GENE PGX

Your genetic guide to

PRECISION MEDICINE

dante labs

INTRODUCTION

Understanding your report

Precision medicine is a pharmacogenomics test that provides the association between an individual's genetic makeup and response to drug therapy. Differences in genetic variants carried by an individual are found to be associated with drug metabolism, activity or absorption. Therefore, though a particular drug therapy may work for one individual, it may not work or result in adverse effects in another. Identifying the individual genetic markers could help physicians design personalised therapy for their patients.

Drug hypersensitivity could lead to adverse events, placing a large burden on healthcare costs. Preventable adverse drug events were found to cost the NHS(UK) up to £2.5 billion every year and were the fourth leading cause of death in the US. A large number of these adverse drug events are due to genetic factors, and so, pharmacogenetic testing could help prevent them.

Some Interesting facts about genes and drug therapy.

- A study conducted on the benefits of pharmacogenomic recommendations in the long term care of patients showed that nearly 50% of the patients had to change one to three drugs, with significant estimated savings annually.
- Clopidogrel is a commonly prescribed drug, with sales exceeding US$ 6 billion. However, individuals who are poor CYP2C19 metabolizers were nearly four times more likely to experience a subtherapeutic antiplatelet response on treatment with clopidogrel, which could increase the risk for adverse cardiovascular events.
- Codeine is a commonly used pain medication. Individuals who are CYP2D6 ultra-rapid metabolizers, when treated with codeine, showed symptoms of extreme sleepiness, shallow breathing and even confusion. Patients that are CYP2D6 poor metabolizers will not have sufficient relief from pain as they will be unable to convert codeine into its active form.
- In a recent review conducted by King's College London, thirty-three economic evaluations (75%) supported PGx-guided treatment while 11 studies (25%) found PGX cost-effective and 22 studies (50%) showed that it was dominant and cost-saving
- In a study conducted by the Medical University of Vienna, the fraction of patients with an actionable genetic profile was 69% for warfarin, 28.5% for clopidogrel, 23% for tacrolimus, 25.7% for simvastatin and 9.1% for thiopurines.

Gene variations are highly influential in metabolic response to various drugs. Other factors include environmental triggers, age, body weight, diet and co-administration of other drugs or influencing chemical and biological compounds.

In this report, we profile gene variants that are associated with your metabolic responses to various drug therapies.

This report will help your physician prescribe for you,

The Right Medication at The Right Dose!

INTRODUCTION

Understanding your report

This report is presented in a user friendly language and format. The following tips will help you get the best information value out of the report.

1. What are the various metabolizer phenotypes?

Ultra Rapid metabolizers (UM) are individuals with variants associated with elevated drug metabolism.

Extensive metabolizers (EM) are individuals with variants associated with fast drug metabolism.

Poor metabolizers (PM) are individuals with variants associated with poor drug metabolism.

Intermediate metabolizers (IM) are individuals with variants associated with moderate rate of drug metabolism.

Normal metabolizers (NM) are individuals with variants associated with normal rate of drug metabolism.

Indeterminate (IN), means that your status could not be determined.

2. Where did the information contained in the report come from?

The information presented in this report is curated by our team of scientists from various high authority sources such as the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and other professional societies and sources.

3. How does genetic variations among individuals affect drug metabolism?

A number of biological pathways are involved in the metabolism and clearance of therapeutic drugs. Inefficiency/deficiency in any of these pathways can lead to non-effective or adversely-effective outcomes.

4. How do I understand the information in the report?

The report is organized by the drug names and areas of use. For example, you will find, "ANALGESIC-TRAMADOL" which means that the drug is Tramadol and its used as an analgesic. Right underneath, you will find your "diplotype" (genetic type) and your Metabolizer status, indicated as NM, PM, EM, etc., (please see question 1 above). Following the metaboliser status, you will find a short description of the nature of guideline (Caution: **This is not a recommendation**, its a description from the guideline agency about the impact of this gene on the metabolism of the drug.)

The Key section **of the report is the** shaded grey box**, which contains your therapeutic recommendations. It includes:**

Activity Score: A score indicating the activity of the drug

Implications: Implications for your therapy

Clinical Effect: Whether its a significant (S) or non-signficant (NS) clinical effect

Classification of Recommendation: The strength of this recommendation based on clinical evidence found in published literature.

METABOLIZER STATUS

GENE NAME	DIPLOTYPE	METABOLIZER STATUS
CYP2C19	*1/*17	RM
CYP2C9	*1/*9	NM
TPMT	*1/*1	NM
CYP3A5	*1/*3	IM
SLCO1B1	*1A/*1A	NM
UGT1A1	*60/*80	IM
CYP2D6	*4xN/*4xN	PM
DPYD	*1/*6	NM
CYP4F2	*1/*1	NA

The metabolizer status is subject to the number and genotype of the genetic markers present in your genome raw data as well as the algorithm used to estimate the metabolizer status. Certain genes such as CYP2D6 are highly complex and ONLY A CLINICAL PHARMACOGENETIC TEST CAN CONFIRM THE METABOLIZER STATUS.

1. ABACAVIR

Genotype-TT
Evidence level: Level 1

In individuals with the HLA-B*57:01 variant allele ("HLA-B*57:01-positive"), abacavir is not recommended and should be considered only under exceptional circumstances. See full guideline for disclaimers, further details and supporting evidence.

Implications
Low or reduced risk of abacavir hypersensitivity

Phenotype (Genotype)
Very low risk of hypersensitivity (~94% of patients) in the absence of *57:01 alleles (reported as "negative" on a genotyping test)

Recommendations
Use abacavir per standard dosing guidelines

Classification of Recommendation
Strong

Genes analyzed: *rs2395029*

Area: *Infectious Diseases*

2. ACENOCOUMAROL

Diplotype is *1/*9
Metabolizer Status is NM
Evidence level: Level 1

DPWG Guideline
Check INR more frequently after initiating or discontinuing NSAIDs in individuals taking acenocoumarol with at least one CYP2C9 *2 or *3 allele.

Implications
Normal Metabolizer - Follow standard dosing guidelines

Genes analyzed: *CYP2C9*

Area: *Cardiology or Hematology*

3. AMITRIPTYLINE

Rapid Metabolizer-Poor Metabolizer
Evidence level: Level 1

CPIC Guideline
The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

Implications

For CYP2D6:
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.

For CYP2C19:
Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.

Genes analyzed: *CYP2C19-CYP2D6* | **Area:** *Psychiatry*

4. ARIPIPRAZOLE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group (DPWG) recommends reducing maximum dose of aripiprazole for patients carrying poor metabolizer alleles of CYP2D6.

Implications
Reduce maximum dose to 10 mg/day (67% of the maximum recommended daily dose).

Clinical effect (S):
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 1.0-1.5x109/l; leucopenia 2.0-3.0x109/l; thrombocytopenia 50-75x109/l.

Genes analyzed: *CYP2D6* | **Area:** *Psychiatry*

5. ATAZANAVIR

Diplotype is *60/*80
Metabolizer status is IM
Evidence level: Level 1

CPIC Guideline

The CPIC dosing guideline recommends considering advising individuals who carry two decreased function UGT1A1 alleles about a substantial likelihood of developing jaundice, which may cause non-adherence. The dosing guideline recommends that alternative agents be considered if the risk of non-adherence due to jaundice is high. The risk of discontinuation is low and very low for individuals carrying one, or no decreased function UGT1A1 alleles, respectively.

Implications

Somewhat decreased UGT1A1 activity; low likelihood of bilirubin- related discontinuation of atazanavir.

Metabolizer Status

Intermediate Metabolizer

Phenotype (Genotype)

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. The term reference function refers to the UGT1A1 alleles to which other alleles are compared. The reference function *1 allele is fully functional and refers to the rs8175347 TA6 allele.

Recommendations

There is no need to avoid prescribing of atazanavir based on UGT1A1 genetic test result. Inform the patient that some patients stop atazanavir because of jaundice -yellow eyes and skin, but that this patient s genotype makes this unlikely -less than about a 1 in 20 chance of stopping atazanavir because of jaundice.

Classification of Recommendation

Strong

Genes analyzed: *UGT1A1*

Area: *Infectious Diseases*

6. ATOMOXETINE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
For CYP2D6 ultrarapid metabolizers, be alert to reduced efficacy of atomoxetine or select an alternative drug. Be alert to ADEs in CYP2D6 poor metabolizers.

Implications
Standard dose. Dose increase probably not necessary; be alert to ADEs.

Clinical effect (S):
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.

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

7. AZATHIOPRINE

Diplotype is *1/*1
Metabolizer status is NM
Evidence level: Level 1

CPIC Guideline
Consider an alternate agent or extreme dose reduction of azathioprine for patients with low or deficient TPMT activity. Start at 30-70% of target dose for patients with intermediate enzyme activity.

Implications
Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern

Metabolizer Status
Normal Metabolizer

Phenotype (Genotype)
Homozygous wild-type or normal, high activity (two functional (normal function) *1 alleles)

Recommendations
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.

Classification of Recommendation
Strong

Genes analyzed: *TPMT*

Area: *Rheumatology*

8. CAPECITABINE

Diplotype is *1/*6
Metabolizer Status is NM
Evidence level: Level 1

DPWG Guideline
Select an alternate drug to capecitabine for DPYD poor metabolizer patients, and reduce capecitabine dose (by 50%) or select an alternate drug for DPYD intermediate metabolizers.

Implications
Normal Metabolizer - Follow standard dosing guidelines

Genes analyzed: *DPYD* | **Area:** *Oncology*

9. CLOMIPRAMINE

Rapid Metabolizer-Poor Metabolizer
Evidence level: Level 1

CPIC Guideline
Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including clomipramine. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

Implications

For CYP2D6:
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.

For CYP2C19:
Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.

Genes analyzed: *CYP2C19-CYP2D6* | **Area:** *Psychiatry*

10. CLOPIDOGREL

Diplotype is *1/*17
Metabolizer status is RM
Evidence level: Level 1

CPIC Guideline
The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers if there is no contraindication.

Implications
Increased platelet inhibition; decreased residual platelet aggregation.

Metabolizer Status
rapid Metabolizer

Phenotype (Genotype)
An individual carrying one increased function alleles

Recommendations
Clopidogrel - label recommended dosage and administration

Classification of Recommendation
Strong

Genes analyzed: *CYP2C19*

Area: *Cardiology*

11. CODEINE

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline
Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers. A label recommended age- or weight-specific codeine dose is warranted for CYP2D6 extensive and intermediate metabolizers.

Activity Score
0

Implications
Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief

Metabolizer Status
Poor Metabolizer

Phenotype (Genotype)
An individual carrying no functional alleles

Recommendations
Avoid codeine use due to lack of efficacy.
Considerations for alternative opioids: Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided. There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol post-surgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable. Some other opioid analgesics are metabolized by CYP2D6, such as hydrocodone and oxycodone. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone, along with non-opioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.

Classification of Recommendation
Strong

Genes analyzed: *CYP2D6*

Area: *Anesthesiology*

12. DESIPRAMINE

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline

Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline/nortriptyline and CYP2C19, CYP2D6 to other tricyclics including desipramine. The CPIC Dosing Guideline update for nortriptyline recommends a 25% dose reduction for CYP2D6 intermediate metabolizers. For CYP2D6 ultrarapid or poor metabolizers, an alternative drug should be considered. If nortriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers.

Activity Score

0

Implications

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.

Metabolizer Status

Poor Metabolizer

Phenotype (Genotype)

An individual carrying only no function alleles

Recommendations

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.g Utilize therapeutic drug monitoring to guide dose adjustments.
Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression.

Classification of Recommendation

Optional

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

13. DOXEPIN

Rapid Metabolizer-Poor Metabolizer
Evidence level: Level 1

CPIC Guideline
Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including doxepin. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

Implications

For CYP2D6:
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.

For CYP2C19:
Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.

Genes analyzed: *CYP2C19-CYP2D6*	**Area:** *Psychiatry*

14. ESCITALOPRAM

Diplotype is *1/*17
Metabolizer status is RM
Evidence level: Level 1

CPIC Guideline

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitors citalopram and escitalopram recommends an alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 ultrarapid metabolizers. 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.

Implications

Increased metabolism when compared to normal metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.

Metabolizer Status

Rapid Metabolizer
*1/*17 is defined as CYP2C19 Rapid Metabolizer based on the CPIC Term Standardization project (07/2016, [Article:27441996]). Please note, in the es-/citalopram guideline, *1/*17 is grouped with *17/*17 under CYP2C19 'ultrarapid' metabolizer.

Phenotype (Genotype)

An individual carrying one increased and one normal function allele.

Recommendations

Consider an alternative drug not predominantly metabolized by CYP2C19.
Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

Classification of Recommendation

Moderate

Genes analyzed: *CYP2C19*

Area: *Psychiatry*

15. FLECAINIDE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
Reduce flecainide dose by 50% for CYP2D6 poor metabolizer (PM) and by 25% for CYP2D6 intermediate metabolizer (IM) patients.

Implications
Reduce dose by 50%, record ECG, monitor plasma concentration.

Minor clinical effect (S):
QTc prolongation (<450 ms female, <470 ms male); INR increase < 4.5; Kinetic effect (S)

Genes analyzed: *CYP2D6* | **Area:** *Cardiology*

16. FLUOROURACIL

Diplotype is *1/*6
Metabolizer Status is NM
Evidence level: Level 1

DPWG Guideline
An alternative drug rather than fluorouracil is recommended for DPYD poor metabolizer patients, and a reduced dose (by 50%) of fluorouracil or use of an alternative drug is recommended for intermediate metabolizer patients.

Implications
Normal Metabolizer - Follow standard dosing guidelines

Genes analyzed: *DPYD* | **Area:** *Dermatology*

17. FLUVOXAMINE

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline
The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor fluvoxamine recommends to consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6 for CYP2D6 poor metabolizers.

Activity Score
0

Implications
Greatly reduced metabolism when compared to normal metabolizers. Higher plasma concentrations may increase the probability of side effects.

Metabolizer Status
Poor Metabolizer

Phenotype (Genotype)
An individual carrying only no functional alleles

Recommendations
Consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6.
Dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 30% dose reduction of fluvoxamine. However, a 30% decrease in dose may not be feasible given the dosage forms, therefore, decreasing the starting dose of fluvoxamine by 25-50% should be considered. Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

Classification of Recommendation
Optional

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

18. HALOPERIDOL

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
Reduce haloperidol dose by 50% or select an alternative drug for CYP2D6 poor metabolizer (PM) genotype patients.

Implications
Reduce dose by 50% or select alternative drug (e.g., pimozide, flupenthixol, fluphenazine, quetiapine, olanzapine, clozapine).

Clinical effect (S):
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 1.0-1.5x109/l; leucopenia 2.0-3.0x109/l; thrombocytopenia 50-75x109/l.

Genes analyzed: *CYP2D6* | **Area:** *Psychiatry*

19. IMIPRAMINE

Rapid Metabolizer-Poor Metabolizer
Evidence level: Level 1

CPIC Guideline
Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including imipramine. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

Implications

For CYP2D6:
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.

For CYP2C19:
Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.

Genes analyzed: *CYP2C19-CYP2D6* | **Area:** *Psychiatry*

20. MERCAPTOPURINE

Diplotype is *1/*1
Metabolizer status is NM
Evidence level: Level 1

CPIC Guideline
Start with reduced doses of mercaptopurine for patients with one nonfunctional TPMT allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles.

Implications
Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern

Metabolizer Status
Normal Metabolizer

Phenotype (Genotype)
Homozygous wild-type or normal, high activity -two functional (normal function) *1 alleles

Recommendations
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, without any special emphasis on mercaptopurine compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.

Classification of Recommendation
Strong

Genes analyzed: *TPMT*	**Area:** *Oncology*

21. METOPROLOL

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
Select another drug or reduce dose of metoprolol for CYP2D6 poor and intermediate metabolizer patients. Use a dose titration of metoprolol for CYP2D6 ultra metabolizers or select an alternative drug.

Implications
Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75%. Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol).

Clinical effect (S):
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 1.0-1.5x109/l; leucopenia 2.0-3.0x109/l; thrombocytopenia 50-75x109/l.

Genes analyzed: *CYP2D6*

Area: *Cardiology*

22. NORTRIPTYLINE

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline
The CPIC Dosing Guideline update for nortriptyline recommends a 25% dose reduction for CYP2D6 intermediate metabolizers. For CYP2D6 ultrarapid or poor metabolizers, an alternative drug should be considered. If nortriptyline is warranted, consider a 50% dose reduction in CYP2D6 poor metabolizers.

Activity Score
0

Implications
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.

Metabolizer Status
Poor Metabolizer

Phenotype (Genotype)
An individual carrying only no function alleles

Recommendations
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.g Utilize therapeutic drug monitoring to guide dose adjustments.
Patients may receive an initial low dose of a tricyclic, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. Titrate dose to observed clinical response with symptom improvement and minimal (if any) side effects. Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression.

Classification of Recommendation
Strong

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

23. ONDANSETRON

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline

The CPIC dosing guideline for ondansetron recommends selecting an alternate drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg. granisetron).

Activity Score

0

Implications

Very limited data available for CYP2D6 poor metabolizers

Metabolizer Status

Poor Metabolizer

Phenotype (Genotype)

An individual carrying no functional alleles

Recommendations

Insufficient evidence demonstrating clinical impact based on CYP2D6 genotype. Initiate therapy with recommended starting dose.

Classification of Recommendation

No recommendation

Genes analyzed: *CYP2D6*	**Area:** *Oncology*

24. OXYCODONE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
Use an alternate drug rather than oxycodone (not codeine or tramadol) for CYP2D6 poor and intermediate metabolizer patients, or be alert to insufficient pain relief. For CYP2D6 ultra metabolizer patients, use an alternate drug rather than oxycodone (not codeine or tramadol), or be alert to adverse drug events.

Implications
Insufficient data to allow calculation of dose adjustment. Select alternate drug - not tramadol or codeine - or be alert to symptoms of insufficient pain relief.

Clinical effect (S):
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.

Genes analyzed: *CYP2D6*	**Area:** *Anesthesiology*

25. PAROXETINE

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline
The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor paroxetine recommends an alternative drug not predominantly metabolized by CYP2D6 for CYP2D6 ultrarapid metabolizers and for CYP2D6 poor metabolizers. For CYP2D6 poor metabolizers, if paroxetine use is warranted, consider a 50% reduction of recommended starting dose and titrate to response.

Activity Score
0

Implications
Greatly reduced metabolism when compared to normal metabolizers. Higher plasma concentrations may increase the probability of side effects.

Metabolizer Status
Poor Metabolizer

Phenotype (Genotype)
An individual carrying only no functional alleles

Recommendations
Select alternative drug not predominantly metabolized by CYP2D6 or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.
Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

Classification of Recommendation
Optional

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

26. PEGINTERFERON ALFA-2A, 2B

Genotype-CT
Evidence level: Level 1

IFNL3 (IL28B) variation (rs12979860) is the strongest baseline predictor of response to PEG-interferon-alpha-containing regimens in HCV genotype 1 patients. Patients with the favorable response genotype (rs12979860 CC) have increased likelihood of response (higher SVR rate) to PEG-interferon-alpha-containing regimens as compared to patients with unfavorable response genotype (rs12979860 CT or TT). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

Implications
For patients treated with PEG-IFN alpha and RBV alone, approximately 30% chance of sustained virologic response (SVR, defined by undetectable serum viral RNA 12-24 weeks after the end of treatment) after 48 weeks of treatment. Consider implications before initiating PEG-IFN alpha and RBV containing regimens.
For patients treated with protease inhibitor combinations with PEG-IFN alpha and RBV therapy, approximately 60% chance for SVR after 24-48 weeks of treatment. Approximately 50% of patients are eligible for shortened therapy (24-28 weeks, with patients receiving boceprevir are eligible for 24-28 weeks instead of the standard 48 weeks if HCV RNA is undetectable by week eight. Patients receiving telaprevir are eligible for 24 weeks of therapy instead of the standard 48 weeks if HCV RNA is undetectable by week four.). Consider implications before initiating PEG-IFN alpha and RBV containing regimens.

Phenotype (Genotype)
Unfavorable response genotype

Classification of Recommendation
Strong

Genes analyzed: *rs12979860* | **Area:** *Infectious Diseases*

27. PHENPROCOUMON

Diplotype is *1/*9
Metabolizer Status is NM
Evidence level: Level 1

DPWG Guideline
For patients treated with phenprocoumon, consider checking INR more frequently in individuals with CYP2C9 2*/2*, 2*/3*, or 3*/3* genotype.

Implications
Normal Metabolizer - Follow standard dosing guidelines

Genes analyzed: *CYP2C9* | **Area:** *Cardiology or Hematology*

28. PHENYTOIN

Diplotype is *1/*9
Metabolizer Status is NM
Evidence level: Level 1

DPWG Guideline
Use the standard starting dose of phenytoin and reduce the maintenance dose based on CYP2C9 genotype; monitor response and serum concentrations and be aware of ADEs.

Implications
Normal Metabolizer - Follow standard dosing guidelines

Genes analyzed: *CYP2C9*

Area: *Neurology*

29. PROPAFENONE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
Reduce the dose of propafenone by 70% for CYP2D6 poor metabolizers, and adjust propafenone dose according to plasma concentrations or use an alternative drug for CYP2D6 intermediate and ultrarapid metabolizers.

Implications
Reduce dose by 70%, record ECG, monitor plasma concentration

Clinical effect (S):
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 9/l; leucopenia 2.0-3.0x10 9/l; thrombocytopenia 50-75x10 9/l

Genes analyzed: *CYP2D6*

Area: *Cardiology*

30. RISPERIDONE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
Select an alternative drug or be extra alert to adverse drug events (ADR) for patients who are CYP2D6 poor metabolizers, intermediate metabolizers, or ultrarapid metabolizers with risperidone. Adjust risperidone dose to clinical response.

Implications
Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., quetiapine,olanzapine, clozapine) or be extra alert to ADEs and adjust dose to clinical response.

Clinical effect (S):
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.

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

31. SERTRALINE

Diplotype is *1/*17
Metabolizer status is RM
Evidence level: Level 1

CPIC Guideline

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor sertraline recommends to consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers.

Implications

Increased metabolism when compared to normal metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.

Metabolizer Status

Rapid Metabolizer
*1/*17 is defined as CYP2C19 Rapid Metabolizer based on the CPIC Term Standardization project (07/2016, PMID: 27441996). Please note, in the sertraline guideline, *1/*17 is grouped with *17/*17 under CYP2C19 'ultrarapid' metabolizer.

Phenotype (Genotype)

An individual carrying one increased and one normal function allele

Recommendations

Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19. Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

Classification of Recommendation

Optional

Genes analyzed: *CYP2C19*

Area: *Psychiatry*

32. SIMVASTATIN

Diplotype is *1A/*1A
Metabolizer status is NM
Evidence level: Level 1

CPIC Guideline
The FDA recommends against 80mg daily simvastatin dosage. In patients with the C allele at SLCO1B1 rs4149056, there are modest increases in myopathy risk even at lower simvastatin doses (40mg daily); if optimal efficacy is not achieved with a lower dose, alternate agents should be considered.

Implications
Normal myopathy risk

Phenotype (Genotype)
Normal Function

Recommendations
Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines.

Classification of Recommendation
Strong

Genes analyzed: *SLCO1B1* | **Area:** *Cardiology*

33. TACROLIMUS

Diplotype is *1/*3
Metabolizer status is IM
Evidence level: Level 1

CPIC Guideline
The CPIC dosing guideline for tacrolimus recommends increasing 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.

Metabolizer Status Possible Intermediate Metabolizer or Normal Metabolizer CPIC Term Standardization Project recommended replacing the term extensive metabolizer with normal metabolizer [Article:27441996] for drug metabolizing enzymes.

Genes analyzed: *CYP3A5* | **Area:** *Transplantation*

34. TAMOXIFEN

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
For CYP2D6 poor and intermediate metabolizers, consider using aromatase inhibitors for postmenopausal women due to increased risk for relapse of breast cancer with tamoxifen. For intermediate metabolizers, avoid concomitant CYP2D6 inhibitor use.

Implications
Increased risk for relapse of breast cancer. Consider aromatase inhibitor for postmenopausal women.

Clinical effect (S):
Failure of lifesaving therapy e.g. anticipated myelosuppression; prevention of breast cancer relapse; arrhythmia; neutropenia < 0.5x109/l; leucopenia < 1.0x109/l; thrombocytopenia < 25x109/l; life-threatening complications from diarrhea.

Genes analyzed: *CYP2D6* | **Area:** *Oncology*

35. TEGAFUR

Diplotype is *1/*6
Metabolizer Status is NM
Evidence level: Level 1

DPWG Guideline
Select an alternate drug (that is not metabolized by DPYD) rather than tegafur for DPYD poor metabolizers.

Implications
Normal Metabolizer - Follow standard dosing guidelines

Genes analyzed: *DPYD* | **Area:** *Oncology*

36. THIOGUANINE

Diplotype is *1/*1
Metabolizer status is NM
Evidence level: Level 1

CPIC Guideline
Start with reduced doses of thioguanine for patients with one nonfunctional TPMT allele, or drastically reduced doses for patients with malignancy and two nonfunctional alleles; adjust dose based on degree of myelosuppression and disease-specific guidelines. Consider alternative nonthiopurine immunosuppressant therapy for patients with nonmalignant conditions and two nonfunctional alleles.

Implications
Lower concentrations of TGN metabolites, but note that TGN after thioguanine are 5-10x higher than TGN after mercaptopurine or azathioprine

Metabolizer Status
Normal Metabolizer

Phenotype (Genotype)
Homozygous wild-type or normal, high activity (two functional (normal function) *1 alleles)

Recommendations
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.

Classification of Recommendation
Strong

Genes analyzed: *TPMT*	**Area:** *Oncology*

37. TRAMADOL

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline

For CYP2D6 poor metabolizers (PM), select an alternative to tramadol (not oxycodone or codeine) and be alert for symptoms of insufficient pain relief. For CYP2D6 intermediate metabolizers (IM), be alert for symptoms of insufficient pain relief, and consider dose increase or select an alternative to tramadol (not oxycodone or codeine). For CYP2D6 ultrarapid metabolizers, use a 30% decreased dose and be alert for ADEs, or use an alternative to tramadol (not oxycodone or codeine).

Implications

Select alternative drug-not oxycodone or codeine- or be alert to symptoms of insufficient pain relief.

Clinical effect (S):

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.

Genes analyzed: *CYP2D6*	**Area:** *Analgesic*

38. TRIMIPRAMINE

Rapid Metabolizer-Poor Metabolizer
Evidence level: Level 1

CPIC Guideline
Tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply the CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6 to other tricyclics including trimipramine. The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for CYP2D6 ultrarapid or poor metabolizers and CYP2C19 ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in CYP2D6 or CYP2C19 poor metabolizers. For CYP2D6 intermediate metabolizers, a 25% dose reduction should be considered.

Implications

For CYP2D6:
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.

For CYP2C19:
Increased metabolism of tertiary amines compared to normal metabolizers. Greater conversion of tertiary amines to secondary amines may affect response or side effects.

Genes analyzed: *CYP2C19-CYP2D6*

Area: *Psychiatry*

39. TROPISETRON

Diplotype is *4xN/*4xN
Metabolizer status is PM
Evidence level: Level 1

CPIC Guideline
The CPIC dosing guideline for tropisetron recommends selecting an alternate drug for CYP2D6 ultrarapid metabolizers. It is recommended that the alternate drug not be predominantly metabolized by CYP2D6 (eg. granisetron).

Activity Score
0

Implications
Very limited data available for CYP2D6 poor metabolizers

Metabolizer Status
Poor Metabolizer

Phenotype (Genotype)
An individual carrying no functional alleles

Recommendations
Insufficient evidence demonstrating clinical impact based on CYP2D6 genotype. Initiate therapy with recommended starting dose.

Classification of Recommendation
No recommendation

Genes analyzed: *CYP2D6*	**Area:** *Oncology*

40. VENLAFAXINE

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline

For CYP2D6 poor (PM) and intermediate metabolizers (IM), select an alternative to venlafaxine or adjust dose to clinical response and monitor patient's plasma metabolite level. For CYP2D6 ultrarapid metabolizers(UM), titrate dose to a maximum of 150% of the normal dose or select an alternative to venlafaxine.

Implications

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.

Clinical effect (S):

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 1.0-1.5x109/l; leucopenia 2.0-3.0x109/l; thrombocytopenia 50-75x109/l.

Genes analyzed: *CYP2D6*

Area: *Psychiatry*

41. VORICONAZOLE

Diplotype is *1/*17
Metabolizer status is RM
Evidence level: Level 1

CPIC Guideline

The CPIC dosing guideline for voriconazole recommends selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers. In pediatric rapid metabolizers, therapy should be initiated at recommended standard case dosing, then therapeutic dosing monitoring should be used to titrate dose to therapeutic trough concentrations.

Implications

In adult patients for whom a rapid metabolizer genotype is identified, the probability of attainment of therapeutic concentrations is modest with standard dosing.
In pediatric patients for whom a rapid metabolizer genotype is identified, the probability of attainment of therapeutic concentrations is variable.

Metabolizer Status

Rapid Metabolizer

Phenotype (Genotype)

An individual carrying one normal function allele and one increased function allele

Recommendations

For adult patients: choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.
For pediatric patients: initiate therapy with recommended standard case dosing. Use therapeutic dose monitoring to titrate dose to therapeutic trough concentrations.
Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, TDM, and comorbidities.
Achieving voriconazole therapeutic concentrations in the pediatric population with ultrarapid and rapid metabolizer phenotypes in a timely manner is difficult. As critical time may be lost in achieving therapeutic concentrations, an alternative antifungal agent is recommended in order that the child receives effective antifungal therapy as soon as possible.
Meticulous therapeutic drug monitoring is critical for rapid metabolizers. There is insufficient evidence to distinguish a CYP2C19*1/*17 and *1/*1 pediatric patient due to large variability in trough concentrations.

Classification of Recommendation

Moderate

Genes analyzed: *CYP2C19*

Area: *Infectious Diseases*

42. ZUCLOPENTHIXOL

Diplotype is *4xN/*4xN
Metabolizer Status is PM
Evidence level: Level 1

DPWG Guideline
For CYP2D6 poor and intermediate metabolizers, reduce zuclopenthixol dose or select an alternative drug. For ultrarapid metabolizers, be alert to low zuclopenthixol plasma concentrations or select an alternative drug.

Implications
Reduce dose by 50% or select alternative drug (e.g., flupenthixol, quetiapine, olanzapine, clozapine).

Minor clinical effect (S):
QTc prolongation (<450 ms , <470 ms); INR increase < 4.5. Kinetic effect (S).

Genes analyzed: *CYP2D6* | **Area:** *Psychiatry*

43. ETHANOL

rs1800497-GG
Evidence level: Level 2B

GG Patients with GG genotype may have a decreased, but not absent, risk for Alcoholism when exposed to ethanol as compared to patients with the AG and AA genotype. Other genetic and clinical factors may influence a patients risk for alcohol dependency.

Genes analyzed: *ANKK1* | **Area:** *Alcoholism*

44. ADALIMUMAB, ETANERCEPT, INFLIXIMAB, TUMOR NECROSIS FACTOR ALPHA (TNF-ALPHA) INHIBITORS

rs1800629-GG
Evidence level: Level 2B

GG Patients with the GG genotype and inflammatory diseases who are treated with anti-TNF therapies may be more likely to have improvement in symptoms as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients response to anti-TNF therapy.

Genes analyzed: *TNF* | **Area:** *Arthritis*

45. SALBUTAMOL

rs7793837-AT
Evidence level: Level 2B

AT Patients with the AT genotype and asthma who are treated with short-acting beta2-antagonists may have a poorer response (decreased acute bronchodilation) as compared to patients with the AA genotype, or may have a better response (increased acute bronchodilation) as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients response to short-acting beta2-antagonists.

Genes analyzed: *CRHR2* | **Area:** *Asthma*

46. SALBUTAMOL

rs6988229-TT
Evidence level: Level 2B

TT Patients with TT genotypes may have increased bronchodilator response (FEV1) when treated with salbutamol in asthma when compared to patients with CC genotypes. Other genetic and clinical factors may also influence a patients response to therapy.

Genes analyzed: *COL22A1* | **Area:** *Asthma*

47. SALBUTAMOL, SALMETEROL

rs1042713-AG
Evidence level: Level 2A

AG Children with the AG genotype with asthma who are treated with salmeterol or salbutamol may have a decreased response to treatment (as measured by increased risk of asthma excerbations and lower quality of life scores) as compared to children with the GG genotype or may have a better response to treatment (as measured by increased risk of asthma excerbations and lower quality of life scores) as compared to patients with the AA genotype. This association does not seem to apply to lung function measurements such as peak expiratory flow rate or FEV1. Other genetic and clinical factors may also influence a patients response to treatment.

Genes analyzed: *ADRB2* | **Area:** *Asthma*

48. ACENOCOUMAROL

rs2108622-CC
Evidence level: Level 2B

CC Patients with the CC genotype who are treated with acenocoumarol may require a lower dose as compared to patients with the CT or TT genotype, although this has been contradicted in some studies. Other genetic and clinical factors may also influence a patients required acenocoumarol dose.

Genes analyzed: *CYP4F2*

Area: *Atrial Fibrillation*

49. AMISULPRIDE, ARIPIPRAZOLE, CLOZAPINE, HALOPERIDOL, OLANZAPINE, PALIPERIDONE, QUETIAPINE, RISPERIDONE, ZIPRASIDONE

rs489693-AC
Evidence level: Level 2B

AC Patients with schizophrenia, schizoaffective disorder, or autism spectrum disorder and genotype AC may have a decreased likelihood of weight gain and hypertriglyceridemia when taking amisulpride, aripiprazole, clozapine, olanzapine, haloperidol, paliperidone, quetiapine, ziprasidone, or risperidone as compared to patients with the AA genotypes, although this is contradicted in one study. Other clinical and genetic factors may also influence likelihood of weight gain in patients taking amisulpride, aripiprazole, clozapine, olanzapine, haloperidol, paliperidone, quetiapine, ziprasidone, or risperidone.

Genes analyzed: *MC4R*

Area: *Autism Spectrum Disorder, Schizophrenia, schizoaffective disorder*

50. CYCLOPHOSPHAMIDE, EPIRUBICIN

rs1695-AA
Evidence level: Level 2A

AA Patients with the AA genotype and Breast Neoplasms who are treated with cyclophosphamide and epirubicin may have 1) increased drug response 2) decreased severity of toxicity as compared to patients with GG genotype. Some patients were additionally treated with fluorouracil. Other genetic and clinical factors may influence a patients response to cyclophosphamide, epirubicin and fluorouracil.

Genes analyzed: *GSTP1*

Area: *Breast Neoplasms*

51. TAMOXIFEN

rs3892097-TT
Evidence level: Level 2A

TT Patients with the TT genotype who are treated with tamoxifen: 1) may have an increased risk of relapse as compared to patients with the CT or CC genotype 2) may have a decreased severity in hot flashes as compared to patients with the CT or CC genotype.

Genes analyzed: *CYP2D6*	**Area:** *Breast Neoplasms*

52. TRASTUZUMAB

rs1801274-AG
Evidence level: Level 2B

AG Patients with the AG genotype may have decreased response to trastuzumab and shorter progression-free survival in people with Breast cancer as compared to patients with genotype AA. Other genetic or clinical factors may also influence the response to trastuzumab.

Genes analyzed: *FCGR2A*	**Area:** *Breast Neoplasms*

53. ANTHRACYCLINES AND RELATED SUBSTANCES, FLUOROURACIL, PLATINUM COMPOUNDS

rs1800566-GG
Evidence level: Level 2A

GG Patients with the GG genotype and Breast Neoplasms and cancer who are treated with chemotherapy regimes that include platinum compounds, anthracyclines and related substances, and nucleoside inhibitors may have a better outcome (overall survival and progression-free survival) as compared to patients with the AA genotype. However, this has been contradicted in some studies. Other genetic and clinical factors may also influence a patients treatment outcome.

Genes analyzed: *NQO1*	**Area:** *Breast Neoplasms, Carcinoma*

54. ANASTROZOLE, CYCLOPHOSPHAMIDE, DOCETAXEL, DOXORUBICIN, EPIRUBICIN, EXEMESTANE, FLUOROURACIL, PACLITAXEL, RADIOTHERAPY, TAMOXIFEN

rs4646-AC
Evidence level: Level 2B

AC The AC genotype in women with breast cancer who are treated with tamoxifen (with or without anastrozole, cyclophosphamide, docetaxel, doxorubicin, epirubicin, exemestane, fluorouracil, letrozole, paclitaxel, radiotherapy) may have DECREASED treatment EFFICACY in PRE-MENOPAUSAL women and INCREASED treatment EFFICACY in POST-MENOPAUSAL women as compared to patients with the AA genotypes. Other genetic and clinical factors may also influence response to tamoxifen and other treatment regimens in pre- and post-menopausal women with breast cancer.

Genes analyzed: *CYP19A1*	**Area:** *Breast Neoplasms, Menopause*

55. ANTINEOPLASTIC AGENTS, CISPLATIN, CYCLOPHOSPHAMIDE, FLUOROURACIL, PACLITAXEL

rs1042522-CC
Evidence level: Level 2B

CC Patients with the CC genotype may have 1) decreased but not absent risk for toxicity 2) increased survival when treated with antineoplastic agents as compared to patients with the CG or GG genotype. Other genetic and clinical factors may also influence a patients response to antineoplastic agents.

Genes analyzed: *TP53*	**Area:** *Breast Neoplasms, Neoplasms, Neutropenia, Ovarian Neoplasms, Stomach Neoplasms*

56. METHOTREXATE

rs1045642-AG
Evidence level: Level 2A

AG Patients with the AG genotype and lymphoma or leukemia who are treated with methotrexate may have an increased risk of toxicity as compared to patients with the GG genotype, or a decreased risk of toxicity as compared to patients with the AA genotype, although this is contradicted in some studies. Other genetic and clinical factors may also influence a patients risk of methotrexate-induced toxicities.

Genes analyzed: *ABCB1*	**Area:** *Burkitt Lymphoma, Drug Toxicity, Lymphoma*

57. CARBOPLATIN

rs1801133-AG
Evidence level: Level 2A

AG Patients with AG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patients response to carboplatin.

Genes analyzed: *MTHFR*	**Area:** *Carcinoma*

58. CARBOPLATIN, CISPLATIN, OXALIPLATIN, PLATINUM, PLATINUM COMPOUNDS

rs25487-CC
Evidence level: Level 2B

CC Patients with cancer and the CC genotype may have increased response (in the form of longer progression-free or overall survival) as compared to patients with the CT or TT genotype. However, a few studies report no association or decreased survival and response for patients with the CC as compared to the TT genotype only. Other genetic and clinical factors may also influence response to platinum-based regimens.

Genes analyzed: *XRCC1*	**Area:** *Carcinoma*

59. CARBOPLATIN, CISPLATIN, OXALIPLATIN, PLATINUM, PLATINUM COMPOUNDS

rs11615-AG
Evidence level: Level 2B

AG Patients with the AG genotype who are treated with platinum-based chemotherapy may have an increased risk for nephrotoxicity as compared to patients with the GG genotype. The findings for response and overall survival are inconclusive. Patients with the AG genotype may have an increased response compared to patients with the AA genotype. However, another study showed an increased response compared to patients with the GG genotype. Additionally, some studies find no association with drug toxicity or survival. Other genetic and clinical factors may also influence a patients response to platinum-based chemotherapy.

Genes analyzed: *ERCC1*	**Area:** *Carcinoma*

60. SUNITINIB

rs1933437-AG
Evidence level: Level 2B

AG Patients with renal cell carcinoma and the AG genotype who are treated with sunitinib may have a decreased risk of experiencing leukopenia, and possibly thrombocytopenia and neutropenia, as compared to patients with the AA genotypes, however, this is contradicted in one study. Other clinical and genetic factors may also influence risk of leukopenia in patients with renal cell carcinoma who are administered sunitinib.

Genes analyzed: *FLT3*	**Area:** *Carcinoma*

61. COCAINE

rs1076560-CC
Evidence level: Level 2B

CC Patients with the CC genotype who abused cocaine may have a decreased risk of death from cocaine intoxication as compared to patients with the AA genotype. Other genetic and clinical factors may also influence cocaine-related death.

Genes analyzed: *DRD2*	**Area:** *Cocaine-Related Disorders*

62. CETUXIMAB

rs4444903-AG
Evidence level: Level 2B

AG Patients with the AG genotype who are treated with cetuximab may have a poorer response as compared to patients with the GG genotype or may have a better response as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients response to cetuximab treatment.

Genes analyzed: *EGF*	**Area:** *Colorectal Neoplasms, Rectal Neoplasms*

63. ASPIRIN

rs10306114-AG
Evidence level: Level 2B

AG Patients with the AG genotype who are treated with aspirin may have an increased risk for non-response to aspirin as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients response to aspirin.

Genes analyzed: *PTGS1*	**Area:** *Coronary Artery Disease, Myocardial Infarction*

64. ATORVASTATIN

rs7412-CT
Evidence level: Level 2A

CT Patients with the CT genotype who are treated with atorvastatin may have a better response (higher reduction in LDL-cholesterol) as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patients response to atorvastatin treatment.

Genes analyzed: *APOE*	**Area:** *Coronary Disease, Hyperlipidemias*

65. ATORVASTATIN

rs20455-AA
Evidence level: Level 2B

AA Patients with the AA genotype may have a lower risk of coronary disease and may be less likely to benefit from atorvastatin treatment as compared to patients with the AG or GG genotype. Other genetic and clinical factors may also influence a patients response to atorvastatin treatment.

Genes analyzed: *KIF6*

Area: *Coronary Disease, Myocardial Infarction*

66. PRAVASTATIN

rs20455-AA
Evidence level: Level 2B

AA Patients with the AA genotype may have a lower risk of coronary disease and may be less likely to benefit from pravastatin treatment as compared to patients with the AG or GG genotype. Other genetic and clinical factors may also influence a patients response to pravastatin treatment.

Genes analyzed: *KIF6*

Area: *Coronary Disease, Myocardial Infarction*

67. AMITRIPTYLINE, ANTIDEPRESSANTS, CLOMIPRAMINE, DESIPRAMINE, DOXEPIN, IMIPRAMINE, NORTRIPTYLINE, TRIMIPRAMINE

rs3892097-TT
Evidence level: Level 1A

TT Patients with the TT genotype (CYP2D6*4/*4) and depression who are treated with tricyclic antidepressants 1) may have an increased likelihood of switching treatment indicating an increased risk of side effects 2) may require a decreased dose of drug as compared to patients with the CC genotype (CYP2D6*1/*1). Other genetic and clinical factors may also influence a patients metabolism of tricyclic antidepressants and risk of adverse effects.

Genes analyzed: *CYP2D6*

Area: *Depression*

68. ANTIDEPRESSANTS, CITALOPRAM, SELECTIVE SEROTONIN REUPTAKE INHIBITORS

rs7997012-GG
Evidence level: Level 2B

GG Patients with the GG genotype and depression who are treated with citalopram may be less likely to have improvement in symptoms as compared to patients with the AA genotype. However, no association has been reported in studies that determined response to different Selective serotonin reuptake inhibitors (SSRIs) or antidepressants as a drug class. Other genetic and clinical factors may also influence a patients response to antidepressants.

Genes analyzed: *HTR2A*

Area: *Depression, Depressive Disorder*

69. ANTIDEPRESSANTS, CITALOPRAM, FLUOXETINE, MIRTAZAPINE, PAROXETINE, SELECTIVE SEROTONIN REUPTAKE INHIBITORS, VENLAFAXINE

rs4713916-GG
Evidence level: Level 2B

GG Patients with the GG genotype may have a reduced response to antidepressants as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients response to antidepressant treatment.

Genes analyzed: *FKBP5*

Area: *Depressive Disorder*

70. CAPECITABINE, FLUOROURACIL, LEUCOVORIN, TEGAFUR

rs1801019-CC
Evidence level: Level 2B

CC Patients with CC genotype and cancer may have an increased risk for toxicity (Diarrhea, any grade 3 adverse event) when treated with leucovorin and tegafur or fluorouracil and leucovorin as compared to patients with the CG and GG genotype. One study found no association between the CC genotype and risk of drug toxicity in patients administered capecitabine and/or fluorouracil. Other genetic and clinical factors may also influence response to leucovorin, tegafur, capecitabine and fluorouracil.

Genes analyzed: *UMPS*

Area: *Drug Toxicity*

71. NEVIRAPINE

rs28399499-TT
Evidence level: Level 2B

TT Patients with the TT genotype and HIV may have a decreased risk for Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN) when treated with nevirapine as compared to patients with the CC or CT genotype, but may not be associated with hepatotoxicity. Other genetic and clinical factors may also influence risk for developing SJS/TEN when receiving nevirapine.

Genes analyzed: *CYP2B6*

Area: *Epidermal Necrolysis*

72. ANTIEPILEPTICS, CARBAMAZEPINE

rs3812718-CT
Evidence level: Level 2B

CT Patients with the CT genotype and epilepsy may be less likely to be resistant to antiepileptic treatment, particularly carbamazepine, as compared to patients with the TT genotype. Other genetic and clinical factors may also influence resistance to antiepileptic drugs.

Genes analyzed: *SCN1A*

Area: *Epilepsy*

73. CARBAMAZEPINE

rs3812718-CT
Evidence level: Level 2B

CT Patients with the CT genotype who are treated with carbamazepine may require a higher dose as compared to patients with the CC genotype. Other genetic and clinical factors may also influence dose of carbamazepine.

Genes analyzed: *SCN1A*

Area: *Epilepsy*

74. CARBAMAZEPINE

rs2234922-AA
Evidence level: Level 2B

AA Patients with the AA genotype may require a decreased dose of carbamazepine as compared to patients with the AG or GG genotype, although this is contradicted in one study. Other genetic and clinical factors may also influence dose of carbamazepine.

Genes analyzed: *EPHX1*

Area: *Epilepsy*

75. CARBAMAZEPINE

rs1051740-CT
Evidence level: Level 2B

CT Patients with the CT genotype and Epilepsy may have higher metabolism of carbamazepine and may require an increased dose of carbamazepine as compared to patients with the the TT genotype, although this is contradicted in some studies. Other genetic and clinical factors may also influence metabolism and dose of carbamazepine.

Genes analyzed: *EPHX1*

Area: *Epilepsy*

76. PHENYTOIN

rs3812718-CT
Evidence level: Level 2B

CT Patients with the CT genotype who are treated with phenytoin may require a higher dose as compared to patients with the CC genotype. Other genetic and clinical factors may also influence dose of phenytoin.

Genes analyzed: *SCN1A*

Area: *Epilepsy*

77. SILDENAFIL

rs5443-CC
Evidence level: Level 2B

CC Patients with the CC genotype and erectile dysfunction who are treated with sildenafil may be less likely to have positive erectile response as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients response to sildenafil.

Genes analyzed: *GNB3*	**Area:** *Erectile Dysfunction*

78. HYDROCHLOROTHIAZIDE

rs7297610-CC
Evidence level: Level 2B

CC Patients with the CC genotype and hypertension who are treated with hydrochlorothiazide may have an increased response as compared to patients with the CT or TT genotype. Other genetic and clinical factors may also influence a patients response to hydrochlorothiazide.

Genes analyzed: *YEATS4*	**Area:** *Essential hypertension, Hypertension*

79. LATANOPROST

rs3753380-TT
Evidence level: Level 2B

TT Patients with the TT genotype and open angle glaucoma, may have a decreased response to latanoprost (as determined by a reduction in intraocular pressure) compared to patients with genotype CC. Other genetic and clinical factors may affect response to latanoprost. *Please note: One study that reported this SNPs association with response to latanoprost compared the haplotype of rs3753380 C and rs3766355 C versus rs3753380 T and rs3766355 A.

Genes analyzed: *PTGFR*	**Area:** *Glaucoma*

80. NEVIRAPINE

rs1045642-AG
Evidence level: Level 2A

AG While patients with the AA genotype and HIV-1 infection who are treated with nevirapine may have a decreased, but not absent, risk for nevirapine hepatotoxicity as compared to patients with the GG genotype, it is not clear what the influence of one A allele with the G allele is. Other genetic and clinical factors may also influence a patients risk for hepatotoxicity with nevirapine treatment.

Genes analyzed: *ABCB1*

Area: *HIV Infections*

81. NEVIRAPINE

rs3745274-GG
Evidence level: Level 2A

GG Patients with the GG genotype and HIV infection may have increased clearance of and decreased exposure to nevirapine as compared to patients with the TT or GT genotype. Other genetic and clinical factors may also influence clearance of nevirapine and exposure to drug.

Genes analyzed: *CYP2B6*

Area: *HIV Infections*

82. PEGINTERFERON ALFA-2B, RIBAVIRIN

rs1127354-CC
Evidence level: Level 2B

CC Patients with chronic hepatitis C and the CC genotype, may have an increased risk of anemia but a decreased risk of thrombocytopenia as compared to patients with the AA or AC genotype who are taking peg interferon alfa-2b and ribavirin. Other clinical and genetic factors may influence risk of anemia in patients with hepatitis C who are taking peg interferon alfa-2b and ribavirin.

Genes analyzed: *ITPA*

Area: *Hepatitis C*

83. PEGINTERFERON ALFA-2B, RIBAVIRIN

rs7270101-AA
Evidence level: Level 2B

AA Patients with chronic hepatitis C and the AA genotype may have an increased risk of anemia but a decreased risk of thrombocytopenia when compared to patients with the AC and CC genotype who are taking peg interferon alfa-2b and ribavirin. Studies have looked at the composite genotypes of rs1127354 CC and rs7270101 AA to identify normal ITPas activity vs. deficient. Normal ITPase activity is associated with increased risk of anemia and possibly decreased risk of thrombocytopenia as compared to deficient activity. Other clinical and genetic factors may influence risk of anemia in patients with hepatitis C who are taking peg interferon alfa-2b and ribavirin.

Genes analyzed: *ITPA*	**Area:** *Hepatitis C*

84. METHADONE

rs3745274-GG
Evidence level: Level 2A

GG Patients with the GG genotype who are being treated with methadone for heroin addiction may require an increased dose of the drug as compared to patients with the TT genotype. Other genetic and clinical factors may also influence dose of methadone.

Genes analyzed: *CYP2B6*	**Area:** *Heroin Dependence*

85. ALFENTANIL, BUPRENORPHINE, DRUGS USED IN OPIOID DEPENDENCE, FENTANYL, HEROIN, MORPHINE, NALTREXONE, OPIOIDS, TRAMADOL

rs1799971-AG
Evidence level: Level 2B

AG Individuals with the AG genotype may experience decreased efficacy of opioids for pain and opioid related drugs to treat addiction, and may require an increased dose of opioids as compared to individuals with the AA genotype. However this has been contradicted in some studies. In some studies, the AA and AG genotypes were found to have a increased efficacy, and to require a decreased dose as compared to the GG genotype. Other genetic and clinical factors may also influence a patients dependence on opioid drugs.

Genes analyzed: *OPRM1*	**Area:** *Heroin Dependence, Opioid-Related Disorders, Pain*

86. ROSUVASTATIN

rs4149056-TT
Evidence level: Level 2A

TT Patients with the TT genotype may have lower plasma concentrations of rosuvastatin as compared to patients with the CC genotype. No association is seen between genotypes of this variant and change in LDL-cholesterol levels in response to rosuvastatin treatment. Other genetic and clinical factors may also influence a patients metabolism and response to rosuvastatin.

Genes analyzed: *SLCO1B1*

Area: *Hypercholesterolemia*

87. ROSUVASTATIN

rs2231142-GG
Evidence level: Level 2B

GG Patients with the GG genotype and who are treated with rosuvastatin 1) may have lower plasma concentrations of rosuvastatin 2) may have a reduced response to treatment as determined by a lower reduction in LDL-C as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients response to rosuvastatin treatment and rosuvastatin pharmacokinetics.

Genes analyzed: *ABCG2*

Area: *Hypercholesterolemia, Myocardial Infarction*

88. ANTIPSYCHOTICS, CLOZAPINE, OLANZAPINE, RISPERIDONE

rs1800497-GG
Evidence level: Level 2B

GG Patients with the GG genotype may have decreased but not non-existant risk of side effects including hyperprolactinemia and weight gain, but increased risk of tardive dyskinesia, during treatment with antipsychotic drugs as compared to patients with the AA or AG genotype. Other genetic and clinical factors may also influence a patients risk for side effects.

Genes analyzed: *ANKK1DRD2*

Area: *Hyperprolactinemia, Weight gain, tardive dyskinesia*

89. DIURETICS, HYDROCHLOROTHIAZIDE

rs4149601-GG
Evidence level: Level 2B

GG White patients with the GG genotype and hypertension who are treated with hydrochlorothiazide may have better response as compared with patients with genotype AA. The opposite result has been seen in Asians (at a lower level of evidence). Other genetic and clinical factors may also influence a patients response to hydrochlorothiazide or other diuretic treatment.

Genes analyzed: *NEDD4L* | **Area:** *Hypertension*

90. HYDROCHLOROTHIAZIDE

rs16960228-GG
Evidence level: Level 2B

GG Patients with the GG genotype and hypertension who are treated with hydrochlorothiazide may have a decreased reduction of diastolic blood pressure as compared to patients with the AA or AG genotypes. Other genetic and clinical factors may also influence a patients response to hydrochlorothiazide treatment.

Genes analyzed: *PRKCA* | **Area:** *Hypertension*

91. SIROLIMUS

rs776746-CT
Evidence level: Level 2A

CT Kidney transplant patients with the CT (CYP3A5 *1/*3) genotype may have increased metabolism, and decreased exposure to sirolimus and require an increased dose as compared to patients with the CC (CYP3A5 *3/*3) genotypes. Other clinical and genetic factors may also influence exposure to and dose of sirolimus.

Genes analyzed: *CYP3A5* | **Area:** *Kidney Transplantation*

92. FUROSEMIDE, IRON, SPIRONOLACTONE

rs4961-GG
Evidence level: Level 2B

GG Patients with the GG genotype and Liver Cirrhosis who are treated with furosemide and spironolactone may be more likely to respond to diuretic treatment as compared to patients with the GT and TT genotype. Other genetic and clinical factors may also influence a patients response to diuretics.

Genes analyzed: *ADD1*

Area: *Liver Cirrhosis*

93. CISPLATIN

rs1695-AA
Evidence level: Level 2B

AA Pediatric patients with the AA genotype and medulloblastoma may have a decreased risk of ototoxicity when treated with cisplatin-based regimens as compared to patients with the AG or GG genotype. Other genetic and clinical factors may also influence risk of ototoxicity in patients receiving cisplatin-based regimens.

Genes analyzed: *GSTP1*

Area: *Medulloblastoma, Testicular Neoplasms*

94. ATORVASTATIN, HMG COA REDUCTASE INHIBITORS, ROSUVASTATIN

rs4693075-CG
Evidence level: Level 2B

CG Patients with the CG genotype may have increased risk of statin-related muscle symptoms as compared to patients with genotype CC. Other genetic and clinical factors may also influence a patients risk of toxicity.

Genes analyzed: *COQ2*

Area: *Muscular Diseases*

95. SIMVASTATIN

rs4149056-TT
Evidence level: Level 1A

TT Patients with the TT genotype may have a lower risk of simvastatin-related myopathy as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patients risk for toxicity.

Genes analyzed: *SLCO1B1*

Area: *Muscular Diseases, Myopathy*

96. CAPECITABINE, FLUOROURACIL, PYRIMIDINE ANALOGUES, TEGAFUR

rs3918290-CC
Evidence level: Level 1A

CC Patients with the CC genotype (DPYD *1/*1) and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) increased clearance of fluoropyrimidine drugs and 2) decreased, but not non-existent, risk for drug toxicity as compared to patients with the CT or TT genotype (DPYD *1/*2A or *2A/*2A). Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine based chemotherapy.

Genes analyzed: *DPYD*

Area: *Neoplasms*

97. CAPECITABINE, FLUOROURACIL, PYRIMIDINE ANALOGUES, TEGAFUR

rs67376798-TT
Evidence level: Level 1A

TT Patients with the TT genotype and cancer who are treated with fluoropyrimidine-based chemotherapy may have 1) increased clearance of the drug and 2) decreased, but not absent, risk and reduced severity of drug toxicity as compared to patients with the AT genotype. Fluoropyrimidines are often used in combination chemotherapy such as FOLFOX (fluorouracil, leucovorin and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan) or FEC (fluorouracil, epirubicin and cyclophosphamide) or with other drugs such as bevacizumab, cetuximab, raltitrexed. The combination and delivery of the drug may influence risk for toxicity. Other genetic and clinical factors may also influence response to fluoropyrimidine-based chemotherapy.

Genes analyzed: *DPYD*	**Area:** *Neoplasms*

98. METHOTREXATE

rs1801133-AG
Evidence level: Level 2A

AG Patients with the AG genotype and leukemia or lymphoma who are treated with methotrexate: 1) may have poorer response to treatment 2) may be at increased risk of toxicity 3) may require a lower dose of methotrexate, and 4) may be at greater risk of folate deficiency as compared to patients with the GG genotype, or 1) may have better response to treatment 2) may be at decreased risk of toxicity, and 3) may require a higher dose of methotrexate as compared to patients with the AA genotype. This association has been contradicted or not found in multiple studies. Other genetic and clinical factors may also influence a patients risk for toxicity and response with methotrexate treatment.

Genes analyzed: *MTHFR*	**Area:** *Neoplasms*

99. CISPLATIN

rs2228001-GT
Evidence level: Level 1B

GT Patients with the GT genotype may have an increased risk for toxicity with cisplatin treatment, including hearing loss and neutropenia, as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients risk for toxicity.

Genes analyzed: *XPC*	**Area:** *Neoplasms, Osteosarcoma, Testicular Neoplasms, Urinary Bladder Neoplasms*

100. CISPLATIN, PLATINUM, PLATINUM COMPOUNDS

rs3212986-CC
Evidence level: Level 2B

CC Patients with the CC genotype may have increased risk for nephrotoxicity with platinum-based regimens as compared to patients with the AA genotypes. Other genetic and clinical factors may also influence response to platinum-based regimens.

Genes analyzed: *ERCC1*

Area: *Neoplasms, Ovarian Neoplasms*

101. TACROLIMUS

rs2740574-TT
Evidence level: Level 2A

TT Transplant recipients with the TT (CYP3A4 (*1/*1) genotype may require a decreased dose of tacrolimus as compared to patients with the CT (*1B/*1) or CC (*1/*1) genotype. Other genetic and clinical factors, such as CYP3A5 *3 (rs776746), may also influence a patients dose requirements.

Genes analyzed: *CYP3A4*

Area: *Organ Transplantation*

102. CYCLOSPORINE

rs776746-CT
Evidence level: Level 2B

CT Patients with the CT (CYP3A5 *1/*3) genotype may require a higher dose of cyclosporine to reach target blood concentration as compared to patients with the CC (CYP3A5 *3/*3) genotype, although this is contradicted in some studies. Other genetic and clinical factors may also influence dose of cyclosporine.

Genes analyzed: *CYP3A5*

Area: *Organ Transplantation, Transplantation*

103. ACENOCOUMAROL

rs1057910-AA
Evidence level: Level 2A

AA Patients with the AA genotype may require increased dose of acenocoumarol as compared to patients with the AC or CC genotype. Other genetic and clinical factors may also influence acenocoumarol dose.

Genes analyzed: *CYP2C9*

Area: *Other*

104. ACENOCOUMAROL, PHENPROCOUMON

rs9923231-CC
Evidence level: Level 1B

CC Patients with the CC genotype who are treated with acenocoumarol or phenprocoumon may require a higher dose as compared to patients with the CT or TT genotypes. Other genetic and clinical factors may also influence a patients acenocoumarol or phenprocoumon maintenance dose requirement.

Genes analyzed: *VKORC1*

Area: *Other*

105. ACENOCOUMAROL, PHENPROCOUMON

rs9934438-GG
Evidence level: Level 2A

GG Patients with the GG genotype may have increased dose of acenocoumarol or phenprocoumon as compared to patients with genotype AA or AG. Other genetic and clinical factors may also influence the dose of acenocoumarol or phenprocoumon.

Genes analyzed: *VKORC1*

Area: *Other*

106. ACENOCOUMAROL, PHENPROCOUMON

rs7294-TT
Evidence level: Level 2A

TT Patients with the TT genotype may require an increased dose of phenprocoumon or acenocoumarol as compared to patients with the CT or CC genotypes, although this has been contradicted in some studies. Other genetic and clinical factors may also influence a patients phenprocoumon or acenocoumarol dose requirement.

Genes analyzed: *VKORC1*

Area: *Other*

107. ALLOPURINOL

rs2231142-GG
Evidence level: Level 2B

GG Patients with the GG genotype and gout may have improved response when treated with allopurinol as compared to patients with the GT or TT genotype. Other genetic and clinical factors may also influence response to allopurinol.

Genes analyzed: *ABCG2*

Area: *Other*

108. AMITRIPTYLINE

rs4244285-GG
Evidence level: Level 1A

GG Patients with the GG genotype who are treated with amitriptyline may have increased metabolism of amitriptyline (decreased amitriptyline plasma concentrations and increased nortriptyline plasma concentrations) as compared to patients with the AA or AG genotype. Other genetic factors, including other CYP2C19 alleles *17 rs12248560 and *3 rs4986893, along with clinical factors, may also influence a patients required dose and should be taken into consideration.

Genes analyzed: *CYP2C19*

Area: *Other*

109. ANTIINFLAMMATORY AGENTS

rs1057910-AA
Evidence level: Level 2A

AA Patients with the AA genotype who are treated with non-steroid antiinflammatory agents, celecoxib or diclofenac may have a decreased, but not absent, risk of gastrointestinal bleeding as compared to patients with the AC and CC genotype. Other genetic and clinical factors may also influence a patients response to Antiinflammatory agents, non-steroids, celecoxib or diclofenac.

Genes analyzed: *CYP2C9*	**Area:** *Other*

110. ASPIRIN

rs6065-CC
Evidence level: Level 2B

CC Patients with the CC genotype may have an increased risk for aspirin resistance as compared to patients with the CT or TT genotype. Other genetic and clinical factors may also influence a patients response to aspirin.

Genes analyzed: *GP1BA*	**Area:** *Other*

111. ATAZANAVIR

rs887829-CT
Evidence level: Level 1A

CT Patients infected with the human immunodeficiency virus (HIV) and the CT genotype who are treated with atazanavir may have a decreased, but not absent, risk of hyperbilirubinemia and bilirubin-related drug discontinuation as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients risk for hyperbilirubinemia, or drug discontinuation.

Genes analyzed: *[]*	**Area:** *Other*

112. BUPRENORPHINE, FENTANYL, MEPERIDINE, MORPHINE, OPIOIDS, PENTAZOCINE

rs2952768-CT
Evidence level: Level 2B

CT Patients with the CT genotype may have decreased opioid analgesic requirements after surgery as compared to patients with the CC genotype. Other genetic and clinical factors may influence a patients opioid dose requirement.

Genes analyzed: *[]*	**Area:** *Other*

113. CAFFEINE

rs2298383-CT
Evidence level: Level 2B

CT Patients with the CT genotype may have decreased anxiety when exposed to caffeine as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patients response to caffeine.

Genes analyzed: *ADORA2A*	**Area:** *Other*

114. CELECOXIB

rs1057910-AA
Evidence level: Level 2A

AA Patients with the AA (CYP2C9 *1/*1) genotype may have increased metabolism of celecoxib as compared to patients with the AC or CC (*1/*3 or *3/*3) genotype. Other genetic and clinical factors may also influence a metabolism of celecoxib.

Genes analyzed: *CYP2C9*	**Area:** *Other*

115. CITALOPRAM

rs4244285-GG
Evidence level: Level 2A

GG Patients with GG genotype may have an increased metabolism of citalopram as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients citalopram metabolism.

Genes analyzed: *CYP2C19*	**Area:** *Other*

116. CITALOPRAM, ESCITALOPRAM

rs12248560-CT
Evidence level: Level 2A

CT Patients with the CT genotype (CYP2C19*1/*17) may have an increased metabolism of citalopram or escitalopram as compared to patients with the CC genotype. Other genetic factors, including other CYP2C19 alleles *2 rs4244285,*3 rs4986893, and clinical factors may also influence a patients citalopram or escitalopram metabolism.

Genes analyzed: *CYP2C19*	**Area:** *Other*

117. CLOMIPRAMINE

rs4244285-GG
Evidence level: Level 2A

GG Patients with the GG genotype may have an increased metabolism of clomipramine as compared to patients with the AG or AA genotype. Other genetic and clinical factors may also influence a patients clomipramine metabolism.

Genes analyzed: *CYP2C19*	**Area:** *Other*

118. DIGOXIN

rs1045642-AG
Evidence level: Level 2A

AG Patients with AG genotype may have decreased metabolism and increased serum concentration of digoxin as compared to patients with the GG genotype. Other genetic and clinical factors may also impact the metabolism of digoxin.

Genes analyzed: *ABCB1*	**Area:** *Other*

119. EFAVIRENZ

rs28399499-TT
Evidence level: Level 2A

TT Patients with the TT genotype may have decreased plasma drug exposure when treated with efavirenz as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patients drug metabolism.

Genes analyzed: *CYP2B6*	**Area:** *Other*

120. EFAVIRENZ

rs3745274-GG
Evidence level: Level 1B

GG Patients with the GG genotype and HIV infection may have decreased plasma concentrations and increased clearance of efavirenz as compared to patients with the GT or TT genotype. Other genetic and clinical factors may also influence a patients exposure to efavirenz.

Genes analyzed: *CYP2B6*	**Area:** *Other*

121. EFAVIRENZ

rs3745274-GG
Evidence level: Level 2A

GG Patients with the GG genotype may have a decreased, but not absent risk of efavirenz-induced side effects, including sleep- and central nervous system-related side effects, as compared to patients with the GT or TT genotype. However, patients with the GG genotype may also have an increased risk for immunological failure, as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients risk for toxicity.

Genes analyzed: *CYP2B6* | **Area:** *Other*

122. EFAVIRENZ

rs4803419-CT
Evidence level: Level 2B

CT Patients with HIV and the CT genotype may have higher plasma concentrations of efavirenz as compared to patients with the CC genotype and lower plasma concentrations as compared to patients with the TT genotype. Other clinical and genetic factors may also influence plasma concentrations of efavirenz in patients with HIV.

Genes analyzed: *CYP2B6* | **Area:** *Other*

123. EFAVIRENZ

rs2279345-CC
Evidence level: Level 2A

CC Patients with the CC genotype and HIV may have increased metabolism of efavirenz resulting in lower efavirenz plasma levels as compared to patients with the TT genotype. Other genetic and clinical factors may also influence metabolism and plasma concentrations of efavirenz.

Genes analyzed: *CYP2B6* | **Area:** *Other*

124. ETHANOL

rs1799971-AG
Evidence level: Level 2B

AG Patients with the AG genotype may have an increased severity of intoxication and an increased response when exposed to ethanol as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients ethanol response.

Genes analyzed: *OPRM1* | **Area:** *Other*

125. FENTANYL, METHADONE, MORPHINE, OPIOIDS, OXYCODONE, TRAMADOL

rs1045642-AG
Evidence level: Level 2B

AG Patients with the AG genotype may experience decreased efficacy of fentanyl, methadone, morphine, tramadol, oxycodone or other opioids and thus may require an increased dose those drugs as compared to patients with the the AA genotype and an improved efficacy and decreased dose of as compared to patients with the GG genotype, athough this has been contradicted in some studies. Other genetic and clinical factors may also influence a patients dose of, or response to, opioids or drugs used to treat opioid disorders.

Genes analyzed: *ABCB1* | **Area:** *Other*

126. FLUOROURACIL, OXALIPLATIN

rs1695-AA
Evidence level: Level 2A

AA Patients with the AA genotype and cancer who are treated with fluorouracil and oxaliplatin may have poorer treatment outcome (reduced responsiveness, lower overall survival time, increased risk of death) as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patients response to fluorouracil and oxaliplatin treatment.

Genes analyzed: *GSTP1* | **Area:** *Other*

127. HMG COA REDUCTASE INHIBITORS, PRAVASTATIN, SIMVASTATIN

rs17244841-AA
Evidence level: Level 2A

AA Patients with the AA genotype who are treated with statins may be more likely to respond as compared to patients with the AT or TT genotype. Other genetic and clinical factors may also influence a patients response when treated with statins.

Genes analyzed: *HMGCR*

Area: *Other*

128. HMG COA REDUCTASE INHIBITORS, SIMVASTATIN

rs1719247-CC
Evidence level: Level 2B

CC Patients with the CC genotype may be more likely to experience myopathy when treated with statins as compared to patients with the CT or TT genotype. Other genetic and clinical factors may also influence the likelihood of myopathy when a patient is treated with statins.

Genes analyzed: *[]*

Area: *Other*

129. HMG COA REDUCTASE INHIBITORS, SIMVASTATIN

rs1346268-TT
Evidence level: Level 2B

TT Patients with the TT genotype may be more likely to experience myopathy when treated with statins as compared to patients with the CC or CT genotype. Other genetic and clinical factors may also influence the likelihood of myopathy when a patient is treated with statins.

Genes analyzed: *[]*

Area: *Other*

130. LORAZEPAM, OXAZEPAM

rs1902023-AA
Evidence level: Level 2B

AA Subjects with the AA genotype may have decreased clearance of oxazepam or lorazepam as compared to subjects with the CC genotype. Other genetic and clinical factors may also influence the oral clearance of oxazepam or lorazepam.

Genes analyzed: *UGT2B15* | **Area:** *Other*

131. NALOXONE

rs1799971-AG
Evidence level: Level 2B

AG Patients with the AG genotype who are treated with naloxone may have increased peak cortisol response as compared to patients with AA genotype.

Genes analyzed: *OPRM1* | **Area:** *Other*

132. NEVIRAPINE

rs28399499-TT
Evidence level: Level 2A

TT Patients with the TT genotype may have decreased plasma drug exposure when treated with nevirapine as compared to patients with the CT or CC genotype. Other genetic and clinical factors may also influence a patients drug metabolism.

Genes analyzed: *CYP2B6* | **Area:** *Other*

133. NEVIRAPINE

rs746647-AA
Evidence level: Level 2B

AA Patients with the AA genotype may have decreased risk of Nevirapine-induced rash when treated with nevirapine in people with HIV as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patients response to nevirapine.

Genes analyzed: *CCHCR1*	**Area:** *Other*

134. NICOTINE

rs1051730-AG
Evidence level: Level 2B

AG Patients with the AG genotype may have an increased risk for nicotine dependency, decreased lung function when exposed to nicotine, but may experience an increased chance of achieving 6 month abstinence if prescribed nicotine replacement therapy as compared to patients with the GG genotype or a decreased risk for nicotine dependency and decreased chance of achieving 6 month abstinence if prescribed nicotine replacement therapy as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patients response to nicotine.

Genes analyzed: *CHRNA3*	**Area:** *Other*

135. ONDANSETRON

rs1045642-AG
Evidence level: Level 2A

AG Patients with genotype AG may have increased likelihood of nausea and vomiting shortly after being treated with treated with ondansetron as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patients response to ondansetron.

Genes analyzed: *ABCB1*	**Area:** *Other*

136. PHENPROCOUMON

rs2108622-CC
Evidence level: Level 2A

CC Patients with the CC genotype who are treated with phenprocoumon may require a lower dose as compared to patients with the TT genotype. Other genetic and clinical factors may also influence a patients required phenprocoumon dose.

Genes analyzed: *CYP4F2* | **Area:** *Other*

137. PRAVASTATIN

rs4149015-GG
Evidence level: Level 2A

GG Patients carrying the GG genotype may have increased chance of response to pravastatin compared to patients carrying the AA or AG genotype. Other genetic and clinical factors may also influence a patients response.

Genes analyzed: *SLCO1B1* | **Area:** *Other*

138. PRAVASTATIN

rs4149056-TT
Evidence level: Level 2A

TT Patients with the TT genotype may have decreased plasma concentrations of pravastatin as compared to patients with the CC or CT genotype. Other genetic and clinical factors may also influence a patients metabolism of pravastatin.

Genes analyzed: *SLCO1B1* | **Area:** *Other*

139. ROSIGLITAZONE

rs10509681-TT
Evidence level: Level 2A

TT Patients with the TT (CYP2C8*1/*1) genotype may have decreased metabolism of rosiglitazone, a larger change in HbA1c, and an increased risk of edema as compared to patients with the CC (CYP2C8*3/*3) or CT (CYP2C8*3/*1) genotype. One study found no association with blood glucose levels. Other genetic and clinical factors may also influence metabolism of rosiglitazone, risk of edema and blood glucose levels.

Genes analyzed: *CYP2C8*	**Area:** *Other*

140. PAROXETINE

rs6295-GG
Evidence level: Level 2B

GG Patients with the GG genotype with panic disorder who are treated with paroxetine may have a better response at 4 weeks of treatment as compared to patients with the CG or CC genotype. Other genetic and clinical factors may also influence a patients response to paroxetine.

Genes analyzed: *HTR1A*	**Area:** *Panic Disorder*

141. ASPARAGINASE, CYCLOPHOSPHAMIDE, DAUNORUBICIN, PREDNISOLONE, VINCRISTINE

rs738409-CG
Evidence level: Level 2B

CG Patients with the CG genotype may have increased risk of hepatotoxicity when treated with remission induction therapy (including asparaginase) in children with acute lymphoblastic leukemia (ALL) as compared to patients with genotype CC. Other genetic and clinical factors may also influence the risk of toxicity to remission induction therapy.

Genes analyzed: *PNPLA3*	**Area:** *Precursor Cell Lymphoblastic Leukemia-Lymphoma*

142. METHOTREXATE

rs11045879-TT
Evidence level: Level 2A

TT Patients with the TT genotype and precursor cell lymphoblastic leukemia-lymphoma who are treated with methotrexate: 1) may have increased clearance of methotrexate as compared to patients with the CC or CT genotype 2) may have an increased risk for GI toxicity when treated with methotrexate as compared to patients with the CC or CT genotype.

Genes analyzed: *SLCO1B1*	**Area:** *Precursor Cell Lymphoblastic Leukemia-Lymphoma*

143. METHOTREXATE

rs1801394-AG
Evidence level: Level 2B

AG Pediatric ALL patients with AG genotypes may have increased likelihood of methotrexate induced toxicity (oral mucositis), increased speed of platelet recovery and increased catalytic activity of TYMS in lymphoblasts when treated with methotrexate as compared to patients with the AA genotype. Allele G is not associated with decreased IQ in pediatric ALL patients treated with methotrexate. Other genetic and clinical factors may also influence response to methotrexate.

Genes analyzed: *FASTKD3MTRR*	**Area:** *Precursor Cell Lymphoblastic Leukemia-Lymphoma*

144. CERIVASTATIN

rs4149056-TT
Evidence level: Level 2A

TT Patients with the TT genotype may have a lower risk of cerivastatin-related rhabdomyolysis as compared to patients with the CC or CT genotype. Other genetic and clinical factors may also influence a patients risk for toxicity. Cerivastatin was withdrawn from the market because of 52 deaths attributed to drug-related rhabdomyolysis that lead to kidney failure.

Genes analyzed: *SLCO1B1*	**Area:** *Rhabdomyolysis*

145. RISPERIDONE

rs1799978-TT
Evidence level: Level 2A

TT Patients with the TT genotype and schizophrenia who are treated with risperidone may be more likely to have improvement in symptoms as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patients response to risperidone.

Genes analyzed: *DRD2*

Area: *Schizophrenia*

146. BUPROPION

rs1800497-GG
Evidence level: Level 1B

GG Patients with the GG genotype who are treated with bupropion may be more likely to quit smoking as compared to patients with the AA or AG genotypes, although this has been contradicted in one study. Other genetic and clinical factors may also influence a patients chance for quitting smoking.

Genes analyzed: *ANKK1*

Area: *Tobacco Use Disorder*

147. NICOTINE

rs4680-GG
Evidence level: Level 2A

GG Patients with the GG genotype who are treated with nicotine replacement therapy may have a decreased likelihood of smoking cessation and increased risk of relapse as compared to patients with the AA genotype. However, some contradictory evidence exists. Other genetic and clinical factors may also influence a patients response to nicotine replacement therapy.

Genes analyzed: *COMT*

Area: *Tobacco Use Disorder*

148. NICOTINE

rs578776-GG
Evidence level: Level 2B

GG Patients with the GG genotype may have an increased risk for tobacco addiction as compared to patients with the AA genotype. Patients with the GG genotype may also show increased levels of cotinine as compared to those with the AA genotype. Other genetic and clinical factors may also influence risk for tobacco addiction and cotinine levels.

Genes analyzed: *CHRNA3*

Area: *Tobacco Use Disorder*

149. NICOTINE

rs2072661-AG
Evidence level: Level 2B

AG Patients with the AG genotype may have a increased risk for smoking addiction, and a decreased likelihood of smoking cessation, as compared to patients with the GG genotype. Other genetic and clinical factors may also influence smoking addiction and cessation.

Genes analyzed: *CHRNB2*

Area: *Tobacco Use Disorder*

150. SIROLIMUS

rs776746-CT
Evidence level: Level 2A

CT Patients with the CT genotype (*1/*3) and who are recipients of transplants may have increased metabolism of sirolimus and require a higher dose as compared to patients with the CC genotype. Other genetic and clinical factors may also influence a patients sirolimus dose requirements.

Genes analyzed: *CYP3A5*

Area: *Transplantation*

151. ETHAMBUTOL, ISONIAZID, PYRAZINAMIDE, RIFAMPIN

rs1799930-AG
Evidence level: Level 2A

AG Patients with the AG genotype and tuberculosis (TB) may have an increased risk of hepatotoxicity when treated with anti-TB drugs as compared to patients with the GG genotype, or a decreased risk as compared to patients with the AA genotype. They also may have increased clearance of isoniazid as compared to those with the AA genotype, and decreased clearance as compared to those with the GG genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity and clearance of isoniazid.

Genes analyzed: *NAT2*

Area: *Tuberculosis*

152. ETHAMBUTOL, ISONIAZID, PYRAZINAMIDE, RIFAMPIN

rs1041983-CC
Evidence level: Level 2A

CC Patients with the CC genotype and tuberculosis (TB) may have a decreased risk for hepatotoxicity when treated with anti-TB drugs as compared to patients with the CT genotype. Other genetic and clinical factors may also influence risk for hepatotoxicity.

Genes analyzed: *NAT2*

Area: *Tuberculosis*

153. ASPIRIN

rs730012-AA
Evidence level: Level 2B

AA Patients with the AA genotype who are treated with aspirin may have a decreased, but not absent, risk of urticaria as compared to patients with the AC or CC genotype. Other genetic and clinical factors may also influence a patients risk for urticaria.

Genes analyzed: *LTC4S*

Area: *Urticaria*

154. TACROLIMUS

rs776746-CT
Evidence level: Level 2A

CT Patients who are recipients of a liver transplantation from a donor with the CT (CYP3A5 *1/*3) genotype may have increased metabolism of tacrolimus resulting in decreased exposure, and may require a higher dose as compared to patients who receive a liver transplantation from a donor with the CC (*3/*3) genotype. Other genetic and clinical factors, such as recipient genotype, may also influence a patients tacrolimus dose requirement.

Genes analyzed: *CYP3A5*

Area: *liver transplantation*

155. TACROLIMUS

rs776746-CT
Evidence level: Level 2A

CT Patients with the CT genotype (*1/*3) and recipients of kidney or hematopoietic stem cell transplant who are treated with tacrolimus may have an increased risk of transplant rejection as compared to patients with the CC genotype (*3/*3) or a decreased risk of transplant rejection as compared to patients with the TT genotype (*1/*1). Other genetic and clinical factors may also influence a patients response to tacrolimus treatment and risk of transplant rejection.

Genes analyzed: *CYP3A5*

Area: *transplant rejection*

DISCLAIMER

This report is to be interpreted only by a qualified and licensed medical practitioner

Ancestry DNA tests do not cover all pharmacogenetic markers and are not considered to be clinically suitable. Medical/therapeutic decisions must only be taken based on certified clinical test results.

This report does not constitute medical advice, diagnosis or treatment. Pharmacogenetics is one among the several factors such as age, sex, ethnicity and medical history that determine a patient's response to medication. Licensed medical practitioners are trained and qualified to make therapeutic decisions based on patient information and medical history, including the pharmacogenetic report. The FDA has recommended pharmacogenetic testing (PGx) only for specific drugs and does not yet mandate it for routine use in guiding therapeutic decisions for all drugs.

Genotyping results do not eliminate the necessity to account for non-genetic factors that can influence dose requirements for medications metabolized by the CYP450 enzymes. CYP450 2C9, 2D6, 3A4, 3A5 and VKORC activity is dependent upon hepatic and renal function status. The results of testing and dose adjustments in the context of renal and hepatic function should be taken into consideration. CYP450 2C9, 2D6, 3A4, 3A5 and VKORC activity can be altered by co-administration of inhibitors and inducers.

This assay includes a limited set of polymorphisms that have been found to exist at high frequencies in the target population. It is possible that tested samples carry a variant that is not included in this panel, in which case the genotype cannot be determined using this assay. These assays are carried out by trained individuals and use standard equipment and laboratory designed protocols. Possibilities exist for inaccuracies in the reported results for various reasons. Licensed practitioners may reorder tests for re-confirmation of results.

The metabolizer status is subject to variation based on the number of genotype calls present in the DNA raw data. Your metabolizer status may change depending upon the genotyping chip used by your raw data provider

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