Biomarkers & Pharmacogenomics in CNS disorders

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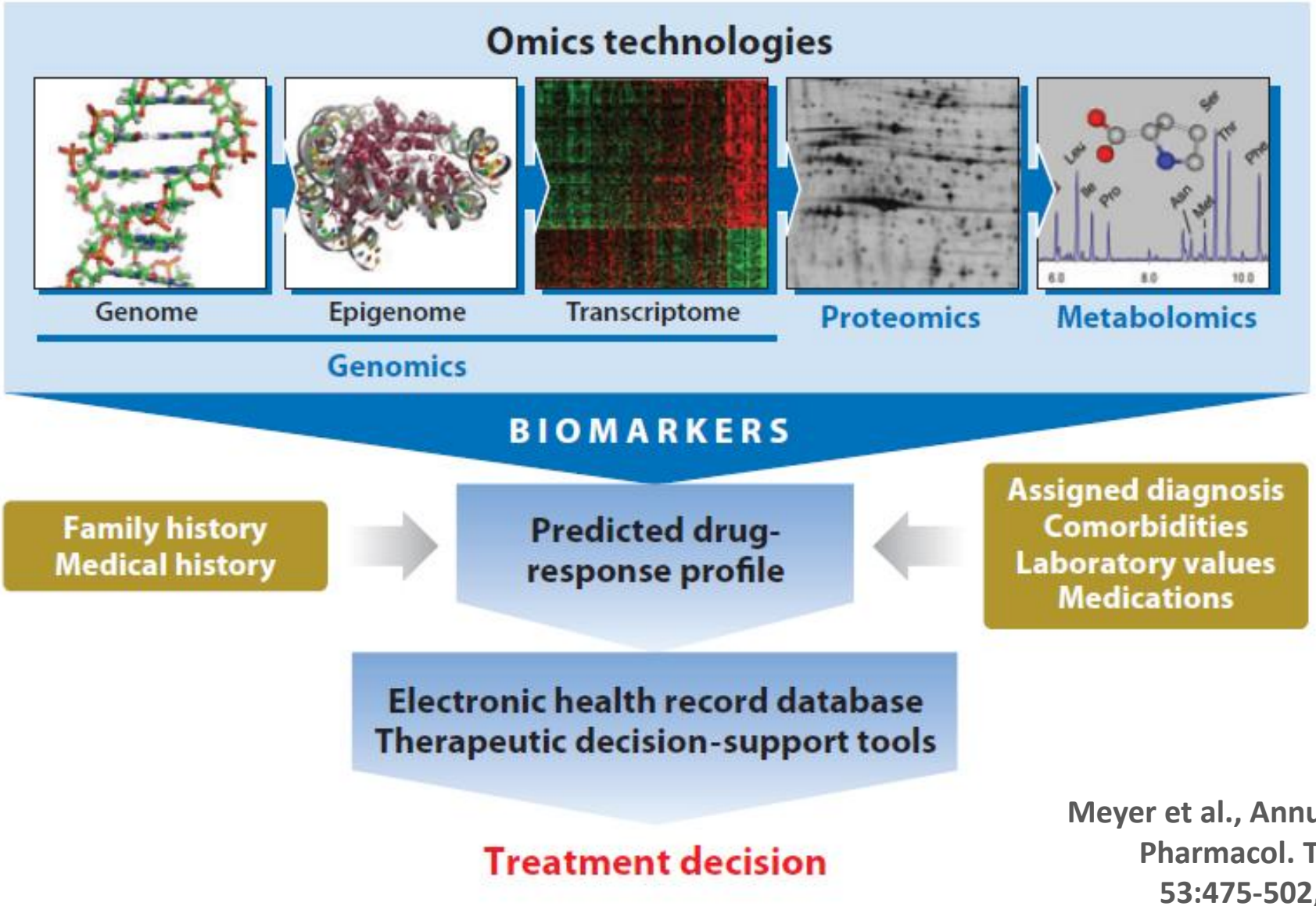
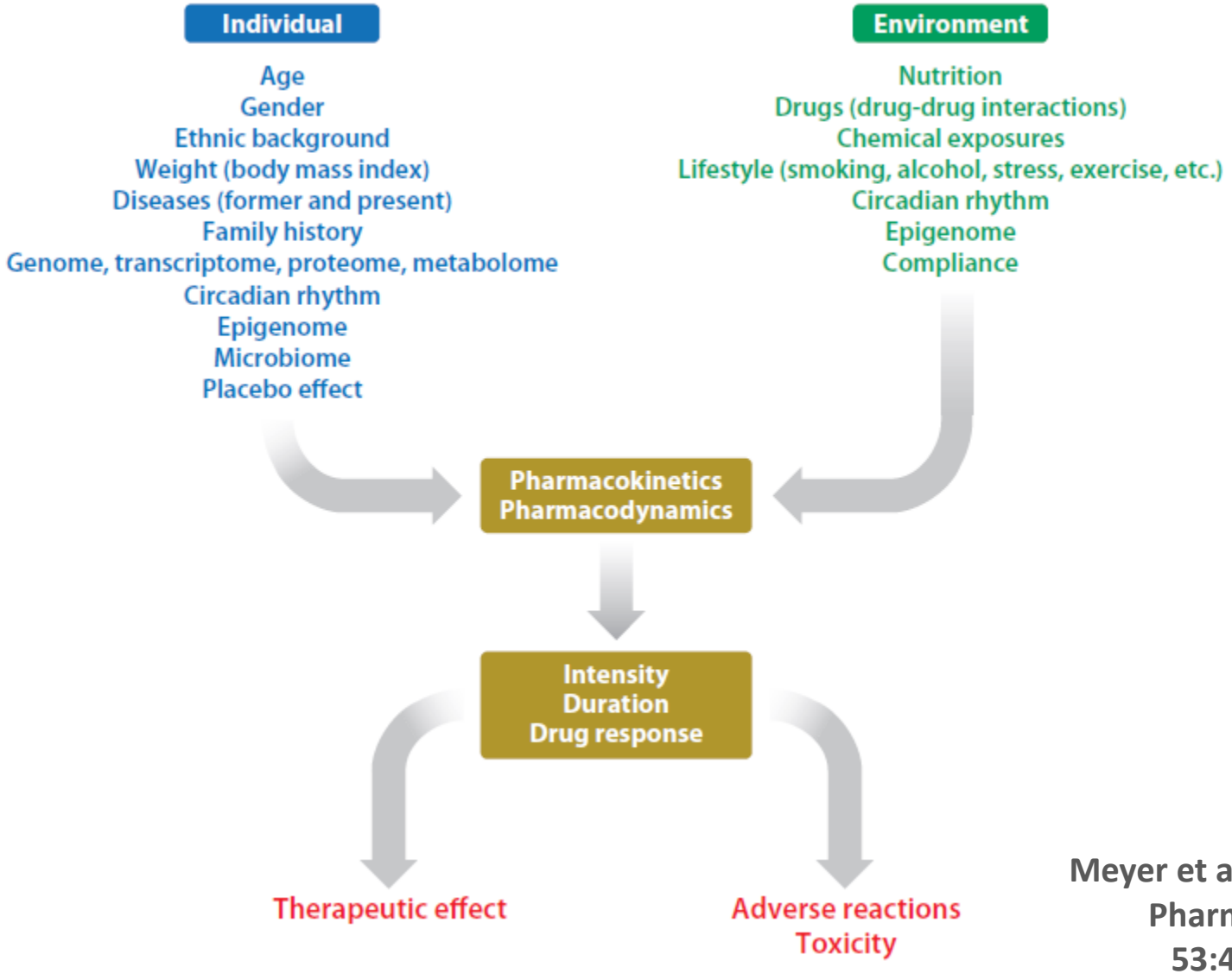
omics based prediction of drug response profiling



Meyer et al., Annu. Rev. Pharmacol. Toxicol 53:475-502, 2013

multiple factors influence drug response



Meyer et al., Annu. Rev. Pharmacol. Toxicol 53:475-502, 2013

challenges in drug therapy

Clinicians frustrations

- Lack of response
- Side effects
- Non-adherence

Patient frustrations

- trial-and-error “roller coaster”
- months/years of ‘trying’
- too many side effects
- multiple medications
- doctor visits etc
- missed work

FDA-pharmacogenomic biomarkers in labeling
Oncology drugs

Ado-Trastuzumab Emtansine	ERBB2
Afatinib	EGFR
Anastrozole	ESR1, PGR
Arsenic Trioxide	PML/RARA
Bosutinib	BCR/ABL1
Brentuximab Vedotin	TNFRSF8
Busulfan	Ph Chromosome
Capecitabine	DPYD
Cetuximab	EGFR
Cetuximab	KRAS
Cisplatin	*TPMT*
Crizotinib	ALK
Dabrafenib (1)	BRAF
Dabrafenib (2)	*G6PD*
Dasatinib	BCR/ABL1
Denileukin Diftitox	IL2RA
Erlotinib (1)	EGFR
Erlotinib (2)	EGFR
Erlotinib (1)	EGFR
Erlotinib (2)	EGFR
Everolimus (1)	ERBB2
Everolimus (2)	ESR1
Exemestane	ESR1
Fluorouracil (2)	DPYD
Fulvestrant	ESR1
Ibritumomab Tiuxetan	MS4A1
Imatinib (1)	KIT
Imatinib (2)	BCR/ABL1
Imatinib (3)	PDGFRB
Imatinib (4)	FIP1L1/PDGFRA
Irinotecan	UGT1A1
Lapatinib	ERBB2
Letrozole	ESR1, PGR
Mercaptopurine	*TPMT*
Nilotinib (1)	BCR/ABL1
Nilotinib (2)	UGT1A1
Obinutuzumab	MS4A1
Ofatumumab	MS4A1
Omacetaxine	BCR/ABL1
Panitumumab (1)	EGFR
Panitumumab (2)	KRAS
Pazopanib	UGT1A1
Pertuzumab	ERBB2
Ponatinib	BCR –ABL T315I
Rituximab	MS4A1
Tamoxifen (1)	ESR1, PGR
Tamoxifen (2)	F5
Tamoxifen (3)	F2
Thioguanine	TPMT
Ticagrelor	*CYP2C19*
Tositumomab	MS4A1
Trametinib	BRAF
Trastuzumab	ERBB2
Tretinoin	PML/RARA

FDA-pharmacogenomic biomarkers in labeling other drugs

Drug	Therapeutic Area	HUGO Symbol
Abacavir	Infectious Diseases	**HLA-B**
Atorvastatin	Endocrinology	**LDLR**
Azathioprine	Rheumatology	TPMT
Boceprevir	Infectious Diseases	**IFNL3**
Carglumic Acid	Metabolic Disorders	**NAGS**
Carisoprodol	Rheumatology	CYP2C19
Carvedilol	Cardiology	CYP2D6
Celecoxib	Rheumatology	CYP2C9
Cevimeline	Dental	CYP2D6
Chloroquine	Infectious Diseases	G6PD
Chlorpropamide	Endocrinology	G6PD
Clopidogrel	Cardiology	CYP2C19
Dapsone	Dermatology	G6PD
Dapsone	Infectious Diseases	G6PD
Dexlansoprazole	Gastroenterology	CYP2C19
Dexlansoprazole	Gastroenterology	CYP1A2
Eltrombopag	Hematology	**F5**
Eltrombopag	Hematology	**SERPINC1**
Esomeprazole	Gastroenterology	CYP2C19
Fluorouracil	Dermatology	DPYD
Flurbiprofen	Rheumatology	CYP2C9
Glimepiride	Endocrinology	G6PD
Glipizide	Endocrinology	G6PD
Glyburide	Endocrinology	G6PD
Ivacaftor	Pulmonary	**CFTR**
Lansoprazole	Gastroenterology	CYP2C19
Lenalidomide	Hematology del (	5q)
Lomitapide	Endocrinology	**LDLR**
Mafenide	Infectious Diseases	G6PD
Maraviroc	Infectious Diseases	**CCR5**
Methylene Blue	Hematology G6PD	
Metoclopramide	Gastroentrology	**CYB5R1-4**
Metoprolol	Cardiology CYP2D6	
Mipomersen	Endocrinology	**LDLR**
Mycophenolic Acid	Transplantation	**HPRT1**
Nalidixic Acid	Infectious Diseases	G6PD
Nitrofurantoin	Infectious Diseases	G6PD
Omeprazole	Gastroenterology	CYP2C19
Pantoprazole	Gastroenterology	CYP2C19
Peginterferon alfa-2b	Infectious Diseases	**IFNL3**
Pegloticase	Rheumatology	G6PD
Perphenazine	Psychiatry CYP2D6	
Phenytoin	Neurology HLA-B	
Prasugrel	Cardiology CYP2C19	
Pravastatin	Endocrinology	**LDLR**
Primaquine	Infectious Diseases	G6PD
Propafenone	Cardiology CYP2D6	
Propranolol	Cardiology CYP2D6	
Quinidine	Cardiology CYP2D6	

FDA-pharmacogenomic biomarkers in labeling other drugs

Drug	Therapeutic Area	HUGO Symbol
Quinidine	Cardiology	CYP2D6
Quinine Sulfate	Infectious Diseases	G6PD
Rabeprazole	Gastroenterology	CYP2C19
Rifampin,	Infectious Diseases	NAT1-2
Rosuvastatin	Endocrinology	**LDLR**
Simeprevir	Infectious Diseases	**IFNL3**
Sodium Nitrite	Antidotal Therapy	G6PD
Sofosbuvir	Infectious Diseases	**IFNL3**
Succimer	Hematology	G6PD
Sulfamethoxazole and Trimethoprim	Infectious Diseases	G6PD
Telaprevir	Infectious Diseases	**IFNL3**
Terbinafine	Infectious Diseases	CYP2D6
Ticagrelor	Cardiology	CYP2C19
Tolterodine	Genitourinary	CYP2D6
Voriconazole	Infectious Diseases	CYP2C19
Warfarin (1)	Cardiology or Hematology	CYP2C9
Warfarin (2)	Cardiology or Hematology	**VKORC1**
Warfarin (3)	Cardiology or Hematology	**PROC**

PharmGKB: http://www.pharmgkb.org

FDA – CNS Drugs: pharmacogenomic biomarkers in labeling

CYP2D6

Amitriptyline
Aripiprazole
Atomoxetine
Citalopram
Clomipramine
Clozapine
Codeine
Desipramine
Dextromethorphan & Quinidine
Diazepam
Doxepin
Fluoxetine
Fluvoxamine
Iloperidone
Imipramine
Modafinil
Nortriptyline
Paroxetine
Perphenazine
Pimozide
Protriptyline
Risperidone
Tetrabenazine
Thioridazine

CYP2C19

Citalopram
Clobazam
Drospirenone
Ethinyl Estradiol

HLA-B

Phenytoin

HLA-A

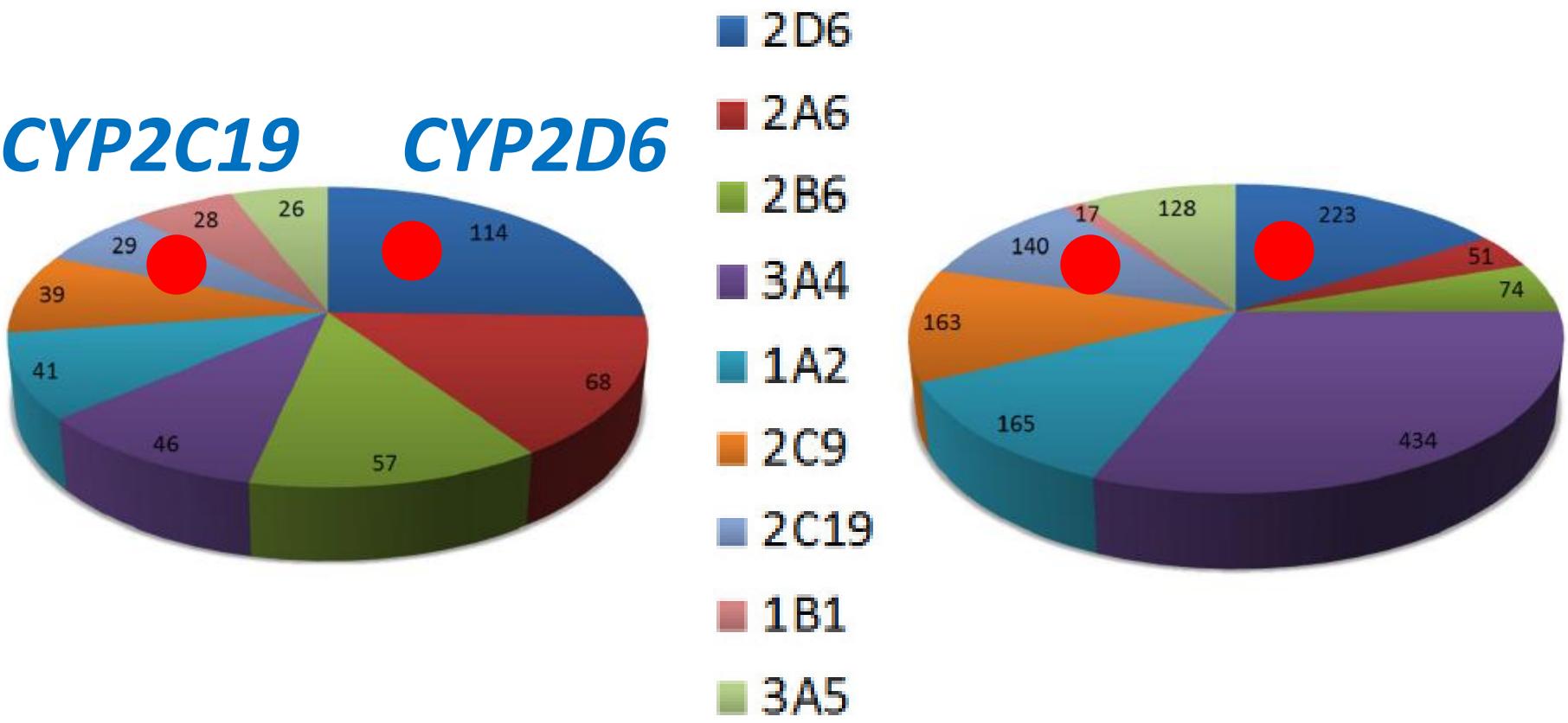
HLA-B

Carbamazepine

cytochrome P450 enzymes (CYPs)

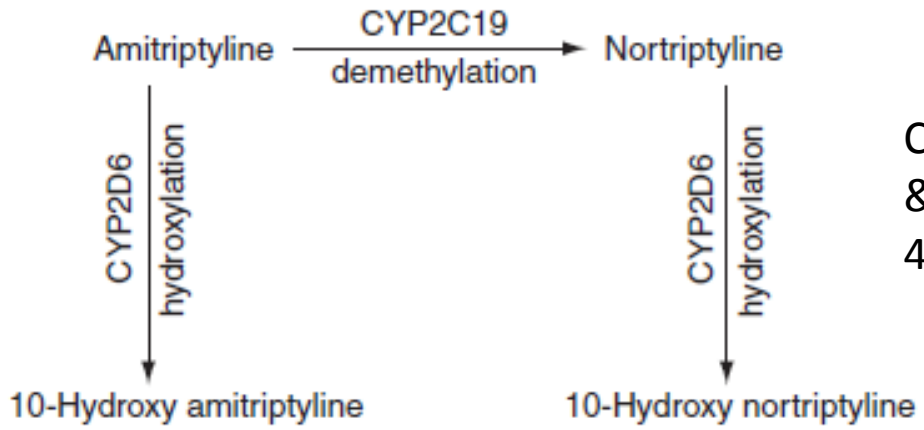
of SNPs per CYP

drugs metabolized per CYP



Preissner et al. 2013
PLOS one : e 8562

Tricyclic antidepressant metabolism by *CYP2D6* and *CYP2C19*



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Parent drug	CYP2C19 metabolite	CYP2D6 metabolite	Therapeutic drug monitoring
Amitriptyline	Nortriptyline	hydroxy-amitriptyline	amitriptyline + nortriptyline
Clomipramine	desmethyl-clomipramine	hydroxy-clomipramine	clomipramine + desmethyl-clomipramine
Desipramine	--------	hydroxy-desipramine	desipramine
Doxepin	desmethyl-doxepin	hydroxy-doxepin	doxepin + desmethyl-doxepin
Imipramine	Desipramine	hydroxy-imipramine	imipramine + desmethyl-imipramine
Nortriptyline	--------	hydroxy-nortriptyline	nortriptyline
Trimipramine	desmethyl-trimipramine	hydroxy-trimipramine	trimipramine + desmethyl-trimipramine

association between allelic variants & enzyme activity

CYP2D6

Functional Status	Activity Value	Alleles
Functional / normal activity / wild-type	1	*1, *2, *27, *33, *35, *45, *46, *39, *48, *53
Reduced function / decreased activity	0.5	*9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, *72
Non-functional / no activity	0	*3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *31, *36, *38, *40, *42, *44, *47, *51, *56, *57, *62

CYP2C19

Functional Status	Alleles
Functional / normal activity / wild-type	*1
Loss-of-function / no or decreased activity	*2, *3, *4, *5, *6, *7, *8
Gain-of-function / increased activity	*17

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CYP2D6 genotypes with resulting activity scores and phenotype classification

Allele 1	Allele 2	CYP2D6 Diplotype	CYP2D6 Activity Score	Phenotype
*1	*1xN	*1/*1xN	≥3.0	UM
*2x2	*41	*2x2/*41	2.5	UM
*1	*2	*1/*2	2.0	EM
*1	*17	*1/*17	1.5	EM
*2	*3	*2/*3	1.0	EM
*1	*4x2	*1/*4x2	1.0	EM
*10	*10	*10/*10	1.0	EM
*4	*10	*4/*10	0.5	IM
*5	*6	*5/*6	0	PM

EM = extensive metabolizer; PM = poor metabolizer
IM = intermediate metabolizer; UM = ultrarapid metabolizer

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predicted metabolizer phenotypes based on *CYP2D6* diplotypes

Predicted Metabolizer Phenotype (Range Multi-Ethnic Frequency[a])											
Allele	*1	*2	*1xN or *2xN	*3	*4 or *4xN	*5	*6	*9	*10	*17	*41
***1**	EM	EM	UM	EM	EM	EM	EM	EM	EM	EM	EM
***2**		EM	UM	EM	EM	EM	EM	EM	EM	EM	EM
***1xN or *2xN**			UM	EM or UM	EM or UM	EM or UM	EM or UM	UM	UM	UM	UM
***3**				PM	PM	PM	PM	IM	IM	IM	IM
***4**					PM	PM	PM	IM	IM	IM	IM
***5**						PM	PM	IM	IM	IM	IM
***6**							PM	IM	IM	IM	IM
***9**								EM	EM	EM	EM
***10**									EM	EM	EM
***17**										EM	EM
***41**											EM

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predicted metabolizer phenotypes based on *CYP2C19* diplotypes

Predicted Metabolizer Phenotype (Range Multi-Ethnic Frequency[a])									
Allele	***1**	***2**	***3**	***4**	***5**	***6**	***7**	***8**	***17**
***1**	EM	IM	IM	IM	IM	IM	IM	IM	UM
***2**		PM	PM	PM	PM	PM	PM	PM	IM
***3**			PM	PM	PM	PM	PM	PM	IM
***4**				PM	PM	PM	PM	PM	IM
***5**					PM	PM	PM	PM	IM
***6**						PM	PM	PM	IM
***7**							PM	PM	IM
***8**								PM	IM
***17**									UM

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frequencies of *CYP2C19* alleles in major race/ethnic groups

C	African	American	East Asian	European	Middle Eastern	Oceanian	South/Central Asian
*1[c]	0.68	0.69	0.60	0.63	0.87	0.24	0.62
*2	0.15	0.12	0.29	0.15	0.12	0.61	0.35
*3	0.0052	0.00028	0.089	0.0042	0.011	0.15	0.024
*4	0.00093	0.0024	0.00049	0.0025	ND	ND	0.00
*5	ND	0.00	0.00062	0.000073	ND	ND	0.00
*6	0.00	0.00	0.00	0.00017	ND	ND	0.00
*8	0.00	0.0012	0.00	0.0035	ND	ND	ND
*17	0.16	0.18	0.027	0.21	ND	ND	ND

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other pathways modulating antidepressant action

5-HT

- *SLC6A4*
- HTR1A
- HTR1B
- HTR2A
- HTR3A
- HTR3B
- HTR6

- TPH1
- TPH2

Norepinephrine

- *COMT*
- *MAO-A*
- *SLCA2*

dopamine

- *SL6A3*
- DRD4

glutamatergic

- GR1K4

HPA axis

- FKBP5
- NR3C1

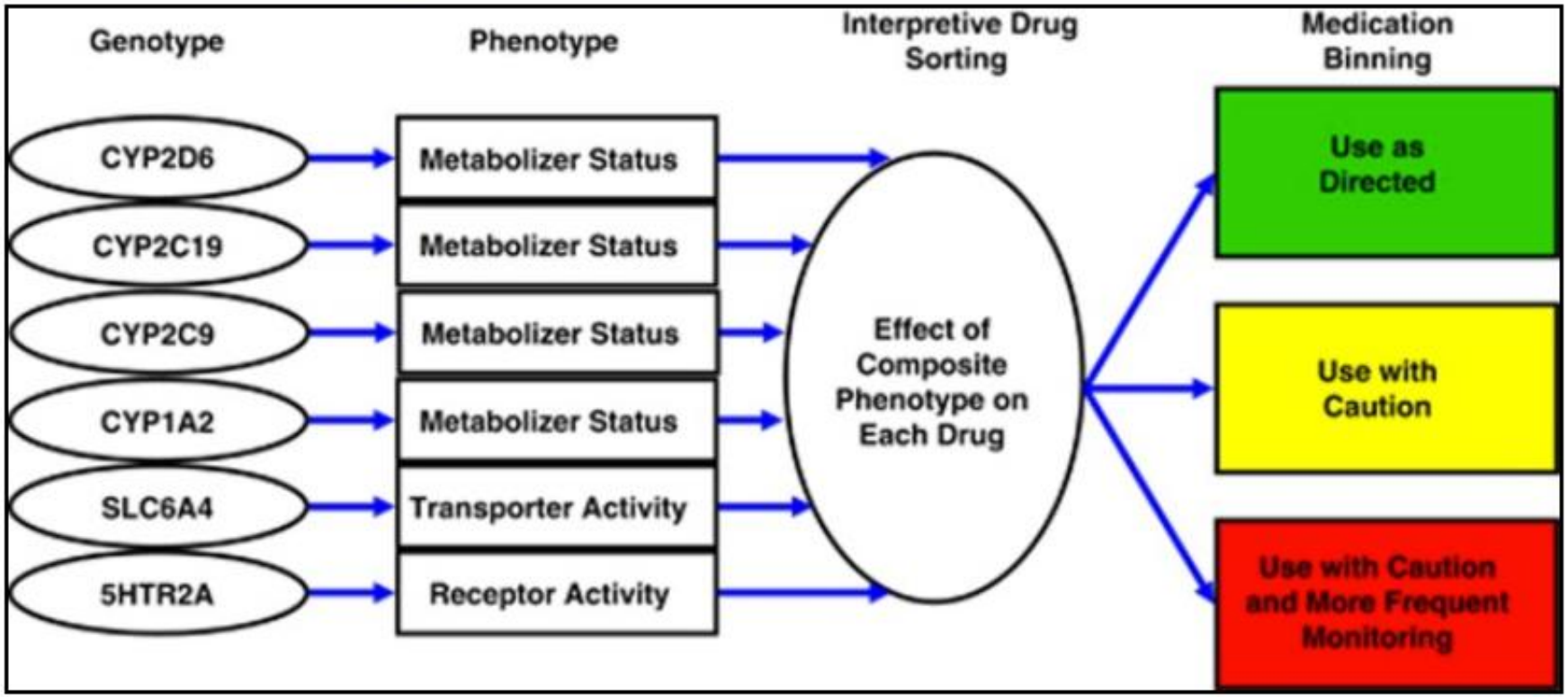
Signal transduction & growth factors

- BDNF
- GNB3
- OPRM1

enzymes

- ACE
- GSK3B
- IDO2

antidepressant treatment algorithms

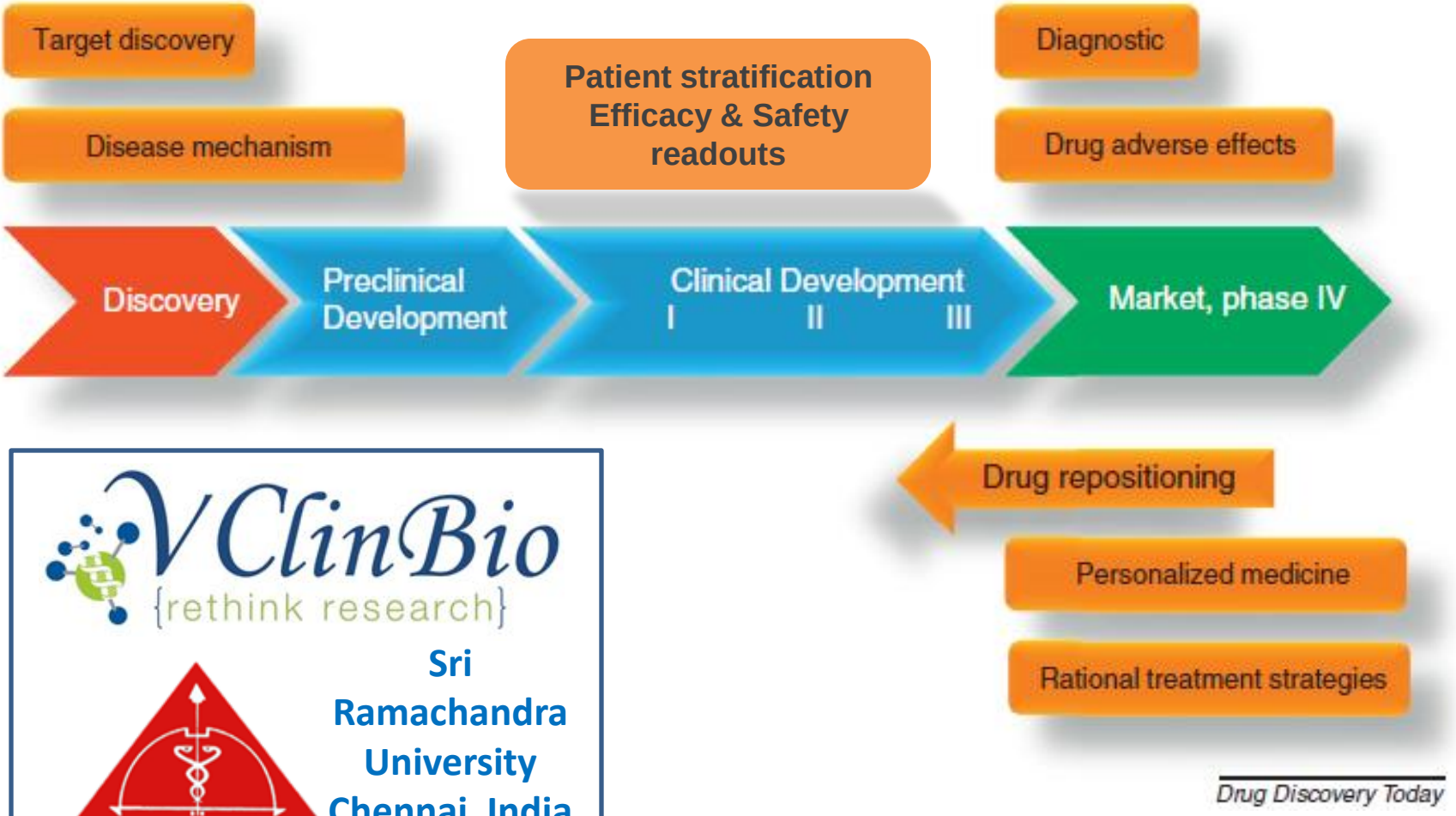


Assurex GeneSight

clinical implications

- Patient stratification procedures in clinical practice will be useful to achieve greater efficacy and safety
- Genotyping (stratification) prior to treatment may provide tailored therapies
- Regional differences in genotypes (stratification) should be investigated to facilitate dosing and regimen

Omic technologies can be applied in different phases of drug discovery and development



VClinBio
{rethink research}

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frequencies of *CYP2D6* alleles in major race/ethnic groups

Allele	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/ Central Asian	Americas	Oceanian
*1[c]	0.39	0.41	0.52	0.59	0.34	0.53	0.62	0.70
*2[d]	0.20	0.12	0.27	0.24	0.12	0.31	0.24	0.012
*3	0.0003	0.0034	0.013	0.0013	0.00	0.00	0.0052	0.00
*4	0.033	0.06	0.18	0.076	0.0045	0.065	0.11	0.011
*5	0.06	0.058	0.028	0.023	0.058	0.025	0.016	0.049
*6	0.00	0.0027	0.0091	0.0096	0.0002	0.00	0.005	0.00
*7	0.00	0.00	0.0012	0.00	0.00	ND	0.00	0.00
*8	0.00	0.00	0.0003	0.00	0.00	ND	0.0015	0.00
*9	0.0010	0.0054	0.02	0.00	0.0008	0.014	0.013	0.00
*10[e]	0.067	0.043	0.028	0.035	0.42	0.19	0.034	0.016
*14	0.0013	0.00	0.00	0.00	0.0092	0.00	0.0047	0.00
*17[f]	0.19	0.18	0.0027	0.014	0.0002	0.0038	0.023	0.0005
*36	0.00	0.0056	0.00	0.00	0.017	ND	ND	0.00
*41[g]	0.10	0.10	0.092	0.22	0.022	0.10	0.057	0.00
xN[h]	0.075	0.043	0.028	0.067	0.015	0.013	0.033	0.088
*1xN[i]	0.014	0.0044	0.0077	0.038	0.0031	0.0050	0.0078	0.11
*2xN[i]	0.015	0.016	0.013	0.036	0.0042	0.0050	0.023	0.00
*4xN[i]	0.014	0.020	0.0028	0.00	0.00	0.00	0.0036	0.00

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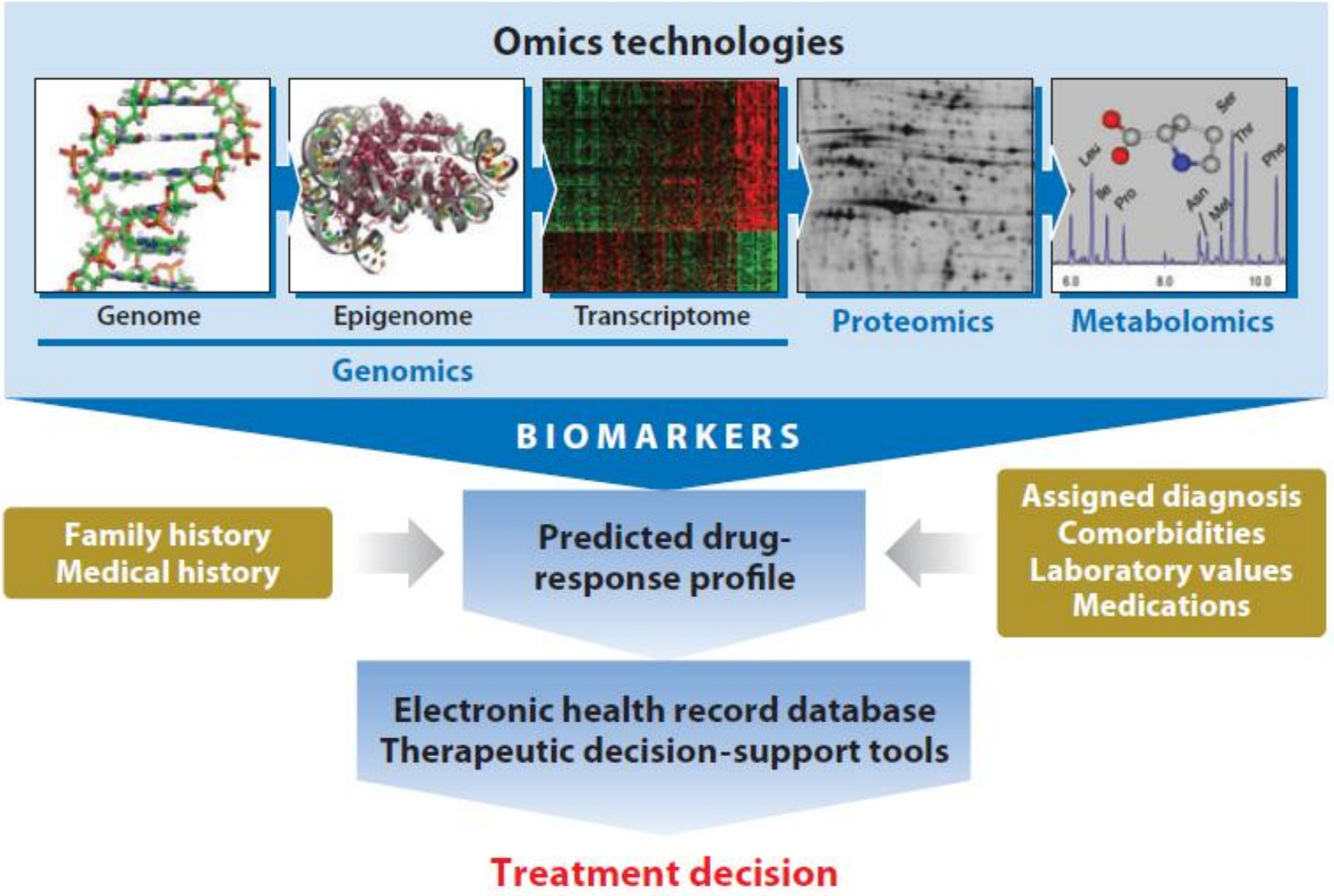
omics based prediction of drug response profiling



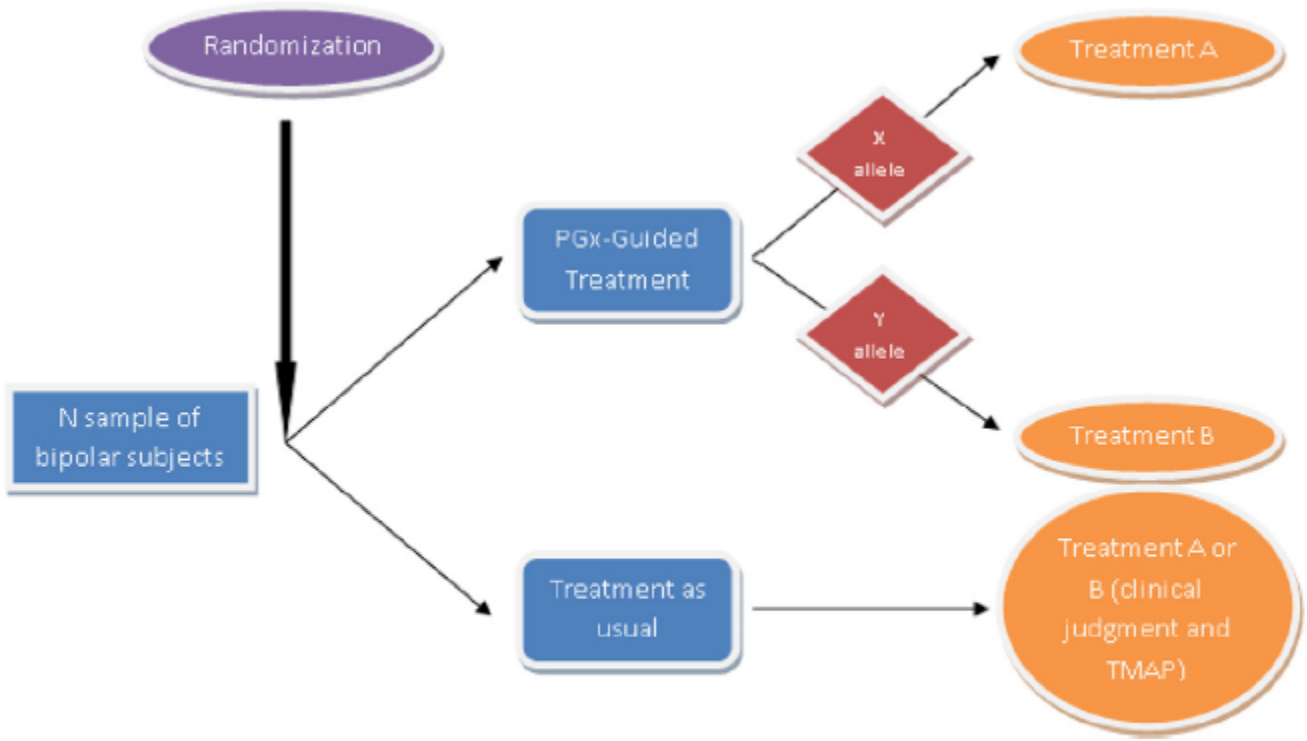
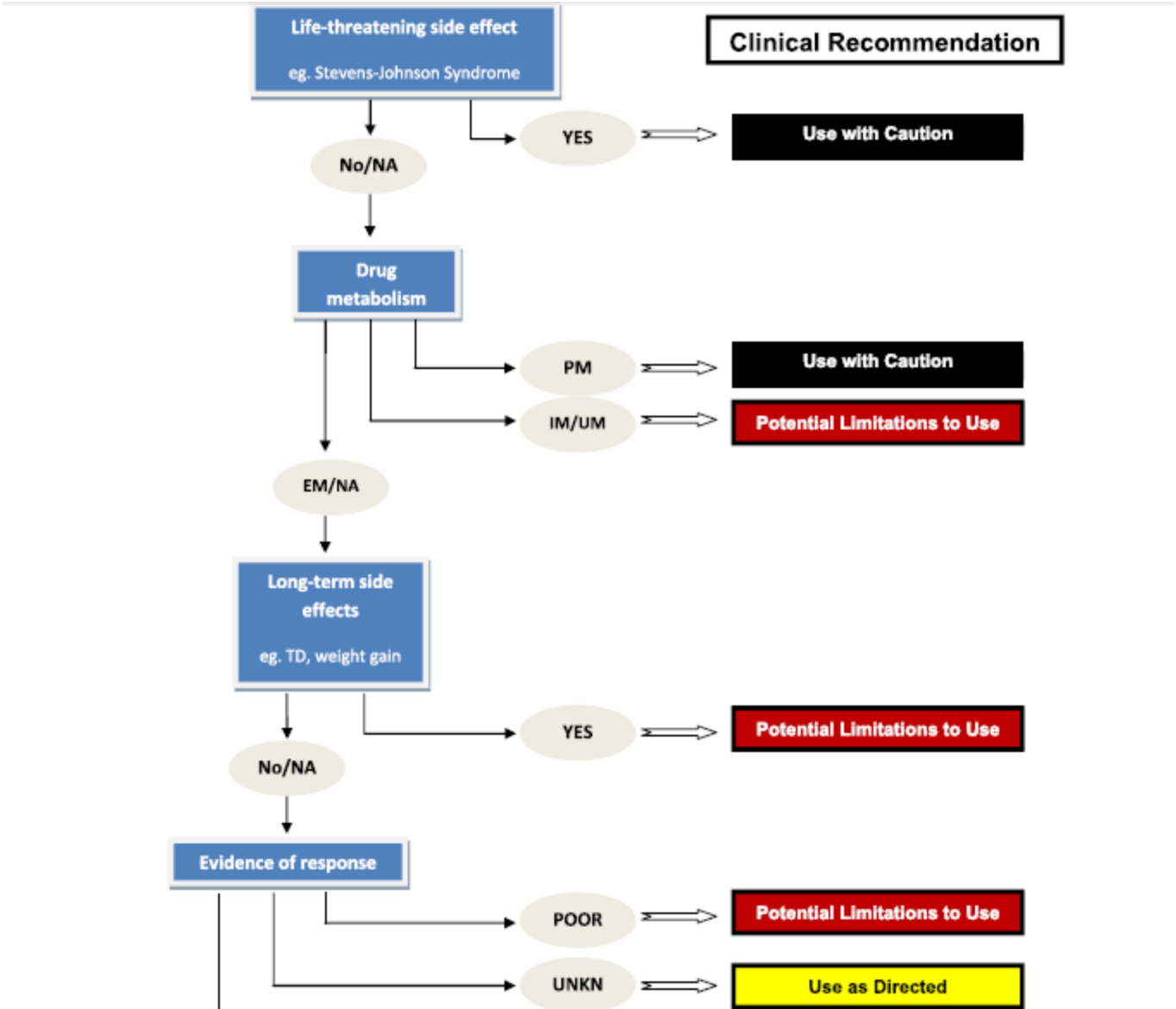


Figure 1 A pharmacogenetics implementation design. Patients are randomized to pharmacogenetic test (PGT) guided treatment or treatment as usual (TAU). For the PGT group, the physician incorporates the results of the test to make treatment decisions; in the TAU group, the physician treats according to usual practice based on evidence-based treatment guidelines. Subjects are assessed longitudinally and outcome compared after the specified treatment interval.


Clinical Recommendation
Life-threatening side effect
eg. Stevens-Johnson Syndrome
YES
Use with Caution
No/NA
Drug metabolism
PM
Use with Caution
IM/UM
Potential Limitations to Use
EM/NA
Long-term side effects
eg. TD, weight gain
YES
Potential Limitations to Use
No/NA
Evidence of response
POOR
Potential Limitations to Use
UNKN
Use as Directed

challenges in antidepressant therapy

Lack of response:~ 50% of patients with depression do not respond to their first treatment

Side effects: In the clinical studies, up to 30% of patients discontinues treatment due to intolerable side effects

Nonadherance: Up to 7% of patients receiving prescription for antidepressant drugs are non-adherent, with side effects most common reason

Patient frustrations

- trial-and-error “roller coaster”
- months/years of ‘trying’
- too many side effects
- multiple medications
- doctor visits etc
- one size fits all

TABLE 3
CYP2D6 Polymorphism and Characteristics

Phenotype	Characteristics	Clinical Consequence
PM	Major variants: CYP2D6*3, -*4, -*5, -*6	High plasma drug level
	Enzyme inactive	Risk of drug-related side effects
	5–10% White; 1–2% Chinese and Japanese	Use of reduced drug dose
IM	Major variants: CYP2D6*9, -*10, -*41	Lower dose for some patients
	Low residual enzyme activity	
EM	Not a uniform group	Standard dose for most patients
	Normal rate of metabolism	
UM	Multiple copies of CYP2D6	Very low plasma drug level
	Very high enzyme activity	Loss of drug efficacy
	1–2% Whites; 30% Ethiopians	Higher drug dose required

IM, intermediate metabolizer.

Arrow From	Arrow To	Controllers
BRL 35961 - metabolite III	glucuronide	
BRL 36583 - metabolite II	glucuronide	
BRL 36610 - metabolite I	BRL 35961 - metabolite III	
BRL 36610 - metabolite I	glucuronide and sulphate	
paroxetine catechol	BRL 35961 - metabolite III	
paroxetine catechol	BRL 36583 - metabolite II	COMT
paroxetine catechol	BRL 36610 - metabolite I	COMT
paroxetine catechol	other polar metabolites	
paroxetine	paroxetine catechol	CYP1A2, CYP2C19, CYP3A4, CYP3A5
paroxetine	paroxetine catechol	CYP2D6
paroxetine	paroxetine	ABCB1

pplemental Table S4. Association between allelic variants[a] and CYP2D6 enzyme activity

Functional Status	Alleles	References
Functional / normal activity / wild-type[a]	*1	57
Loss-of-function / no or decreased activity	*2, *3, *4, *5, *6, *7, *8	58-64
Gain-of-function / increased activity	*17	65-67

Tricyclic antidepressant metabolism by *CYP2D6* and *CYP2C19*

Table 2 Dosing recommendations for amitriptyline and nortriptyline based on CYP2D6 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation
CYP2D6 ultrarapid metabolizer	Increased metabolism of tricyclics to less active compounds as compared with extensive metabolizers	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6	Strong
	Lower plasma concentrations will increase probability of pharmacotherapy failure	If a tricyclic is warranted, consider increasing the starting dose.[b] Use therapeutic drug monitoring to guide dose adjustments	
CYP2D6 extensive metabolizer	Normal metabolism of tricyclics	Initiate therapy with recommended starting dose[b]	Strong
CYP2D6 intermediate metabolizer	Reduced metabolism of tricyclics to less active compounds as compared with extensive metabolizers	Consider 25% reduction of recommended starting dose.[b] Use therapeutic drug monitoring to guide dose adjustments	Moderate
	Higher plasma concentrations will increase the probability of side effects		
CYP2D6 poor metabolizer	Greatly reduced metabolism of tricyclics to less active compounds as compared with extensive metabolizers	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6	Strong
	Higher plasma concentrations will increase the probability of side effects	If a tricyclic is warranted, consider a 50% reduction of recommended starting dose.[b] Use therapeutic drug monitoring to guide dose adjustments	

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Tricyclic antidepressant metabolism by *CYP2D6* and *CYP2C19*

Table 3 Dosing recommendations of amitriptyline based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 ultrarapid metabolizer	Increased metabolism of amitriptyline as compared with extensive metabolizers	Consider alternative drug not metabolized by CYP2C19 If a tricyclic is warranted, use therapeutic drug monitoring to guide dose adjustments	Optional
CYP2C19 extensive metabolizer	Normal metabolism of amitriptyline	Initiate therapy with recommended starting dose[b]	Strong
CYP2C19 intermediate metabolizer	Reduced metabolism of amitriptyline as compared with extensive metabolizers	Initiate therapy with recommended starting dose[b]	Strong
CYP2C19 poor metabolizer	Greatly reduced metabolism of amitriptyline as compared with extensive metabolizers Higher plasma concentrations of amitriptyline will increase the probability of side effects	Consider a 50% reduction of recommended starting dose.[b] Use therapeutic drug monitoring to guide dose adjustments	Moderate

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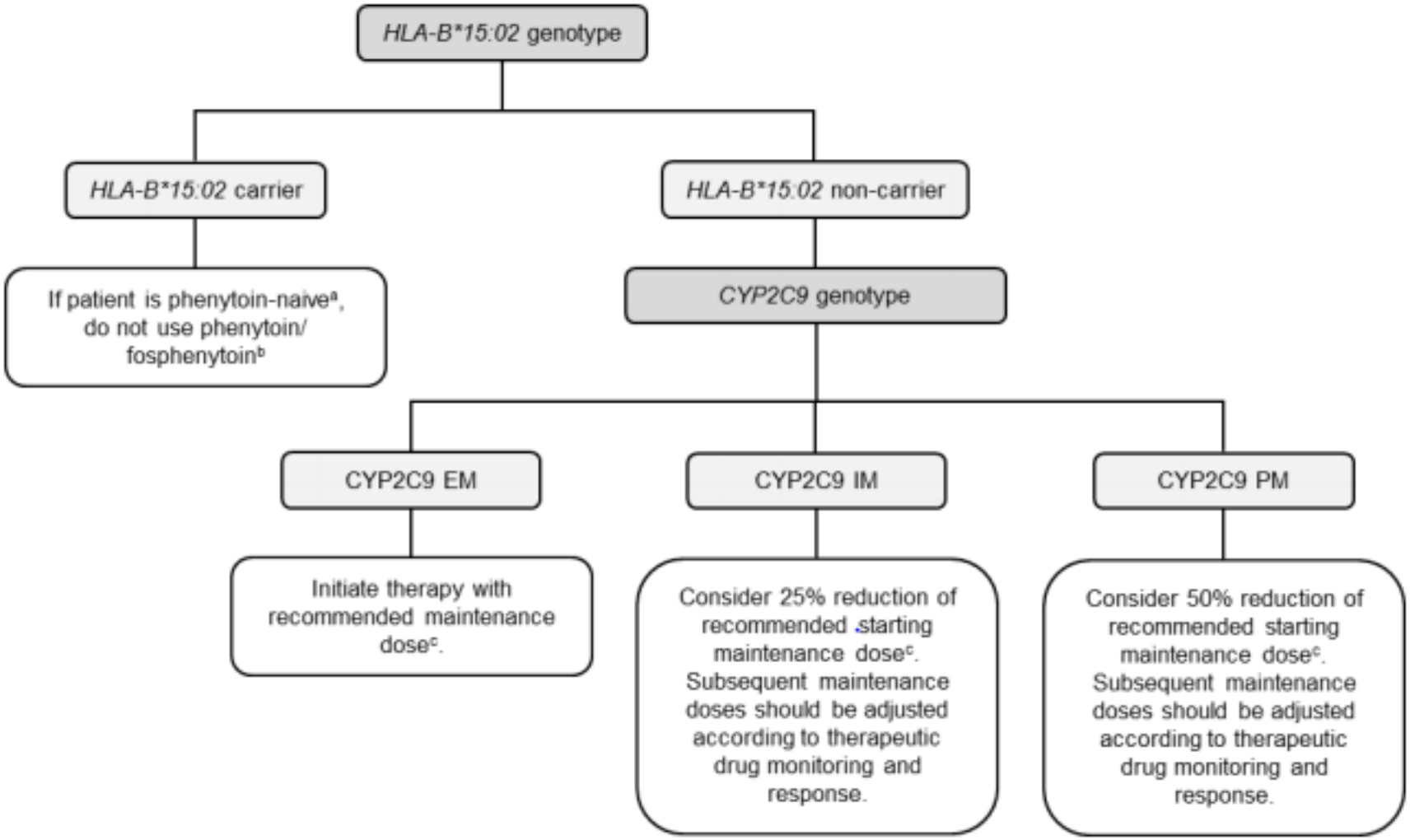
GWAS studies

Table 2 Top genome-wide association markers found within the STAR*D study, the GENDEP project, and the MARS project

Study	Diagnosis	Sample size and ethnicity	AD	Top markers (Chr, gene)	Outcome: phenotypic value	Pathway analysis
Garriock et al[76] (STAR*D study)	MDD	*N* = 1491 for RE and *N* = 1351 for RM Non-Hispanic Caucasian: *n* = 1067 (71.5%) African Americans: *n* = 241 (16.2%) Hispanic Caucasians: *n* = 183 (12.3%)	Citalopram	rs6966038 (7, *UBE3C*) rs6127921 (20, *BMP7*) rs809736 (15, *RORA*)	RE, compared with NRE: 4.65E-07 RM, compared with NRM: 3.63E-07 RE, compared with NRE: 3.45E-06 RM, compared with NRM: 1.07E-06 RE, compared with NRE: 8.19E-06 RM, compared with NRM: 7.64E-05	—
Uher et al[77] (GENDEP project)	MDD	*N* = 706 Caucasian (European)	Escitalopram (*N* = 394) or nortriptyline (*N* = 312)	rs1126757 (6, *IL11*) rs2500535 (6, *UST*)	% change in MADRS during escitalopram treatment: 2.83E-06 % change in MADRS during nortriptyline treatment: 3.56E-08	—
Ising et al[78] (MARS project)	MDD, BP	MARS sample[a]: *n* = 339 Caucasian (European) German replication sample: *n* = 361 STAR*D: *n* = 832 white subjects	Mixed	rs6989467 (8, *CDH17*)[a] rs1502174 (3, *EPHB1*)[a]	Early partial RE: 7.60E-07 Early partial RE: RE, RM: 8.50E-05	3 clusters: 1. *FN1* 2. *ADAMTSL1* 3. *EDN1*

pharmacogenomics: phenytoin



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