Supplementary information 2.1
Table of actionable pharmacogenes and associated prescribing guidance

Gene Symbol	% patients	Genotype/ Allele/ Diplotype	Effect	Drug Name	CPIC/ DPWG	Result	Adverse Effects	Dosage Recommendations	Evidence
CFTR	66% European CF patients	F508del/ F508del	Ivacaftor non-responder	Ivacaftor- used to treat cystic fibrosis	CPIC	Little clinical response to Ivacaftor	n/a	Do not use Ivacaftor	(1-7)
CFTR		Homozygous or heterozygous in combination with any other allele for any of the following: G1244E; G1349D; G178R; G551D, G551S; S1251N; S1255P; S549N; S549R; R117H, E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q/W, F1074L,	Ivacaftor responder	Ivacaftor- used to treat cystic fibrosis	CPIC	Clinical response to Ivacaftor- improvement in lung function, weight gain, reduced risk of pulmonary exacerbation	n/a	Use Ivacaftor	(1-7)
CYP2C19	Varies with ethnicity (8)	All genotypes	all	Rabeprazole (proton-pump inhibitor)- inhibition of gastric acid production, used to treat dyspepsia, GORD, treatment and prevention of GI ulceration and acid hypersecretion	DPWG	n/a	n/a	Insufficient evidence to make a therapeutic recommendation	(9-11)

CYP2C19	Varies with ethnicity (8)	*1/*2, *1/*3, *2/*17	Intermediate metaboliser	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine (tricyclic antidepressant) mainly used to treat major depressive disorders. Some also used to treat obsessive compulsive disorder, depressive disorder, chronic pain	CPIC	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Initiate therapy with standard dose. Advice should be given in conjunction with *CYP2D6* haplotypes	(8, 12-16)
CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Citalopram, escitalopram- (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	CPIC	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness, confusion, coma, rarely death	None but monitor for adverse drug effects	(17-21)
CYP2C19	Varies with ethnicity (8)	*1/*2, *1/*3, *2/*17, *3/*17	Intermediate metaboliser	Citalopram, escitalopram- (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	DPWG	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness, confusion, coma, rarely death	None	(11, 17-20)

CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Clopidogrel- (thienopyridine-class antiplatelet agent)- used for prophylaxis and treatment of thrombosis	CPIC	Reduced metabolism increases reduces conversion to active metabolites	Reduced bioactivation of clopidogrel resulting in reduced levels of active metabolites. Get reduced platelet inhibition and increased residual platelet inhibition. Increased risk for adverse cardiovascular events	Consider using an alternative antiplatelet agent such as prasugrel or ticagrelor	(11, 22-27)
CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Clopidogrel- (thienopyridine-class antiplatelet agent)- used for prophylaxis and treatment of thrombosis	DPWG	Reduced metabolism increases reduces conversion to active metabolites	Reduced bioactivation of clopidogrel resulting in reduced levels of active metabolites. Get reduced platelet inhibition and increased residual platelet inhibition. Increased risk for adverse cardiovascular events	Consider alternative drug e.g. prasugrel which is not predominantly metabolised by *CYP2C19* but is, however, associated with an increased risk of bleeding	(11, 22-27)
CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Esomeprazole, lansoprazole, omeprazole, pantoprazole (proton-pump inhibitor)- inhibition of gastric acid production, used to treat dyspepsia, GORD, treatment and prevention of GI ulceration, oesophagitis and acid hypersecretion	DPWG	Reduced clearance of drug resulting in increased plasma levels which increases the risk of AEDs	Dry mouth, ptosis, vomiting, sedation, seizures, coma	None but monitor for adverse drug effects	(11, 28-31)

CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Imipramine (tricyclic antidepressant)- used to treat depression and enuresis	DPWG	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Insufficient evidence to calculate dose adjustment. Consider another drug such as mirtazapine or fluvoxamine	(11, 32, 33)
CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic disorder, social anxiety disorder	CPIC	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness	None but monitor for adverse drug effects	(21, 34, 35)
CYP2C19	Varies with ethnicity (8)	See above	Intermediate metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic disorder, social anxiety disorder	DPWG	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness	Insufficient data to consider dose adjustment. Monitor closely for adverse drug effects	(11)
CYP2C19	2-11%	See above	Intermediate metaboliser	Voriconazole (triazole antifungal)- used to treat infections such as aspergillosis	CPIC	Reduced metabolism leads to increased plasma drug levels and risk of side effects. Increased metabolism leads to rapid drug clearance and reduced efficacy	Hepatotoxicity, seizures, visual disturbance, salivation, shortness of breath, weakness, altered level of consciousness.	Initiate treatment at standard dose and monitor	(36, 37)

CYP2C19	Varies with ethnicity (8)	All genotypes	n/a	Moclobemide (RIMA)- used to treat depression and social anxiety	DPWG	Reduced metabolism increases risk of side effects. Increased metabolism results in lower plasma concentrations and reduced efficacy	Reduced metabolism: serotonin syndrome (hyperthermia, sweating, agitation, tremor, diarrhoea, dilated pupils), dizziness, headache, dry mouth, nausea. Increased metabolism: ineffective treatment of anxiety and depression	None as insufficient evidence to calculate alternate dosing schedule	(11, 38, 39)
CYP2C19	Varies with ethnicity (8)	All genotypes	n/a	Voriconazole (triazole antifungal)- used to treat infections such as aspergillosis	DPWG	Reduced metabolism leads to increased plasma drug levels and risk of side effects. Increased metabolism leads to rapid drug clearance and reduced efficacy	Reduced metabolism: hepatotoxicity, seizures, visual disturbance, salivation, shortness of breath, weakness, altered level of consciousness. Increased metabolism: failure to treat disease	Monitor serum levels and be alert for adverse drug effects	(11, 36, 37)
CYP2C19	Varies with ethnicity (8)	*1/*1	Normal metaboliser	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine (tricyclic antidepressant) mainly used to treat major depressive disorders. Some also used to treat obsessive compulsive disorder, depressive disorder, chronic pain	CPIC	Normal metabolism	No increased risk	Initiate therapy with standard dose. Advice should be given in conjunction with *CYP2D6* haplotypes	(8, 12-16)

CYP2C19	Varies with ethnicity (8)	See above	Normal metaboliser	Citalopram, escitalopram- (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	CPIC	Normal metabolism	None	None	(17-21)
CYP2C19	Varies with ethnicity (8)	See above	Normal metaboliser	Clopidogrel- (thienopyridine-class antiplatelet agent)- used for prophylaxis and treatment of thrombosis	CPIC	Normal metabolism	Normal platelet inhibition and normal residual platelet aggregation	Normal dosing	(22-27, 40)
CYP2C19	Varies with ethnicity (8)	See above	Normal metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic and anxiety disorder	CPIC	Normal metabolism	None	None	(21, 34, 35)
CYP2C19	77-92%	See above	Normal metaboliser	Voriconazole (triazole antifungal)- used to treat infections such as aspergillosis	CPIC	Increased metabolism leads to rapid drug clearance and reduced efficacy	Failure to adequately treat fungal disease	Initiate treatment at standard dose	(11, 36, 37)

CYP2C19	Varies with ethnicity (8)	*2/*2, *2/*3, *3/*3	Poor metaboliser	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine (tricyclic antidepressant) mainly used to treat major depressive disorders. Some also used to treat obsessive compulsive disorder, depressive disorder, chronic pain	CPIC	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Avoid tertiary amine use and consider alternative drug not predominantly metabolised by *CYP2C19* such as nortriptyline and desipramine. If prescribing tertiary amines start at 50% of recommended dose and use plasma levels to decide maintenance dosing. Advice should be given in conjunction with *CYP2D6* haplotypes	(8, 12-16)
CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Citalopram, escitalopram- (SSRI)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	CPIC	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness, confusion, coma, rarely death	Consider 50% dose reduction and titrate dose according to response. Be aware of adverse drug effects. Alternatively select a drug not predominantly metabolised by *CYP2C19*	(17-21)
CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Citalopram, escitalopram- (SSRI)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	DPWG	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness, confusion, coma, rarely death	None	(11, 17-21)

CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Clopidogrel-(thienopyridine-class antiplatelet agent)-used for prophylaxis and treatment of thrombosis	CPIC	Greatly reduced metabolism increases reduces conversion to active metabolites	Significantly reduced bioactivation of clopidogrel and reduced levels of active metabolites. Significantly reduced platelet inhibition and increased residual platelet inhibition. Increased risk for adverse cardiovascular events	Consider using an alternative antiplatelet agent such as prasugrel or ticagrelor	(22-27, 40)
CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Clopidogrel-(thienopyridine-class antiplatelet agent)-used for prophylaxis and treatment of thrombosis	DPWG	Greatly reduced metabolism increases reduces conversion to active metabolites	Significantly reduced bioactivation of clopidogrel resulting in reduced levels of active metabolites. Get significantly reduced platelet inhibition and increased residual platelet inhibition. Increased risk for adverse cardiovascular events	Consider alternative drug e.g. prasugrel which is not predominantly metabolised by *CYP2C19* but is, however, associated with an increased risk of bleeding	(11, 22-26)

CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Esomeprazole, lansoprazole, omeprazole, pantoprazole (proton-pump inhibitor)- inhibition of gastric acid production, used to treat dyspepsia, GORD, treatment and prevention of GI ulceration, oesophagitis and acid hypersecretion	DPWG	Reduced clearance of drug resulting in increased plasma levels which increases the risk of adverse drug effects	Dry mouth, ptosis, vomiting, sedation, seizures, coma	None but monitor for adverse drug effects	(11, 28-31)
CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Imipramine (tricyclic antidepressant)- used to treat depression and enuresis	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Reduce dose by 30%. Monitor plasma imipramine and desipramine levels. Alternatively select another drug such as mirtazapine or fluvoxamine	(11, 32, 33)
CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic disorder, social anxiety disorder	CPIC	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness	Consider 50% dose reduction and titrate according to response. Can reduce or increase dose according to response. Be aware of adverse drug effects. Alternatively select a drug not predominantly metabolised by *CYP2C19*	(21, 34, 35)
CYP2C19	Varies with ethnicity (8)	See above	Poor metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic disorder, social anxiety disorder	DPWG	Reduced metabolism leads to increased plasma drug levels and risk of side effects	Emesis, seizures, arrhythmia, reduced level of consciousness	Reduce dose by 50%	(11, 34, 35)

CYP2C19	5-10%	See above	Poor metaboliser	Voriconazole (triazole antifungal)- used to treat infections such as aspergillosis	CPIC	Reduced metabolism leads to increased plasma drug levels and risk of side effects. Increased metabolism leads to rapid drug clearance and reduced efficacy	Hepatotoxicity, seizures, visual disturbance, salivation, shortness of breath, weakness, altered level of consciousness.	Choose alternative anti-fungal agent not predominantly metabolised by *CYP2C19* such as isavuconazole, amphotericin B or posaconozole. If using voriconazole, dose should be reduced and therapeutic drug monitoring should be performed	(11, 36, 37)
CYP2C19	Varies with ethnicity (8)	*17/*17, *1/*17	Ultra-rapid metaboliser	Amitriptyline, clomipramine, doxepin, imipramine, trimipramine (tricyclic antidepressant) mainly used to treat major depressive disorders. Some also used to treat obsessive compulsive disorder, depressive disorder, chronic pain	CPIC	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Avoid tertiary amine use and consider alternative drug not predominantly metabolised by *CYP2C19* such as nortriptyline and desipramine. If prescribing tertiary amines use plasma levels to decide dosing. Advice should be given in conjunction with *CYP2D6* haplotypes	(8, 12-15)
CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Citalopram, escitalopram- (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	CPIC	Increased metabolism leads to rapid drug clearance and reduced efficacy	Failure to control psychiatric symptoms	Consider alternative drug not predominantly metabolised by *CYP2C19*	(17-21)

CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Citalopram, escitalopram- (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, depressive episodes, panic disorder, agoraphobia	DPWG	Increased metabolism leads to rapid drug clearance and reduced efficacy	Failure to control psychiatric symptoms	Monitor plasma levels. Can increase dose to 150% of standard dose. Alternatively select another drug e.g. fluoxetine, paroxetine	(11, 17-20)
CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Clopidogrel- (thienopyridine-class antiplatelet agent)- used for prophylaxis and treatment of thrombosis	CPIC	Lower conversion of drug to active metabolites	Catalyses the bioactivation of clopidogrel to form active metabolites. Get increased platelet inhibition which results in decreased residual platelet aggregation	Normal dosing	(22-27, 40)
CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Clopidogrel- (thienopyridine-class antiplatelet agent)- used for prophylaxis and treatment of thrombosis	DPWG	Lower conversion of drug to active metabolites	Catalyses the bioactivation of clopidogrel to form active metabolites. Get increased platelet inhibition which results in decreased residual platelet aggregation	None	(11, 22-26)

CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Esomeprazole, lansoprazole, omeprazole, pantoprazole (proton-pump inhibitor)- inhibition of gastric acid production, used to treat dyspepsia, GORD, treatment and prevention of GI ulceration, oesophagitis and acid hypersecretion	DPWG	Rapid clearance of drug resulting in insufficient therapeutic levels	Ineffective gastric acid inhibition	For *H. Pylori* eradication, increase dose by 50-100% (esomeprazole), by 200% (lansoprazole), by 100-200% (omeprazole) and by 400% (pantoprazole). Monitor closely for insufficient response. For indications other than *H. Pylori* eradication monitor for insufficient response and consider dose increase of 50-100% (esomeprazole), by 200% (lansoprazole), by 100-200% (omeprazole) and by 400% (pantoprazole)	(11, 28-31)
CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Imipramine (tricyclic antidepressant)- used to treat depression and enuresis	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	None	(11, 32, 33)
CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic disorder, social anxiety disorder	CPIC	Increased metabolism leads to rapid drug clearance and reduced efficacy	Failure to control psychiatric symptoms	Normal dosing. Consider alternative drug not predominantly metabolised by CYP2C19 if patient does not respond	(21, 34, 35)
CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Sertraline (selective serotonin reuptake inhibitor)- used to treat major depressive disorder, OCD, panic disorder, social anxiety disorder	DPWG	Increased metabolism leads to rapid drug clearance and reduced efficacy	Failure to control psychiatric symptoms	None but monitor for lack of therapeutic effect	(11, 34, 35)

CYP2C19	Varies with ethnicity (8)	See above	Ultra-rapid metaboliser	Voriconazole (triazole antifungal)- used to treat infections such as aspergillosis	CPIC	Increased metabolism leads to rapid drug clearance and reduced efficacy	Failure to adequately treat fungal disease	Choose an alternative anti-fungal agent not predominantly metabolised by *CYP2C19* such as isavuconazole, amphotericin B or posaconozole	(11, 36, 37)
CYP2C9	2%	*1/*2, *1/*3, *2/*2, *2/*3	Intermediate metaboliser	Acenocoumarol (Coumarin anticoagulant)- used to treat thrombosis and prothrombotic state	DPWG	Intermediate drug metabolism	Intermediate risk of sub-therapeutic INR and thrombosis	Check INR more frequently after initiation or discontinuation of NSAIDS. Dosage recommendations not given	(11, 41-43)
CYP2C9	2%	*1/*2, *1/*3	Intermediate metaboliser	Phenprocoumon (Coumarin anticoagulant)- used to treat thrombosis and prothrombotic state	DPWG	Intermediate drug metabolism	Intermediate risk of sub-therapeutic INR and thrombosis	None	(11, 44-46)
CYP2C9	2%	*2/*2, *2/*3	Intermediate metaboliser	Phenprocoumon (Coumarin anticoagulant)- used to treat thrombosis and prothrombotic state	DPWG	Intermediate drug metabolism	Lower risk of sub-therapeutic INR and thrombosis	Increased frequency of INR checks	(11, 44-46)
CYP2C9	8%	*1/*2 , *2/*2, *1/*3, *2/*3	Intermediate metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	CPIC	Slower drug metabolism leads to increased levels and toxicity	Ataxia, nystagmus, dysarthria, sedation, severe cutaneous adverse reactions	If *HLA-B* 15:02 negative, consider 25% dose reduction and monitor. If *HLA-B* 15:02 positive do not use phenytoin or fosphenytoin	(47-52)
CYP2C9	2%	*1/*2, *1/*3	Intermediate metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	DPWG	Slower drug metabolism leads to increased levels and toxicity	Ataxia, nystagmus, dysarthria, sedation, severe cutaneous adverse reactions	Standard loading dose. Reduce maintenance dose by 25% and monitor	(11, 49-51, 53, 54)

CYP2C9	2%	See above	Intermediate metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	DPWG	Slower drug metabolism leads to increased levels and toxicity	Ataxia, nystagmus, dysarthria, sedation, severe cutaneous adverse reactions	Standard loading dose. Reduce maintenance dose by 50% and monitor	(11, 49-51, 53, 54)
CYP2C9	Varies with ethnicity	Any diplotype that includes *5, *6, *8, *11	Intermediate metaboliser	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Intermediate drug metabolism	Lower risk of sub-therapeutic INR and thrombosis	VKORC1 GG: 3-4mg daily; VKORC1 GA: 0.5-2mg daily; VKORC1 AA: 0.5-2mg daily. In Europeans, consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as algorithms may not be validated. reduce dose by 10-25%	(55-63)

CYP2C9	2%	*1/*2	Intermediate metaboliser	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Intermediate drug metabolism	Intermediate risk of sub-therapeutic INR and thrombosis	*VKORC1* GG: 5-7mg daily; *VKORC1* GA: 3-4mg daily; *VKORC1* AA: 3-4mg daily. In Europeans consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as calculators/algorithms may not be validated.	(55-63)

CYP2C9	2%	*2/*2	Intermediate metaboliser	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Intermediate drug metabolism	Lower risk of sub-therapeutic INR and thrombosis	*VKORC1* GG: 3-4mg daily; *VKORC1* GA: 3-4mg daily; *VKORC1* AA: 0.5-2mg daily. In those of European ancestry consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as calculators/algorithms may not be validated.	(55-63)

CYP2C9	2%	*1/*3	Intermediate metaboliser	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Intermediate drug metabolism	Lower risk of sub-therapeutic INR and thrombosis	*VKORC1* GG: 3-4mg daily; *VKORC1* GA: 3-4mg daily; *VKORC1* AA: 0.5-2mg daily. In Europeans consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as calculators/algorithms may not be validated.	(55-63)

CYP2C9	2%	*2/*3	Intermediate metaboliser	Warfarin- Anticoagulant used to treat thrombosis	CPIC	Intermediate drug metabolism	Lower risk of sub-therapeutic INR and thrombosis	*VKORC1* GG: 3-4mg daily; *VKORC1* GA: 0.5-2mg daily; *VKORC1* AA: 0.5-2mg daily. In those of European ancestry consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as calculators/algorithms may not be validated.	(55-63)
CYP2C9	n/a	All genotypes	n/a	Glibenclamide, gliclazide, glimepiride, tolbutamide (sulfonylurea)- used to treat hyperglycaemia in diabetes	DPWG	Slow or fast drug metabolism	Risk of hyperglycaemia in fast metabolisers and hypoglycaemia in slow metabolisers	Reviewed but no recommendations made in respect to CYP2C9. Monitor blood glucose levels	(11, 64-66)
CYP2C9	91%	*1/*1	Normal metaboliser	Acenocoumarol (Coumarin anticoagulant) used to treat thrombosis and prothrombotic state	DPWG	Increased drug metabolism	Risk of sub-therapeutic INR with risk of thrombosis	Dosing recommendations not given	(11, 41-43)

CYP2C9	91%	See above	Normal metaboliser	Phenprocoumon (Coumarin anticoagulant)- used to treat thrombosis and prothrombotic state	DPWG	Increased drug metabolism	Risk of sub-therapeutic INR with risk of thrombosis	None	(11, 44-46)
CYP2C9	91%	See above	normal metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	CPIC	Normal drug metabolism	None	If *HLA-B* 15:02 negative, initiate therapy with standard dose and monitor. If *HLA-B* 15:02 positive do not use phenytoin or fosphenytoin	(47-52)
CYP2C9	91%	See above	normal metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	DPWG	Normal drug metabolism	None	Standard dosing	(11, 49-51, 53, 54)
CYP2C9	91%	See above	Normal metaboliser	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Increased drug metabolism	Risk of sub-therapeutic INR with risk of thrombosis	*VKORC1* GG: 5-7mg daily; *VKORC1* GA: 5-7mg daily; *VKORC1* AA: 3-4mg daily. Europeans consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as calculators/algorithms may not be validated.	(55-62, 67)

CYP2C9	1%	*3/*3	Poor metaboliser	Acenocoumarol (Coumarin anticoagulant)- used to treat thrombosis and prothrombotic state	DPWG	Slow drug metabolism	Risk of high INR and haemorrhage	Check INR more frequently during initiation of therapy after initiation or discontinuation of NSAIDS. Dosage recommendations not given	(11, 41-43)
CYP2C9	1%	See above	Poor metaboliser	Phenprocoumon (Coumarin anticoagulant)- used to treat thrombosis and prothrombotic state	DPWG	Slow drug metabolism	Risk of high INR and haemorrhage	Increased frequency of INR checks	(11, 44-46)
CYP2C9	1%	See above	Poor metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	CPIC	Significantly slower drug metabolism leads to increased levels and toxicity	Ataxia, nystagmus, dysarthria, sedation, severe cutaneous adverse reactions	If *HLA-B* 15:02 negative, consider 50% dose reduction and monitor. If *HLA-B* 15:02 positive do not use phenytoin or fosphenytoin	(47-52)
CYP2C9	1%	See above	Poor metaboliser	Phenytoin (anti-epileptic)- used to treat epilepsy	DPWG	Significantly slower drug metabolism leads to increased levels and toxicity	Ataxia, nystagmus, dysarthria, sedation, severe cutaneous adverse reactions	Standard loading dose. Reduce maintenance dose by 50% and monitor	(11, 49-51, 53, 54)

CYP2C9	1%	See above	Poor metaboliser	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Slow drug metabolism	Risk of high INR and haemorrhage	*VKORC1* GG: 0.5-2mg daily; *VKORC1* GA: 0.5-2mg daily; *VKORC1* AA: 0.5-2mg daily. In those of European ancestry consider *CYP4F2* rs2108622. If T allele present, consider increasing dose by 5-10%. In individuals of African ancestry, dose clinically unless *5/*6/*8/*11 tested. If present reduce dose by 15-30%. In addition consider *CYP2C* rs12977823. If A allele present, reduce dose by 10-25%. Ideally dose using calculator such as GAGE or IWPC. Caution in non-Europeans as calculators/algorithms may not be validated.	(55-62, 67)

CYP2D6	2-11%	IM (two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele)	Intermediate metaboliser	Amitriptyline (tricyclic antidepressant)- mainly used to treat major depressive disorders	DPWG	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Consider 25% dose reduction and monitor amitriptyline and nortriptyline plasma concentrations.	(11-13, 68-70)
CYP2D6	2-11%	*4/*10, *5/*10, *6/*10,*4/*17, *5/*17, *6/*17, *4/*41 *5/*41, *6/*41	Intermediate metaboliser	Anti-emetics- ondansetron and tropisetron	CPIC	Limited data available	Unknown	Insufficient evidence to make recommendation	(71)
CYP2D6	2-11%	See above	Intermediate metaboliser	Aripiprazole (atypical antipsychotic)- used to treat schizophrenia and bipolar disorder	DPWG	None	None	None	(11, 72-74)
CYP2D6	2-11%	See above	Intermediate metaboliser	Atomoxetine (norepinephrine reuptake inhibitor)- used to treat ADHD	DPWG	None	None	None	(11, 75-78)
CYP2D6	2-11%	See above	Intermediate metaboliser	Clomipramine (tricyclic antidepressant)- used to treat obsessive compulsive disorder, depressive disorder, chronic pain	DPWG	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	No recommendation for dose reduction due to insufficient evidence. Consider plasma desmethylclomipramine level monitoring	(11-13, 68-70, 79)

CYP2D6	2-11%	See above	Intermediate metaboliser	Codeine (opioid analgesic)- used to treat pain	CPIC	Reduced metabolism increases risk of non-efficacy and poor pain relief	Inadequate pain relief	Standard dosing but monitor response and consider morphine or non-opioid analgesics	(80-89)
CYP2D6	2-11%	See above	Intermediate metaboliser	Codeine (opioid analgesic)- used to treat pain	CPNDS	Intermediate metabolism	Inadequate pain relief	Codeine can be given at standard doses but should be monitored for efficacy. Exercise extra caution with opioid naïve children and breastfeeding mothers	(80-87, 90)
CYP2D6	2-11%	See above	Intermediate metaboliser	Codeine (opioid analgesic)- used to treat pain	DPWG	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Monitor effect and consider alternative drug such as morphine, NSAID, acetaminophen (paracetamol)	(11, 80-87)
CYP2D6	2-11%	See above	Intermediate metaboliser	Doxepin (tricyclic antidepressant)- used to treat depression, anxiety and insomnia	DPWG	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	20% dose reduction and adjust dose according to plasma nordoxepin levels	(11-13, 68-70, 91)
CYP2D6	2-11%	See above	Intermediate metaboliser	Flecainide (antiarrhythmic)- used for SVT, VT, RVVOT, ARVD	DPWG	Increased plasma levels increase risk of adverse drug effects	Lethal arrhythmias, cardiac failure, lung toxicity	Reduce dose by 25% monitor plasma drug levels and ECG	(11, 92-94)
CYP2D6	2-11%	See above	Intermediate metaboliser	Haloperidol (typical antipsychotic)- used to treat schizophrenia, mania, acute psychosis	DPWG	Increased plasma levels increase risk of adverse drug effects	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms, anti-cholinergic symptoms	None	(11, 73, 95, 96)

CYP2D6	2-11%	See above	Intermediate metaboliser	Imipramine (tricyclic antidepressant)- used to treat depression and enuresis	DPWG	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	30% dose reduction and plasma imipramine and desipramine level monitoring	(11-13, 32, 68-70)
CYP2D6	2-11%	See above	Intermediate metaboliser	Metoprolol (β-blocker)- used to treat heart failure, tachycardias and hypertension	DPWG	Increased plasma levels increase risk of adverse drug effects	Cardiorespiratory arrest, metabolic acidosis, seizures	Ideally, select alternate drug e.g. carvedilol or bisoprolol, especially if treating heart failure. If prescribing metoprolol reduce dose by 50% and be aware of risk of adverse drug effects	(11, 97-100)
CYP2D6	2-11%	See above	Intermediate metaboliser	Nortriptyline (2nd generation tricyclic)- used to treat depression	DPWG	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Reduce dose by 40%. Monitor plasma nortriptyline and 10-hydroxynortryptyline concentrations	(11, 12, 69, 70, 101)
CYP2D6	2-11%	See above	Intermediate metaboliser	Other tricyclic antidepressants- used to treat depression. Drugs include desipramine, fluvoxamine, nortriptyline (2nd-generation tricyclic)	CPIC	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Consider 25% dose reduction	(8, 12, 13, 68-70)
CYP2D6	2-11%	See above	Intermediate metaboliser	Oxycodone (opioid)- pain relief	DPWG	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Insufficient evidence to recommend dose alteration. Suggests selection of alternative drug but not tramadol or codeine. Be alert to symptoms of insufficient pain relief	(11, 102-104)

CYP2D6	2-11%	See above	Intermediate metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	CPIC	Reduced drug metabolism increases plasma drug concentrations and risk of adverse effects	Seizures, arrhythmia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure	Give standard dose, monitoring for adverse effects	(21, 69, 105-107)
CYP2D6	2-11%	See above	Intermediate metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	DPWG	Reduced drug metabolism increases plasma drug concentrations and risk of adverse effects	Seizures, arrhythmia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure	None but be alert for adverse drug effects	(11, 69, 105-108)
CYP2D6	2-11%	See above	Intermediate metaboliser	Propafenone (class 1c anti-arrhythmic drug)- used to treat atrial and ventricular arrhythmias	DPWG	Increased plasma levels increase risk of adverse drug effects	Lethal arrhythmias, cardiac failure, death	Insufficient evidence to recommend dose adjustment. Monitor plasma levels and ECG. Consider alternative drug including amiodarone, soltalol, disopyramide, quinidine	(11, 109-111)
CYP2D6	2-11%	See above	Intermediate metaboliser	Risperidone (atypical antipsychotic)- used to treat schizophrenia, bipolar disorder and occasionally features of autism	DPWG	Increased plasma levels increase risk of adverse drug effects	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms, anti-cholinergic symptoms	Insufficient evidence to recommend dose increase. Monitor plasma levels. Monitor for adverse drug effects and titrate to clinical response. Consider selecting alternative drug e.g. clozapine, quetiapine, olanzapine	(11, 72, 112-114)
CYP2D6	2-11%	See above	Intermediate metaboliser	Tamoxifen (hormonal anti-cancer agent)- used to treat breast cancer	DPWG	Slow metabolism of tamoxifen to its active metabolites can increase risk of cancer relapse	Relapse of breast cancer	Avoid use of CYP2D6 inhibitors. In post-menopausal women consider aromatase inhibitor as an alternative treatment	(11, 115-118)

CYP2D6	2-11%	See above	Intermediate metaboliser	Tramadol (opioid)- pain relief	DPWG	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Consider dose increase if pain relief insufficient. Consider selection of alternative drug but not oxycodone or codeine	(11, 119-123)
CYP2D6	2-11%	See above	Intermediate metaboliser	Tricyclic antidepressants including amitriptyline, clomipramine, doxepin, imipramine, trimipramine- mainly used to treat major depressive disorders	CPIC	Reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Consider 25% dose reduction and use monitoring to guide dose adjustments. Advice should be given in conjunction with *CYP2C19* haplotypes	(8, 12, 13, 68-70)
CYP2D6	2-11%	See above	Intermediate metaboliser	Venlafaxine (serotonin norepinephrine reuptake inhibitor)- used to treat major depressive disorder, anxiety disorder, social phobia, panic disorder	DPWG	None	None	Insufficient evidence for dose reduction. Consider alternative e.g. sertraline, citalopram or if using venlafaxine monitor plasma O-desmethylvenlafaxine levels and adverse drug effects and adjust dose accordingly	(11, 18, 124-126)
CYP2D6	2-11%	See above	Intermediate metaboliser	Zuclopenthixol (typical thioxanthane antipsychotic)- used to treat psychotic illness such as schizophrenia	DPWG	Somewhat reduced metabolism increases risk of side effects	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms	Reduce dose by 25% and monitor for adverse drug effects. Alternatively consider another antiopsychotic such as flupenthixol, clozapine, olanzapine or quetiapine	(11, 127)

CYP2D6	100%	All genotypes	n/a	Carvedilol (β-blocker)- used to treat heart failure and hypertension	DPWG	Uncertain	Toxicity: metabolic-hypoglycaemia, hyperkalaemia, neurological-seizures, reduced consciousness, cardiovascular-bradycardia, hypotension, AV block, respiratory-bronchospasm; Efficacy: possible undertreatment	Consideration of the literature led to the conclusion that there is insufficient evidence to recommend dose adjustment	(11, 128-130)
CYP2D6	100%	All genotypes	n/a	Clozapine (atypical antipsychotic)	DPWG	Uncertain	Respiratory depression, coma, tachycardia, hypotension, delirium	Consideration of the literature led to the conclusion that there is insufficient evidence to recommend dose adjustment	(11, 131, 132)
CYP2D6	100%	All genotypes	n/a	Duloxetine (serotonin norepinephrine reuptake inhibitor)- depression, anxiety, neuropathic pain	DPWG	Uncertain	As per SSRI-seizures, arrhythmia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure	Consideration of the literature led to the conclusion that there is insufficient evidence to recommend dose adjustment	(11, 133-135)
CYP2D6	100%	All genotypes	n/a	Flupenthixol (typical antipsychotic, thioxanthane class)- used to treat schizophrenia	DPWG	Uncertain	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms	Consideration of the literature led to the conclusion that there is insufficient evidence to recommend dose adjustment	See zuclopenthixol(11, 127)

CYP2D6	100%	All genotypes	n/a	Mirtazapine (atypical antidepressant)- used to treat mood disorders and major depressive episodes	DPWG	Uncertain	As per SSRI- seizures, arrhythmia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure	Consideration of the literature led to the conclusion that there is insufficient evidence to recommend dose adjustment	(11, 136-138)
CYP2D6	100%	All genotypes	n/a	Olanzapine (atypical antipsychotic)- used to treat schizophrenia and bipolar disorder	DPWG	Uncertain	Cardiac toxicity including arrhythmias and prolonged QT interval, neurological problems including seizures, delirium, coma	Consideration of the literature led to the conclusion that there is insufficient evidence to recommend dose adjustment	(11, 139-141)
CYP2D6	77-92%	*1/*1, *1/*2, *1/*3, *1/*4, *1/*5, *1/*6, *1/*9, *1/*10, *1/*17, *1/*41, *2/*2, *2/*3, *2/*4, *2/*5, *2/*6, *2/*9, *2/*10, *2/*17, *2/*41, *10/*10, *10/*17, *10/*41, *17/*17, *17/*41, *41/*41,	Normal metaboliser	Anti-emetics- ondansetron and tropisetron	CPIC	Normal metabolism of ondansetron	None	Start treatment at standard dose	(71)
CYP2D6	77-92%	See above	Normal metaboliser	Codeine (opioid analgesic)- used to treat pain	CPIC	Normal metabolism	None	None	(80-89)

CYP2D6	77-92%	See above	Normal metaboliser	Other tricyclic antidepressants- used to treat depression. Drugs include desipramine, fluvoxamine, nortriptyline (2nd-generation tricyclic)	CPIC	Normal metabolism	No increased risk	None	(8, 12, 13, 68-70)
CYP2D6	77-92%	See above	Normal metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	CPIC	Normal drug metabolism	None	Give standard dose	(21, 69, 105-107)
CYP2D6	77-92%	See above	Normal metaboliser	Tricyclic antidepressants including amitriptyline, clomipramine, doxepin, imipramine, trimipramine- mainly used to treat major depressive disorders	CPIC	Normal metabolism	No increased risk	None. Advice should be given in conjunction with *CYP2C19* haplotypes	(8, 12, 13, 68-70)
CYP2D6	5-10%	PM (two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles)	Poor metaboliser	Amitriptyline (tricyclic antidepressant)- mainly used to treat major depressive disorders	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Select alternative drug e.g. citalopram, sertraline OR monitor amitriptyline and nortriptyline plasma concentrations.	(11-13, 68-70)
CYP2D6	5-10%	Any 2 poor metaboliser alleles e.g. *3/*3, *3/*4, *3/*5, *3/*6, *4/*4, *4/*4N, *4/*5, *5/*5, *4/*6, *5/*6, *6/*6	Poor metaboliser	Anti-emetics- ondansetron and tropisetron	CPIC	Limited data available	Unknown	Insufficient evidence to make recommendation	(71)

CYP2D6	5-10%	See above	Poor metaboliser	Aripiprazole (atypical antipsychotic)- used to treat schizophrenia and bipolar disorder	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiac toxicity including arrhythmias and prolonged QT interval, neurological problems including seizures, delirium, coma	Reduce to 67% of recommended maximum daily dose i.e. 10mg.day	(11, 72-74)
CYP2D6	5-10%	See above	Poor metaboliser	Atomoxetine (norepinephrine reuptake inhibitor)- used to treat ADHD	DPWG	Greatly reduced metabolism increases risk of side effects	Anticholinergic symptoms, seizures, prolonged QT interval, altered level of consciousness	None but beware of possible adverse effects	(11, 75-78)
CYP2D6	5-10%	See above	Poor metaboliser	Clomipramine (tricyclic antidepressant)- used to treat obsessive compulsive disorder, depressive disorder, chronic pain	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	50% dose reduction and plasma desmethylclomipramine level monitoring	(11-13, 68-70, 79)
CYP2D6	5-10%	See above	Poor metaboliser	Codeine (opioid analgesic)- used to treat pain	CPIC	Greatly reduced metabolism increases risk of non-efficacy and poor pain relief	Inadequate pain relief	Avoid codeine, tramadol hydrocodone and oxycodone. Use morphine or non-opioid analgesics.	(80-89)
CYP2D6	5-10%	See above	Poor metaboliser	Codeine (opioid analgesic)- used to treat pain	CPNDS	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Do not give codeine for pain relief	(80-87, 90)
CYP2D6	5-10%	See above	Poor metaboliser	Codeine (opioid analgesic)- used to treat pain	DPWG	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Select alternative drug such as morphine, NSAID, acetaminophen (paracetamol). Avoid codeine, tramadol, hydrocodone and oxycodone.	(11, 80-87)

CYP2D6	5-10%	See above	Poor metaboliser	Doxepin (tricyclic antidepressant)- used to treat depression, anxiety and insomnia	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	60% dose reduction and plasma nordoxepin level monitoring	(11-13, 68-70, 91)
CYP2D6	5-10%	See above	Poor metaboliser	Flecainide (antiarrhythmic)- used for SVT, VT, RVVOT, ARVD	DPWG	Increased plasma levels increase risk of adverse drug effects	Lethal arrhythmias, cardiac failure, lung toxicity	Reduce dose by 50% monitor plasma drug levels and ECG	(11, 92-94)
CYP2D6	5-10%	See above	Poor metaboliser	Haloperidol (typical antipsychotic)- used to treat schizophrenia, mania, acute psychosis	DPWG	Increased plasma levels increase risk of adverse drug effects	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms, anti-cholinergic symptoms	Reduce dose by 50% or consider selecting alternative drug e.g. pimozide, quetiapine, flupenthixol, olanzapine, clozapine, fluphenazine	(11, 73, 95, 96)
CYP2D6	5-10%	See above	Poor metaboliser	Imipramine (tricyclic antidepressant)- used to treat depression and enuresis	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	70% dose reduction and plasma imipramine and desipramine level monitoring	(11-13, 32, 68-70)
CYP2D6	5-10%	See above	Poor metaboliser	Metoprolol (β-blocker)- used to treat heart failure, tachycardias and hypertension	DPWG	Increased plasma levels increase risk of adverse drug effects	Cardiorespiratory arrest, metabolic acidosis, seizures	Ideally, select alternate drug e.g. carvedilol or bisoprolol, especially if treating heart failure. If prescribing metoprolol reduce dose by 75% and be aware of risk of adverse drug effects	(11, 97-100)
CYP2D6	5-10%	See above	Poor metaboliser	Nortriptyline (2nd generation tricyclic)- used to treat depression	DPWG	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Reduce dose by 60%. Monitor plasma nortriptyline and 10-hydroxynortryptyline concentrations	(11, 12, 69, 70, 101)

CYP2D6	5-10%	See above	Poor metaboliser	Other tricyclic antidepressants- used to treat depression. Drugs include desipramine, fluvoxamine, nortriptyline (2nd-generation tricyclic)	CPIC	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Avoid tricyclics or consider 50% dose reduction	(8, 12, 13, 68-70)
CYP2D6	5-10%	See above	Poor metaboliser	Oxycodone (opioid)- pain relief	DPWG	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Insufficient evidence to recommend dose alteration. Consider alternative drug but not tramadol or codeine. Be alert to symptoms of insufficient pain relief	(11, 102-104)
CYP2D6	5-10%	See above	Poor metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	CPIC	Significantly reduced drug metabolism increases plasma drug concentrations and risk of adverse effects	Seizures, arrhythmia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure	Consider alternative drug not predominantly metabolised by CYP2D6 or 50% reduction in paroxetine dose and titrate to response	(21, 69, 105-107)
CYP2D6	5-10%	See above	Poor metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	DPWG	Significantly reduced drug metabolism increases plasma drug concentrations and risk of adverse effects	Seizures, arrhythmia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, respiratory failure	None but be alert for adverse drug effects	(11, 69, 105-108)
CYP2D6	5-10%	See above	Poor metaboliser	Propafenone (class 1c anti-arrhythmic drug)- used to treat atrial and ventricular arrhythmias	DPWG	Increased plasma levels increase risk of adverse drug effects	Lethal arrhythmias, cardiac failure, death	Reduce dose by 70% monitor plasma drug levels and ECG	(11, 109-111)

CYP2D6	5-10%	See above	Poor metaboliser	Risperidone (atypical antipsychotic)- used to treat schizophrenia, bipolar disorder and occasionally features of autism	DPWG	Increased plasma levels increase risk of adverse drug effects	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms, anti-cholinergic symptoms	Insufficient evidence to recommend dose adjustment. Monitor plasma levels. Monitor for adverse drug effects and titrate to clinical response. Consider selecting alternative drug e.g. clozapine, quetiapine, olanzapine	(11, 72, 112-114)
CYP2D6	5-10%	See above	Poor metaboliser	Tamoxifen (hormonal anti-cancer agent)- used to treat breast cancer	DPWG	Slow metabolism of tamoxifen to its active metabolites can increase risk of cancer relapse	Relapse of breast cancer	In post-menopausal women consider aromatase inhibitor as an alternative treatment	(11, 115-118)
CYP2D6	5-10%	See above	Poor metaboliser	Tramadol (opioid)- pain relief	DPWG	Reduced metabolism decreases efficacy of pain relief	Inadequate pain relief	Insufficient evidence to recommend dose alteration. Suggests selection of alternative drug but not oxycodone or codeine. Monitor for symptoms of insufficient pain relief	(11, 119-123)
CYP2D6	5-10%	See above	Poor metaboliser	Tricyclic antidepressants including amitriptyline, clomipramine, doxepin, imipramine, trimipramine- mainly used to treat major depressive disorders	CPIC	Greatly reduced metabolism increases risk of side effects	Cardiotoxicity, anticholinergic effects, seizures, altered consciousness, delirium, coma, death	Avoid tricyclics or consider 50% dose reduction and use monitoring to guide dose adjustments. Advice should be given in conjunction with CYP2C19 haplotypes	(8, 11-13, 68-70)

CYP2D6	5-10%	See above	Poor metaboliser	Venlafaxine (serotonin norepinephrine reuptake inhibitor)- used to treat major depressive disorder, anxiety disorder, social phobia, panic disorder	DPWG	Greatly reduced metabolism increases risk of side effects	Anticholinergic symptoms, seizures, prolonged QT interval, altered level of consciousness	Insufficient evidence for dose reduction. Consider alternative e.g. sertraline, citalopram or if using venlafaxine monitor plasma O-desmethylvenlafaxine levels and adverse drug effects and adjust dose accordingly	(11, 18, 124-126)
CYP2D6	5-10%	See above	Poor metaboliser	Zuclopenthixol (typical thioxanthane antipsychotic)- used to treat psychotic illness such as schizophrenia	DPWG	Greatly reduced metabolism increases risk of side effects	Somnolence, altered state of consciousness, arrhythmias, extra-pyramidal symptoms	Reduce dose by 50% and monitor for adverse drug effects. Alternatively consider another antiopsychotic such as flupenthixol, clozapine, olanzapine or quetiapine	(127)
CYP2D6	1-2%	UM (a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles)	Ultra-rapid metaboliser	Amitriptyline (tricyclic antidepressant)- mainly used to treat major depressive disorders	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Select alternative drug e.g. citalopram, sertraline OR monitor E-10-hydroxy-amitriptyline plasma concentration.	(11-13, 68-70)
CYP2D6	1-2%	*1/*1xN, *1/*2xN	Ultra-rapid metaboliser	Anti-emetics- ondansetron and tropisetron	CPIC	Increased metabolism to less active compounds- decreased response to ondansetron	Ineffective treatment of vomiting	Select alternative drug e.g. granisetron. Palonosetron, dolasetron and ramosetron are all metabolised by CYP2D6 so should not be used	(71)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Aripiprazole (atypical antipsychotic)- used to treat schizophrenia and bipolar disorder	DPWG	Lower plasma concentrations result in reduced efficacy	None	No dose adjustment recommended but be alert to possibility of adverse effects	(11, 72-74)

CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Atomoxetine (norepinephrine reuptake inhibitor)- used to treat ADHD	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy, possible undertreatment	Dose adjustment not recommended due to insufficient evidence. Be aware of possibility of adverse drug effects and consider alternative e.g. methylphenidate or clonidine	(11, 75-78)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Clomipramine (tricyclic antidepressant)- used to treat obsessive compulsive disorder, depressive disorder, chronic pain	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Select alternative drug e.g. citalopram, sertraline or plasma desmethylclomipramine level monitoring	(11-13, 68-70, 79)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Codeine (opioid analgesic)- used to treat pain	CPIC	Rapid metabolism to morphine increases risk of side effects	Respiratory depression, coma, death	Avoid codeine, tramadol, hydrocodone and oxycodone. Consider morphine or non-opioid pain relief.	(80-89)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Codeine (opioid analgesic)- used to treat pain	CPNDS	Increased metabolism to morphine increases risk of adverse drug effects	Respiratory depression, coma, death	Do not give codeine for pain relief. Avoid other opioids metabolised by *CYP2D6*, including tramadol, oxycodone, hydrocodone	(80-87, 90)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Codeine (opioid analgesic)- used to treat pain	DPWG	Increased metabolism to morphine increases risk of adverse drug effects	Respiratory depression, coma, death	Monitor for effects of opiate overdose or select alternate drug such as morphine, NSAID, acetaminophen (paracetamol). Alternative drugs should not include tramadol, hydrocodone or oxycodone	(11, 80-87)

CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Doxepin (tricyclic antidepressant)- used to treat depression, anxiety and insomnia	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Select alternative drug e.g. citalopram, sertraline or 100% dose increase. Monitor plasma nordoxepin levels to determine maintenance dose	(11-13, 68-70, 91)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Flecainide (antiarrhythmic)- used for SVT, VT, RVVOT, ARVD	DPWG	Reduced plasma levels may result in undertreatment and non-control of symptoms	Failure to control tachycardias	Monitor plasma levels and ECG OR consider alternative drug including amiodarone, soltalol, disopyramide, quinidine	(11, 92-94)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Haloperidol (typical antipsychotic)- used to treat schizophrenia, mania, acute psychosis	DPWG	Reduced plasma levels may result in undertreatment and non-control of symptoms	Ineffective treatment of psychosis	Insufficient evidence to recommend dose increase. Monitor plasma levels and adjust dose accordingly OR consider selecting alternative drug e.g. pimozide, quetiapine, flupenthixol, olanzapine, clozapine, fluphenazine	(73, 95, 96)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Imipramine (tricyclic antidepressant)- used to treat depression and enuresis	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Select alternative drug e.g. citalopram, sertraline or 70% dose increase. Monitor plasma imipramine and desipramine levels	(11-13, 32, 68-70)

CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Metoprolol (β-blocker)- used to treat heart failure, tachycardias and hypertension	DPWG	Reduced plasma levels may result in undertreatment and non-control of symptoms	Insufficient treatment of indication	Ideally, select alternate drug e.g. carvedilol or bisoprolol, especially if treating heart failure. If prescribing metoprolol titrate dose to a maximum of 250% of standard dose and monitor for efficacy and adverse drug effects	(11, 97-100)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Nortriptyline (2nd generation tricyclic)- used to treat depression	DPWG	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Select alternative drug e.g. sertraline, citalopram. If prescribing nortriptyline increase dose by 60% and monitor plasma nortriptyline and 10-hydroxynortryptyline concentrations	(11, 12, 69, 70, 101)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Other tricyclic antidepressants- used to treat depression. Drugs include desipramine, fluvoxamine, nortriptyline (2nd-generation tricyclic)	CPIC	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Consider using non-tricyclic antidepressant or if using, titrate to a higher dose	(8, 12, 13, 68-70)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Oxycodone (opioid)- pain relief	DPWG	Increased metabolism to morphine increases risk of adverse drug effects	Urinary retention, nausea & vomiting, confusion, respiratory depression, coma , death	Insufficient evidence to recommend dose alteration. Suggests selection of alternative drug but not tramadol or codeine. Be alert to symptoms of adverse drug effects	(11, 102-104)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	CPIC	Rapid metabolism reduces plasma concentrations of SSRI	Increased likelihood of ineffective treatment	Select alternative drug not predominantly metabolised by CYP2D6	(21, 69, 105-107)

CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Paroxetine (selective serotonin reuptake inhibitor)- used to treat depression and anxiety	DPWG	Rapid metabolism reduces plasma concentrations of SSRI	Increased likelihood of ineffective treatment	Insufficient data to recommend dose adjustment. Consider therapy with alternative agent e.g. sertraline, citalopram	(11, 69, 105-108)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Propafenone (class 1c anti-arrhythmic drug)- used to treat atrial and ventricular arrhythmias	DPWG	Reduced plasma levels may result in undertreatment and non-control of symptoms	Lethal arrhythmias, cardiac failure, death	Insufficient evidence to recommend dose adjustment. Monitor plasma levels and ECG. Consider alternative drug including amiodarone, soltalol, disopyramide, quinidine	(11, 109-111)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Risperidone (atypical antipsychotic)- used to treat schizophrenia, bipolar disorder and occasionally features of autism	DPWG	Reduced plasma levels may result in undertreatment and non-control of symptoms	Ineffective treatment of psychosis	Insufficient evidence to recommend dose increase. Monitor plasma levels. Consider selecting alternative drug e.g. clozapine, quetiapine, olanzapine. Monitor for efficacy	(11, 72, 112-114)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Tamoxifen (hormonal anti-cancer agent)- used to treat breast cancer	DPWG	None	None	Standard dosing	(11, 115-118)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Tramadol (opioid)- pain relief	DPWG	Increased metabolism to morphine increases risk of adverse drug effects	Urinary retention, nausea & vomiting, confusion, respiratory depression, coma , death	Consider 30% dose reduction. Consider selection of alternative drug such as paracetamol, NSAIDS or morphine but not oxycodone or codeine. Watch for symptoms of adverse drug effects	(11, 119-123)

CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Tricyclic antidepressants including amitriptyline, clomipramine, doxepin, imipramine, trimipramine- mainly used to treat major depressive disorders	CPIC	Lower plasma concentrations result in reduced efficacy	Reduced chance of therapeutic levels, lack of efficacy	Consider non tricyclic antidepressant consider titrating to higher dose and monitoring closely. Advice should be given in conjunction with *CYP2C19* haplotypes	(8, 12, 13, 68-70)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Venlafaxine (serotonin norepinephrine reuptake inhibitor)- used to treat major depressive disorder, anxiety disorder, social phobia, panic disorder	DPWG		Reduced chance of therapeutic levels, lack of efficacy, possible undertreatment	Increase dose by 150% and monitor plasma O-desmethylvenlafaxine levels. Consider alternative e.g. sertraline, citalopram	(11, 18, 124-126)
CYP2D6	1-2%	See above	Ultra-rapid metaboliser	Zuclopenthixol (typical thioxanthane antipsychotic)- used to treat psychotic illness such as schizophrenia	DPWG	Increased metabolism leads to rapid drug clearance and reduced efficacy	Ineffective treatment of psychosis	Insufficient data to allow calculation of dose adjustment. Be alert to low zuclopenthixol concentrations or select alternative drug (flupenthixol, quetiapine, olanzapine, clozapine)	(11, 127)
CYP3A5	Varies with ethnicity (142)	*1/*3, *1/*6, *1/*7 (one functional and one non-functional allele)	Intermediate metaboliser	Tacrolimus (macrolide lactone immune suppressant)- predominantly used in suppression of transplant rejection	CPIC	Lower concentrations of tacrolimus	Reduced chance of achieving therapeutic levels, risk of undertreatment with increased risk of transplant rejection	1.5 to 2-fold dose increase with monitoring. Maximum tacrolimus dose not to exceed 0.3mg/kg/day	(142-146)
CYP3A5	Varies with ethnicity (142)	Any other combination of alleles apart from *1/*1	Intermediate metaboliser	Tacrolimus (macrolide lactone immune suppressant)- predominantly used in suppression of transplant rejection	DPWG	Lower concentrations of tacrolimus	Reduced chance of achieving therapeutic levels, risk of undertreatment with increased risk of transplant rejection	No dose recommendation. Dose should be adjusted according to therapeutic monitoring	(11, 143-146)

CYP3A5	Varies with ethnicity (142)	*1/*1 (2 functional alleles)	Normal metaboliser	Tacrolimus (macrolide lactone immune suppressant)- predominantly used in suppression of transplant rejection	CPIC	Lower concentrations of tacrolimus	Reduced chance of achieving therapeutic levels, risk of undertreatment with increased risk of transplant rejection	1.5 to 2-fold dose increase with monitoring. Maximum tacrolimus dose not to exceed 0.3mg/kg/day	(142-146)
CYP3A5	Varies with ethnicity (142)	*1/*1 (2 functional alleles)	Normal metaboliser	Tacrolimus (macrolide lactone immune suppressant)- predominantly used in suppression of transplant rejection	DPWG	Lower concentrations of tacrolimus	Reduced chance of achieving therapeutic levels, risk of undertreatment with increased risk of transplant rejection	No dose recommendation. Dose should be adjusted according to therapeutic monitoring	(11, 143-146)
CYP3A5	Varies with ethnicity (142)	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7 (two non-functioning alleles)	Poor - CYP3A5 non-expressor	Tacrolimus (macrolide lactone immune suppressant)- predominantly used in suppression of transplant rejection	CPIC	Normal concentrations of tacrolimus	Increased chance of achieving therapeutic levels with reduced risk of undertreatment and transplant rejection	Standard dosing and monitoring	(142-146)
CYP3A5	Varies with ethnicity (142)	*1 plus any of *2, *4, *5, *8, *9	Possible intermediate metaboliser	Tacrolimus (macrolide lactone immune suppressant)- predominantly used in suppression of transplant rejection	CPIC	Lower concentrations of tacrolimus	Reduced chance of achieving therapeutic levels, risk of undertreatment with increased risk of transplant rejection	1.5 to 2-fold dose increase with monitoring. Maximum tacrolimus dose not to exceed 0.3mg/kg/day	(142-146)
DPYD	3-5%	*1/*2A, *1/*13, *1/ rs67376798A	Heterozygous - one functional and one non-functional allele, intermediate DPD activity	Fluorouracil, capecitabine, tegafur (fluoropyrimidines)- used as chemotherapeutic agents in cancer e.g. breast, colorectal etc.	CPIC	Decreased DPD activity (30-70% of wild type). Increased risk of severe/ fatal drug toxicity	Mucositis, neutropenia, thrombocytopenia , renal toxicity, diarrhoea, alopecia, neurological damage, death	Reduce starting dose by at least 50% and adjust dose based on toxicity and/or pharmacokinetic test	(147-153)

DPYD	0.2%	*2A/*2A, *13/*13, rs67376798A / rs67376798A	Homozygous-2 non-functional alleles, complete DPD deficiency	Fluorouracil, capecitabine, tegafur (fluoropyrimidines)-used as chemotherapeutic agents in cancer e.g. breast, colorectal etc.	CPIC	Complete DPD deficiency and increased risk of severe/ fatal drug toxicity	Mucositis, neutropenia, thrombocytopenia, renal toxicity, diarrhoea, alopecia, neurological damage, death	Select alternate drug	(147-153)
DPYD		IM (1 active allele and 1 decreased activity allele OR 1 active and 1 inactive allele (see notes)	Intermediate metaboliser	Fluorouracil, capecitabine, tegafur (fluoropyrimidines)-used as chemotherapeutic agents in cancer e.g. breast, colorectal etc.	DPWG	Low DPD activity. High risk of severe/ fatal drug toxicity	Mucositis, neutropenia, thrombocytopenia, renal toxicity, diarrhoea, alopecia, neurological damage, death	Reduce dose by 50% and increase or decrease depending on response. Monitor for adverse drug effects. Alternatively, select drug not predominantly metabolised by *DPYD* (not tegafur)	(11, 147-152)
DPYD		See above	Intermediate metaboliser	Tegafur (Fluorpyrimidine)-used as chemotherapeutic agent in cancer e.g. breast, colorectal etc.	DPWG	Low DPD activity. High risk of severe/ fatal drug toxicity	Mucositis, neutropenia, thrombocytopenia, renal toxicity, diarrhoea, alopecia, neurological damage, death	None	(11, 147-152)
DPYD		PM (2 inactive alleles OR 2 decreased activity alleles OR 1 inactive and 1 decreased activity allele (see notes)	Poor metaboliser	Fluorouracil, capecitabine (fluoropyrimidines)-used as chemotherapeutic agents in cancer e.g. breast, colorectal etc.	DPWG	Low or absent DPD activity. High risk of severe/ fatal drug toxicity	Mucositis, neutropenia, thrombocytopenia, renal toxicity, diarrhoea, alopecia, neurological damage, death	Select alternative drug not predominantly metabolised by *DPYD* (not tegafur)	(11, 147-152)
DPYD		See above	Poor metaboliser	Tegafur (fluoropyrimidine)-used as chemotherapeutic agent in cancer e.g. breast, colorectal etc.	DPWG	Low or absent DPD activity. High risk of severe/ fatal drug toxicity	Mucositis, neutropenia, thrombocytopenia, renal toxicity, diarrhoea, alopecia, neurological damage, death	Select alternate drug not predominantly metabolised by DPYD (not capecitabine or fluorouracil)	(11, 147-152)

DPYD	95-97%	*1/*1 (or any combination of *1, *4, *5, *6, *9A)	Wild type- 2 functional alleles, high DPD activity	Fluorouracil, capecitabine, tegafur (fluoropyrimidines)- used as chemotherapeutic agents in cancer e.g. breast, colorectal etc.	CPIC	Normal DPD activity and normal risk for toxicity	None	No adjustment	(147-153)
F5	Varies with ethnicity	CT, A534Q heterozygote OR TT, A534Q homozygote	Factor V resistant to inactivation due to abolition of a cleavage site. Prothrombotic genotype	Hormonal contraceptive (oestrogen and progesterone containing hormonal contraceptive)- use to prevent pregnancy, regulation of menstruation	DPWG	Increased risk of coagulopathy	Increased risk of thrombotic events.	If positive family history of thrombotic event, avoid and select alternative contraception e.g. progesterone only, copper IUD. If negative family history, avoid other risk factors such as smoking and obesity and use with caution	(11, 154-157)
F5	Varies with ethnicity	CC	Normal factor V inactivation. Non-prothrombotic genotype	Hormonal contraceptive (oestrogen and progesterone containing hormonal contraceptive)- use to prevent pregnancy, regulation of menstruation	DPWG	Wild type. No increased risk of thrombotic events	No increased risk of thrombotic events	None	(11, 154-157)
G6PD	Varies with ethnicity - Class I is very rare	Normal- a male carrying a non-deficient (class IV) allele or a female carrying two non-deficient (class IV) alleles. Class IV alleles include B, Sao Boria	Normal levels of G6PD	Rasburicase (recombinant urate oxidase)- used in tumour lysis syndrome (occasionally off licence in rhabdomyolysis, gout)	CPIC	Cells have normal response to drug-induced oxidative stress	Normal risk of acute haemolytic anaemia	Rasburicase may be used	(158-164)

G6PD	See above	Deficient- a male carrying a deficient (class I-III) allele or a female carrying 2 deficient (class I-III) alleles. Examples of class I-III alleles include A-, Bangkok, Canton, Chatham, Kalyan-Kerala, Mediterranean, Orissa, Villeurbanne	Reduced levels of G6PD	Rasburicase (recombinant urate oxidase)- used in tumour lysis syndrome (occasionally off licence in rhabdomyolysis, gout)	CPIC	Cells have an abnormal response to drug-induced oxidative stress	Increased risk of acute haemolytic anaemia	Avoid rasburicase. Use alternative such as allopurinol	(158-164)
G6PD	See above	Variable- a female carrying one normal (class IV) and one deficient (class I-III) allele. For examples see above	Variable levels of G6PD	Rasburicase (recombinant urate oxidase)- used in tumour lysis syndrome (occasionally off licence in rhabdomyolysis, gout)	CPIC	Cells may have an abnormal response to drug-induced oxidative stress	Unknown risk of acute haemolytic anaemia	Measure enzyme levels before administration of rasburicase. If levels are low prescribe alternative e.g. allopurinol	(158-164)

*HLA-A *31:01*	Varies with ethnicity	One or two *31:01 alleles (positive genotyping test)	Abnormal interaction between carbamazepine and *HLA-A*	Carbamazepine (benzodiazepine)-used as analgesic and anticonvulsant	CPNDS	Increased risk of carbamazepine SCAR	SCAR including toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia. Also hepatitis and acute renal failure	Do not use in carbamazepine naïve patients. Also avoid structurally similar drugs including primidone, oxycarbazepine, lamotrigine, phenytoin and phenonbarbitol. If patient has previously used for >3 months there is no need for genetic testing and it can be continued/ reintroduced with caution. If patient has used for <3 months consider genetic testing	(165-167)
*HLA-A *31:01*	Varies with ethnicity	No *31:01 alleles (negative genotyping test)	Normal interaction between carbamazepine and *HLA-A*	Carbamazepine (benzodiazepine)-used as analgesic and anticonvulsant	CPNDS	Normal or reduced risk of carbamazepine SCAR	None	Standard dosing but monitor response and consider morphine or non-opioid analgesics. Consider *HLA-B*	(165-167)
*HLA-B *15:02*	Varies with ethnicity	One or two *15.02 alleles (positive genotyping test)	Abnormal interaction between carbamazepine and *HLA-B*	Carbamazepine (benzodiazepine)-used as analgesic and anticonvulsant	CPIC	Increased risk of carbamazepine SCAR	SCAR including toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia. Also hepatitis and acute renal failure	Do not use in carbamazepine naïve patients. If patient has previously used for >3 months without any cutaneous adverse reactions, can continue or reintroduce with caution	(47, 166, 168-172)

*HLA-B *15:02*	Varies with ethnicity	See above	Abnormal interaction between carbamazepine and *HLA-B*	Carbamazepine (benzodiazepine)- used as analgesic and anticonvulsant	CPNDS	Increased risk of carbamazepine SCAR	SCAR including toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia. Also hepatitis and acute renal failure	Do not use in carbamazepine naïve patients. Also avoid structurally similar drugs including primidone, oxycarbazepine, lamotrigine, phenytoin and phenonbarbitol. If patient has previously used for >3 months there is no need for genetic testing and it can be continued/ reintroduced with caution. If patient has used for <3 months consider genetic testing	(47, 166-171)
*HLA-B *15:02*	Varies with ethnicity	See above	Abnormal interaction between phenytoin and *HLA-B*	Phenytoin (anti-epileptic)- used to treat epilepsy	CPIC	Increased risk of phenytoin SCAR	SCAR including toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia. Also hepatitis, acute renal failure, Ataxia, nystagmus, dysarthria and sedation	CPIC recommends that phenytoin prescribing should take into account both *HLA-B* and *CYP2C9* genotypes. See advice for Phenytoin and *CYP2C9* but phenytoin should not be used in *HLA-B 15:02* positive patients	(47-52)
*HLA-B *15:02*	Varies with ethnicity	No *15.02 alleles (negative genotyping test)	Normal interaction between carbamazepine and *HLA-B*	Carbamazepine and oxcarbazepine (benzodiazepine)- used as analgesic and anticonvulsant	CPIC	Normal or reduced risk of carbamazepine SCAR	None	Standard dosing	(47, 166, 168-172)
*HLA-B *15:02*	Varies with ethnicity	No *15.02 alleles (negative genotyping test)	Normal interaction between carbamazepine and *HLA-B*	Carbamazepine and oxcarbazepine (benzodiazepine)- used as analgesic and anticonvulsant	CPNDS	Normal or reduced risk of carbamazepine SCAR	None	Standard dosing but consider HLA-A	(47, 166-171)

*HLA-B *15:02*	Varies with ethnicity	No *15.02 alleles (negative genotyping test)	Normal interaction between phenytoin and *HLA-B*	Phenytoin (anti-epileptic)- used to treat epilepsy	CPIC	Normal risk of phenytoin SCAR	None	CPIC recommends that phenytoin prescribing should take into account both *HLA-B* and *CYP2C9* genotypes. See advice for Phenytoin and *CYP2C9*	(47-52)
*HLA-B *44*	Varies with ethnicity	One or two *44 alleles (positive genotyping test)	Abnormal interaction between Ribavirin and *HLA-B*	Ribavirin (nucleoside inhibitor)- used to treat viral infections including Hepatitis B and RSV	DPWG	Reduced response to Ribavirin	Reduced likelihood of viral clearance	No dose adjustment but be alert to non-response. Currently no alternative treatment available	(11, 173)
*HLA-B *44*	Varies with ethnicity	No *44 alleles (negative genotyping test)	Normal interaction between Ribavirin and *HLA-B*	Ribavirin (nucleoside inhibitor)- used to treat viral infections including Hepatitis B and RSV	DPWG	Normal response to Ribavirin	Standard likelihood of viral clearance	None	(11, 173)
*HLA-B *57:01*	6% but varies with ethnicity	One or two *57:01 alleles (positive genotyping test)	Abnormal interaction between abacavir and *HLA-B*	Abacavir (NRTI)- used in treatment of HIV	CPIC	High risk of hypersensitivity	Nausea, vomiting, diarrhoea, rash	Avoid abacavir	(174-180)
*HLA-B *57:01*	6% but varies with ethnicity	One or two *57:01 alleles (positive genotyping test)	Abnormal interaction between abacavir and *HLA-B*	Abacavir (NRTI)- used in treatment of HIV	DPWG	High risk of hypersensitivity	Nausea, vomiting, diarrhoea, rash	Avoid abacavir	(11, 174-179)
*HLA-B *57:01*	94% but varies with ethnicity	No *57:01 alleles (negative genotyping test)	Normal interaction between abacavir and *HLA-B*	Abacavir (NRTI)- used in treatment of HIV	CPIC	Very low risk of hypersensitivity	None	Standard dosing	(174-180)
*HLA-B *57:01*	94% but varies with ethnicity	No *57:01 alleles (negative genotyping test)	Normal interaction between abacavir and *HLA-B*	Abacavir (NRTI)- used in treatment of HIV	DPWG	Very low risk of hypersensitivity	None	Standard dosing	(11, 174-179)

*HLA-B *58:01*	Varies with ethnicity	One or two *58:01 alleles (positive genotyping test)	Abnormal interaction between allopurinol and *HLA-B*	Allopurinol (xanthine oxidase inhibitor)-used to treat gout	CPIC	Increased risk of allopurinol SCAR	SCAR including toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia. Also hepatitis and acute renal failure	Avoid allopurinol	(181-189)
*HLA-B *58:01*	Varies with ethnicity	One or two *58:01 alleles (positive genotyping test)	Abnormal interaction between allopurinol and *HLA-B*	Allopurinol (xanthine oxidase inhibitor)-used to treat gout	PRO	Increased risk of allopurinol SCAR	SCAR including toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia. Also hepatitis and acute renal failure	If *HLA-B 58:01* positive AND of Korean descent AND Stage III-V CKD OR HLA-B 58:01 positive AND of Han Chinese or Thai descent with or without CKD should not be prescribed allopurinol	(181-190)
*HLA-B *58:01*	Varies with ethnicity	No *58:01 alleles (negative genotyping test)	Normal interaction between allopurinol and *HLA-B*	Allopurinol (xanthine oxidase inhibitor)-used to treat gout	CPIC	Low risk of allopurinol SCAR	None	Standard dosing	(181-189)
IFNL3 (IL28B)	Varies with ethnicity	CC	Favourable genotype	Peginterferon α-2a, peginterferon α-2b, Ribavirin (Interferons, nucleoside inhibitor)-used to treat viral infections e.g. hepatitis and in case of interferons, MS	CPIC	Increased chance of responding to treatment	None	Increased chance of response when used alone or with protease inhibitor (approximately 70% chance of sustained virologic response when used alone, increased to 90% if combined with protease inhibitor). Patients more likely to be eligible for shortened therapy regimes. Adds weight to prescription of these drugs	(191-195)

IFNL3 (IL28B)	Varies with ethnicity	CT or TT	Unfavourable genotype	Peginterferon α-2a, peginterferon α-2b, Ribavirin (Interferons, nucleoside inhibitor)- used to treat viral infections e.g. hepatitis and in case of interferons, MS	CPIC	Reduced chance of responding to treatment	Less likely to respond to treatment but still exposed to risks of treatments	Reduced chance of response when used alone or with protease inhibitor (approximately 30% chance of sustained virologic response when used alone, increased to 60% if combined with protease inhibitor) and patients unlikely to be eligible for shortened therapy regimes. Makes prescription of these drugs less favourable. Weigh up risks and benefits before prescribing	(191-195)

RARG	Varies with ethnicity	A	High risk allele	Daunorubicin, doxorubicin (anthracycline chemotherapeutic agent)- used in treatment of malignancy including haematological, neuroblastoma, sarcoma	CPNDS	Increased risk of anthracycline-associated cardiotoxicity	Increased risk of anthracycline-associated cardiotoxicity	*RARG, UTG1A6* and SLC28A3 should all be considered together in paediatric patients. If low risk allele in SLC28A3 and no high risk alleles in *RARG, UTG1A6,* then patient should be considered low risk for AAC and should have normal follow up. If patient carries a high risk allele then management and follow up as follows: should be prescribed dexrasoxane (iron chelation, have serial echocardiography, aggressive management of cardiovascular risk factors, have liposomal anthracyclines prescribed and at lower rate of infusion. Use of other cardioprotective agents should be considered. If moderate risk e.g. no high risk or protective alleles, should have increased echocardiography, close monitoring for cardiotoxicity and increased follow up	(196-198)

SLC28A3	Varies with ethnicity	A	Low risk allele	Daunorubicin, doxorubicin (anthracycline chemotherapeutic agent)- used in treatment of malignancy including haematological, neuroblastoma, sarcoma	CPNDS	Reduced risk of anthracycline-associated cardiotoxicity	Reduced risk of anthracycline-associated cardiotoxicity	*RARG, UTG1A6* and SLC28A3 should all be considered together in paediatric patients. If low risk allele in SLC28A3 and no high risk alleles in *RARG, UTG1A6,* then patient should be considered low risk for AAC and should have normal follow up. If patient carries a high risk allele then management and follow up as follows: should be prescribed dexrasoxane (iron chelation, have serial echocardiography, aggressive management of cardiovascular risk factors, have liposomal anthracyclines prescribed and at a lower rate of infusion. Use of other cardioprotective agents should be considered. If moderate risk e.g. no high risk or protective alleles, should have increased echocardiography, close monitoring for cardiotoxicity and increased follow up	(196-198)

SLCO1B1	55-88%	TT (two normal, possibly increased, possibly decreased or unknown function alleles)	High activity- fast metaboliser (wild type)	Simvastatin (statin)- used to treat hypercholesterolaemia	CPIC	Normal statin metabolism	Low risk of myopathy	None	(199-206)
SLCO1B1	11-36%	TC (one decreased function allele (*5, *15, *16, *17) and one normal, possibly increased, possibly decreased or unknown function alleles)	Intermediate activity- intermediate metaboliser	Simvastatin (statin)- used to treat hypercholesterolaemia	CPIC	Slower than normal statin metabolism	Intermediate risk of myopathy	Prescribe lower dose of simvastatin or consider alternative e.g. pravastatin	(199-206)
SLCO1B1	0-6%	CC (two decreased function alleles (*5, *15, *16, *17))	Low activity- slow metaboliser	Simvastatin (statin)- used to treat hypercholesterolaemia	CPIC	Slow statin metabolism	High risk of myopathy	Prescribe lower dose of simvastatin or consider alternative e.g. pravastatin	(199-206)
TPMT	86-97%	1/*1	High activity- fast metaboliser (wild type)	6-Mercaptopurine (thiopurine immune-suppressant)- used in treatment of haematological malignancy and inflammatory bowel disease	CPIC	Lower concentrations of TGN metabolites, higher methylTIMP	Insufficient treatment of malignancy or insufficient immune suppression	Start at normal dose and monitor, wait two weeks for dose increase	(11, 207-216)
TPMT	86-97%	See above	High activity- fast metaboliser (wild type)	Azathioprine (thiopurine immune-suppressant)- used in treatment of organ transplant and autoimmune disease	CPIC	Lower concentrations of TGN metabolites, higher methylTIMP	Insufficient treatment of malignancy or insufficient immune suppression	Start at normal dose and monitor, wait two weeks for dose increase	(212, 213, 215-218)
TPMT	86-97%	See above	High activity- fast metaboliser (wild type)	Thioguanine (thiopurine immune-suppressant)- used in treatment of leukaemia, inflammatory bowel disease autoimmune disease	CPIC	Lower concentrations of TGN metabolites, higher methylTIMP	Insufficient treatment of malignancy or insufficient immune suppression	Start at normal dose and monitor, wait two weeks for dose increase	(211, 215, 216, 219, 220)

TPMT	3-14%	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4	Intermediate activity- intermediate metaboliser	6-Mercaptopurine (thiopurine immune-suppressant)- used in treatment of haematological malignancy and inflammatory bowel disease	CPIC	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Risk of fatal myelo-suppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Start at 30-70% of normal dose, monitor and wait 2-4 weeks before adjusting	(11, 207-216)
TPMT	3-14%	See above	Intermediate activity- intermediate metaboliser	Azathioprine (thiopurine immune-suppressant)- used in treatment of organ transplant and autoimmune disease	CPIC	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Risk of fatal myelosuppressio n and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Start at 30-70% of normal dose, monitor and wait 2-4 weeks before adjusting	(212, 213, 215-218)
TPMT	3-14%	See above	Intermediate activity- intermediate metaboliser	Thioguanine (thiopurine immune-suppressant)- used in treatment of leukaemia, inflammatory bowel disease autoimmune disease	CPIC	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Risk of fatal myelosuppressio n and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Start at 30-50% of normal dose, monitor and wait 2-4 weeks before adjusting	(211, 215, 216, 219, 220)
TPMT	3-14%	IM (one inactive allele: *2, *3, *4-*18)	Intermediate metaboliser	6-Mercaptopurine (thiopurine immune-suppressant)- used in treatment of haematological malignancy and inflammatory bowel disease	DPWG	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Risk of fatal myelo-suppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Select alternative or reduce dose by 50%. Increased monitoring	(11, 207-214)
TPMT	3-14%	See above	Intermediate metaboliser	Azathioprine (thiopurine immune-suppressant)- used in treatment of organ transplant and autoimmune disease	DPWG	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Risk of fatal myelo-suppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Select alternative or reduce dose by 50%. Increased monitoring	(11, 212, 213, 217, 218)

TPMT	3-14%	See above	Intermediate metaboliser	Thioguanine (thiopurine immune-suppressant)- used in treatment of leukaemia, inflammatory bowel disease autoimmune disease	DPWG	Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP	Risk of fatal myelo-suppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Alternative drugs should be chosen as evidence if insufficient to adjust dosage	(11, 211, 219, 220)
TPMT	up to 15%	Any **paediatric** patient heterozygous or homozygous for any of *2, *3A, *3B and *3C	Intermediate or poor metaboliser	Cisplatin-chemotherapeutic agent used in treatment of childhood and adult malignancy	CPNDS	Raised levels of cisplatin, possible increase in reactive oxygen species	High risk of ototoxicity and permanent hearing loss	Select alternative such as carboplatin) or used otoprotectants such as amifostine, sodium thiosulfate (note: depends on tumour type)	(221)
TPMT	<1%	*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4	Low activity-slow metaboliser	6-Mercaptopurine (thiopurine immune-suppressant)- used in treatment of haematological malignancy and inflammatory bowel disease	CPIC	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	High risk of fatal myelosuppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Reduce to 10% of normal dose and reduce frequency to 3 times weekly, monitor and wait 4-6 weeks before adjusting dose	(11, 207-216)
TPMT	<1%	See above	Low activity-slow metaboliser	Azathioprine (thiopurine immune-suppressant)- used in treatment of organ transplant and autoimmune disease	CPIC	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	High risk of fatal myelosuppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Reduce to 10% of normal dose and reduce frequency to 3 times weekly, monitor and wait 4-6 weeks before adjusting dose	(212, 213, 215-218)
TPMT	<1%	See above	Low activity-slow metaboliser	Thioguanine (thiopurine immune-suppressant)- used in treatment of leukaemia, inflammatory bowel disease autoimmune disease	CPIC	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	High risk of fatal myelosuppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Reduce to 10% of normal dose and reduce frequency to 3 times weekly, monitor and wait 4-6 weeks before adjusting dose	(211, 215, 216, 219, 220)

TPMT	86-97%	*1/*1	Normal metaboliser	6-Mercaptopurine (thiopurine immune-suppressant)- used in treatment of haematological malignancy and inflammatory bowel disease	DPWG	Lower concentrations of TGN metabolites, higher methylTIMP	Insufficient treatment of malignancy or insufficient immune suppression	None	(11, 207-214)
TPMT	86-97%	See above	Normal metaboliser	Azathioprine (thiopurine immune-suppressant)- used in treatment of organ transplant and autoimmune disease	DPWG	Lower concentrations of TGN metabolites, higher methylTIMP	Insufficient treatment of malignancy or insufficient immune suppression	None	(11, 212, 213, 217, 218)
TPMT	86-97%	See above	Normal metaboliser	Thioguanine (thiopurine immune-suppressant)- used in treatment of leukaemia, inflammatory bowel disease autoimmune disease	DPWG	Lower concentrations of TGN metabolites, higher methylTIMP	Insufficient treatment of malignancy or insufficient immune suppression	None	(11, 211, 219, 220)
TPMT	<1%	PM (two inactive alleles: *2, *3, *4-*18)	Poor metaboliser	6-Mercaptopurine (thiopurine immune-suppressant)- used in treatment of haematological malignancy and inflammatory bowel disease	DPWG	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	High risk of fatal myelo-suppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Select alternative or reduce dose by 90%. Increased monitoring	(11, 207-214)
TPMT	<1%	See above	Poor metaboliser	Azathioprine (thiopurine immune-suppressant)- used in treatment of organ transplant and autoimmune disease	DPWG	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	High risk of fatal myelosuppressio n and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Select alternative or reduce dose by 90%. Increased monitoring	(11, 212, 213, 217, 218)

TPMT	<1%	See above	Poor metaboliser	Thioguanine (thiopurine immune-suppressant)- used in treatment of leukaemia, inflammatory bowel disease autoimmune disease	DPWG	Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylTIMP metabolites	High risk of fatal myelosuppression and bone marrow toxicity, liver toxicity and risk of discontinuation of treatment	Alternative drugs should be chosen as evidence if insufficient to adjust dosage	(11, 211, 219, 220)
UGT1A1	Varies with ethnicity	1 reference function (*1) or increased function (*36) allele with 1 decreased function (*6, *28, *37) allele OR genotype CT at rs887829	Intermediate metaboliser	Atazanavir (protease inhibitor)- used to treat HIV infection	CPIC	Decreased levels of UGT1A1. Low likelihood of hyperbilirubinaemia	Low possibility of hyperbilirubinaemia and jaundice leading to discontinuation of atazanavir	Prescribe azatanavir but warn patient of possibility of adverse drug effects including hyperbilirubinaemia and jaundice	(222-227)
UGT1A1	Varies with ethnicity	*1/*28	Intermediate metaboliser	Irinotecan (topoisomerase inhibitor)- used as anti-cancer agent, particularly in the treatment of colorectal malignancy	DPWG	Toxicity risk moderately increased	Diarrhoea, neutropenia and myelosuppression	No dose adjustment recommended but be alert to possibility of adverse effects	(11, 228-232)
UGT1A1	Varies with ethnicity	Heterozygous *1/*28 OR *1/*27 OR *36/*28 OR *36/*27	Intermediate metaboliser	Irinotecan (topoisomerase inhibitor)- used as anti-cancer agent, particularly in the treatment of colorectal malignancy	PRO	Toxicity risk moderately increased	Diarrhoea, neutropenia and myelosuppression	Genotyping unnecessary for doses <180mg/m2. For standard dosing (180-230mg/m^2) and intensification regimes (>230mg/m^2) there should be rigorous biological and clinical surveillance dose may need to be reduced.	(11, 228-232)
UGT1A1	Varies with ethnicity	See above	Normal metaboliser	Atazanavir (protease inhibitor)- used to treat HIV infection	CPIC	Normal levels of *UGT1A1*. Very low likelihood of hyperbilirubinaemia	None	None	(222-227)

UGT1A1	Varies with ethnicity	*1/*1, *1/*36, *36/*36	Normal metaboliser	Irinotecan (topoisomerase inhibitor)- used as anti-cancer agent, particularly in the treatment of colorectal malignancy	DPWG	Toxicity risk not increased	None	Normal dosing	(11, 228-232)
UGT1A1	Varies with ethnicity	Homozygous wild type *1/*1 OR 1*36 OR *36/36	Normal metaboliser	Irinotecan (topoisomerase inhibitor)- used as anti-cancer agent, particularly in the treatment of colorectal malignancy	PRO	Toxicity risk not increased	None	Genotyping unnecessary for doses <180mg/m^2. Standard dosing (180-230mg/m^2) and intensification regimes (>230mg/m^2) possible	(11, 228-232)
UGT1A1	Varies with ethnicity	2 decreased function (*6, *28, *37) alleles or genotype TT at rs887829	Poor metaboliser	Atazanavir (protease inhibitor)- used to treat HIV infection	CPIC	Markedly decreased levels of UGT1A1. High likelihood of hyperbilirubinaemia	Possibility of hyperbilirubinaemia and jaundice leading to discontinuation of atazanavir	Consider alternative antiviral	(222-227)
UGT1A1	Varies with ethnicity	*28/*28	Poor metaboliser	Irinotecan (topoisomerase inhibitor)- used as anti-cancer agent, particularly in the treatment of colorectal malignancy	DPWG	Toxicity risk significantly increased	Diarrhoea, neutropenia and myelosuppression	If dose is >250mg reduce initial dose by 30%. Dose may be increased in response to neutrophil count. Dose adjustment is not required if dose ≤250mg	(11, 228-232)
UGT1A1	Varies with ethnicity	Homozygous mutated *28/*28 or *27/*28 OR *27/*27	Poor metaboliser	Irinotecan (topoisomerase inhibitor)- used as anti-cancer agent, particularly in the treatment of colorectal malignancy	PRO	Toxicity risk significantly increased	Diarrhoea, neutropenia and myelosuppression	Genotyping unnecessary for doses <180mg/m^2. Reduce starting dose by 30% and there should be rigorous biological and clinical surveillance. Dose intensification is contraindicated	(228-233)

								RARG, UTG1A6 and SLC28A3 should all be considered together in paediatric patients. If low risk allele in SLC28A3 and no high risk alleles in *RARG, UTG1A6,* then patient should be considered low risk for AAC and should have normal follow up. If patient carries a high risk allele then management and follow up as follows: should be prescribed dexrasoxane (iron chelation, have serial echocardiography, aggressive management of cardiovascular risk factors, have liposomal anthracyclines prescribed and at a lower rate of infusion. Use of other cardioprotective agents should be considered. If moderate risk e.g. no high risk or protective alleles, should have increased echocardiography, close monitoring for cardiotoxicity and increased follow up	
UGT1A6	Varies with ethnicity	See above	High risk allele	Daunorubicin, doxorubicin (anthracycline chemotherapeutic agent)- used in treatment of malignancy including haematological, neuroblastoma, sarcoma	CPNDS	Increased risk of anthracycline-associated cardiotoxicity	Increased risk of anthracycline-associated cardiotoxicity		(196-198)

VKORC1	Varies with ethnicity	GA	Lower expression of VKORC1 which is the target enzyme of warfarin	Warfarin-Anticoagulant used to treat thrombosis	CPIC	very low risk of hypersensitivity	Risk of high INR and haemorrhage	See *CYP2C9* and warfarin.	(55-62, 67)
VKORC1	Varies with ethnicity	GG	Normal expression of VKORC1 which is the target enzyme of warfarin	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Normal sensitivity to warfarin	None	See *CYP2C9* and warfarin.	(55-62, 67)
VKORC1	Varies with ethnicity	AA	Significantly lower expression of VKORC1 which is the target enzyme of coumarins	Acenocoumarol, phenprocoumon (Coumarin anticoagulant) used to treat thrombosis and prothrombotic state	DPWG	Increased sensitivity to coumarins so lower dose required	Risk of high INR and haemorrhage	Monitor INR more frequently	(11, 234-236)
VKORC1	Varies with ethnicity	AG	Significantly lower expression of VKORC1 which is the target enzyme of coumarins	Acenocoumarol, phenprocoumon (Coumarin anticoagulant) used to treat thrombosis and prothrombotic state	DPWG	Increased sensitivity to coumarins so lower dose required	Risk of high INR and haemorrhage	None	(11, 234-236)
VKORC1	Varies with ethnicity	AA	Significantly lower expression of VKORC1 which is the target enzyme of coumarins	Warfarin-Anticoagulant used to treat thrombosis	CPIC	Increased sensitivity to coumarins so lower dose required	Risk of high INR and haemorrhage	See *CYP2C9* and warfarin.	(55-62, 67)

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