.	CONVINCING evidence that HLA-B*57:01 is more frequent in clinically diagnosed abacavir hypersensitivity patients, compared to abacavir tolerant patients. Discriminative accuracy of the genetic marker determined from the studies to which the guidelines refer [median (range)]: Sensitivity 46% (14%-78%) Specificity 99% (96%-100%) PPV 82% (61%-100%) NPV 90% (85%-96%).	CONVINCING evidence of reduced incidence of abacavir hypersensitivities if abacavir is not used in HLA-B*5701 allele carriers. Estimate of the number needed to genotype determined from the studies to which the guidelines refer [mean (range)]: NNG 21 (19-23).
	HLA-B*5701	CPIC 2014 In individuals with the *HLA-B**57:01 variant allele, abacavir is not recommended and should be considered only under exceptional circumstances.		CONVINCING evidence of reduced incidence of abacavir hypersensitivities if abacavir is not used in HLA-B*5701 allele carriers. Estimate of the number needed to genotype determined from the studies to which the guidelines refer [mean (range)]: NNG 17 (9-23).
Acenocoumarol	VKORC1	DPWG 2019 Patients with the VKORC1 -1639 (rs9923231) AA genotype should be given 50% of the standard initial dose of acenocoumarol and undergo more frequent INR monitoring. There is no recommendation for patients with the VKORC1 -1639 AG genotype.	CONVINCING Evidence of a higher risk of overanticoagulation in variant genotypes with concomitant use of NSAID's (CYP2C9 inhibitor), but no significantly higher risk of bleeding. Considerable evidence of a strong association between CYP2C9 variant alleles and a reduced clearance of AC and therefore, lower required dose regimen.	ADEQUATE evidence of significant association between CYP2C9 genotype-guided dosing and a higher percentage of patients with steady dose and time in the therapeutic INR range. Estimate of the number needed to genotype determined from the studies to which the guidelines refer [mean (range)]: NNG 45 (7-112)
Allopurinol	HLA-B*5801	CPIC 2016 Allopurinol is contraindicated in individuals with the HLA-B*58:01 variant allele	CONVINCING evidence that HLA-B*58:01 is more frequent in patients with allopurinol-induced severe cutaneous adverse reactions. Discriminative accuracy of the genetic marker determined from the studies to which the guidelines refer [median (range)]: Sensitivity 66% (33%-100%) Specificity 89% (87%-100%) PPV 12% (2%-22%) NPV 100% (100%-100%).	ADEQUATE evidence of reduced incidence of severe allopurinol hypersensitivity reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, if allopurinol is not used in HLA-B*5801 allele carriers. Estimate of the number needed to genotype determined from the study to which the CPIC guideline refers: NNG 417 (Asian population).
	HLA-B*5801	ACR 2012 *HLA-B**5801 positive individuals of Korean descent with stage 3 or worse CKD, or of Han Chinese or Thai extraction irrespective of renal function are recommended an alternative prescription to allopurinol.		
Azathioprine	TPMT	CPIC 2018 TPMT PM (2 nonfunctional *TPMT* alleles): reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines; TPMT IM (one functional plus one nonfunctional allele): Start at	CONVINCING Evidence of significant association between TPMT (PM, IM) genotype and risk of adverse drug reaction such as myelosuppression. Discriminative accuracy of the genetic marker determined from the studies to which the guidelines refer [median (range)]:	CONVINCING Evidence of significant benefit of TPMT-based dosing to reduce toxicity and maintain drug efficacy. Estimate number needed to genotype determined from the study to which the guideline refers: NNG 189.

continued

Table 8 (continued) Drugs mentioned in following guidelines which considered clinical utility studies.

Drug	Genetic marker	Guideline	Clinical validity	Clinical utility
		30-70% of target dose and titrate based on tolerance.	Sensitivity 23% (5%- 91%) Specificity 97% (75%- 100%) PPV 54% (13%-100%) NPV 86% (60%-98%)	
	TPMT	DPWG 2019 TPMT PM (2 nonfunctional *TPMT* alleles): Choose an alternative or start with 10% of the standard dose; TPMT IM (one functional plus one nonfunctional allele): Start with 50% of the standard dose; adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness.		Not applicable
Capecitabine	DPYD	CPIC 2017 Alternative drug for patients who are DPYD poor metabolizers with an activity score of 0. In those who are poor metabolizers with an activity score of 0.5, an alternative drug is also recommended	CONVINCING Significant association between DPYD (PM, IM) genotype and risk of toxicity such as myelosuppression and skin toxicity.	Not applicable
	DPYD	DPWG 2019 An alternative drug or reduction in dose is recommended for patients with DPYD activity scores of 0.0, 1.0 and 1.5.	ADEQUATE Evidence of significant association between DPYD (PM, IM) genotype and risk of toxicity such as myelosuppression and skin toxicity.	ADEQUATE evidence that DPYD*2A genotype-guided dosing results in adequate systemic drug exposure. Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 10 (9-10)
Carbamazepine	HLA-B	Canadian Pharmacogenomics Network for Drug Safety 2014	CONVINCING Evidence of significant association between HLA-B*15:02 genotype and IDR risk like CBZ- induced Stevens- Johnson syndrome or toxic epidermal necrolysis.	ADEQUATE Carbamazepine should not be prescribed for CBZ-naive patients who carry at least one HLA-B*15:02 allele.
	HLA-B	CPIC 2017 An alternative drug for carbamazepine-naive patients carrying at least one copy of either *HLA-B*15:02* or *HLA-A*31:01* should be used due to the association of those alleles with an increased risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In addition, *HLA-A*31:01* is associated with an increased risk of drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE).		ADEQUATE Evidence of significant benefit of prospective screening of HLA-B*15:02 and therefore prevention of carbamazepine-induced SJS/TEN. Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 227 (38-415).
	HLA-A	CPIC 2017	ADEQUATE Evidence of significant association between HLA-A*31:01 genotype and IDR risk like CBZ- induced hypersensitivity syndrome or maculopapular exanthema.	Not applicable

continued

Table 8 (continued) Drugs mentioned in following guidelines which considered clinical utility studies.

Drug	Genetic marker	Guideline	Clinical validity	Clinical utility
Clopidogrel	CYP2C19	CPIC 2013 Alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers if there is no contraindication.	ADEQUATE Evidence of significant association between CYP2C19 (PM, IM) genotype and lack of efficacy due to reduced plasma concentrations of the active metabolite.	Not applicable
	CYP2C19	DPWG 2019 Avoid clopidogrel use in patients who are CYP2C19 poor metabolizers and are undergoing percutaneous coronary intervention, stroke or TIA. For CYP2C19 intermediate metabolizers who are undergoing percutaneous coronary intervention, stroke, or TIA, choose an alternative drug or double the dose to 150 mg/day (600 mg loading dose). No action is required for patients who are CYP2C19 ultra-rapid metabolizers	CONVINCING evidence of significant association between CYP2C19 (PM, IM) genotype and lack of efficacy due to reduced plasma concentrations of the active metabolite and therefore elevated risk of adverse cardiovascular events.	ADEQUATE evidence that patients would profit from a genotype guided dosing regimen to significantly reduce the rate of major adverse cardiovascular events. Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 18 (16-20)
Escitalopram	CYP2C19	CPIC 2018 An alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 ultrarapid metabolizers should be used. For CYP2C19 poor metabolizers, consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.	CONVINCING Evidence of significant association between CYP2C19 UM genotype and lower serum concentration of escitalopram. CONVINCING Evidence of significant association between CYP2C19 genotype and pharmacokinetics of escitalopram like elevated plasma concentrations concerning PM with risk of ADR and lower serum concentration in UM. Evidence of significant association between CYP2C19 PM genotype and risk of adverse drug reaction.	Not applicable
	CYP2C19	DPWG 2019 Do not exceed the below mentioned doses for intermediate metabolizer (for IM = 75% of the standard maximum dose) and poor metabolizer (for PM = 50% of the standard maximum dose). For CYP2C19 ultrarapid metabolizer, the recommendation is to avoid escitalopram.	INADEQUATE evidence of a significant association between CYP2C19 genotype and pharmacokinetics of escitalopram.	INADEQUATE Evidence of significant association between CYP2C19 and CYP2D6 genotype and ADR. Evidence of significant association between CYP2C19 UM (*17/*17) genotype and reduced plasma serum levels therefore lack efficacy.
Fluorouracil	DPYD	DPWG 2019 An alternative drug to fluorouracil is recommended for patients with a DPYD activity score of 0. For patients with a DPYD activity score of 1 or 1.5, start with 50% of the standard dose or choose an alternative drug; adjustment of subsequent doses should be guided by toxicity and effectiveness	CONVINCING Evidence of significant association between DPYD genotype (PM, IM) and risk of toxicity (myelosuppression, gastrointestinal and skin toxicity).	ADEQUATE Evidence of significant benefit of DPYD genotyping and dose reduction to reduce adverse side effects before administering fluorouracil. Estimate number needed to genotype determined from the study to which the guideline refers: NNG 101
	DPYD	CPIC 2017 Patients who are intermediate metabolizers with an activity score of 1 or 1.5 should receive a dose reduction of 50%. Patients with the c.[2846A>T];[2846A>T] genotype may require a	CONVINCING Evidence of significant association between DPYD genotype (PM, IM) and risk of toxicity (myelosuppression, gastrointestinal and skin toxicity).	INADEQUATE Evidence of significant benefit of DPYD genotyping and dose reduction to reduce adverse side effects before administering fluorouracil.

continued

Table 8 (continued) Drugs mentioned in following guidelines which considered clinical utility studies.

Drug	Genetic marker	Guideline	Clinical validity	Clinical utility
		>50% dose reduction. Patients who are intermediate metabolizers with an activity score of 1 or 1.5 should receive a dose reduction of 50%. Patients with the c.[2846A>T];[2846A>T] genotype may require a >50% dose reduction.		Estimate number needed to genotype determined from the study to which the guideline refers: NNG 101
Lansoprazole	CYP2C19	DPWG 2019 For CYP2C19 ultrarapid metabolizers who are undergoing *H. pylori* eradication therapy, use a 4-fold higher dose. For CYP2C19 ultrarapid metabolizers with other indications, be alerted to reduced effectiveness and, if necessary, use a 4-fold higher dose.	ADEQUATE evidence of significant association between CYP2C19 genotype and the therapeutic effect and efficacy of lansoprazole on erosive reflux esophagitis.	INADEQUATE evidence for significant improving of eradication rates with pharmacogenomics-based tailored treatment. Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 8 (4-12)
Mercaptopurine	TPMT	DPWG 2019 Select an alternative drug or reduce the initial dose of mercaptopurine for patients that are TPMT poor metabolizers and reduce initial dose for patients that are TPMT intermediate metabolizers. Select an alternative drug or reduce the initial dose of mercaptopurine for patients that are NUDT15 poor metabolizers and reduce initial dose for patients that are NUDT15 intermediate metabolizers.	CONVINCING Evidence of significant association between TPMT genotype and risk of toxicity (myelosuppression) of mercaptopurine.	Not applicable
	TPMT	CPIC 2016 Consider an alternate agent or extreme dose reduction of mercaptopurine for patients who are TPMT or NUDT15 poor metabolizers. Start at 30-80% of target dose for patients who are TPMT or NUDT15 intermediate metabolizers.	CONVINCING Evidence of significant association between TPMT genotype and risk of toxicity (myelosuppression) of mercaptopurine.	INADEQUATE Significant benefit of genotyping for the major TPMT variant alleles as a valuable tool to prevent AZA toxicity.
Phenprocoumon	VKORC1	DPWG 2019 Patients with the VKORC1 -1639 (rs9923231) AA genotype is recommended to be given 50% of the standard initial dose of phenprocoumon and more frequent monitoring of INR.	ADEQUATE Evidence of significant association between CP2C9 (PM, *2/*2, *2/*3, *3/*3) genotype and risk of adverse drug reactions. CONVINCING evidence of significant association of phenprocoumon maintenance dosage and polymorphisms in the VKORC1 gene. ADEQUATE Evidence of significant association between VKORC1 (rs9934438 AA) genotype and risk of adverse drug reaction.	INADEQUATE evidence of significant benefit of genotype-guided dosing in order to increase the mean percentage of time in the therapeutic INR range Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 20 (7-40)
Tacrolimus	CYP3A5	DPWG 2019 Increased doses of tacrolimus are recommended for CYP3A5 heterozygous and homozygous expressors and adjusted as needed.	CONVINCING Evidence of significant association between CYP3A5 (IM, EM) genotype and lack of efficacy due to reduced plasma concentrations. CONVINCING evidence of significant association between CYP3A5 expression and affection of	INADEQUATE evidence of pharmacogenetic adaptation of the daily dose of tacrolimus is associated with improved achievement of the target.

continued

Table 8 (continued) Drugs mentioned in following guidelines which considered clinical utility studies.

Drug	Genetic marker	Guideline	Clinical validity	Clinical utility
			tacrolimus pharmacokinetics thus higher mean tacrolimus daily doses.	Estimate number needed to genotype determined from the study to which the guideline refers: NNG 8
	CYP3A5	CPIC 2018 Increase the starting dose by 1.5 to 2 times the recommended starting dose in patients who are CYP3A5 intermediate or extensive metabolizers, though total starting dose should not exceed 0.3 mg/kg/day. Therapeutic drug monitoring should also be used to guide dose adjustments.	CONVICING Evidence of significant association between CYP3A5 (IM, EM) genotype and lack of efficacy due to reduced plasma concentrations.	ADEQUATE Evidence of significant benefit of CYP3A5 genotyping for tacrolimus dose adjustments in order to improve achievement of target drug blood levels. Estimate number needed to genotype determined from the study to which the guideline refers: NNG 8
Voriconazole	CYP2C19	DPWG 2019 Patients who are CYP2C19 poor metabolizers should receive 50% of the standard dose, and CYP2C19 ultrarapid metabolizers should receive a 1.5 times higher initial dose. Monitor voriconazole plasma concentrations for CYP2C19 poor, intermediate and ultrarapid metabolizers.	INADEQUATE evidence of a significant association between CYP2C19 genotype and pharmacokinetics (plasma concentrations, clearance) of voriconazole.	INADEQUATE evidence for significant benefits of genotype-directed dosing algorithms to reach the voriconazole target range sooner. Estimate number needed to genotype determined from the study to which the guideline refers: NNG 13
	CYP2C19	CPIC 2018 Select an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers.	ADEQUATE evidence of a significant association between CYP2C19 genotype and pharmacokinetics (plasma concentrations, clearance) of voriconazole. Evidence of a lack of association between CYP2D6 genotype and hepatotoxic side effects of voriconazole. ADEQUATE evidence of a lack of association between CYP2D6 genotype and hepatotoxic side effects of voriconazole	not applicable
Warfarin	VKORC1 CYP2C9	DPWG 2019 Patients with the VKORC1 -1639 (rs9923231) AA genotype should be given 60% of the standard initial dose of warfarin. Reduce warfarin dose in CYP2C9 poor and intermediate metabolizers (PM and IM) and patients with CYP2C9*1/*3, *2/*3, *2/*2 or *3/*3 genotype.	CONVINCING Evidence of significant association between VKORC1 polymorphism and a variance up to 30% in stable warfarin dose among patients of European ancestry. CONVINCING Evidence of significant association between CYP2C9 polymorphism and a variance up to 17% in stable warfarin dose among patients of European ancestry. CYP2C9 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.	CONVINCING VKORC1 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin. INADEQUATE evidence that genotype- guided dosing strategies would improve percentage of time that the INR is within the therapeutic range or to reduce ADR.
	VKORC1	CPIC 2017 The recommendations for dosing are for adult and pediatric patients that are specific to continental ancestry, and are based on genotypes from CYP2C9, VKORC1, CYP4F2, and rs12777823 including pharmacogenetic warfarin dosing algorithms.	CONVINCING evidence of significant association between CYP2C9 polymorphism and a variance up to 17% in stable warfarin dose among patients of European ancestry. CYP2C9 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.	CONVINCING VKORC1 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.

continued

Table 8 (continued) Drugs mentioned in following guidelines which considered clinical utility studies.

Drug	Genetic marker	Guideline	Clinical validity	Clinical utility
				Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 37 (6-63)
	CYP4F2			not applicable
	CYP2C9			CONVINCING CYP2C9 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.
	CYP2C9 VKORC1	Canadian Pharmacogenomics Network for Drug Safety 2017 They recommend testing for the VKORC1 SNP -1639G>A (rs9923231) and the CYP2C9 alleles *2 and *3 in order to better guide warfarin dosage.	CONVINCING evidence of significant association between VKORC1 gene polymorphisms and warfarin dosage.	CONVINCING CYP2C9 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin. Estimate number needed to genotype determined from the studies to which the guideline refer [mean (range)]: NNG 18 (6-42)

The reference studies behind the guidelines most frequently examined the effect of polymorphisms in genes coding for the metabolizing enzymes of a particular drug on the pharmacodynamics or kinetics of the drug. The majority of the studies analyzed were association or cohort studies.

In a total of 40 studies referenced in the guidelines, the clinical benefit of pharmacogenetic tests was analyzed for a total of 15 drugs. Overall, the studies provided strong evidence for a significant benefit of genotype-controlled dosing, with improved clinical outcome of the patients, a lower risk of adverse drug reactions, or better control of blood drug levels. Major genetic-marker drug pairs on which these clinical benefit analyses focused included HLA-A and HLA-B (abacavir, allopurinol, carbamazepine), thiopurine S-methyltransferase (TPMT; azathioprine, mercaptopurine), CYP2C19 (clopidogrel, escitalopram, lansoprazole, voriconazole), and VKORC1 (warfarin, phenprocoumon). Full results are presented in Table 9.

Applying the EGAPP criteria has shown that scientific evidence is missing due to limited clinical utility data, whereas the guidelines recommend dose adjustments for azathioprine (DPWG 2019), fluorouracil (CPIC 2017), lansoprazole (DPWG 2019), mercaptopurine (CPIC 2016), phenprocoumon (DPWG 2019), tacrolimus (DPWG 2019) and voriconazole (DPWG 2019).

Mean values of NNG varied between 4 and 417 (Figure 4). The maximum and minimum NNG values for the genetic-marker drug pairs Acenocoumarol VKORC1, Carbamazepine HLA-B and Warfarin CYP2C9/VKORC1 differ by over 100. The maximum NNG values of Allopurinol HLA-B*5801 and Carbamazepine HLA-B are greater than 415, therefore out of plot range. The smallest NNG values calculated for Abacavir HLA-B*5701, Acenocoumarol VKORC1, Capecitabine DPYD, Lansoprazole CYP2C19, Phenprocoumon VKORC1, Tacrolimus CYP3A5 and Warfarin VKORC1/CYP2C9 are less than 10.

OR in mean varied between zero and 6.13 (Figure 5). The maximum and minimum OR values for the genetic-marker drug pairs Acenocoumarol VKORC1, Lansoprazole CYP2C19 and Warfarin CYP2C9/VKORC1 differ by over 1. The maximum value of Lansoprazole CYP2C19 is 6.13, therefore out of plot range.

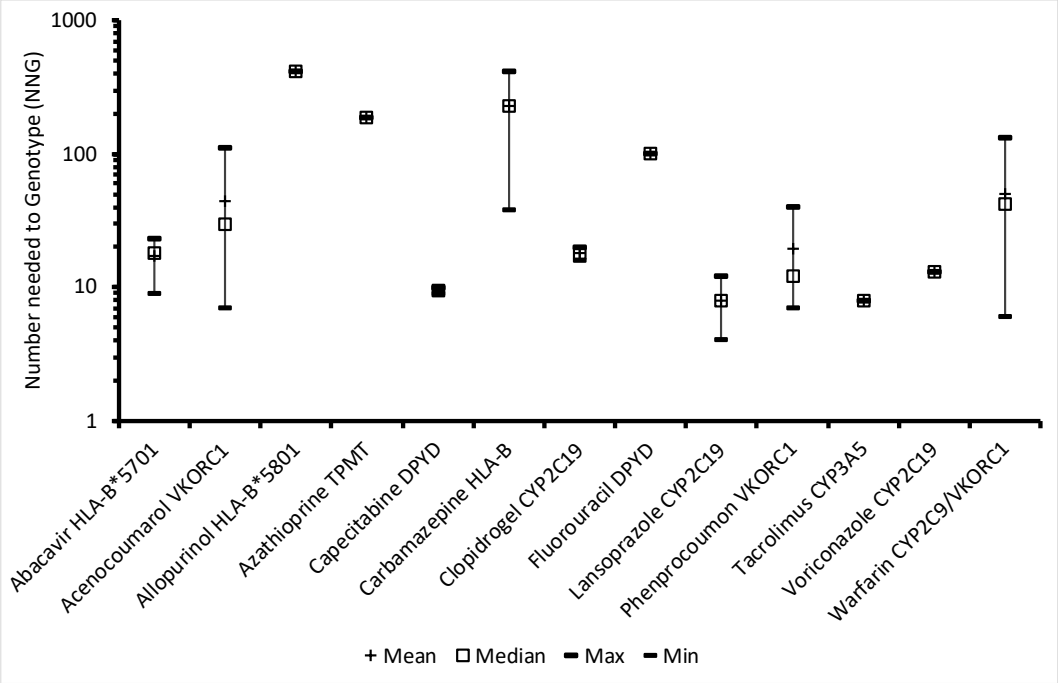

Figure 4 The number needed to genotype (NNG) for drug-genetic marker pairs. The reference literature of the guidelines was searched for data on NNG and summarized as mean, median, maximum and minimum values.

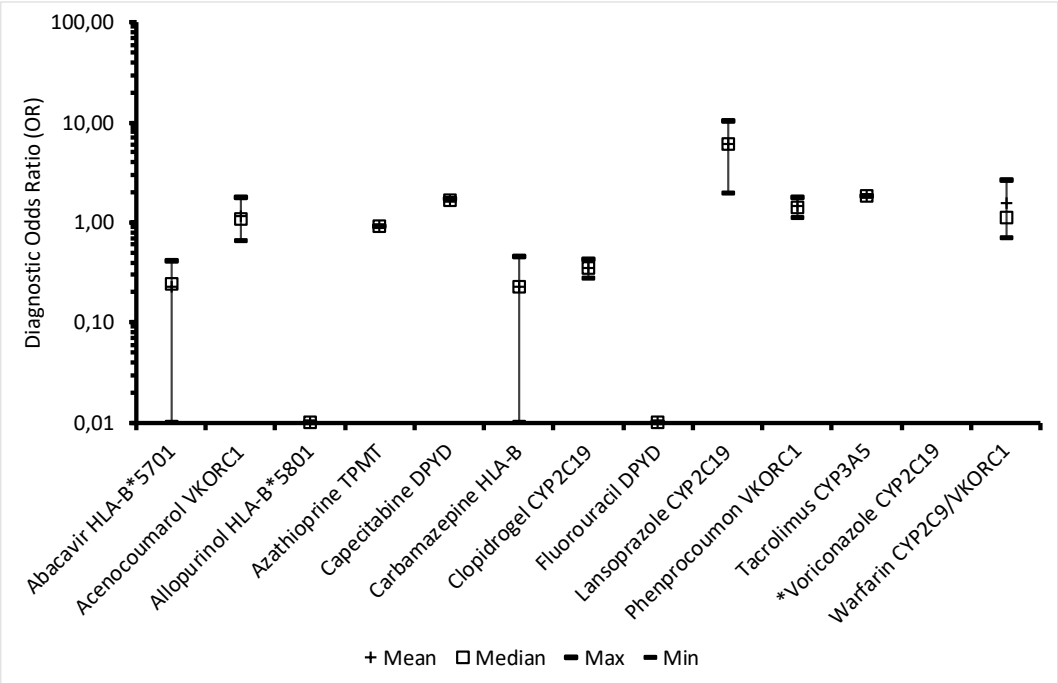

Figure 5 The diagnostic odds ratio (OR) for drug-genetic marker pairs. The reference literature of the guidelines was searched for data on OR (see Table 8). The x axis shows drug-genetic marker pair; the y axis shows the mean OR ± 95% CI. *OR for Voriconazole CYP2C19 is not applicable (division by zero).

Abacavir, a carbocyclic, nucleoside reverse transcriptase inhibitor, is used to treat patients infected with HIV-1 (human immunodeficiency virus) as part of an antiretroviral combination therapy. The presence of at least one *57:01 allele (reported as "positive" on a genotyping test, ~6% of patients affected) is strongly associated with a high risk of hypersensitivity (OR < 0.41). Therefore, the guidelines [37, 52] do not recommend Abacavir in carriers of HLA-B*5701 [58]. Referential studies showed CONVINCING evidence of reduced incidence of Abacavir hypersensitivities if avoided in HLA-B*5701 allele carriers (see Table 8).
Azathioprine is an analog of the nucleobase's adenine and guanine used as a cytostatic in the chemotherapy of leukemia and long-term treatment of chronic intestinal inflammation. It shows CONVINCING evidence for TPMT-based dosing algorithm to reduce toxicity and maintain drug efficacy (see Table 8, NNG 189).

Summary of genetic-marker drug pairs recommended for testing according to CONVINCING evidence:

- Abacavir HLA-B*5701 (reduce hypersensitivity)
- Acenocoumarol VKORC1 (therapeutic INR-range)
- Allopurinol HLA-B*5801(reduce Steven-Johnson-Syndrome)
- Azathioprine TPMT (reduce toxicity)
- Capecitabine DPYD (reduce myelosupression)
- Carbamazepine HLA-B (reduce Steven-Johnson-Syndrome)
- Clopidogrel CYP2C19 (reduce major cardiovascular events)
- Fluorouracil DPYD (reduce toxicity)
- Tacrolimus CYP3A5 (achieve target drug blood levels)
- Warfarin VKORC1 CYP2C9 (achieve stable dose)

Table 9 shows our concluding evaluation for each genotype-drug pair based on the evaluation of the clinical validity and utility, the assessment of the net benefit of genotype-based adjustments, and the certainty of evidence.

3.3. Assessment of the Quality of the Guidelines with the AGREE 2 Instrument

The AGREE II tool was used to evaluate the process of practice guideline development and the quality of reporting. AGREE II comprises 23 items organized into 6 quality domains. The rating of these 23 items for each of the 32 included guideline documents is summarized in the net diagram (Figure 6). Overall, domain 6

of AGREE II (editorial independence) and domain 3 (rigor of development) had the highest average quality scores, while the lowest average quality score was for domain 2 (stakeholder involvement).

The guideline quality assessment reveals overall comprehensive adequacy in three domains: Clarity of Presentation, Scope and Purpose, Editorial Independence. **(a)** As part of Domain 4, Clarity of Presentation, the guidelines [3, 11, 30, 33, 51] show specific and unambiguous recommendations. To be pointed out, the guideline [30] clearly presents options for managing the condition or health issue. **(b)** In regard to the Domain 1, Scope and Purpose, precise description of the overall objectives is given by the guideline [30]. **(c)** Domain 6, Editorial Independence rates the bias between recommendations and conflicting interests. The guidelines [17, 30, 33] state giving recommendations independently of the funding body and received high AGREE II rating scores.

Overall comprehensive deficits are revealed in three domains: Stakeholder Involvement, Rigor of Development, Applicability. **(a)** As part of Domain 2, Stakeholder Involvement, the guidelines [11, 36, 47, 51] ranked low scores respecting target population views and preferences. **(b)** In regard to Domain 3, Rigor of Development, the following guidelines scored the lowest concerning the items recommendation formulation [16, 28, 51], external reviews [17, 33, 51], and update procedures [17, 33]. In regard to **(c)** Domain 5, Applicability, the guidelines [5, 30, 44] lack considering the potential resource implications of applying the recommendations.

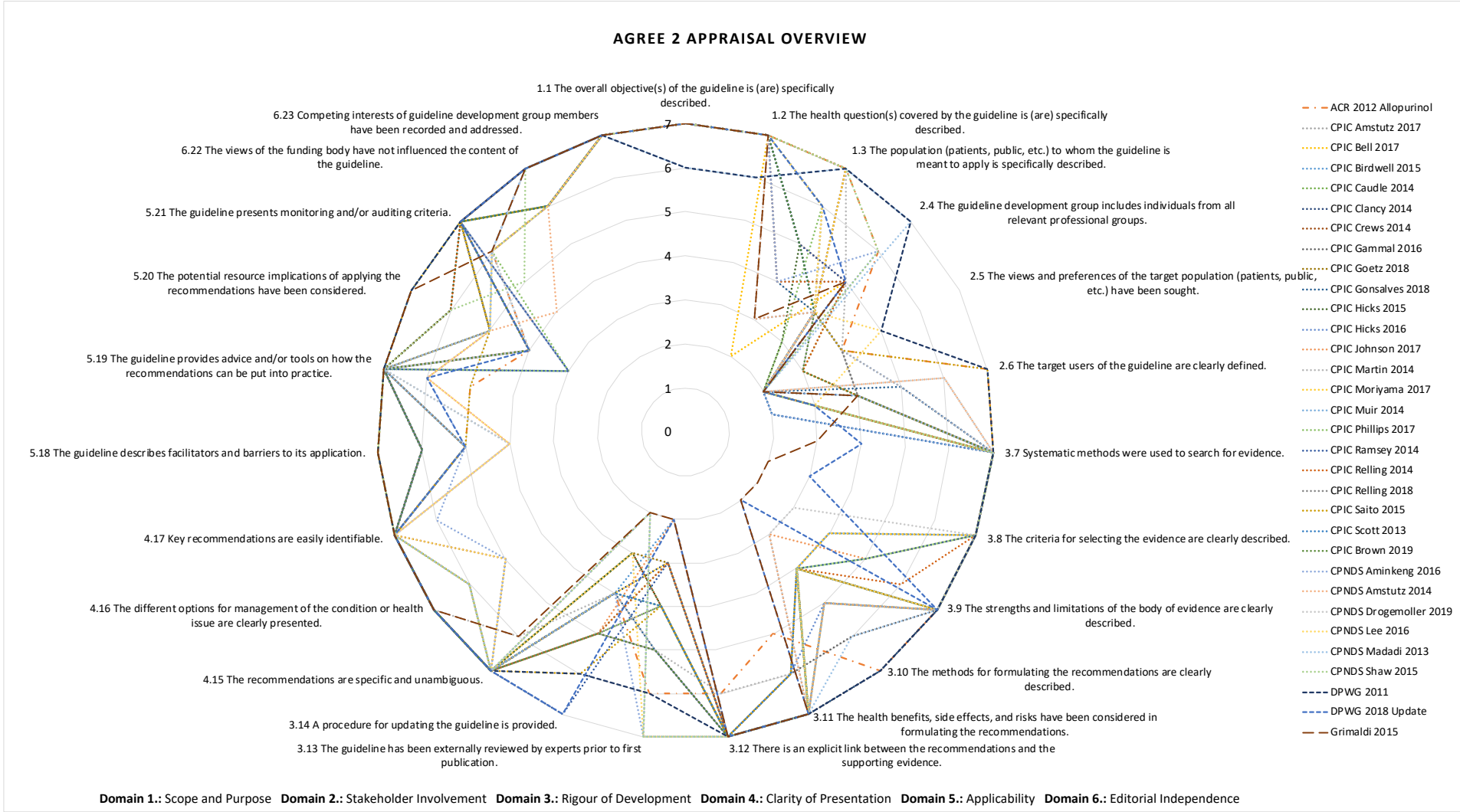

Figure 6 Visualized guideline quality assessment: The Appraisal of Guidelines for Research & Evaluation II (AGREE II) net diagram. For assessment a 7-point rating scale (1: strongly disagree to 7: strongly agree) was used.

4. Discussion

This systematic review aims to systematically assess the quality of published guidelines on the use of inherited (germline) pharmacogenetic biomarkers to guide drug selection or dose adjustment. This analysis of guidelines with regard to pharmacogenetic interaction and concomitant profile should facilitate dosing in the future and, above all, make drug treatment safer. Our aim was to avoid harmful side effects for the patient and to make the use of the drug safer and provide a detailed overview for practitioners.

Quality and Strength of Scientific Evidence

Pharmacogenetic testing is an emerging field and individual drug dosing seems promising for optimizing therapy and reducing adverse drug reactions. However, the quality of the data and statistical power related to the sample size varies. Hence, study outcomes do not necessarily fit all patients equally, making it difficult to decide on appropriate, cost-effective, safe treatments and justified genetic testing [32].

A common basis for evaluating the scientific evidence of the studies is defined by the ACCE project from the Centers for Disease Control and Prevention. The key criteria of the ACCE project are analytic and clinical validity, clinical utility and ethical/legal/social implications. The EGAPP Working Group improves the evaluation tool by focusing on genetic testing and defining more precise criteria for clinical validity and clinical utility [54]. Therefore, the approach presented in Section 2.4 evaluates studies used for guideline recommendations based on the EGAPP method.

The results of abacavir can be used exemplarily for a comparison between the convincing scientific evidence (shown in Table 8) of significant benefit of genotype stratified dosing to minimize hypersensitivity reaction and guideline recommendations of DPWG 2019 [30] and CPIC 2014 [30]. Both guidelines advise not to administer abacavir to patients with HLA-B*5701 genotype. This consensus emphasizes strong evidence to justify the guideline recommendations. Additionally, high-ranked agencies, such as the FDA [56] or European Medicines Agency (EMA) [18], both advise genetic screening for the HLA-B*5701 gene prior to initiating therapy with abacavir. The FDA categorizes biomarker information in three types: testing prior to drug prescription, testing recommended, and testing for

information purposes only. Although clopidogrel is labeled to have a reduced effect for CYP2C19 PM, testing is categorized for information purposes only. The hereby presented classification shows adequate evidence. As a consequence additional tests will not be funded although the outcome could be improved [32].
The differences mentioned in Section 3.2 between results from the EGAPP analyses and guideline recommendations might occur from the differences in the applied criteria, medication utilization patterns by country, and guideline's focus on studies considering the clinical validity [39]. Studies on the clinical validity of many other genetic marker-drug pairs only show indications. Although these associations between genetic variants and blood plasma levels or even health outcomes can suggest a course of action, they cannot provide a clear recommendation. In the future, the focus should therefore shift to evaluate their clinical utility. The EGAPP criteria help to evaluate the clinical utility and address the problem of missing consensus on precise definition and adequate demonstration of clinical utility [35, 42].

Healthcare insurers demand not only for clinical utility but also for cost-effectiveness. The per-patient costs are an important measurement for comparing a desired clinical outcome by pharmacogenomic guided therapy versus the standard care. However, it might be desirable to aggregate real-world clinical data too. Besides economically aspects, this could include data on healthcare utilization, e.g., emergency room visits and hospitalizations in relation to adverse-drug reactions or the patients' genotypes [31]. Randomized clinical trials analyzing the cost-effectiveness are available for a few drugs and specific patient populations only. However, a full test coverage for all gene-drug interactions and patient specifics is not feasible [1, 31]. Reimbursement for testing is not yet in scope of the healthcare insurers, as they demand for clinical guidelines on which patients to test. The DPWG then established the Clinical Implication Score to categorize the strength of recommendation for testing. The criteria include the severity of side effects, level of evidence of the side effect, the inclusion of genotype information in the product characteristics, and the NNG [1, 53].

The determination of the NNG as described in Section 2.5 reflects the goal of this work to avoid adverse events. The NNG was calculated for each genetic marker-

drug pair based on data from clinical utility studies. This allows conclusions to be drawn as to when genetic testing is beneficial. The lower the NNG, the more beneficial the testing would be. The DPWG grades a NNG <10 the highest score, >1,000 the lowest score, with a gradation at 100 [53]. Considering the range of the calculated NNG values (4 to 417) in Figure 4, this seems to be a reasonable approach. In combination with the calculation of the diagnostic odds ratio the effectiveness of genotyping is determined.
Based on the EGAPP evaluation criteria (Table 2) and quality of evidence (Table 3), genetic testing was recommended for, e.g., allopurinol and carbamazepine. The NNG of these agents (values >400) indicate a reduced effectiveness compared to most other substances (Figure 4). Limited availability of data might reduce the significance of the NNG, i.e. the calculation for azathioprine is based on a single study only.

This systematic review features a unique and broad scope of an up-to-date overview of guideline publications and genetic marker-drug pairs. The EGAPP criteria-based re-evaluation of the level of evidence enables an unprecedented summarization of recommendations to guide clinicians and facilitate stratification of drug therapy. It was possible to create precise recommendations under consideration of an extensive number of studies for each genetic marker-drug pair.

Systematic Assessment of Methodological Guideline Quality

Another quality measure used in this work to assess the internal, methodological quality of pharmacogenetic guidelines is the AGREE II tool [10]. It is proven internationally and known to be sensitive to differences in important aspects of guidelines [2]. Applying AGREE II has the advantage of evaluating the development process of a guideline and is a decisive factor for the overall quality. The resulting score grades the quality of the CPGs and if it is recommended for use in clinical practice. The analysis of a total of 23 items ensures that deficits are identified, and particularly trustworthy sources highlighted.

The guideline of DPWG is ranked very high in all six AGREE II domains. Only a minor lack in considering the views and preferences of the target population (Domain 2, Stakeholder Involvement) could be found. This item seems to be a general deficit since related CPGs also show weaknesses in this particular domain. Additional deficits could be seen in Domain 3 Rigor of Development, and especially in Domain 5 Applicability. Domain 5 evaluates whether the available resources for implementing the recommendations into clinical practice are considered. The quality of guidelines published by CPIC are generally high and often include a workflow on how to implement the pharmacogenetic test results into clinical practice and the electronic health record. This approach should be adapted by other guidelines with a low score in Domain 5. Comparable results for, e.g., CPIC, DPWG, CPNDS were found in [6], showing the lowest score for Domain 2 and Domain 5 too.

The AGREE II tool targets traditional disease-based clinical practice guideline and might need to be improved for pharmacogenomic testing. Yet, it provides valuable feedback for evaluating the guidelines, especially as there seems to be a no more targeted tool.

Accelerate scientific work

The process of a systematic review involves many manually performed tasks, such as literature search, data extraction, statistically synthesizing the data and filtering as well as storing the information in a suitable structure. Pharmacological guidelines reference a large number of papers, making this process time-consuming and hardly manageable, which proved itself to be very true in the course of this work. In general, scientists demand faster, automated, and more efficient processes. This led the way to create a solution to this challenge.

As part of this work, an application for semiautomatic extraction of quantitative and qualitative data from PharmGKB and PubMed to facilitate the conduction of systematic reviews was created.

The proposed solution based on Python scripts allows the automated data extraction of relevant source for the systematic review, mainly PharmGKB and PubMed. Such modern databases can be accessed by APIs, publicly available over the web. Research processes can be greatly improved and supported by finding strategies and solutions like this in order to use the data as efficiently as possible. The created tool is modular and easy to extend and fit to the purposes of a literature review. The programming language Python is cross-compatible for all major operating systems and offers a rich set of modules for further data extraction, modification, filtering, synthesizing and exports. At the same time, systematically reviewed findings could be applied more quickly to everyday clinical practice, thus patients can benefit from it.

Outlook

It is unclear at what point in time or treatment progress the data should be collected, whether they should be evaluated preventively for all or for selected cases only. Preemptive pharmacogenetics testing can result in fewer required genetic tests, immediate availability of test results when starting a treatment, and lower barriers to consider pharmacogenomics data in clinical practice. The additional costs for testing a panel of genes instead of a single gene is negligible [42, 57]. The Ubiquitous Pharmacogenomics consortium (U-PGx) investigates preemptive genotyping approach and its clinical implementation in Europe. The study aims to provide evidence for selecting the right drug and right dose. As a result of the project, the participating countries adapted a clinical decision support for patient-specific drug

dosing recommendations based on the U-PGx Genetic Information Management Suite. Currently, the suite only uses DPWG recommendations. A comparable platform based on CPIC recommendations was established by the University of Chicago, called the 1200 Patients Project. The project aims to personalize medical care by preemptive pharmacogenetics testing too [39]. The study [48] shows an example implementation of a medicine safety code for storing patients' genotyping results on a printable card. It offers the potential to make individual pharmacogenomic data and decision support available in a wide variety of healthcare settings using quick response codes while giving patients full control over their genetic data and independent of centralized databases [48].

It would be favorable to include the results of this meta-analysis into the U-PGx system instead of focusing on a single source. Guidelines have unique profiles and strengths and considering the totality of guidelines are of added value [1]. The U-PGx system is financed by funds from the EU, therefore the data set containing up to date DPWG recommendations is available on demand. To enhance the current data aggregation and recommendation table generation solution, the results from Table 9 could be incorporated with the U-PGx data. Provided that the U-PGx suite source code is publicly available, an extended portal could be established with genotyping recommendations based on the results from this meta-analysis.

Physicians, pharmacists and pharmacogenomics experts raise concerns on data privacy regarding pharmacogenetic testing [34, 55]. Genetic data belongs to the special categories of personal data. In the European Union, the General Data Protection Regulation (GDPR), Art. 4 No. 13 defines the term "genetic data". Genetic data are personal data relating to the inherited or acquired genetic characteristics of a natural person which provide unique information about the physiology or health of that natural person and which have been obtained, in particular, from the analysis of a biological sample from the natural person concerned. Accordingly, pharmacogenetic DNA analyses, for example, fall under Art. 9 GDPR [19]. The Genetic Diagnostics Act (Gendiagnostikgesetz, GenDG) determines the requirements for genetic examinations in humans and for the genetic analyses performed in the course of these examinations, as well as the use of genetic samples and data in Germany. Pharmacogenetic tests are also covered by

the provisions of the GenDG [12]. These regulations must be applied for genetic data collection, storage and deletion when implementing supporting software. Educational information about regulatory requirements and assurance when the genotype data is used would potentially increase the acceptance of pharmacogenetic testing. Other studies discuss on how to raise awareness of clinicians as well as patients and possibly increase patient's medication adherence [21, 34].

Pharmacogenetic testing is preceded by a multifactorial decision. The determination should be based on the scientific evidence and current guidelines, calculation of the NNG from clinical utility studies and overall consideration of financial and ethical aspects. Tests can ideally save costs by making a therapy safer and more effective and thus improve healing and save resources. In the sense of evidence-based medicine, only such tests should be considered for practical application, where the test quality (e.g. positive and negative predictive value) and ideally also the utility is well proven. The biggest problem for the implementation currently seems to be the lack of evidence of sufficient test quality (e.g. minor sensitivity and specificity). Therefore, forfeiting the benefits of the postulated pharmacogenetic tests but overall, also a lack of existing hypotheses, sample-size requirements, operational and logistic issues [32, 59].

To conclude, this extensive evidence-based clinical practice guideline for pharmacogenetic testing was developed with a high degree of methodical approach in order to formulate clear statements and recommendations. It is essential to make the results and recommendations quickly available and easily accessible for physicians. This work provides a guideline on how to deal with genotype data in order to improve patient's safety, minimize side effects and avoid mortalities.

5. Summary

Pharmacogenetics claim to offer the potential to improve health outcomes by identifying individuals who are at greater risk of harm or treatment failure from certain drugs. Routine adoption of pharmacogenetic tests requires evidence of their clinical validity and utility. This study aims to systematically assess the quality of published guidelines on the use of inherited (germline) pharmacogenetic biomarkers to guide drug selection or dose adjustment.

A protocol of the study was registered on PROSPERO (registration CRD42016046258). A systematic literature search (EMBASE, MEDLINE, the Pharmacogenomics Knowledge Base, and the International Guideline Library) was performed. Inclusion criteria were: The article must be a guideline, which contains a recommendation for dose or therapy modification for a defined drug based on at least one genetic variant in the patient's germline genome. The process of the systematic review was supported by self-developed Python scripts for data extraction, synthesizing, filtering and exporting, accessing the web application programming interfaces (APIs) from the literature databases and using RefWorks literature management as a database programmatically. It was possible to extract and individually export data from the Pharmacogenomics Knowledge Base (PharmGKB) to ensure a faster process for the systematic evaluation of this data.

The level of evidence and the strength of recommendation for each genetic marker-drug pair was re-evaluated by applying predefined scales published by the "Evaluation of Genomic Applications in Practice and Prevention" (EGAPP) working group. The focus was on two key questions, namely the clinical validity and the clinical utility.

A total of 32 guideline publications were identified, which included recommendations on genotype-stratified prescription for 84 drugs. The guidelines were systematically reviewed on their evidence that particular genetic markers were associated with pharmacokinetics or pharmacodynamics of the drug and how factors such as ethnicity affect these associations. However, for only a few drugs (e.g., abacavir-HLA-B, allopurinol-HLA-B, warfarin-VKORC1/CYP2C9, tacrolimus-CYP3A5) the guidelines identified sufficient evidence supporting benefits outweigh negative

effects when genotype-stratified prescribing was applied. For several drugs, guidelines recommended genotype-based dose adjustments despite lack of evidence that pharmacogenetic dose adjustment would improve outcome (e.g. irinotecan dose reductions in UGT1A1 *28/*28 carriers would increase tumor response and survival).

Most guideline recommendations are based solely on associations between genetic variants and either blood concentrations of the drug or health outcomes (e.g. adverse drug reactions) of the treatment. Prospective studies investigating the impact of genetic testing on the clinical outcome of patients and data on the number needed to genotype (NNG) or the cost-effectiveness are scarce. Characteristics of clinical utility, however, play an important role in the translation into clinical care.

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Appendix

Table 9 Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
Abacavir	CPIC (Martin et al. 2014) [37]	*HLA-B*	Absence of *57:01 alleles	Use abacavir per standard dosing guidelines.	Very low risk of hypersensitivity (constitutes ~94% of patients).	**CONVINCING** Evidence of reduced incidence of abacavir hypersensitivities if abacavir is not used in HLA-B*5701 allele carriers. **CONVINCING** Evidence of a significant association between HLA-B*57:01 genotype and the incidence of abacavir hypersensitivities.
			Presence of at least one *57:01 allele	Abacavir is not recommended.	High risk of hypersensitivity (~6% of patients).	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*HLA-B*	HLA-B*57:01	Select alternative drug.	HLA-B*5701-positive patients have a strongly increased risk of a hypersensitivity reaction to abacavir.	**CONVINCING** Evidence of reduced incidence of abacavir hypersensitivities if abacavir is not used in HLA-B*5701 allele carriers. **CONVINCING** Evidence of a significant association between HLA-B*57:01 genotype and the incidence of abacavir hypersensitivities.
Acenocoumarol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	Check INR more frequently after initiating or discontinuing NSAIDs.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5. Kinetic effect.	**CONVINCING** Evidence of a higher risk of over anticoagulation in variant genotypes with concomitant use of NSAID's (CYP2C9 inhibitor), but no significantly higher risk of bleeding. Considerable evidence of a strong association between CYP2C9 variant alleles and a reduced clearance of AC and therefore lower required dose regimen. Adequate evidence of significant association between CYP2C9 genotype-guided dosing and a higher percentage of patients with steady dose and time in the therapeutic INR range.
			CYP2C9 *2/*2	Check INR more frequently after initiating or discontinuing NSAIDs.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5. Kinetic effect.	
			CYP2C9 *1/*3	Check INR more frequently after initiating or discontinuing NSAIDs.	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite,	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
					insomnia, sleep disturbance etc.); neutropenia >1.5x10/l; leucopenia >3.0x10/l; thrombocytopenia > 75x10/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	
			CYP2C9 *2/*3	Check INR more frequently after initiating or discontinuing NSAIDs.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5. Kinetic effect.	
			CYP2C9 *3/*3	Check INR more frequently during dose titration and after initiating or discontinuing NSAIDs.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5. Kinetic effect.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*VKORC1*	VKORC1 rs9934438 AG	NO action is needed for this gene-drug interaction.	The genetic variation results in a reduction of the required dose, but with the current practice of initiating or reviewing treatment this results in little or no increased risk of bleeding or excessive anticoagulation.	**INSUFFICIENT** Evidence of significant association of VKORC1 genotype and acenocoumarol dose variability.
			VKORC1 rs9934438 AA	Check INR more frequently.	An INR >= 6, resulting in an increased risk of bleeding, occurs in 8-12% of these patients during the first weeks of treatment with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to acenocoumarol.	
Allopurinol	CPIC (Saito et al. 2016) [47]	*HLA-B*	Absence of *58:01 alleles	Use allopurinol per standard dosing guidelines.	Low or reduced risk of allopurinol SCAR	**CONVINCING** Evidence of significant association between HLA-B*58:01 genotype and a susceptibility of allopurinol induced severe cutaneous adverse reactions.
			Presence of at least one *58:01	Allopurinol is contraindicated.	Significantly increased risk of allopurinol SCAR	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	ACR (Khanna et al. 2012) [29]	*HLA-B*	HLA-B*58:01-positive	HLA-B*58:01-positive individuals should be prescribed an alternative drug to allopurinol.	High risk for severe allopurinol hypersensitivity reaction	**CONVINCING** Evidence of significant association between HLA-B*58:01 genotype and a susceptibility of allopurinol induced severe cutaneous adverse reactions.
Amitriptyline	CPIC (Hicks et al. 2017) [26]	*CYP2C19*	CYP2C19 Ultrarapid metabolizer (~2-5% of patients	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.	**INADEQUATE** association between CYP2C19 UM genotype and a lack of efficacy due to reduced plasma concentration. **INADEQUATE** association between CYP2D6 UM genotype and a lack of efficacy due to reduced plasma concentration. **CONVINCING** Significant association between CYP2D6 (PM, IM) genotype and risk of adverse drug reaction.
			CYP2C19 Rapid metabolizer (~2-30% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.	
			CYP2C19 Normal metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of tertiary amines.	
			CYP2C19 Intermediate metabolizer (~18-45% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism of tertiary amines compared to normal metabolizers.	
			CYP2C19 Poor metabolizer (~2-15% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. For tertiary amines, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments	Greatly reduced metabolism of tertiary amines compared to normal metabolizers. Decreased conversion of tertiary amines to secondary amines may affect response or side effects.	
		CYP2D6	CYP2D6 Ultrarapid metabolizer (~1-20% of patients)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose	Increased metabolism of TCAs to fewer active compounds compared to normal metabolizers. Lower plasma concentrations of active drug will increase	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				(compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	probability of pharmacotherapy failure.	
			CYP2D6 Normal metabolizer (~72-88% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	
			CYP2D6 Intermediate metabolizer (~1-13% of patients)	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Reduced metabolism of TCAs to fewer active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients)	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose, e.g. utilize therapeutic drug monitoring to guide dose adjustments.	Greatly reduced metabolism of TCAs to fewer active compounds compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Use 70% of the standard dose and monitor the effect and side effects or the plasma concentrations of amitriptyline and nortriptyline to adjust the maintenance dose.	In theory, risk of side effects is increased, because the genetic variation results in higher plasma concentrations of the active metabolite nortriptyline and to a lesser extent of amitriptyline	**ADEQUATE** evidence that PMs are associated with a slower metabolism and thus higher concentrations of the drug. **INADEQUATE** and insufficient evidence of a correlation between UM (more than two copies of a functional allele) and a significantly higher plasma concentration. **ADEQUATE** evidence of higher plasma concentration in IMs. **INADEQUATE** evidence of significant association between CYP2D6 UM genotype and a lack of efficacy due to reduced plasma concentration. **CONVINCING** evidence of significant association between CYP2D6 (PM, IM) genotype and risk of adverse drug reaction.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-	Reduce dose by 25% and monitor plasma concentration or select alternative drug (e.g., citalopram, sertraline).	The risk of side effects is increased, because the gene variation leads to higher plasma concentrations of the active metabolite nortriptyline and to a lesser extent of amitriptyline.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			*16, *19-*21, *38, *40, *42) allele)			
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	1. Increase the dose to 1.4 times the standard dose, monitor the effect and side effects or the plasma concentrations and be alerted to increased plasma concentrations of the cardiotoxic Z-10-hydroxy metabolites. Plasma concentrations of Z-hydroxy nortriptyline or Z-hydroxy amitriptyline higher than 40 ng/mL are considered toxic. 2. If a dose increase is not desirable due to the cardiotoxic hydroxy metabolite: avoid amitriptyline.	The risk of ineffectiveness is increased and the risk of cardiotoxic side effects may be increased. The gene variation leads to increased conversion of amitriptyline and the active metabolite nortriptyline to less active and inactive metabolites.	
Aripiprazole	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Administer no more than 10 mg/day or 300 mg/month (67-75% of the standard maximum dose of aripiprazole).	The risk of side effects is increased. The genetic variation leads to an increase in the sum of the plasma concentrations of aripiprazole and the active metabolite.	**CONVINCING** evidence of significant association between CYP2D6 allele and serum levels and development of ADR. Especially significant in PMs.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	NO action is needed for this gene-drug interaction. The genetic variation increases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is insufficient evidence that this increases the risk of side effects.	--	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	NO action is needed for this gene-drug interaction. The genetic variation increases the plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole to a limited degree. There is insufficient evidence that this increases the risk of side effects.	--	
Atazanavir	CPIC (Gammal et al. 2016) [20]	*UGT1A1*	An individual carrying 2 reference function and/or increased function alleles; or individuals of genotype CC at rs887829	There is no need to avoid prescription of atazanavir based on UGT1A1 genetic test result.	Reference UGT1A1 activity; very low likelihood of bilirubin-related discontinuation of atazanavir.	**CONVINCING** Strong Evidence of an association between PM UGT1A1 and severe hyperbilirubinemia and jaundice. Evidence of significant association between UGT1A1 PM genotype and risk of adverse drug reactions such as hyperbilirubinemia. **INADEQUATE** Evidence of significant benefit of UGT1A1 genetic testing to reduce Atazanavir - associated hyperbilirubinemia.
			An individual carrying one reference function (*1) or increased function allele (*36) plus one decreased function allele (*6, *28, *37). Alternatively identified by heterozygosity for rs887829 C/T.	There is no need to avoid prescription of atazanavir based on UGT1A1 genetic test result.	Somewhat decreased UGT1A1 activity; low likelihood of bilirubin-related discontinuation of atazanavir.	
			An individual carrying two decreased function alleles (*6, *28, *37). Alternatively identified by homozygosity for rs887829 T/T (*80/*80)	Consider an alternative agent particularly where jaundice would be of concern to the patient.	Markedly decreased UGT1A1 activity; high likelihood of bilirubin-related discontinuation of atazanavir.	
Atomoxetine	CPIC (Brown et al. 2019) [11]	*CYP2D6*	CYP2D6 Ultrarapid Metabolizer	Initiate with a dose of 0.5 mg/kg/day and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional	No adequate serum concentrations for the intended effect at standard dosing.	**INADEQUATE** Scarce Evidence of independency of the metabolism of CYP2D6 activity. Evidence of significant association between CYP2D6 PM genotype and risk of adverse drug reaction. Evidence of significant association between CYP2D6 UM

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				increase in dose to approach 400 ng/ml.		genotype and lack of efficacy due to reduced plasma concentrations.
			CYP2D6 Normal metabolizer	Initiate with a dose of 0.5 mg/kg and increase to 1.2 mg/kg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml.	Normal metabolizers of atomoxetine have a lower likelihood of response as compared to poor metabolizers. Lack of efficacy.	
			CYP2D6 Normal metabolizer or Intermediate metabolizer	Initiate with a dose of 0.5 mg/kg and increase to 1.2 mg/kg/day after 3 days If no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a peak plasma concentration (1 to 2 hours after dose administered). If <200 ng/ml, consider a proportional increase in dose to approach 400 ng/ml	Normal metabolizers may be at an increased risk of increased discontinuation as compared to poor metabolizers.	
			CYP2D6 Normal metabolizer or Intermediate metabolizer	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 2-4 h after dosing. If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml. If unacceptable side effects are present at any time, consider a reduction in dose.	Decreased metabolism of atomoxetine and higher atomoxetine concentrations as compared to normal metabolizers.	
			CYP2D6 Intermediate metabolizer	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a	Decreased metabolism of atomoxetine and higher atomoxetine concentrations as compared to normal metabolizers.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				plasma concentration 2-4 h after dosing. If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml. If unacceptable side effects are present at any time, consider a reduction in dose.		
			CYP2D6 Poor metabolizer	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 4 h after dosing. If response is inadequate and concentration is <200 ng/ml, consider a proportional dose increase to achieve a concentration to approach 400 ng/ml. If unacceptable side effects are present at any time, consider a reduction in dose.	Significantly decreased metabolism of atomoxetine may result in higher concentrations as compared to non-poor metabolizers. This may increase the occurrence of treatment-emergent side effects, but also a greater improvement of ADHD symptoms as compared to non-poor metabolizers in those who tolerate treatment. Poor metabolizer status is associated with lower final dose requirements as compared to non-poor metabolizers.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Standard dose. Doses increase probably not necessary.	The genetic variation increases the plasma concentration of atomoxetine and thereby the risk of side effects. .	**INADEQUATE**/ Scarce Evidence of independency of the metabolism of CYP2D6 activity. **INADEQUATE** evidence of significant association between CYP2D6 genotype and higher systemic exposure and thus concentration- related adverse events. **INADEQUATE** evidence of significant association between CYP2D6 UM genotype and lack of efficacy due to reduced plasma concentrations.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-	In the event of side effects occurring and/or a response later than 9weeks: reduce the dose and check whether the effect is conserved. The plasma concentration of atomoxetine is a factor of 2-3 times higher for IM than for EM at the same dose.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); INR increase <4.5; Kinetic effect.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			*16, *19-*21, *38, *40, *42) allele)			
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Be alerted to reduced efficacy or select alternative drug (e.g., methylphenidate, clonidine).	The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy.	
Atorvastatin	DPWG (update 2018) [52]	*SLCO1B1*	512 CC	- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy: 1. Choose an alternative. Rosuvastatin and pravastatin are influenced to a similar extent by SLCO1B1 polymorphisms but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors. 2. If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms. - Patient has no additional significant risk factors for statin-induced myopathy: Advise the patient to contact their doctor in the event of muscle symptoms.	The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy.	**CONVINCING** evidence of significant association between SLCBO1B1 genotype and significant association with myopathy (ADR). **CONVINCING** evidence of significant association between elevated plasma levels and ADR in patients who received simvastatin. **INADEQUATE** evidence of significant association between SLCO1B1 genotype and myopathy in rouvastatin-treated patients.
			512 TC	Choose an alternative for patients with the SLCO1B1 521 CC or TC (rs4149056) genotype and with ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy.	The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
Azathioprine	CPIC (Relling et al. 2018) [45]	*TPMT*	Homozygous wild-type or normal, high activity (two functional *1 alleles)	Start with normal starting dose (e.g., 2-3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.	Lower concentrations of TGN metabolites, higher methylITIMP	**CONVINCING** Evidence of significant association between TPMT (PM, IM) genotype and risk of adverse drug reaction such as myelosuppression. Evidence of significant benefit of TMOT-based dosing to reduce toxicity and maintain drug efficacy.
			Heterozygote or intermediate activity (one functional allele - *1, plus one nonfunctional allele - *2, *3A, *3B, *3C, or *4)	Consider starting at 30-70% of target dose (e.g., 1-1.5 mg/kg/d), and titrate based on tolerance. Allow 2-4 weeks to reach steady state after each dose adjustment.	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	
			Homozygous variant, mutant, low, or deficient activity (two nonfunctional alleles - *2, *3A, *3B, *3C, or *4)	Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment.	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*TPMT*	IM (one inactive allele: *2, *3, *4-*18)	Select alternative drug or reduce dose by 50%. Increase dose in response of hematology monitoring and efficacy.	The genetic variation reduces the conversion of azathioprine and mercaptopurine to mainly inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression.	**CONVINCING** Evidence of significant association between TPMT (PM, IM) genotype and risk of adverse drug reaction such as myelosuppression.
			PM (two inactive alleles: *2, *3, *4-*18)	Select alternative drug or reduce dose by 90%. Increase dose in response of hematology monitoring and efficacy.	Clinical effect : death; arrhythmia; unanticipated myelosuppression.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
Capecitabine	CPIC (Amstutz et al. 2018) [4]	*DPYD*	An individual carrying two normal alleles	Use label-recommended dosage and administration.	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity	**CONVINCING** Significant association between DPYD (PM, IM) genotype and risk of toxicity such as myelosuppression and skin toxicity.
			An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles	Reduce starting dose by 50% followed by titration of dose based on toxicity or therapeutic drug monitoring (if available). Patients with the c.[2846A>T];[2846A>T] genotype may require >50% reduction in starting dose.	Decreased DPD activity and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	
			An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele	Activity score 0.5: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. 5-fluorouracil should be administered at a strongly reduced dose with early therapeutic drug monitoring. Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*DPYD*	PM (2 inactive alleles, 2 decreased activity alleles, or one inactive and one decreased activity alleles)	Select alternative drug.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	**ADEQUATE** Evidence of significant association between DPYD (PM, IM) genotype and risk of toxicity such as myelosuppression and skin toxicity following fluoropyrimidine treatment. **ADEQUATE** evidence that DPYD*2A genotype- guided dosing results in adequate systemic drug exposure.
			IM (1 active allele and 1 inactive or decreased activity allele)	Reduce dose by 50% or select alternative drug. Tegafur is not a suitable alternative because this drug is also a substrate for DPD. Increase dose in response to toxicity and efficacy.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	
Carbamazepine	CPIC (Phillips et al. 2017) [43]	*HLA-A* *HLA-B*	Non-carrier of HLA-B*15:02 or HLA-A*31:01. No HLA-B*15:02 or HLA-A*31:01 alleles reported, often	Use carbamazepine per standard dosing guidelines.	Normal or reduced risk of carbamazepine induced SJS/TEN, DRESS and MPE.	**ADEQUATE** Evidence of significant association between HLA-A*31:01 genotype and IDR risk like CBZ-induced hypersensitivity syndrome or maculopapular exanthema. **ADEQUATE** Evidence of significant

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			reported as "negative" on genotyping tests.			benefit of prospective screening of HLA-B*15:02 and therefore prevention of carbamazepine-induced SJS/TEN. **CONVINCING** Evidence of significant association between HLA-B*15:02 genotype and IDR risk like CBZ-induced Stevens- Johnson syndrome or toxic epidermal necrolysis.
			Carrier of HLA-A*31:01. One or two *31:01 alleles, often reported as "positive" on a genotyping test.Non-carrier of HLA-B*15:02. No HLA-B*15:02 alleles reported, often reported as "negative" on genotyping tests.	A. If patient is carbamazepine-naive and alternative agents are available, do not use carbamazepine. B. If patient is carbamazepine-naive and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction.	Increased risk of carbamazepine-induced SJS/TEN, DRESS and MPE	
			Carrier of HLA-B*15:02. One or two *15:02 alleles, often reported as "positive" on a genotyping test.	A. If patient is carbamazepine-naive, do not use carbamazepine. B. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within 3 months of dosing.	Increased risk of carbamazepine-induced SJS/TEN	
	Canadian Pharmacoge-nomics Network for Drug Safety (Amstutz et al. 2014) [5]	*HLA-A*	patients who are positive for HLA-A*31:01	Alternative medications should be used as first-line therapy.	HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions	
		HLA-B	CBZ-naive patients who carry at least one HLA-B*15:02 allele.	Genetic testing for HLA-B*15:02 is recommended for all CBZ-naive patients before initiation of CBZ therapy.		
Carvedilol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	No recommendations.	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc); neutropenia > 1.5x109/l;	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
					leucopenia > 3.0x109/l; thrombocytopenia > 75x109/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	No recommendations.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); INR increase <4.5; Kinetic effect.	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	No recommendations.	--	
Cisplatin	Canadian Pharmacogenomics Network for Drug Safety (Lee et al. 2016) [33]	*TPMT*	functional TPMT variants (*3A, *3B, *3C), functionally inactive TPMT *2 variant	testing for the TPMT alleles *2, *3A, *3B or *3C in all pediatric cancer patients.	TPMT risk variants, which account for approximately 25% of patients with ototoxicity.	**ADEQUATE** Evidence of significant association between genetic variants in TPMT and COMT and cisplatin-induced hearing loss in children.
Citalopram	CPIC (Hicks et al. 2015) [25]	*CYP2C19*	Ultrarapid metabolizer (~5-30% of patients)	Consider an alternative drug not predominantly metabolized by CYP2C19.	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	**Convincing** Consistent evidence that UM of citalopram accumulate a significantly lower concentration of the drug, lower AUC and concentration maximum.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Extensive metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism	**Adequate** Evidence of significant association between CYP2C19 UM genotype and lack of efficacy due to reduced plasma concentrations.
			Intermediate metabolizer (~18-45% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism when compared to extensive metabolizers.	
			Poor metabolizer (~2-15% of patients)	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	**Adequate** Evidence of significant association between CYP2C19 PM genotype and risk of adverse drug reaction.
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Do not exceed the following daily doses (50% of the standard maximum dose): 1. adults up to 65 years: 20 mg as tablets or 16 mg as drops, 2. Adults 65 years or older: 10 mg as tablets or 8 mg as drops.	The risk of QT prolongation and therefore also the theoretical risk of torsades de pointes is increased as the gene variation leads to an increased citalopram plasma concentration.	
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	Do not exceed the following daily doses: 1. Adults up to 65 years: 30 mg as tablets or 22 mg as drops, 2. Adults 65 years or older: 15 mg as tablets or 10 mg as drops.	The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased citalopram plasma concentration.	**ADEQUATE** evidence of significant association between CYP2C19 UM genotype and lack of efficacy due to reduced plasma concentrations.
			CYP2C19 UM (*17/*17)	NO action is needed for this gene-drug interaction.	--	
Clomipramine	CPIC (Hicks et al. 2017) [26]	*CYP2D6*	CYP2D6 Ultrarapid metabolizer (~1-20% of patients)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring.	Increased metabolism of TCAs to less active compounds compared to normal metabolizers. Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	**CONVINCING** Evidence of significant association between CYP2D6 genotype and Clomipramine metabolism including side effects and therapy failure.

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2D6 Normal metabolizer (~72-88% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	
			CYP2D6 Intermediate metabolizer (~1-13% of patients)	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Reduced metabolism of TCAs to less active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose, e.g. utilize therapeutic drug monitoring to guide dose adjustments.	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
		CYP2C19	CYP2C19 Ultrarapid metabolizer (~2-5% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.	
			CYP2C19 Rapid metabolizer (~2-30% of patients)			
			CYP2C19 Normal metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of tertiary amines	
			CYP2C19 Intermediate metabolizer (~18-45% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism of tertiary amines compared to normal metabolizers.	
			CYP2C19 Poor metabolizer (~2-15% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. For tertiary amines, consider a 50% reduction of the recommended starting dose. Utilize therapeutic	Greatly reduced metabolism of tertiary amines compared to normal metabolizers. Decreased conversion of tertiary amines to secondary amines may affect response or side effects.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				drug monitoring to guide dose adjustments.		
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Reduce dose by 50% and monitor (desmethyl) clomipramine plasma concentration.	Clinical effect: long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); INR 4.5-6.0; neutropenia 1.0-1.5x10/l; leucopenia 2.0-3.0x10/l; thrombocytopenia 50-75x10/l.	**INADEQUATE** No quality evidence of an association of a mutated CYP2D6 genotype and ADRs or drug efficacy. **INADEQUATE** Evidence of significant association between CYP2D6 (PM, IM) genotype and risk of ADR or lack of efficacy.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	Insufficient data to allow calculation of dose adjustment. Monitor (desmethyl)clomipramine plasma concentration.	Clinical effect: long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); INR 4.5-6.0; neutropenia 1.0-1.5x10/l; leucopenia 2.0-3.0x10/l; thrombocytopenia 50-75x10/l.	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Select alternative drug (e.g., citalopram, sertralin) or monitor (desmethyl)clomipramine plasma concentration.	Clinical effect: long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; ADE resulting from	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
					increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); INR 4.5-6.0; neutropenia 1.0-1.5x10/l; leucopenia 2.0-3.0x10/l; thrombocytopenia 50-75x10/l.	
Clopidogrel	CPIC (Scott et al. 2013) [50]	*CYP2C19*	Ultrarapid metabolizer (UM) (~5-30% of patients)	Clopidogrel - label recommended dosage and administration.	Increased platelet inhibition; decreased residual platelet aggregation	**ADEQUATE** Evidence of significant association between CYP2C19 (PM,IM) genotype and lack of efficacy due to reduced plasma concentrations of the active metabolite.
			Extensive metabolizer (EM) (~35-50% of patients)	Clopidogrel - label recommended dosage and administration.	Normal platelet inhibition; normal residual platelet aggregation	
			Intermediate metabolizer (IM) (~18-45% of patients)	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor.	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	
			Poor metabolizer (PM) (~2-15% of patients)	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor.	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	**ADEQUATE** CYP2C19 loss-of-function allele carriers have an increased risk of adverse events. Dose escalation studies show that this risk can be overcome by higher maintenance doses of clopidogrel or a switch to alternative drugs (i.e. prasugrel).
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Increased risk for reduced response to clopidogrel. Consider alternative drug.	Clinical effect (statistically significant difference): death; arrhythmia; unanticipated myelosuppression	**CONVINCING** evidence of significant association between CYP2C19 (PM,IM) genotype and lack of efficacy due to reduced plasma concentrations of the active metabolite and therefore elevated risk of adverse cardiovascular events. **ADEQUATE** evidence that patients would profit from a genotype guided dosing regimen to significantly reduce the rate of major adverse cardiovascular events.
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	choose an alternative or double the dose to 150 mg/day (600 mg loading dose). Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolised by CYP2C19 (or to a lesser extent).	Clinical effect (statistically significant difference): death; arrhythmia; unanticipated myelosuppression	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2C19 UM (*17/*17)	NO action is required for this gene-drug interaction.	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); international normalized ratio increase < 4.5 Kinetic effect (statistically significant difference)	
Clozapine	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	No recommendations.	Clinical effect (not statistically significant difference).	
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	No recommendations.	Clinical effect (not statistically significant difference).	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	No recommendations.	Clinical effect (not statistically significant difference).	
Codeine	CPIC (Crews et al. 2014) [15]	*CYP2D6*	Ultrarapid metabolizer (~1-2% of patients)	Avoid codeine use due to potential for toxicity.	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	**ADEQUATE** Risk of toxicity due to increased plasma concentrations of the active metabolite (morphine) (UM).
			Extensive metabolizer (~77-92% of patients	Use label recommended age- or weight-specific dosing.	Normal morphine formation	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Intermediate metabolizer (~2-11% of patients)	Use label recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a non-opioid.	Reduced morphine formation	**ADEQUATE** Lack of efficacy due to reduced plasma concentrations of the active metabolite (PM,IM).
			Poor metabolizer (~5-10% of patients)	Avoid codeine use due to lack of efficacy.	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	
	Canadian Pharmacogenomics Network for Drug Safety (Madadi et al. 2013) [36]	*CYP2D6*		poor metabolizers of CYP2D6 should not receive codeine for pain relief, and ultrametabolizers of CYP2D6 should avoid codeine for pain relief.		ADEQUATE Increasing CYP2D6 activity was associated with increased risk. Lack of efficacy due to reduced plasma concentrations of the active metabolite.
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine-not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief.	The genetic variation reduces the conversion of codeine to morphine. This can result in reduced analgesia	**ADEQUATE** Evidence of significant association concerning lack of efficacy due to reduced plasma concentrations of the active metabolite (PM,IM). **INADEQUATE** evidence that genotyping of (CYP2D6) would predict codeine response in breastfeeding mother/infant pairs when following the safety guidelines.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine-not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief.	The genetic variation reduces the conversion of codeine to morphine. This can result in reduced analgesia.	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9,	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine-not tramadol or oxycodone) or be alert to ADE.	The genetic variation increases the conversion of codeine to morphine. This can result in an increase in side effects. Death has occurred in children who	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			*10, *17, *29, *36, *41) alleles)		received analgesic doses. One adult with reduced kidney function and co-medication with two CYP3A4 inhibitors became comatose after use of codeine for a cough.	
Daunorubicin	Canadian Pharmacogenomics Network for Drug Safety (Aminkeng et al. 2016) [3]	*RARG*	RARG rs2229774	Pharmacogenomic testing should be performed in all pediatric cancer patients who are treated with doxorubicin or daunorubicin for the following genetic variants RARG rs2229774, SLC28A3 rs7853758, UGT1A6*4 rs17863783.	Anthracycline associated cardiotoxicity (ACT).	**ADEQUATE** Evidence of significant association between RARG/UGT1A6/SLC28A3 genotype and risk of anthracycline- induced cardiotoxicity.
		SLC28A3	SLC28A3 rs7853758			
		UGT1A6	UGT1A6 *4 (rs17863783)			
Desflurane	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible	**ADEQUATE** Evidence of sigificant association between CACNA1S gene mutation and a MH susceptibility.
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility	
		RYR1	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible	**CONVINCING** Evidence of sigificant association between CACNA1S gene mutation and a MH susceptibility. **CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS.

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility	**CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. Evidence of significant association between RYR1 gene mutations and risk of adverse drug reaction (MHS).
Desipramine	CPIC (Hicks et al. 2017) [26]	*CYP2D6*	CYP2D6 Ultrarapid metabolizer (~1-20% of patients)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	Increased metabolism of TCAs to less active compounds compared to normal metabolizers. Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	
			CYP2D6 Normal metabolizer (~72-88% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	
			CYP2D6 Intermediate metabolizer (~1-13% of patients)	Consider 25% reduction of recommended starting dose, e.g. utilize therapeutic drug monitoring to guide dose adjustments.	Reduced metabolism of TCAs to less active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients)	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose, e.g utilize therapeutic drug monitoring to guide dose adjustments.		**ADEQUATE** Evidence of significant association between CYP2D6 PM and a decreased metabolism of desipramine, higher plasma concetrations and therefore risk of adverse drug reactions.
Doxepin	CPIC (Hicks et al. 2017) [26]	*CYP2D6*	CYP2D6 Ultrarapid metabolizer (~1-20% of patients)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers).	Increased metabolism of TCAs to less active compounds compared to normal metabolizers. Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				Utilize therapeutic drug monitoring to guide dose adjustments.		
			CYP2D6 Normal metabolizer (~72-88% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	
			CYP2D6 Intermediate metabolizer (~1-13% of patients	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Reduced metabolism of TCAs to less active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients)	Avoid tricyclic use due to potential side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose, e.g. utilize therapeutic drug monitoring to guide dose adjustments.	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects	INADEQUATE Significant evidence that CYP2D6 PM phenotypes are at special risk for high serum antidepressant concentrations and for clinical symptoms of toxcity.
		CYP2C19	CYP2C19 Ultrarapid metabolizer (~2-5% of patients)	Avoid tertiary amine use due to potential of sub-optimal response. Consider alternative drug not metabolized by CYP2C19. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.	
			CYP2C19 Rapid metabolizer (~2-30% of patients)			
			CYP2C19 Normal metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of tertiary amines.	
			CYP2C19 Intermediate metabolizer (~18-45% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism of tertiary amines compared to normal metabolizers.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2C19 Poor metabolizer (~2-15% of patients	Avoid tertiary amine use due to potential of sub-optimal response. Consider alternative drug not metabolized by CYP2C19. For tertiary amines, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Greatly reduced metabolism of tertiary amines compared to normal metabolizers. Decreased conversion of tertiary amines to secondary amines may affect response or side effects	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Reduce dose by 60%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	**INADEQUATE** Evidence of adverse drug reaction in CYP2D6 PM, IM and UM genotype.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	Reduce dose by 20%. Adjust maintenance dose in response to (nor)doxepin plasma concentration.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); INR increase <4.5 Kinetic effect	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Select alternative drug (citalopram, sertraline) or double the standard dose and monitor the effect and side effects or the plasma concentrations of doxepin and nordoxepin in order to set the maintenance dose.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); INR increase <4.5 Kinetic effect. The risk of ineffectiveness and cardiotoxic side effects may be increased.	
Doxorubicin	Canadian Pharmacogenomics Network	*RARG*	RARGrs2229774	Pharmacogenomic testing should be performed in all pediatric cancer patients who are treated with	Anthracycline associated cardiotoxicity (ACT).	**ADEQUATE** Evidence of significant association between RARG/

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	for Drug Safety (Aminkeng et al. 2016) [3]	*SLC28A3*	SLC28A3 rs7853758	doxorubicin or daunorubicin for the following genetic variants RARGrs2229774, SLC28A 3 rs7853758, UGT1A6*4 rs1786378 3.		UGT1A6/SLC28A3 genotype and risk of anthrazykline induced cardiotoxicity.
		UGT1A6	UGT1A6*4 rs17863783			
Duloxetine	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	No recommendation.	Clinical effect (not statistically significant difference).	
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)		--	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)		--	
Efavirenz	DPWG (update 2018) [52]	*CYP2B6*	IM	Determine the efavirenz plasma concentration if side effects occur and reduce the dose if needed. In 14 IM adults, a dose reduction to 400 mg/day (2/3rd of the standard dose) was sufficient to achieve therapeutic plasma concentrations and to reduce or resolve side effects. The therapeutic range	Genetic variations increase the efavirenz plasma concentration and therefore the risk of side effects. However, the efavirenz plasma concentration remains within the therapeutic range for the majority of patients.	**CONVINCING** evidence of significant association between CYP2B6*6 genotyp and higher plasma efavirenz concentration.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				established for efavirenz is 1000-4000 ng/ml.		
			PM	Genetic variations increase the risk of side effects. The standard dose leads to an efavirenz concentration in the toxic range in the majority of patients with this genotype.	The recommended initial dose is 400 mg/day and this dose should be titrated to plasma concentration if needed (further reduction to 200 mg/day or in rare cases an increase to 600 mg/day). The therapeutic range established for efavirenz is 1000-4000 ng/ml.	
Eliglustad	DPWG (update 2018) [52]	*CYP2D6*	UM	Eliglustat is contra-indicated. Choose an alternative if possible.	This gene variation increases the conversion of eliglustat to inactive metabolites. As a result, a normal dose is not effective.	
			IM	Co-medication with both a moderate to strong CYP2D6 inhibitor and a moderate to strong CYP3A inhibitor: Eliglustat is contra-indicated.	This gene variation reduces the conversion of eliglustat to inactive metabolites. However, in the absence of CYP2D6 and CYP3A inhibitors, this does not result in a clinically significant increased risk of side effects.	
			PM	NO co-medication with a CYP3A inhibitor or strong CYP3A inducer: Use a dose of 84 mg once daily.	This gene variation reduces the conversion of eliglustat to inactive metabolites. This increases the risk of side effects, such as a (small, dose-dependent) elongation of the QT interval. CYP3A inhibitors increase this risk even further.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
Enflurane	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible	
				Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility	
		RYR1		Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible	
				Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility	
Escitalopram	CPIC (Hicks et al. 2015) [25]	*CYP2C19*	Ultrarapid metabolizer (~5-30% of patients).	Consider an alternative drug not predominantly metabolized by CYP2C19.	Lower plasma concentrations will increase probability of pharmacotherapy failure.	**CONVINCING** Evidence of significant association between CYP2C19 UM genotype and lower serum concentration of escitalopram.
			Extensive metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism	
			Intermediate metabolizer (~18-45% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism when compared to extensive metabolizers.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Poor metabolizer (~2-15% of patients)	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	**CONVINCING** Evidence of significant association between CYP2C19 genotype and pharmacokinetics of escitalopram like elevated plasma concentrations concerning PM with risk of ADR and lower serum concentration in UM. Evidence of significant association between CYP2C19 PM genotype and risk of adverse drug reaction.
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Avoid escitalopram.	The risk of conversion to another antidepressant is increased as the gene variation leads to a reduction in the escitalopram plasma concentration.	**INADEQUATE** evidence of a significant association between CYP2C19 genotype and pharmacokinetics of escitalopram.
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	Do not exceed the following doses (75% of the standard maximum dose): adults < 65 years 15 mg/day, =65 years 7.5 mg/day	The risk of QT prolongation and torsades de pointes is theoretically increased because the gene variation leads to an increased escitalopram plasma concentration. If you follow the dose recommendation below, the increased plasma concentration and the theoretically increased risk of QT prolongation will be offset.	**INADEQUATE** evidence of significant association between CYP2C19 UM (*17/*17) genotype and reduced plasma serum levels therefore lack of efficacy.
			CYP2C19 UM (*17/*17)	Avoid escitalopram.	The risk of conversion to another antidepressant is increased as the gene variation leads to a reduction in the escitalopram plasma concentration.	
Esomeprazole	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	None	Positive clinical effects.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	None	Positive clinical effects.	**INADEQUATE** Evidence of a significant association between CYP2C19 genotype and pharmacokinetics of esomeprazole, meaning UM(*17/*17) associated with lack of efficacy due to reduced plasma concentrations. Evidence of a significant association between CYP2C19 genotype and a adverse drug reaction risk of esomeprazole. Evidence of lack of efficacy due to reduced plasma concetration.
			CYP2C19 UM (*17/*17)	Helicobacter pylori eradication: increase dose by 50-100%. Be extra alert to insufficient response.	No data was retrieved with the literature search.	
Flecainide	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Reduce dose by 50%, record ECG, monitor plasma concentration.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); INR increase < 4.5; Kinetic effect.	**ADEQUATE** Evidence of significant association between CYP2D6 genotype and Flecainide pharmacokinetics like risk of ADR in PM/IM and reduced plasma concentrations in UM. **ADEQUATE** evidence of significant association between time- dependent variability of ECG such as change in QTc interval and CYP2D6 variants.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	Reduce dose by 25%, record ECG, monitor plasma concentration.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); INR increase < 4.5; Kinetic effect.	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Monitor the plasma concentration as a precaution and record an ECG or select an alternative. Examples of anti-arrhythmic drugs that are not metabolized via CYP2D6 (or to a lesser extent) include sotalol,	The genetic variation increases conversion of flecainide to inactive metabolites. A higher dose is possibly required as a result.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				disopyramide, quinidine and amiodarone.		
Flucloxacillin	DPWG (update 2018) [52]	*HLA-B*	HLA-B*5701	1. Regularly monitor the patient's liver function 2. Choose an alternative if liver enzymes and/or bilirubin levels are elevated.	HLA-B*5701-positive patients have an 80-fold elevated risk of flucloxacillin-induced liver injury. However, the incidence is low (1-2 per 1000 individuals).	**INADEQUATE** evidence of significant associaton between HLA-B*5701 and ADR.
Fluorouracil	CPIC (Amstutz et al. 2018) [4]	*DPYD*	DPYD Normal Metabolizer	Use label-recommended dosage and administration.	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	**CONVINCING** Evidence of significant association between DPYD genotype (PM, IM) and risk of toxicity (myelosupression, gastrointestinal and skin toxicity). **INADEQUATE** Evidence of significant benefit of DPYD genotyping and dose reduction to reduce adverse side effects before administering fluorouracil.
			DPYD Intermediate Metabolizer	Reduce starting dose by 50% followed by titration of dose based on toxicity or therapeutic drug monitoring (if available). Patients with the c.[2846A>T];[2846A>T] genotype may require >50% reduction in starting dose.	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	
			DPYD Poor Metabolizer	Activity score 0.5: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose with early therapeutic drug monitoring. Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*DPYD*	PM (2 inactive alleles, 2 decreased activity alleles, or one inactive	Select alternative drug. Tegafur is not a suitable alternative because this drug is also metabolized by DPD.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	**CONVINCING** Evidence of significant association between DPYD genotype (PM, IM) and risk of toxicity (myelosupression, gastrointestinal and

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			and one decreased activity alleles)			skin toxicity). **ADEQUATE** Evidence of significant benefit of DPYD genotyping and dose reduction to reduce adverse side effects before administering fluorouracil. **ADEQUATE** evidence of no significant drawback on effectiveness when DPYD*2A genotype guided dosing is administered.
			IM (1 active allele and 1 inactive or decreased activity allele)	Reduce dose by 50% or select alternative drug. Tegafur is not a suitable alternative because this drug is also a substrate for DPD. Increase dose in response to toxicity and efficacy.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	
Flupenthixol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	None.	None.	
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	None.	None.	
			UM (gene duplication in absence of inactive or decreased activity alleles)	None.	None.	
Fluvoxamine	CPIC (Hicks et al. 2015) [25]	*CYP2D6*	Ultrarapid metabolizer (~1-2% of patients)	No recommendation due to lack of evidence.	No data available for CYP2D6 Ultrarapid Metabolizers.	
			Extensive metabolizer (~77-92% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism.	
			Intermediate metabolizer (~2-11% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	
			Poor metabolizers (~5-10% of patients)	Consider a 25-50% reduction f of recommended starting dose and titrate to response or use an	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma	**INADEQUATE** Evidence of significant association between CYP2D6 PM

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				alternative drug not metabolized by CYP2D6.	concentrations may increase the probability of side effects.	genotype and risk of adverse drug reaction.
Glibenclamide	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	None.	-	
			CYP2C9 *2/*2	None.	-	
			CYP2C9 *1/*3	None.	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc); neutropenia > 1.5x10/l; leucopenia >3.0x10/l; thrombocytopenia >75x10/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	
			CYP2C9 *2/*3	None.	-	
			CYP2C9 *3/*3	None.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase < 4.5 Kinetic effect.	
Gliclazide	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	None.	-	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2C9 *2/*2	None.	-	
			CYP2C9 *1/*3	None.	-	
			CYP2C9 *2/*3	None.	-	
			CYP2C9 *3/*3	None.	-	
Glimepiride	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	None.	-	**CONVINCING** Evidence of significant association between CYP2C9 genotype and Glimepirid pharmacokinetics.
			CYP2C9 *2/*2	None.	-	
			CYP2C9 *1/*3	None.	-	
			CYP2C9 *2/*3	None.	Clinical effect: long-standing discomfort (> 168 hr), permanent symptom or invalidating injury e.g. failure of prophylaxis of atrial fibrillation; venous thromboembolism; decreased effect of clopidogrel on inhibition of platelet aggregation; ADE resulting from increased bioavailability of phenytoin; INR > 6.0; neutropenia 0.5-1.0x10/l; leucopenia 1.0-2.0x10/l; thrombocytopenia 25-50x10/l; severe diarrhea.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2C9 *3/*3	None	Clinical effect: long-standing discomfort (> 168 hr), permanent symptom or invalidating injury e.g. failure of prophylaxis of atrial fibrillation; venous thromboembolism; decreased effect of clopidogrel on inhibition of platelet aggregation; ADE resulting from increased bioavailability of phenytoin; INR > 6.0; neutropenia 0.5-1.0x10/l; leucopenia 1.0-2.0x10/l; thrombocytopenia 25-50x10/l; severe diarrhea.	
Haloperidol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	Reduce dose by 50% or select alternative drug (e.g., pimozide, flupenthixol, fluphenazine, quetiapine, olanzapine, clozapine).	The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased plasma concentrations of haloperidol and the active metabolite.	**INADEQUATE** Evidence of a significant association between pharmakoninetics and pharmacodynamics of haloperidol and CYP2D6 PM genotype like adverse drug reactions or CYp2D6 UM genotyoe and reduced plasma concentrations.
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	NO action is required for this gene-drug interaction.	Minor clinical effect: QTc prolongation (<450 ms women, <470 ms men); INR increase < 4.5 Kinetic effect.	
			UM (gene duplication in absence of inactive or decreased activity alleles)	1. be alert to possible reduced plasma concentrations of haloperidol and reduced haloperidol and increase the dose based on results of therapeutic drug monitoring, 2. or prescribe an alternative according to the current guidelines.	The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause decreased plasma concentrations of haloperidol and the active metabolite reduced haloperidol.	
Halothane	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used,	Malignant Hyperthermia susceptible.	**CONVINCING** Evidence of sigificant association between CACNA1S gene mutation and a MH suscepibility. **CONVINCING** Halogenated volatile anesthetics or depolarizing muscle

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				except in extraordinary circumstances where the benefits outweigh the risks.		relaxants succinylcholine are relatively contraindicated in persons with MHS.
				Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
		RYR1		Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. Evidence of significant association between RYR1 gene mutations and risk of adverse drug reaction (MHS).
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
Hormonal contraceptives for systemic use	DPWG (Swen et al. 2011, update 2018) [30, 52]	*F5*	F5 homozygous rs6025 TT	Positive (family) history of thrombotic events: avoid estrogen-containing oral contraceptives and select alternative (e.g., copper intrauterine device, progestin-only contraceptive). Negative (family) history of thrombotic events: avoid additional risk factors (e.g., obesity, smoking).	The homozygously present genetic polymorphism "factor V Leiden" causes an increased tendency to coagulation, resulting in an increased risk of venous thromboembolism. Contraceptives containing oestrogens can increase this risk even further.	**CONVINCING** Evidence of a significant association between Factor V Leiden, an increased risk of thrombosis (VTE) an oral contraceptives. Evidence of significant association between homozygous rs6025TT/CT genotype and risk of adverse drug reactions like venous thromboembolism in association with oral contraceptive.
Imipramine	CPIC (Hicks et al. 2016) [26]	CYP2C19	CYP2C19 Ultrarapid metabolizer (~2-5% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Greater conversion of tertiary amines to secondary amines may affect response or side effects.	**ADEQUATE** Evidence of significant association between CYP2C19 genotype and pharmacokinetics of imipramine.
			CYP2C19 Rapid metabolizer (~2-30% of patients)			

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2C19 Normal metabolizer (~35-50% of patients)d	Initiate therapy with recommended starting dose.	Normal metabolism of tertiary amines.	
			CYP2C19 Intermediate metabolizer (~18-45% of patients)		Reduced metabolism of tertiary amines compared to normal metabolizers.	
			CYP2C19 Poor metabolizer (~2-15% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. For tertiary amines, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Decreased conversion of tertiary amines to secondary amines may affect response or side effects.	
		CYP2D6	CYP2D6 Ultrarapid metabolizer (~1-20% of patients	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	**ADEQUATE** Evidence of significant association between CYP2D6 genotype and pharmacokinetics of imipramine.
			CYP2D6 Normal metabolizer (~72-88% of patients)d	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	
			CYP2D6 Intermediate metabolizer (~1-13% of patients)d	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Reduced metabolism of TCAs to less active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients)	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				monitoring to guide dose adjustments.		
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Reduce dose by 30% and monitor plasma concentration of imipramine and desipramine or select alternative drug (e.g. fluvoxamine, mirtazapine)	The risk of side effects is increased. The gene variation results in an increase in the plasma concentration of imipramine+desipramine.	**ADEQUATE** Evidence of significant association between CYP2C19 genotype and pharmacokinetics of imipramine.
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	No action is required for this gene-drug interaction.	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); international normalized ratio increase < 4.5 Kinetic effect (statistically significant difference)	
			CYP2C19 UM (*17/*17)	No action is required for this gene-drug interaction.	No data was retrieved with the literature search.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	Reduce dose by 70% and monitor imipramine and desipramine plasma concentrations.	The risk of side effects may be increased, because the gene variation leads to increased plasma concentrations of imipramine and the active metabolite desipramine.	**ADEQUATE** Evidence of significant association between CYP2D6 genotype and pharmacokinetics of imipramine.
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	Reduce dose by 30% and monitor imipramine and desipramine plasma concentrations.	Minor clinical effect: QTc prolongation (<450 ms men, <470 ms women); INR increase < 4.5. Kinetic effect.	
			UM (gene duplication in absence of inactive or decreased activity alleles)	Use 1.7 times the standard dose and monitor the effect and side effects or the plasma concentrations of imipramine and desipramine in order to set the maintenance dose. If a dose increase is not desired due	The risk of ineffectiveness and cardiotoxic side effects may be increased. The gene variation leads to reduced plasma concentrations of imipramine and the active metabolite desipramine	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				to the potentially cardiotoxic hydroxy metabolites: avoid imipramine. Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, citalopram and sertraline.	and to increased plasma concentrations of the potentially cardiotoxic hydroxy metabolites.	
Irinotecan	DPWG (Swen et al. 2011, update 2018) [30, 52]	*UGT1A1*	*1/*28	NO action is needed for this gene-drug interaction.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	
			*28/*28	Start with 70% of the standard dose If the patient tolerates this initial dose, the dose can be increased, guided by the neutrophil count.	Clinical effect: Failure of lifesaving therapy e.g. anticipated myelosuppression; prevention of breast cancer relapse; arrhythmia; neutropenia <0.5x10/l; leucopenia <1.0x10/l; thrombocytopenia <25x10/l; life-threatening complications from diarrhea.	**CONVINCING** Evidence of a significant association between UGT1A1 (UGT1A1*28) genotype and risk of toxicity (hematological and / or digestive toxicity) when administering Irinotecan. **INADEQUATE** Evidence of advantage of UGT1A1 genotyping as a useful prognostic indicator of severe toxicity for patients treated with this irinotecan dosage and schedule.
	Professional Society (Etienne-Grimaldi et al. 2015) [17]	*UGT1A1*	UGT1A1*28/*28 , UGT1A1*1/*1	Reduce dose of irinotecan in patients with the UGT1A1*28/*28 genotype, and prescribe high-dose irinotecan (>=240 mg/m2) only to patients with the UGT1A1*1/*1 genotype.	Hematological and gastrointestinal toxicities.	**CONVINCING** Evidence of a significant association between UGT1A1 (UGT1A1*28) genotype and risk of toxicity (hematological and / or digestive toxicity) and irinotecan. **INADEQUATE** Evidence of advantage of UGT1A1 genotyping as a useful prognostic indicator of severe toxicity for patients treated with this irinotecan dosage and schedule.
Isoflurane	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Evidence of significant association between CACNA1S gene mutation and a MH susceptibility. **CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
		RYR1	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. Evidence of significant association between RYR1 gene mutations and risk of adverse drug reaction (MHS).
				Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
Ivacaftor	CPIC (Clancy et al. 2014) [14]	*CFTR*	Homozygous or Heterozygous G551D-CFTR, rs75527207 genotype AA or AG	Use ivacaftor according to the product label .	Significant improvement in lung function, weight, risk of pulmonary exacerbation, patient reported outcomes, and reduction in sweat chloride concentrations through enhanced CFTR channel activity (increase probability of open channel).	**INADEQUATE** Considerable evidence of an association between G551D-CFTR mutation and a lack of efficacy due to pharmacodynamics mechanisms and therefore Ivacaftor is not recommended.
			Homozygous for F508del-CFTR, rs113993960 or rs199826652 genotype del/del	Ivacaftor is not recommended.	No significant reduction in sweat chloride concentrations; no changes in other clinical measurements including spirometric measurements, pulmonary exacerbations, or body weight. Unlikely to respond to treatment.	**ADEQUATE** Considerable evidence of an association between F508del-CFTR homozygous mutation and a lack of efficacy due to pharmacodynamics mechanisms and therefore Ivacaftor is not recommended.
			Homozygous or heterozygous for one of the following CFTR variants: E56K, P67L, R74W, D110E, D110H, R117C, R117H,	Use ivacaftor according to the product label.	Significantly enhanced channel open probability in vitro. In vitro assays with CFBEo-cells expressing S549N-CFTR showed ivacaftor potentiated chloride channel function, improved lung	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			G178R, E193K, L206W, R347H, R352Q, A455E, S549N, S549R, G551D, G551S, D579G, S945L, S997F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, G1244E, S1251N, S1255P, D1270N, G1349D		function after ivacaftor treatment in a 12-year-old girl with CF with a copy of the S549N variant. Improvement in sweat chloride and CFQ-R respiratory domain scores in patients with the R117H variant.	
Lansoprazole	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	NO action is needed for this gene-drug interaction.	The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.	**ADEQUATE** evidence of significant association between CYP2C19 genotype and the therapeutic effect and efficacy of lansoprazole on erosive reflux esophagitis. **INADEQUATE** evidence for significant improving of eradication rates with pharmacogenomics-based tailored treatment.
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	NO action is needed for this gene-drug interaction.	The higher plasma concentration of lansoprazole results in an increase in the therapeutic effectiveness, without an increase in the incidence of side effects.	
			CYP2C19 UM (*17/*17)	Helicobacter pylori eradication: increase dose by 200%. Be extra alert to insufficient response.	The genetic variation may reduce lansoprazole plasma concentrations and therefore lansoprazole effectiveness.	
Mercaptopurine	CPIC (Relling et al. 2018) [45]	*TPMT*	Homozygous wild-type or normal, high activity (two functional *1 alleles)	Start with normal starting dose (e.g., 75 mg/m2/d or 1.5 mg/kg/d) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy).	Lower concentrations of TGN metabolites, higher methyl TIMP.	**CONVINCING** Evidence of significant association between TPMT genotype and risk of toxicity (myelosuppression) of mercaptopurin. Significant benefit of genotyping for the major TPMT variant

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Heterozygote or intermediate activity (one functional allele - *1, plus one nonfunctional allele - *2, *3A, *3B, *3C, or *4)	Start with reduced doses (start at 30-70% of full dose: e.g., at 50 mg/m2/d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2-4 weeks to reach steady state after each dose adjustment.	Moderate to high concentrations of TGN metabolites; low concentrations of methyl TIMP.	alleles as a valuable tool to prevent AZA toxicity.
			Homozygous variant, mutant, low, or deficient activity (two nonfunctional alleles - *2, *3A, *3B, *3C, or *4)	For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m2/d given just thrice a week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methyl TIMP metabolites.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*TPMT*	IM (one inactive allele: *2, *3, *4-*18)	Select alternative drug or reduce dose by 50%. Increase dose in response of hematologic monitoring and efficacy.	The genetic variation reduces the conversion of azathioprine and mercaptopurine to mainly inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression.	**CONVINCING** Evidence of significant association between TPMT genotype and risk of toxicity (myelosuppression) of mercaptopurin.
			PM (two inactive alleles: *2, *3, *4-*18)	Select alternative drug or reduce dose by 90%. Increase dose in response of hematology monitoring and efficacy.	Clinical effect : death; arrhythmia; unanticipated myelosuppression.	
Methoxyflurane	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used,	Malignant Hyperthermia susceptible.	**CONVINCING** Evidence of significant association between CACNA1S gene mutation and a MH susceptibility. **CONVINCING** Halogenated volatile anesthetics or depolarizing muscle

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				except in extraordinary circumstances where the benefits outweigh the risks.		relaxants succinylcholine are relatively contraindicated in persons with MHS.
				Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
		RYR1	An individual negative for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. Evidence of significant association between RYR1 gene mutations and risk of adverse drug reaction (MHS).
				Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
Metoprolol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75%. Be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol).	The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.	**CONVINCING** Evidence of a significant association between CYP2D6 genotype (PM, IM) and pharmacokinetics (plasma concentrations) of metoprolol and his major active metabolite a-hydroxymetoprolol and which furthermore contributes to interindividual differences in metoprolol response. **ADEQUATE** Evidence of a significant association between CYP2D6 genotype and the risk of adverse drug reactions.
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 50%. Be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol).	The gene variation reduces the conversion of metoprolol to inactive metabolites. However, the clinical consequences are limited mainly to the occurrence of asymptomatic bradycardia.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			UM (gene duplication in absence of inactive or decreased activity alleles)	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE. Select alternative drug (e.g., atenolol, bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE.	The gene variation increases the conversion of metoprolol to inactive metabolites. This can increase the dose requirement. However, with a target dose of 200 mg/day, there was no effect on the blood pressure and hardly any effect on the reduction of the heart rate.	
Mirtazapine	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	None.	Clinical effect: short-lived discomfort (< 48 h) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc); neutropenia > 1.5x10/l; leucopenia >3.0x10/l; thrombocytopenia >75x10/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	None.	Minor clinical effect: QTc prolongation (<450 ms men, <470 ms women); INR increase < 4.5. Kinetic effect.	
			UM (gene duplication in absence of inactive or decreased activity alleles)	None.	Minor clinical effect: QTc prolongation (<450 ms men, <470 ms women); INR increase <4.5. Kinetic effect.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
Moclobemide	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	None.	Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); international normalized ratio increase < 4.5. Kinetic effect (statistically significant difference)	
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	None.	No data was retrieved with the literature search.	
			CYP2C19 UM (*17/*17)	None.	No data was retrieved with the literature search.	
Nortriptyline	CPIC (Hicks et al. 2017) [26]	*CYP2D6*	CYP2D6 Ultrarapid metabolizer (~1-20% of patients)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	Increased metabolism of TCAs to less active compounds compared to normal metabolizers. Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	**CONVINCING** Evidence of significant association between CYP2D6 (UM) genotype and lack of efficacy due to reduced plasma concentrations.
			CYP2D6 Normal metabolizer (~72-88% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	
			CYP2D6 Intermediate metabolizer (~1-13% of patients)	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Reduced metabolism of TCAs to less active compounds when compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients)	Avoid tricyclic use due to potential side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose.g Utilize therapeutic drug	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers. Higher plasma concentrations of active drug will increase the probability of side effects.	**INADEQUATE** Evidence of significant association between CYP2D6 (PM, IM) genotype and the risk of adverse drug reaction.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				monitoring to guide dose adjustments.		
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	Reduce dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations.	The risk of side effects may be increased, because the gene variation leads to an increased plasma concentration of nortriptyline.	**INADEQUATE** Evidence of significant association between CYP2D6 (PM, IM) genotype and the risk of adverse drug reaction. I**NADEQUATE** evidence of significant relationship between the CYP450 genotype and serum concentrations of nortriptyline and genotypes as predictive for differences in treatment response.
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	Reduce dose by 40% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations.	The risk of side effects may be increased because the gene variation leads to an increased plasma concentration of nortriptyline.	**ADEQUATE** Evidence that CYP2D6 genotype influences the interindividual variance in oral clearance and steady-state plasma concentrations.
			UM (gene duplication in absence of inactive or decreased activity alleles)	Select alternative drug (e.g., citalopram, sertraline) or increase dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations.	The risk of ineffectiveness and cardiotoxic effects may be increased. The gene variation leads to a decrease in the plasma concentration of nortriptyline and an increase in the plasma concentration of the cardiotoxic metabolite Z-10-hydroxynortriptyline.	**ADEQUATE** Evidence of significant association between CYP2D6 (UM) genotype and lack of efficacy due to reduced plasma concentrations.
Olanzapine	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	None.	-	
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	None.	-	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			UM (gene duplication in absence of inactive or decreased activity alleles)	None.	None.	
Omeprazole	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	No action is required for this gene-drug interaction.	The higher plasma concentration of omeprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.	
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	No action is required for this gene-drug interaction.	Positive clinical effects.	
			CYP2C19 UM (*17/*17)	Helicobacter pylori eradication: increase dose by 100-200%. Be extra alert to insufficient response.	The genetic variation may lead to a reduced omeprazole plasma concentration and therefore reduced effectiveness. Minor clinical effect (statistically significant difference): QTc prolongation (<450 ms female, <470 ms male); international normalized ratio increase < 4.5 Kinetic effect (statistically significant difference).	**CONVINCING** Evidence of significant association between CYP2C19 (UM) genotype and lack of efficacy due to reduced plasma concentrations. **CONVINCING** evidence of significant association between CYP2C19 polymorphism and therapeutic efficacy of omeprazole. Furthermore CYP2C19*2 and *3 influence the PKs and PDs of omeprazole.
Ondansetron	CPIC (Bell et al. 2017) [7]	*CYP2D6*	Ultrarapid metabolizer	Select and alternative drug not predominantly metabolized by CYP2D6 (i.e. granisetron).	Increased metabolism to less active compounds when compared to normal metabolizers and is associated with decreased response to ondansetron and tropisetron (i.e. vomiting).	**INADEQUATE** Evidence of significant association between CYP2D6 genotype and pharmacokinetics of ondansetron.
			Normal metabolizer	Initiate therapy with recommended starting dose.	Normal metabolism.	
			Intermediate metabolizer	Initiate therapy with recommended starting dose.	Very limited data available for CYP2D6 intermediate metabolizers.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Poor metabolizer	Initiate therapy with recommended starting dose	Very limited data available for CYP2D6 poor metabolizers.	
Oxcarbazepine	CPIC (Phillips et al. 2017) [43]	*HLA-B*	Non-carrier of HLA-B*15:02. No HLA-B*15:02 alleles reported, often reported as "negative" on genotyping tests.	Use oxcarbazepine per standard dosing guidelines.	Normal or reduced risk of oxcarbazepine-induced SJS/TEN.	**ADEQUATE** Evidence of significant association between HLA-B*15:02 genotype and OXC-induced MPE (maculopapular eruption) OXC-SJS (Steve-Johnson-Syndrome). Evidence of significant association between HLA-B*15:02 genotype and OXC-induced MPE (maculopapular eruption) OXC-SJS (Steve-Johnson-Syndrome).
			Carrier of HLA-B*15:02. One or two *15:02 alleles, often reported as "positive" on a genotyping test.	If patient is oxcarbazepine-naive, do not use oxcarbazepine. If the patient has previously used oxcarbazepine consistently for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of oxcarbazepine in the future.	Increased risk of oxcarbazepine-induced SJS/TEN.	
Oxycodone	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	Insufficient data to allow calculation of dose adjustment. Select alternate drug - not tramadol or codeine.	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc); neutropenia > 1.5x109/l; leucopenia > 3.0x109/l; thrombocytopenia > 75x10^9/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	**ADEQUATE** Evidence of significant association between CYP2D6 genotype (PM, IM) and lack of efficacy due to reduced formation of the active metabolite oxymorphone.
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	Insufficient data to allow calculation of dose adjustment. Select alternate drug - not tramadol or codeine.	-	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			UM (gene duplication in absence of inactive or decreased activity alleles)	Insufficient data to allow calculation of dose adjustment. Select alternate drug (NOT tramadol or codeine).	Minor clinical effect: QTc prolongation (<450 ms men, <470 ms women); INR increase < 4.5. Kinetic effect.	**INADEQUATE** Evidence of significant association between CYP2D6 genotype (UM) and ADR risk due to enhanced formation of metabolites.
Pantoprazole	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	NO action is required for this gene-drug interaction.	The higher plasma concentration of pantoprazole results in an increase in the therapeutic effectiveness, without an increase in the side effects.	
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	NO action is required for this gene-drug interaction.	Positive clinical effects.	
			CYP2C19 UM (*17/*17)	For Helicobacter pylori ERADICATION THERAPY: 1. use a 5-fold higher dose. 2. advise the patient to contact their doctor if symptoms of dyspepsia persist. OTHER INDICATIONS:1. be alert to reduced effectiveness. 2. if necessary, use a 5-fold higher dose. 3. advise the patient to report persisting symptoms of dyspepsia.	The genetic variation may lead to a reduced pantoprazole plasma concentration and therefore reduced pantoprazole effectiveness.	**ADEQUATE** Evidence of significant association between CYP2C19 (UM) genotype and lack of efficacy due to reduced plasma concentrations.
Paroxetine	CPIC (Hicks et al. 2015) [25]	*CYP2D6*	Ultrarapid metabolizer (~1-2% of patients	Select alternative drug not predominantly metabolized by CYP2D6.	Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure.	**CONVINCING** Evidence of significant association between CYP2D6 genotype (UM) and the lack of efficacy due to reduced plasma concentrations
			Extensive metabolizer (~77-92% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism.	
			Intermediate metabolizer (~2-11% of patients)	Initiate therapy with recommended starting dose.	Higher plasma concentrations may increase the probability of side effects.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Poor metabolizers (~5-10% of patients)	Select alternative drug not predominantly metabolized by CYP2D6 d or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Higher plasma concentrations may increase the probability of side effects.	**INADEQUATE** Evidence of significant association between CYP2D6 genotype (UM, PM) and risk of adverse drug reaction.
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	NO action is needed for this gene-drug interaction.	The plasma concentration of paroxetine can increase as a result of the reduced activity of CYP2D6.	
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	NO action is needed for this gene-drug interaction.	The plasma concentration of paroxetine can increase as a result of the reduced activity of CYP2D6.	
			UM (gene duplication in absence of inactive or decreased activity alleles)	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline).	Efficacy will probably be lacking. The genetic variation increases the conversion of paroxetine.	**CONVINCING** Evidence of significant association between CYP2D6 genotype (UM) and the lack of efficacy due to reduced plasma concentrations.
Peginterferon alfa-2a	CPIC (Muir et al. 2014) [41]	*IFNL3*	CC	Approximately 80-90% of patients are eligible for shortened therapy (24-28 weeks vs. 48 weeks). Weighs in favor of using PEG-IFN alpha and RBV containing regimens.	Approximately 70% chance for SVR c after 48 weeks of treatment. Consider implications before initiating PEG-IFN alpha and RBV containing regimens.	CONVINCING Evidence of significant association between IFNL3 (rs12979860 CC) genotype and a 90% chance for SVR (sustained viral response) after 24-48 weeks of treatment with protease inhibitor combinations with peginterferon- alpha and ribavirin therapy in HCV genotype 1 patients. Evidence of significant association between IFNL3 (rs12979860 CT/TT) genotype and a 60% chance for SVR (sustained viral response) after 24-48 weeks of treatment with protease inhibitor combinations with peginterferon- alpha and ribavirin therapy in HCV genotype 1 patients.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
		IFNL3	CT or TT	Approximately 50% of patients are eligible for shortened therapy (24-28 weeks). Consider implications before initiating PEG-IFN and RBV containing regimens.	Approximately 30% chance for SVR c after 48 weeks of treatment.	
Phenprocoumon	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	None.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	**ADEQUATE** Evidence of significant association between CP2C9 (PM, *2/*2, *2/*3, *3/*3) genotype and risk of adverse drug reactions. **CONVINCING** evidence of significant association of phenprocoumon maintenance dosage and polymorphisms in the VKORC1 gene. **INADEQUATE** evidence of significant benefit of genotype-guided dosing in order to increased the mean percentage of time in the therapeutic INR range.
			CYP2C9 *2/*2	Check INR more frequently.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	
			CYP2C9 *1/*3	None.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	
			CYP2C9 *2/*3	Check INR more frequently.	Clinical effect: death; arrhythmia; unanticipated myelosuppression.	
			CYP2C9 *3/*3	Check INR more frequently.	Clinical effect: long-standing discomfort (> 168 hr), permanent symptom or invalidating injury e.g. failure of prophylaxis of atrial fibrillation; venous thromboembolism; decreased effect of clopidogrel on inhibition of platelet aggregation; ADE resulting from increased bioavailability of phenytoin; INR > 6.0; neutropenia 0.5-1.0x10{}9/l; leucopenia 1.0-2.0x10{}9/l; thrombocytopenia 25-50x10{}9/l; severe diarrhea.	
		VKORC1	VKORC1 rs9934438 AG	No action is needed for this gene-drug interaction	The gene variation leads to a lower dose requirement, but regular monitoring of patients ensures that this does not lead to a distinct increase in the risk of bleeding.	**ADEQUATE** Evidence of significant association between VKORC1 (rs9934438 AA) genotype and risk of adverse drug reaction.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			VKORC1 rs9934438 AA	Check INR more frequently.	An INR = 6, resulting in an increased risk of bleeding, occurs in 17% of these patients with standard regulation by the Anticoagulation Clinic. The genetic variation increases the sensitivity to phenprocoumon.	
Phenytoin	CPIC (Caudle et al. 2014) [13]	*CYP2C9*	CYP2C9 Extensive Metabolizer	If patient is phenytoin-naive, do not use phenytoin/fosphenytoin.	Increased risk of phenytoin-induced SJS/TEN.	ADEQUATE Evidence of significant association between CYP2C9 genotype (PM, IM) and a risk of toxicity.
			CYP2C9 Intermediate Metabolizer			
			CYP2C9 Poor Metabolizer			
		HLA-B	Normal activity ~91% of patients; An individual carrying 2 normal activity alleles; Example diplotype:*1/*1	Initiate therapy with recommended maintenance dose.	Normal phenytoin metabolism.	CONVINCING Evidence of significant association between HLA-B (15:02) genotype and IDR risk (increased risk of phenytoin induced SJS/TEN).
			Heterozygote ~8% of patients; An individual carrying one normal activity allele plus one decreased function allele; Example diplotypes: *1/*3, *1/*2	Consider 25% reduction of recommended starting maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring and response.	Reduced phenytoin metabolism, higher plasma concentrations will increase probability of toxicities.	
			Homozygous variant ~1% of patients; An individual carrying 2 decreased function alleles; Example diplotypes: *2/*2, *3/*3, *2/*3	Consider 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.		

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days.	Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects.	**INADEQUATE** Evidence of significant association between CYP2C9 genotype (PM, IM) and a risk of toxicity.
			CYP2C9 *2/*2	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5 Kinetic effect	**ADEQUATE** Evidence of significant association between CYP2C9 genotype and increased phenytoin plasma levels.
			CYP2C9 *1/*3	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days.	Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients.	
			CYP2C9 *2/*3	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5 Kinetic effect	
			CYP2C9 *3/*3	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days.	Genetic variation reduces conversion of phenytoin to inactive metabolites. This increases the risk of side effects. The life-threatening cutaneous side effects Stevens-Johnson Syndrome and toxic epidermal necrolysis may occur, especially in Asian patients.	**ADEQUATE** evidence of significant association between CYP2C9*3 genotype and phenytoin related SJS/TEN.
Pimozide	DPWG (update 2018) [52]	*CYP2D6*	UM	No action is required for this gene-drug interaction.	This gene variation can result in lower pimozide concentrations. However, there is no evidence of reduced effectiveness.	**INADEQUATE** evidence of significant association between CYP3A4 genotype and increased serum levels of CYP3A4 metabolized antipsychotic drugs**.**
			IM	Use no more than the following doses (80% of the standard maximum dose): adults 16 mg/day	The risk of QT-prolongation – and thereby also the risk of torsade de points – is theoretically increased, because the genetic variation results in an increase in the	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				children 0.08 mg/kg per day to a maximum of 3 mg/day	plasma concentration of pimozide. The risk of an excessively high plasma concentration can be negated by following the dose recommendations provided.	
			PM	Use no more than the following doses (50% of the standard maximum dose): adults 10 mg/day children 0.05 mg/kg per day to a maximum of 2 mg/day.	The risk of QT-prolongation – and thereby also the risk of torsade de points – is theoretically increased, because the genetic variation results in an increase in the plasma concentration of pimozide. The risk of an excessively high plasma concentration can be negated by following the dose recommendations provided.	
Propafenone	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (2 inactive alleles)	Reduce dose by 70%, record ECG, monitor plasma concentration.	Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of side effects.	**INADEQUATE** Evidence of significant association between CYP2D6 (PM, IM) genotype and risk of adverse drug reaction.
			IM (2 decreased activity alleles, or 1 active and 1 inactive allele, or 1 decreased activity and 1 inactive allele)	Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone).	Genetic variation increases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This may increase the risk of side effects. Minor clinical effect: QTc prolongation (<450 ms male, <470 ms female); INR increase < 4.5, Kinetic effect.	
			UM (gene duplication in absence of inactive or decreased activity alleles)	Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone).	Genetic variation decreases the sum of the plasma concentrations of propafenone and the active metabolite 5-hydroxypropafenone. This increases the risk of reduced or no efficacy.	**INADEQUATE** Evidence of significant association between CYP2D6 (UM) genotype and a lack of efficacy due to reduced plasma concentrations.

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
Rabeprazole	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	None.	Positive clinical effects.	
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	None.	-	
			CYP2C19 UM (*17/*17)	None.	No data was retrieved with the literature search.	
Rasburicase	CPIC (Relling et al. 2014) [46]	*G6PD*	Normal. A male carrying a non-deficient (class IV) allele or a female carrying two non-deficient (class IV) alleles.	No reason to withhold rasburicase based on G6PD status.	Low or reduced risk of hemolytic anemia.	**INADEQUATE** Evidence of significant association between G6PD genotype and the suggestion to select an alternative drug (allopurinol) since Rasuricase is contraindicated. Evidence of significant association between G6PD genotype and the suggestion to measure the enzyme activity to ascertain that G6PD status is normal.
			Deficient or Deficient with CNSHA. A male carrying a class I, II or III allele, a female carrying two deficient class I-III alleles.	Rasburicase is contraindicated; alternatives include allopurinol.	At risk of acute hemolytic anemia.	
			A female carrying one non-deficient (class IV) and one deficient (class I-III variants) allele.	To ascertain that G6PD status is normal, enzyme activity must be measured; alternatives include allopurinol.	Unknown risk of hemolytic anemia.	
Ribavirin	CPIC (Muir et al. 2014) [41]	*IFNL3*	CC	Approximately 80-90% of patients are eligible for shortened therapy (24-28 weeks vs. 48 weeks). Weighs in favor of using PEG-IFN alpha and RBV containing regimens.	Approximately 70% chance for SVR c after 48 weeks of treatment.	**CONVINCING** Evidence of significant association between IFNL3 (rs12979860 CC) genotype and a approximately 90% chance for SVR after 24-48 weeks of treatment with protease inhibitor combinations with

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CT or TT	Approximately 50% of patients are eligible for shortened therapy (24-28 weeks)d. Consider implications before initiating PEG-IFN and RBV containing regimens.	Approximately 30% chance for SVR c after 48 weeks of treatment.	peginterferon- alpha and ribavirin therapy in HCV genotype 1 patients. **CONVINCING** evidence of significant association between IFNL3 (rs12979860 CT, TT) genotype and a approximately 60% chance for SVR after 24-48 weeks of treatment with protease inhibitor combinations with peginterferon- alpha and ribavirin therapy in HCV genotype 1 patients. **CONVINCING** Evidence of significant association between IFNL3(rs12979860 CC) genotype and higher rates of rapid virological response.
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*HLA-B*	HLA-B*44	None.	Clinical effect: long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); INR 4.5-6.0; neutropenia 1.0-1.5x10/l; leucopenia 2.0-3.0x10/l; thrombocytopenia 50-75x10/l.	
Risperidone	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	No action is needed for this gene-drug interaction.	The genetic variation can result in both an increase in side effects and a stronger decrease in schizophrenia symptoms. In addition to this, the genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.	**ADEQUATE** Evidence of significant association between CYP2D6 (PM, IM) and risk of adverse drug reaction.

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	No action is needed for this gene-drug interaction.	The genetic variation may lead to a decrease in the required maintenance dose. However, as the effect on the dose is smaller than that of the normal biological variation, action is not useful.	
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	No action is needed for this gene-drug interaction.	Genetic variation may lead to an increase in the required maintenance dose. However, as the effect is smaller than that of the normal biological variation, action is not useful.	**INADEQUATE** Evidence of significant association between CYP2D6 (UM) and a lack of efficacy due to reduced plasma concentrations.
Sertraline	CPIC (Hicks et al. 2015) [25]	*CYP2C19*	Ultrarapid metabolizer (~5-30% of patients)	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.	Increased metabolism when compared to extensive metabolizers.	**INADEQUATE** Evidenc of significant association between CYP2C19 (UM) genotype and a lack of efficacy due to reduced plasma concentrations.
			Extensive metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism.	
			Intermediate metabolizer (~18-45% of patients)	Initiate therapy with recommended starting dose.	Reduced metabolism when compared to extensive metabolizers.	
			Poor metabolizer (~2-15% of patients)	Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Do not give doses exceeding 75 mg/day. Guide the dose by response and side effects and/or sertraline plasma concentration.	The risk of side effects is increased. The gene variation leads to increased plasma concentrations of sertraline.	**INADEQUATE** Evidenc of significant association between CYP2C19 (PM, IM) genotype and higher plasma levels and therefore risk of ADR.
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	No action is needed for this gene-drug interaction.	The gene variation has a minor effect on the sertraline plasma concentration. No effect on side effects was found.	I**NADEQUATE** evidence of significant association between CYP2C19 metabolizer status and response to sertraline.
			CYP2C19 UM (*17/*17)	No action is needed for this gene-drug interaction.	The gene variation has a negligible effect on the plasma concentration of sertraline. Moreover, no significant effect on response and side effects has been found.	
Sevoflurane	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Evidence of sigificant association between CACNA1S gene mutation and a MH susceptibility. **CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS.
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
		RYR1	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. Evidence of significant association between RYR1 gene mutations and risk of adverse drug reaction (MHS).

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
Simvastatin	CPIC (Ramsey et al. 2014) [44]	*SLCO1B1*	Normal function, Homozygous wild-type (two normal function alleles)	Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines.	Normal myopathy risk.	**CONVINCING** Evidence of significant association between SLCO1B1 (rs4149056 CC, TC) genotype and a risk of adverse drug reaction (simvastatin- induced myopathy). **ADEQUATE** evidence of significant association between SLCO1B1 genotype and ADR and drug efficacy.
			Intermediate function, Heterozygous (one normal function allele plus one decreased function allele)	Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin); Consider routine CK surveillance.	Intermediate myopathy risk.	
			Low function, Homozygous variant or mutant (two decreased function alleles)		High myopathy risk.	
Simvastatin	DPWG (update 2018) [52]	*SLCO1B1*	512 CC	Choose an alternative. Consider any additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by SLCO1B1 polymorphisms.	The genetic polymorphism leads to reduced simvastatin transport to the liver. This increases simvastatin plasma concentrations and therefore the risk of myopathy.	**ADEQUATE** evidence of significant association between SLCO1B1 genotype and ADR and drug efficacy.
			512 TC	1. Choose an alternative. Consider any additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by SLCO1B1 polymorphisms. 2. If an alternative is not an option: Avoid simvastatin doses exceeding 40 mg/day.	The genetic polymorphism may lead to reduced simvastatin transport to the liver. This may increase simvastatin plasma concentrations and therefore the risk of myopathy.	
Succinylcholine	CPIC (Gonsalves et al. 2018) [23]	*CACNA1S*	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used,	Malignant Hyperthermia susceptible.	**CONVINCING** Evidence of sigificant association between CACNA1S gene mutation and a MH susceptibility. **CONVINCING** Halogenated volatile anesthetics or depolarizing muscle

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				except in extraordinary circumstances where the benefits outweigh the risks.		relaxants succinylcholine are relatively contraindicated in persons with MHS.
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
		RYR1	An individual heterozygous for a RYR1 or CACNA1S	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used except in extraordinary circumstances where the benefits outweigh the risks.	Malignant Hyperthermia susceptible.	**CONVINCING** Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. Evidence of significant association between RYR1 gene mutations and risk of adverse drug reaction (MHS).
			An individual negative for a RYR1 or CACNA1S	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.	Uncertain susceptibility.	
Tacrolimus	CPIC (Birdwell et al. 2015) [8]	*CYP3A5*	Extensive metabolizer (CYP3A5 expresser)	Increase starting dose 1.5 to 2 times recommended starting dose. Total starting dose should not exceed 0.3mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Lower dose-adjusted through concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	**CONVICING** Evidence of significant association between CYP3A5 (IM, EM) genotype and lack of efficacy due to reduced plasma concentrations. **ADEQUATE** Evidence of significant benefit of CYP3A5 genotyping for tacrolimus dose adjustments in order to improve achievement of target drug blood levels.
			Intermediate metabolizer (CYP3A5 expresser)			
			Poor metabolizer (CYP3A5 non-expresser)	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Higher (“normal”) dose-adjusted through concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP3A5*	CYP3A5 homozygous expressor	Start with 2.5 times the standard initial dose that would yield the desired result in non-expressors Adjustment of the dose should then be based on therapeutic drug monitoring.	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc); neutropenia >1.5x109/l; leucopenia >3.0x109/l; thrombocytopenia >75x109/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	**CONVINCING** Evidence of significant association between CYP3A5 (IM, EM) genotype and lack of efficacy due to reduced plasma concentrations. **CONVINCING** Evidence of significant association between CYP3A5 expression and affection of tacrolimus pharmacokinetics therefore higher mean tacrolimus daily doses. **INADEQUATE** Evidence of pharmacogenetic adaptation of the daily dose of tacrolimus is associated with improved achievement of the target.
			CYP3A5 heterozygote expressor	Start with 1.75 times of the standard initial dose that would yield the desired result in non-expressors. Adjustment of the dose should then be based on therapeutic drug monitoring.	Clinical effect: long-standing discomfort (>168 hr), permanent symptom or invalidating injury e.g. failure of prophylaxis of atrial fibrillation; venous thromboembolism; decreased effect of clopidogrel on inhibition of platelet aggregation; ADE resulting from increased bioavailability of phenytoin; INR >6.0; neutropenia 0.5-1.0x109/l; leucopenia 1.0-2.0x109/l; thrombocytopenia 25-50x109/l; severe diarrhea.	
Tamoxifen	CPIC (Goetz et al. 2018) [22]	*CYP2D6*	CYP2D6 Ultrarapid Metabolizer. An individual carrying duplications of functional alleles (*1/*1xN, *1/*2xN, *2/*2xN)	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Therapeutic endoxifen concentrations.	
			CYP2D6 Normal metabolizer.	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy	Therapeutic endoxifen concentrations.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			(*1/*1, *1/*2, *1/*9, *1/*41, *2/*2)	with recommended standard of care dosing (tamoxifen 20 mg/day).		
			CYP2D6 Normal metabolizer or Intermediate metabolizer.. (*1/*4, *1/*5, *41/*41)	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women. If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day).	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	**ADEQUATE** Evidence of significant association between CYP2D6 (IM) genotype and increased risk for relapse of breast cancer.
			CYP2D6 Normal metabolizer or Intermediate metabolizer. (*10/*10, *10/*41)			
			CYP2D6 Intermediate metabolizer (*4/*10,*4/*41, *5/*9).			
			CYP2D6 Poor metabolizer (*3/*4,*4/*4, *5/*5, *5/*6)	Recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of CYP2D6 genotype and based on knowledge that CYP2D6 poor metabolizers switched from tamoxifen to anastrozole do not have an increased risk of recurrence. Higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy.		**ADEQUATE** Evidence of significant association between CYP2D6 (PM) genotype and lack of efficacy due to reduced formation of the active metabolite.
	Canadian Pharmacogenomics Network for Drug Safety	*CYP2D6*		Alternatives to standard tamoxifen treatments may be considered in CYP2D6 poor or intermediate metabolizers with an emphasis on the use of comprehensive CYP2D6	Testing of all common genetic CYP2D6 variants is RECOMMENDED	**ADEQUATE** Evidence of significant association between CYP2D6 (PM) genotype and lack of efficacy due to reduced formation of the active metabolite. Evidence of significant association between CYP2D6 (IM)

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	(Drogemoller et al. 2019) [16]			genotyping panels in guiding treatment decisions.		genotype and increased risk for relapse of breast cancer.
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Select an alternative or increase the dose to 40 mg/day and monitor the endoxifen concentration. Aromatase inhibitors are a possible alternative for post-menopausal women.	This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness	**CONVINCING** Evidence of significant association between CYP2D6 (PM) genotype and lack of efficacy due to reduced formation of the active metabolite.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	1. Select an alternative or measure the endoxifen concentration and increase the dose if necessary by a factor of 1.5-2. Aromatase inhibitors are a possible alternative for post-menopausal women. 2. If TAMOXIFEN is selected: avoid co-medication with CYP2D6 inhibitors such as paroxetine and fluoxetine.	This gene variation reduces the conversion of tamoxifen to the active metabolite endoxifen. This can result in reduced effectiveness.	**CONVINCING** Evidence of significant association between CYP2D6 (IM) genotype and increased risk for relapse of breast cancer.
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	NO action is needed for this gene-drug interaction.	Minor clinical effect: the plasma concentration of the active metabolites 4-hydroxytamoxifen and endoxifen can increase. However, there is no evidence that this results in an increase in the side effects.	
Tegafur	CPIC (Amstutz et al. 2018) [4]	*DPYD*	Homozygous wild-type or normal, high DPD activity (two or more functional *1 alleles)	Use label-recommended dosage and administration.	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Heterozygous or intermediate activity (~3-5% of patients), (one functional allele *1, plus one nonfunctional allele - *2A, *13 or rs67376798A)	Start with at least a 50% reduction in starting dose followed by titration of dose based on toxicity b or pharmacokinetic test (if available).	Increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	
			Homozygous variant, DPD deficiency (~0.2% of patients), (2 nonfunctional alleles - *2A, *13 or rs67376798A)	Select alternate drug.	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*DPYD*	PM (2 inactive alleles, 2 decreased activity alleles, or one inactive and one decreased activity alleles)	Select alternative drug. Fluorouracil or capecitabine are not suitable alternatives because both are also metabolized by DPD.	-	**INADEQUATE** evidence of significant association between DPYD deficiency and ADR like toxicities.
			IM (1 active allele and 1 inactive or decreased activity allele)	None.		
Thioguanine	CPIC (Relling et al. 2018) [45]	*TPMT*	Homozygous wild-type or normal, high activity (two functional *1 alleles)	Start with normal starting dose. Adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine . Allow 2 weeks to reach steady state after each dose adjustment.	Lower concentrations of TGN metabolites, but note that TGN after thioguanine are 5-10x higher than TGN after mercaptopurine or azathioprine.	**CONVINCING** Evidence of significant association between TPMT (PM/IM) genotype and risk of toxicity (severe and life-threatening myelosuppression due to high levels of thioguanine nucleotides).
			Heterozygote or intermediate activity (one functional allele - *1, plus one nonfunctional allele - *2, *3A, *3B, *3C, or *4)	Start with reduced doses (reduce by 30-50%) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 2-4 weeks to reach steady state after each dose adjustment.	Moderate to high concentrations of TGN metabolites; but note that TGN after thioguanine are 5-10x higher than TGN after mercaptopurine or azathioprine.	
			Homozygous variant, mutant, low, or deficient activity (two	Start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily)	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			nonfunctional alleles - *2, *3A, *3B, *3C, or *4)	and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 4-6 weeks to reach steady state after each dose adjustment. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.		
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*TPMT*	IM (one inactive allele: *2, *3, *4-*18)	Start with 75% of the standard dose. Adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and efficacy. The frequency of monitoring should be increased. .	Genetic variation reduces conversion of thioguanine to inactive metabolites. This increases the risk of serious adverse events such as myelosuppression.	**ADEQUATE** Evidence of significant association between TPMT (PM/IM) genotype and risk of toxicity (severe and life-threatening myelosuppression due to high levels of thioguanine nucleotides).
			PM (two inactive alleles: *2, *3, *4-*18)	Choose an alternative or start with 6-7% of the standard dose. Any adjustment of the initial dose should be guided by toxicity (monitoring of blood counts) and effectiveness. The frequency of monitoring should be increased.	Genetic variation reduces conversion of thioguanine to inactive metabolites. This increases the risk of serious, life-threatening adverse events such as myelosuppression.	
Tolbutamide	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C9*	CYP2C9 *1/*2	None.	-	
			CYP2C9 *2/*2	None.	-	
			CYP2C9 *1/*3	None.	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc); neutropenia >1.5x10/l; leucopenia >3.0x10/l; thrombocytopenia >75x10/l; moderate diarrhea not	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
					affecting daily activities; reduced glucose increase following oral glucose tolerance test.	
			CYP2C9 *2/*3	None.	-	
			CYP2C9 *3/*3	None.	Minor clinical effect: QTc prolongation (<450 ms females, <470 ms males); INR increase <4.5	
Tramadol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	1. be alert to a reduced effectiveness 2. in the case of inadequate effectiveness: a. try a dose increase. b. if this does not work: choose an alternative Do not select codeine,	Clinical effect: short-lived discomfort (<48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance etc.); neutropenia >1.5x10/l; leucopenia >3.0x10/l; thrombocytopenia > 75x10/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test.	**ADEQUATE** Evidence of a significant association between CYP2D6 genotype and pharmacokinetics of tramadol and its active O-desmethyl metabolite. Evidence of a significant association between CYP2D6 genotype and response to tramadol treatment. **INADEQUATE** Evidence of a significant association between CYP2D6 genotype and side effects of tramadol.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	1. be alert to a reduced effectiveness 2. in the case of inadequate effectiveness: a. try a dose increase b. if this does not work: choose an alternative. Do not select codeine, as this is also metabolized by CYP2D6.		
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	1. Select an alternative. Do not choose codeine, as it is contra-indicated for CYP2D6 UM. 2. If an alternative is not possible, use 40% of the standard dose. Advise the patient to report side effects (such as drowsiness, confusion, constipation, nausea and vomiting,	The genetic variation increases the conversion of tramadol to a metabolite with a stronger opioid effect. This can result in an increase in potentially life-threatening side effects.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
				respiratory depression or urine retention).		
Trimipramine	CPIC (Hicks et al. 2017) [26]	*CYP2C19*	CYP2C19 Ultrarapid metabolizer (~2-5% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Greater conversion of tertiary amines to secondary amines may affect response or side effects.	**INADEQUATE** Evidence of significant association between CYP2C19 genotype and pharmacokinetics of trimipramine.
			CYP2C19 Rapid metabolizer (~2-30% of patients)			
			CYP2C19 Normal metabolizer (~35-50% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of tertiary amines.	
			CYP2C19 Intermediate metabolizer (~18-45% of patients)		Reduced metabolism of tertiary amines compared to normal metabolizers.	
			CYP2C19 Poor metabolizer (~2-15% of patients)	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. For tertiary amines, consider a 50% reduction of the recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Decreased conversion of tertiary amines to secondary amines may affect response or side effects.	
		CYP2D6	CYP2D6 Ultrarapid metabolizer (~1-20% of patients)	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure.	**ADEQUATE** Evidence of significant association between CYP2D6 genotype and pharmacokinetics of trimipramine.
			CYP2D6 Normal metabolizer (~72-88% of patients)	Initiate therapy with recommended starting dose.	Normal metabolism of TCAs.	

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Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			CYP2D6 Intermediate metabolizer (~1-13% of patients)	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	Higher plasma concentrations of active drug will increase the probability of side effects.	
			CYP2D6 Poor metabolizer (~1-10% of patients)	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.		
Tropisetron	CPIC (Bell et al. 2017) [7]	*CYP2D6*	Ultrarapid metabolizer (**1/*1xN, *1/*2xN, *2/*2xN)*	Select and alternative drug not predominantly metabolized by CYP2D6 (i.e. granisetron).	Increased metabolism to less active compounds when compared to normal metabolizers and is associated with decreased response to ondansetron and tropisetron (i.e. vomiting).	**ADEQUATE** Evidence of significant association between CYP2D6 genotype and pharmacokinetics of tropisetron.
			Normal metabolizer (v **1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41)*	Initiate therapy with recommended starting dose.	Normal metabolism.	
			Intermediate metabolizer (**4/*10,*4/*41, *5/*9*)	Initiate therapy with recommended starting dose.	Very limited data available for CYP2D6 intermediate metabolizers	
			Poor metabolizer (**3/*4,*4/*4, *5/*5, *5/*6*)		Very limited data available for CYP2D6 poor metabolizers	
Venlafaxine	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or adjust dose to clinical response and monitor (O-desmethyl)venlafaxine plasma concentration.	There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, while an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.	**ADEQUATE** Evidence of a significant association between CYP2D6 genotype and pharmacokinetics (plasma concentrations) of venlafaxine and is major active metabolite, O-desmethylvenlafaxine.

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or adjust dose to clinical response and monitor (O-desmethyl) venlafaxine plasma concentration.	There are indications of an increased risk of side effects and a reduced chance of efficacy. The gene variation reduces the conversion of venlafaxine to the active metabolite O-desmethylvenlafaxine, while an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.	**ADEQUATE** Evidence of a significant association between CYP2D6 genotype and side effects of venlafaxine. **ADEQUATE** Evidence of a significant association between CYP2D6 genotype and response to depression treatment with venlafaxine.
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Titrate dose to a maximum of 150% of the normal dose or select alternative drug (e.g., citalopram, sertraline).	Minor clinical effect: The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O-desmethylvenlafaxine.	
Voriconazole	CPIC (Moriyama et al. 2017) [40]	*CYP2C19*	Ultrarapid metabolizer (~2-5% of patients)	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole.	In patients for whom an ultrarapid metabolizer genotype is identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing.	**ADEQUATE** evidence of a significant association between CYP2C19 genotype and pharmacokinetics (plasma concentrations, clearance) of voriconazole. Evidence of a lack of association between CYP2D6 genotype and hepatotoxic side effects of voriconazole.
			Rapid metabolizer (~2-30% of patients)		In patients for whom a rapid metabolizer genotype is identified, the probability of attainment of therapeutic concentrations is modest with standard dosing.	
			Normal metabolizer (~35-50% of patients)	Initiate therapy with recommended standard of care dosage.	Normal voriconazole metabolism.	
			Intermediate metabolizer (~18-45% of patients)		Higher dose-adjusted through concentrations of voriconazole compared to normal metabolizers.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			Poor metabolizer (~2-15% of patients)	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	Higher dose-adjusted through concentrations of voriconazole and may increase probability of adverse events.	
	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2C19*	CYP2C19 PM (*2/*2, *2/*3, *3/*3)	Use 50% of the standard dose and monitor the plasma concentration.	Minor clinical effect: QTc prolongation (<450 ms female, <470 ms male); international normalized ratio increase <4.5 ; Kinetic effect.	**INADEQUATE** evidence of a significant association between CYP2C19 genotype and pharmacokinetics (plasma concentrations, clearance) of voriconazole.
			CYP2C19 IM (*1/*2, *1/*3, *17/*2, *17/*3)	Monitor the plasma concentration.	The gene variation can reduce the conversion of voriconazole and consequently increase the plasma concentration. This could result in improved efficacy or an increase in the risk of side effects.	**ADEQUATE** evidence of a lack of association between CYP2D6 genotype and hepatotoxic side effects of voriconazole. **INADEQUATE** evidence for significant benefits of genotype- directed dosing algorithms to reach the voriconazole target range sooner.
			CYP2C19 UM (*17/*17)	Use an initial dose that is 1.5x higher and monitor the plasma concentration.	The gene variation increases the conversion of voriconazole, which increases the risk of ineffectiveness.	
Warfarin	CPIC (Johnson et al. 2017) [28]	*CYP2C9*	GG		CYP2C9 and VKORC1 polymorphisms account for up to 18 and 30% respectively, of the variance in stable warfarin dose among patients of European ancestry.	**CONVINCING** evidence of significant association between CYP2C9 polymorphism and a variance up to 17% in stable warfarin dose among patients of European ancestry. CYP2C9 genotype guided dosing has significant
			GA			

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			AA			advantage in order to estimate the anticipated stable dose of warfarin.
		CYP4F2	GG			
			GA			
			AA			
		VKORC1	GG		CYP2C9 and VKORC1 polymorphisms account for up to 18 and 30% respectively, of the variance in stable warfarin dose among patients of European ancestry.	**CONVINCING** Evidence of significant association between VKORC1 polymorphism and a variance up to 30% in stable warfarin dose among patients of European ancestry. VKPRC1 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.
			GA			
			AA			
	Canadian Pharmacogenomics Network for Drug Safety (Shaw et al. 2015) [51]	*CYP2C9*	CYP2C9 alleles *2 and *3	Testing of all warfarin-naive patients for VKORC1 (-1639G>A), CYP2C9*2, and CYP2C9*3 should be considered before initiation of therapy and within the first 2 weeks of therapy.		**CONVINCING** Evidence of significant association between CYP2C9 polymorphism and a variance up to 17% in stable warfarin dose among patients of European ancestry. CYP2C9 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.
		VKORC1	VKORC1 SNP -1639G>A (rs9923231)	Testing of all warfarin-naive patients for VKORC1 (-1639G>A), CYP2C9*2, and CYP2C9*3 should be considered before initiation of therapy and within the first 2 weeks of therapy.		**CONVINCING** Evidence of significant association between VKORC1 polymorphism and a variance up to 30% in stable warfarin dose among patients of European ancestry. VKPRC1 genotype guided dosing has significant advantage in order to estimate the anticipated stable dose of warfarin.

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
	DPWG (update 2018) [52]	*CYP2C9*	CYP2C9 IM	Use 65% of the standard initial dose. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm.	This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.	
			CYP2C9 PM	Use 20% of the standard initial dose. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm.	This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.	
			CYP2C9*1/*2	No action is required for this gene-drug interaction.	Genetic variation may lead to a decrease in the required maintenance dose. However, there is insufficient evidence that this could cause problems when the therapy is initiated in the usual manner.	
			CYP2C9*1/*3	Use 65% of the standard initial dose. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT.	This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.	
			CYP2C9*2/*2	Use 65% of the standard initial dose. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT.	This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.	
			CYP2C9*2/*3		This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.	
			CYP2C9*3/*3	Use 20% of the standard initial dose. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT.	This gene variation reduces the conversion of warfarin to inactive metabolites. This can increase the risk of bleeding.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
		VKORC1	VKORC1 -1639 AA	Use 60% of the standard initial dose. The genotype-specific initial dose and maintenance dose can be calculated using an algorithm, as used in EU-PACT. From day 6 on the standard algorithm without genotype information can be used to calculate the dose.	The genetic variation results in increased sensitivity to warfarin. This results in an increase in the risk of excessively severe inhibition of blood clotting (INR >4) during the first month of the treatment.	**CONVINCING** evidence of significant association between VKORC1 gene polymorphisms and warfarin dosage. **INADEQUATE** evidence that genotype-guided dosing strategies would improve percentage of time that the INR is within the therapeutic range or to reduce ADR.
			VKORC1 -1639 AG	No action is needed for this gene-drug interaction.	The genetic variation results in a reduction in the required dose and an increase in the risk of excessively severe inhibition of blood clotting during the first month of the treatment. However, the effect is small and GA is also the most common genotype, meaning that the standard treatment will primarily be based on patients with this genotype.	
Zuclopenthixol	DPWG (Swen et al. 2011, update 2018) [30, 52]	*CYP2D6*	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Reduce dose by 50% or select alternative drug (e.g., flupenthixol, quetiapine, olanzapine, clozapine).	The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopentixol plasma concentrations.	**ADEQUATE** Evidence of a significant association between CYP2D6 genotype and pharmacokinetics (plasma concentrations, clearance) of zuclopenthixol**. INADEQUATE** Evidence of a significant association between CYP2D6 genotype and neurological side effects (parkinsonism, tardive dyskinesia) of zuclopenthixol.
			IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-	Reduce dose by 25% or select alternative drug (flupenthixol, quetiapine, olanzapine, clozapine).	The genetic polymorphism leads to decreased metabolic capacity of CYP2D6, which may cause increased zuclopentixol plasma concentrations.	

continued

Table 9 (continued) Published guideline recommendations for genotype-based therapy modification.

Drug	Guideline	Gene	Genotype / metabolizer phenotype	Recommendation	Rationale	Class of recommendations and level of evidence
			*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)			
			UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Insufficient data to allow calculation of dose adjustment.	The genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may cause decreased zuclopentixol plasma concentrations.	

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