药物基因组学在精准医疗中的研究与应用

蒋正欣，PhD
先声诊断 高级医学经理

9.21.2019

精准医疗成败在于：精准用药

为何要做药物基因组学检测？

如何使患者精准用药获益最大化？

为何选择先声诊断和MassARRAY®平台？

精准医疗成败在于：精准用药

最新研究进展：临床证据与指南

重要临床获益性研究列举

先声诊断和MassARRAY®平台优势

为何要做药物基因组学检测？

为何药物反应存在显著个体化差异?

➢ **药代动力学（PK）：**

- 药物在体内吸收、分布、代谢和清除的动态规律

➢ **药效动力学（PD）：**

- 药物对机体的作用及其机制，包括疗效和不良反应

➢ **药物基因组学（PGx）检测的目的:**

- 明确引起个体药物反应差异的基因多态性
- 指导临床合理用药
- 疗效最大化+不良反应最小化
- 减少药物治疗费用

Drug	
Pharmacokinetic mechanisms	
CYP2B6	Efavirenz
CYP2C19	Clopidogrel, SSRIs, TCAs, voriconazole, proton pump inhibitors*
CYP2C9	Celecoxib*, phenytoin, warfarin
CYP2D6	Codeine, oxycodone, tramadol, SSRIs, TCAs, ondansetron, tamoxifen, atomoxetine
CYP3A5	Tacrolimus
DPYD	5-fluorouracil, capecitabine, tegafur
TPMT and *NUDT15*	Azathioprine, mercaptopurine, thioguanine
SLCO1B1	Simvastatin
UGT1A1	Atazanavir
Pharmacodynamic mechanisms	
CFTR	Ivacaftor
CYP4F2	Warfarin
G6PD	Rasburicase
HLA-B	Abacavir, allopurinol, carbamazepine, phenytoin
IFNL3 (IL28B)	Interferon
RYR1 and *CACNA1S*	Inhaled anesthetics, succinylcholine
VKORC1	Warfarin

SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant.
*Guidelines in progress.

Table 1: **Drugs and genes with guidelines from the Clinical Pharmacogenetics Implementation Consortium for use in clinical practice**

99种药物 + 132个PGx用药剂量指南 + 309种药物的标签有PGx信息

PharmGKB

CPIC® Clinical Pharmacogenetics Implementation Consortium

KNMP Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group

Canadian Pharmacogenomics Network for Drug Safety

FDA U.S. FOOD & DRUG ADMINISTRATION

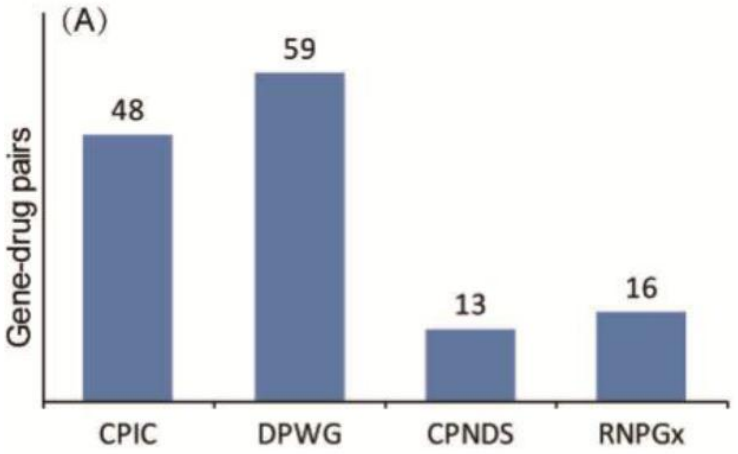
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Health Canada Santé Canada

Pmda Pharmaceuticals and Medical Devices Agency

根据GRADE和AGREE II指南制定标准，推荐临床优先采用CPIC和CPNDS指南

Guideline	Scope and purpose (%)	Stakeholder involvement (%)	Rigor of development (%)	Clarity of presentation (%)	Applicability (%)	independence (%)	Overall score	Recommendation for use
CPIC	79.6	44.4	77.8	79.6	47.2	86.1	6/7	Recommended
RNPGX	66.7	29.6	43.1	72.2	33.3	38.9	3/7	Recommended with modifications
CPNDS	85.2	53.7	68.8	77.8	43.1	77.8	6/7	Recommended
DPWG	75.9	40.7	54.2	83.3	43.1	58.3	4/7	Recommended with modifications
Median (range)	77.8 (66.7–85.2)	42.6 (29.6–53.7)	61.5 (43.1–77.8)	78.7 (72.2–83.3)	43.1 (33.3–47.2)	68.1 (38.9–86.1)		



Guo C, et al., Clin Exp Pharmacol Physiol. 2019

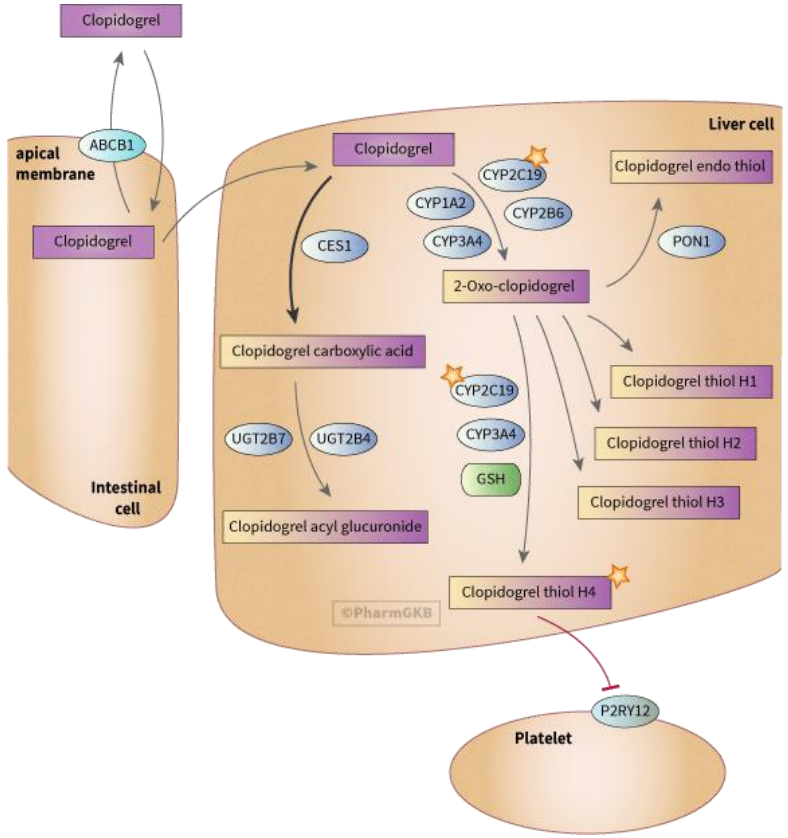
24种最重要的药物基因检测有指南或药物标签支持改变临床用药方案

VIP	Clinical Genetic Testing [1,2]	Drug (Guideline/Drug Label Organizations [3])	Clinical Impact
BRCA1	Genetic testing for *BRCA1* mutations	Olaparib, rucaparib (FDA drug label)	Targeted treatment specific to genetic status
BRCA2	Genetic testing for *BRCA2* mutations	Olaparib, rucaparib (FDA drug label)	Targeted treatment specific to genetic status
CACNA1S	Genetic testing for *CACNA1S* mutations	Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine (CPIC [2])	Alternate choice of medication to prevent serious ADR (risk of death)
CFTR	Genetic testing for presence of *CFTR* G551D, F508del variants (+32 other variants now approved—found on ivacaftor drug label)	Ivacaftor (CPIC [7]), lumacaftor (when in formulation with ivacaftor) (FDA drug label)	Targeted treatment specific to genetic status
CYP2C19	Genetic testing for presence of increased and decreased function alleles	Clopidogrel (DPWG [3,4], CPIC [10]) Amitriptyline, clomipramine, doxepin, imipramine, trimipramine (CPIC [32]—all tricyclic antidepressants listed, DPWG [3,4])—only imipramine) Citalopram, escitalopram, sertraline (CPIC [31], DPWG [3,4]) Voriconazole (CPIC [6], DPWG [3,4])	Dosing adjustment/alternate choice of medication (risk of poor efficacy/ADRs)
		Lansoprazole, omeprazole, pantoprazole (DPWG [3,4])	Increase attention/monitoring dose
CYP2C9	Genetic testing for presence of decreased function alleles	Phenytoin (CPIC [20], DPWG [3,4])	Dosing adjustment to prevent serious ADR
	Genetic testing for presence of decreased function alleles	Warfarin (CPIC [9], CPNDS [11], DPWG [3])	Dosing adjustment for optimal efficacy (avoiding excessive bleeding/clotting)
CYP2D6	Genetic testing for presence of increased and decreased function alleles (recommendation may be based on genotype activity score)	Amitriptyline, also likely applicable to other TCAs: Clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine (CPIC [32]—as listed, DPWG [3,4]—only amitriptyline, clomipramine, doxepin, imipramine, nortriptyline) Aripiprazole, haloperidol, pimozide, zuclopenthixol (DPWG [3,4]), fluvoxamine (CPIC), paroxetine (CPIC [31]—both SSRIs listed, DPWG [3,4]—only paroxetine) Venlafaxine (DPWG [3,4]) Codeine (CPIC [23], DPWG [3,4], CPNDS [24]), tramadol (DPWG [3,4]) Flecainide, propafenone (DPWG [3,4]) Metoprolol (DPWG [3,4]) Tamoxifen (CPIC [26], DPWG [3,4], CPNDS [29]) Eliglustat (DPWG [3]) Tetrabenazine (FDA drug label)	Dosing adjustment/alternate choice of medication (risk of poor efficacy/ADRs)
		Ondansetron, tropisetron (CPIC [8])	Alternate choice of medication to reduce risk of poor efficacy for UMs
UGT1A1	Genetic testing for presence of two decreased function alleles	Atazanavir (CPIC [13])	Dosing adjustment to prevent serious ADR (jaundice)
	Genetic testing for presence of *UGT1A1*1,*28, *36, *37* variants	Irinotecan (DPWG [3,4], French Group of Clinical Oncopharmacology (GPCO-Unicancer) & National Pharmacogenetics Network (RNPGx) [30])	Dosing adjustment to prevent serious ADR (hematological/gastrointestinal toxicity)
UGT1A6	Genetic testing for presence of *UGT1A6*4* (rs17863783) variant	Daunorubicin, doxorubicin (CPNDS [28])	Pediatric patients: Dosing adjustment to prevent serious ADR (cardiotoxicity)
VKORC1	Genetic testing for homozygous *VKORC1* rs9934438 status	Acenocoumarol, phenprocoumon (DPWG [3,4])	Increase attention/monitoring dose
	Genetic testing for presence of *VKORC1* rs9923231 variant	Warfarin (CPIC [9], CPNDS [11], DPWG [3])	Dosing adjustment for optimal efficacy (avoiding excessive bleeding/clotting)
		Atomoxetine (CPIC [33], DPWG [3,4])	Increase attention/monitoring dose
CYP3A5	Genetic testing for presence of "normal" function and decreased function alleles	Tacrolimus (CPIC [16], DPWG [3,4])	Dosing adjustment to reduce risk of poor efficacy
CYP4F2	Genetic testing for presence of *CYP4F2*3* allele	Warfarin (CPIC [9])	Dosing adjustment for optimal efficacy (avoiding excessive bleeding/clotting)
DPYD	Genetic testing for presence of decreased function alleles (recommendation based on genotype activity score)	Capecitabine, fluorouracil, tegafur (CPIC [25]—only capecitabine and fluorouracil, DPWG [3,4]—all three anti-neoplastics listed)	Dosing adjustment/alternate choice of medication (risk of ADR—death)
DMD	Genetic testing for presence of *DMD* mutation that is amenable to exon 51 skipping	Eteplirsen (FDA drug label)	Targeted treatment specific to genetic status
F5	Genetic testing for *F5* alleles	Estrogen-containing hormonal contraceptives (DPWG [3,4])	Alternate choice of contraceptive method to prevent serious ADR (venous thrombo-embolism)
G6PD	Genetic testing for presence of decreased function (class I, II, or III) alleles [x-linked—males 1 allele, females—2 alleles; if ambiguous result or female heterozygote—enzymatic testing to confirm activity levels]	Rasburicase (CPIC [18]) Pegloticase (FDA drug label, European Medicines Agency drug label) Primaquine (FDA drug label)	Alternate choice of medication to prevent serious ADR (acute hemolytic anemia)
HLA-A	Genetic testing for presence of *HLA-A*31:01* variant	Carbamazepine (CPIC [21], CPNDS [22])	Dosing adjustment to prevent serious ADR (SCAR)
HLA-B	Genetic testing for presence of *HLA-B*15:02* variant	Carbamazepine (CPIC [21], CPNDS [22]), phenytoin (CPIC [20]), oxcarbazepine (CPIC [21])	Dosing adjustment to prevent serious ADR (SCAR)
	Genetic testing for presence of *HLA-B*57:01* variant	Abacavir (CPIC [12], DPWG [3,4])	Dosing adjustment/alternate choice of medication (risk of poor efficacy/ADR—SCAR)
	Genetic testing for presence of *HLA-B*58:01* variant	Allopurinol (CPIC [17], American College of Rheumatology [19])	Dosing adjustment to prevent serious ADR (SCAR)
IFNL3	Genetic testing for presence of *IFNL3* (IL28B) variant (rs12979860)	Peginterferon alfa-2a, peginterferon alfa-2b, ribavirin (CPIC [14])	Anticipated efficacy—consider in context of SDM and likely side effects
POLG	Mitochondrial genetic testing for *POLG* mutations	Divalproex sodium (FDA drug label, Health Canada/Santé Canada drug label)	Alternate choice of medication to prevent serious ADR (acute liver failure and death)
RARG	Genetic testing for presence of *RARG* rs2229774 variant	Daunorubicin, doxorubicin (CPNDS [28])	Pediatric patients: Dosing adjustment to prevent serious ADR (cardiotoxicity)
RYR1	Genetic testing for *RYR1* mutations	Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine (CPIC [2])	Alternate choice of medication to prevent serious ADR (risk of death)
SLCO1B1	Genetic testing for presence of C allele at *SLCO1B1* rs4149056	Simvastatin (CPIC [5], DPWG [3])	Dosing adjustment/alternate choice of medication to prevent serious ADR (myopathy)
TPMT	Genetic testing for presence of decreased function alleles	Azathioprine, mercaptopurine, thioguanine (CPIC [15], DPWG [3,4])	Dosing adjustment/alternate choice of medication (risk of poor efficacy/ADRs)
	Genetic testing for presence of *TPMT *2, *3A, *3B, *3C* alleles	Cisplatin (CPNDS [27])	Pediatric patients: Dosing adjustment to prevent serious ADR (ototoxicity)

Hippman C, Nislow C, J. Pers. Med. 2019

PGx最新研究进展 | 心血管疾病

药物	基因	PGx指南
氯吡格雷	*CYP2C19*	CPIC, DPWG
华法林	*CYP2C9, VKORC1, CYP4F2*	CPIC, DPWG, CPNDS
辛伐他汀	*SLCO1B1*	CPIC, DPWG



*CYP2C19*与高危人群（PCI-stent）的主要心脏副作用相关，与低危人群无显著相关性

Ref	Year	Ethnic	Population studied	n	PCI-stent (%)	Follow up	Endpoint	Polymorphisms	Outcomes (LOF vs no LOF)
High-risk patients (PCI-stent)									
Collet (29)	2009	Europeans	ACS	259	86	>4 years	MACE (CV death, ACS, urgent PCI)	CYP2C19*2	HR 5.38 (2.32-12.47) p ≤ 0.0001
							ST definite	CYP2C19*2	HR 6.04 (1.75-20.80) p = 0.004
Mega (22)	2009	84% Europeans	ACS stent (TRITON)	1477	100	15 months	MACE (CV death, ACS, stroke)	CYP2C19*2	HR 1.53 (1.07-2.19) p = 0.01
							ST definite	CYP2C19*2	HR 3.09 (1.19-8.0) p = 0.02
Mega (17)	2010	84% Europeans	ACS stent (TRITON)	2905	100	15 months	MACE (CV death, ACS, stroke)	CYP2C19*2 and ABCB1	ABCB1 TT vs CT/CC: HR 1.72 (1.22-2.44) p = 0.002 CYP2C19*2 + ABCB1 HR 1.97 (1.38-2.82) p = 0.0002
Simon (30)	2009	Europeans	ACS	2208	68.7	12 months	MACE (death any cause, ACS, stroke)	CYP2C19 and ABCB1	CYP2C19: HR 1.98 (1.10-3.58) ABCB1: HR 1.72 (1.20-2.47)
Sorich (33)	2010	84% Europeans	ACS stent (TRITON)	13608	100	15 months	MACE (CV death, ACS, stroke)	CYP2C19 LOF	OR 1.63 (1.45-1.81) p < 0.0001
Shuldiner (31)	2009	Europeans	PCI	227	100	12 months	MACE (CV death, ACS, stroke, PCI)	CYP2C19*2	HR 2.42 (1.18-4.99) p = 0.02
Wallentin (35)	2010	Europeans	ACS	10285	60	12 months	MACE (CV death, ACS, stroke)	CYP2C19	HR at 30 days: p = 0.028
								CYP2C19 and ABCB1	HR 1.2 (1.0-1.4) p = 0.047**
Low-risk patients									
Pare (53)	2010	Europeans-latin american	ACS stable	5059	14.5	12 months	MACE (CV death, ACS, stroke)	CYP2C19*2	p = 0.32

Data are showed as: OR: odds ratio, HR: hazard ratio, (95%CI), p-value

Davila-Fajardo CL, et al., Genes. 2019

*CYP2C19*与高危人群的主要心脏副作用相关，CPIC和DPWG指南建议高危人群检测

Ref	Year	Ethnic	Population studied	n	PCI-stent (%)	Follow up	Endpoint	Polymorphisms	Outcomes (intervention group vs control group)
Non RCT									
Sánchez-Ramos (37)	2016	Europeans	ACS-PCI-stent	719	100	1 year	MACE (CV death, ACS, stroke)	CYP2C19*2, *3 and ABCB1	HR 0.63 (0.41-0.97) p=0.037 HR 0.61 (0.39-0.94) p=0.02**
							ST definite	CYP2C19 *2, *3 and ABCB1	HR 1.27 (0.08-20.2) p=0.87
							Urgent revascularization*	CYP2C19 *2, *3 and ABCB1	HR 0.63 (0.31-1.28) p=0.20
RCT									
Shen (39)	2016	Asians	CAD-PCI	628	100	1 month 6 months 12 months	MACE (composite of death from any cause, myocardial infarction, or target vessel revascularization)	CYP2C19*2	1.3% vs. 5.6%, P = 0.003 3.2% vs. 7.8%, P = 0.012 4.2% vs. 9.4%, P = 0.010
Roberts (Rapid Gene) (40)	2012	Europeans	ACS or stable angina/ stent	187	100	7 days	high on-treatment platelet reactivity	CYP2C19*2	0% vs 30% p=0.0092
Roberts (RAPID STEMI study) (41)	2016	Europeans	STEMI- stent	102	100	1 month	high on-treatment platelet reactivity	CYP2C19*2, *17 and ABCB1 TT	OR=0.15 p=0.03
Xie (42)	2013	Asians	CAD-PCI	600	100	180 days	MACE (death from any cause, MI, stroke, ischemia)	CYP2C19*2,*3	1.0% and 6.2%, P<0.01
Notarangelo Pharmclo (43)	2018	Europeans	ACS	888	No data	12 months	MACE (CV death, nonfatal IM, nonfatal stroke)	CYP2C19*2, *17 and ABCB1	HR 0.58 (0.43-0.78) p<0.001
Bergmeijer (Popular genetics) (44)	ongoing	Europeans	STEMI-stent	2500	100	15 months	MACE (CV death, ACS, stroke)	CYP2C19*2, *3	
Tailor-PCI (NCT01742117)	ongoing	Europeans	ACS or CAD/ stent	5000	100	12 months	MACE (non-fatal MI, non-fatal stroke, severe recurrent ischemia, CV death, and ST)	CYP2C19*2,*17	

Data are showed as: OR: odds ratio, HR: hazard ratio, (95%CI), p-value

Davila-Fajardo CL, et al., Genes. 2019

CPIC和DPWG指南建议检测*CYP2C19*指导氯吡格雷用药方案

PGx指南	基因代谢型	风险描述	适用人群	治疗建议
CPIC	CYP2C19 EM	血小板抑制和聚集正常	ACS-PCI	按照药物标签常规使用
	CYP2C19 IM	血小板抑制减弱、血小板聚集和心血管不良反应风险升高	ACS-PCI	选择替代药物（例如：普拉格雷、替格瑞洛）
	CYP2C19 PM	血小板抑制极大减弱、血小板聚集和心血管不良反应风险升高	ACS-PCI	选择替代药物（例如：普拉格雷、替格瑞洛）
	CYP2C19 UM	血小板抑制增强、血小板聚集减弱	ACS-PCI	按照药物标签常规使用
DPWG	CYP2C19 IM	活性代谢物减少，严重心脑血管不良反应风险升高	PCI, Stroke, TIA	选择替代药物（例如：普拉格雷、替格瑞洛）或增加剂量至150 mg/d（初始剂量600 mg）
	CYP2C19 PM	活性代谢物减少，严重心脑血管不良反应风险升高	PCI, Stroke, TIA	选择替代药物（例如：普拉格雷、替格瑞洛）
	CYP2C19 UM	活性代谢物增加，严重心脑血管不良反应风险可能降低，出血风险可能升高	普适	按照药物标签常规使用

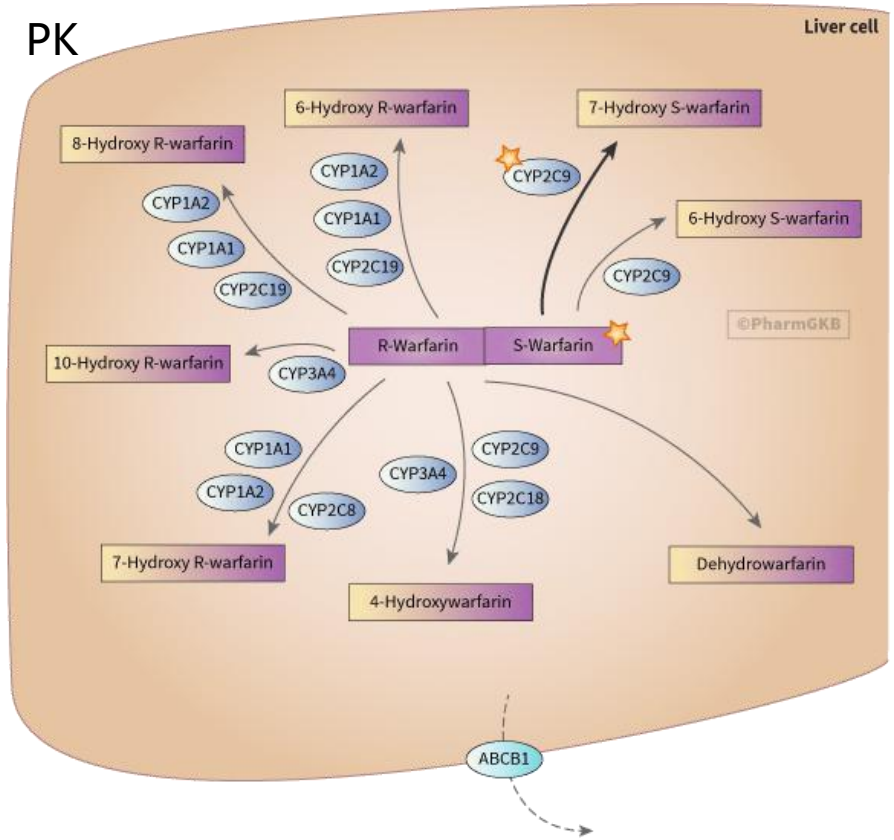
CPIC 2013 update: Scott SA, et al., Clin Pharmacol Ther. 2013

DPWG 2018 update

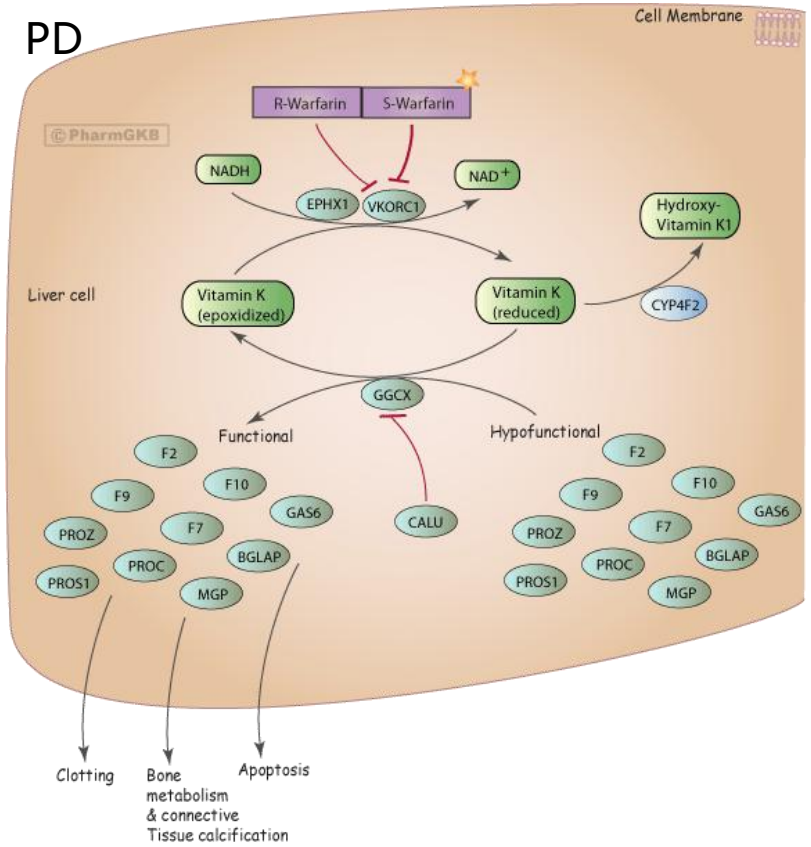
PGx最新研究进展 | 心血管疾病

药物	基因	PGx指南
氯吡格雷	*CYP2C19*	CPIC, DPWG
➡ 华法林	*CYP2C9, VKORC1, CYP4F2*	CPIC, DPWG, CPNDS
辛伐他汀	*SLCO1B1*	CPIC, DPWG

PK



PD



PGx最新研究进展 | 华法林随机临床实验

CYP2C19, *VKORC1*, *CYP4F2*基因检测指导华法林剂量调整:

- 可改善治疗范围时间比例 (%TTR)
- 降低出血和静脉血栓风险

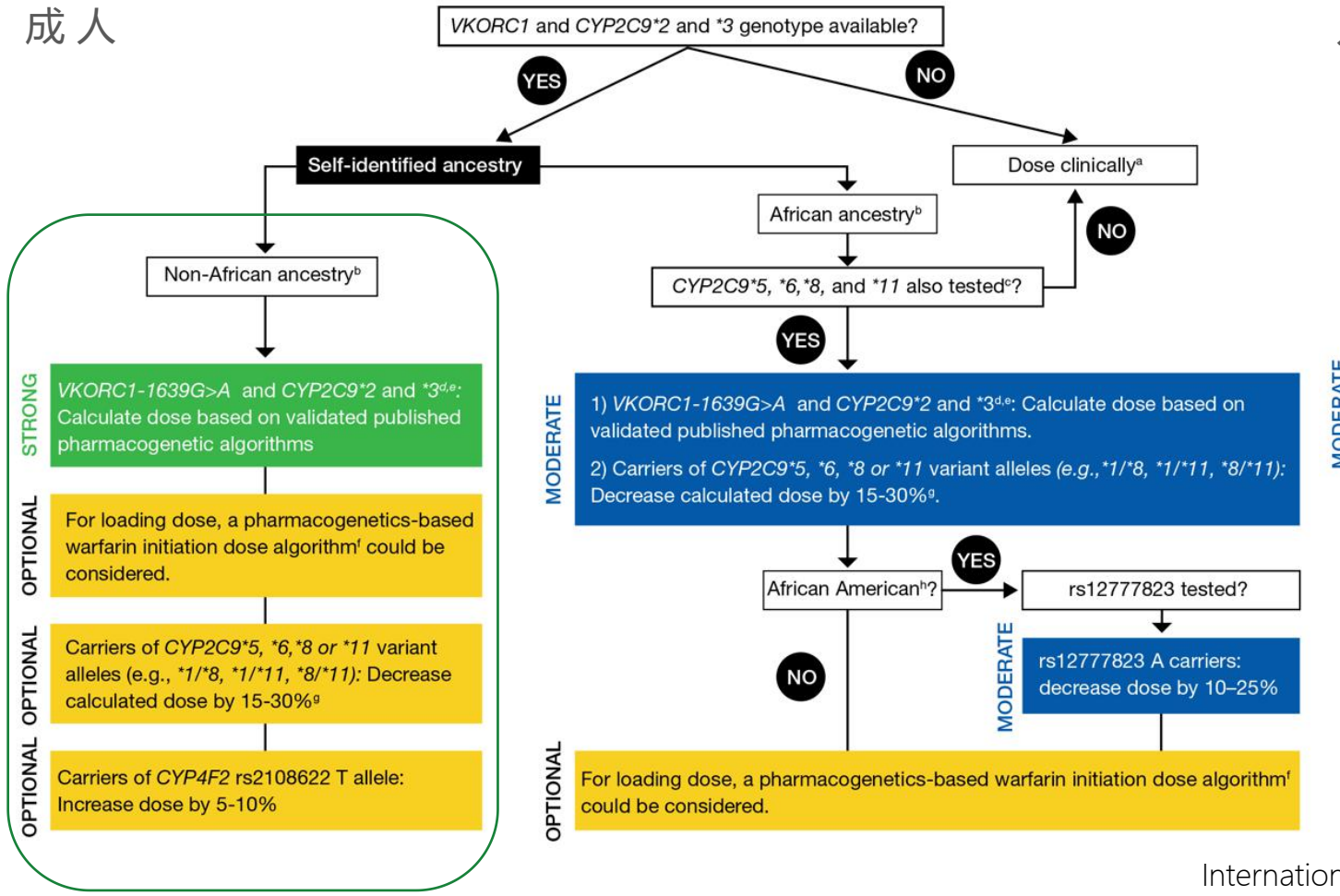
Ref	Year	Ethnic	Population studied	n	Follow up	Endpoint	Polymorphisms	Homozygotes action required	Outcomes (intervention group vs control group)	Availability test	Dose in non-genotype group
Pirmohamed (EU-PACT) (3)	2015	2% non-European	**AF (72.1%) VT (27.9%)**	455	12 weeks	%TTR	CYP2C9*2,*3 VKORC1	VKORC1: 17% CYP2C9*2 and *3: 3.4%	67.4% vs 60.3%, p < 0.001	2h	Fixed-dose strategy
Kimel (COAG) (79)	2015	33% non-European	AF (23%) DVT or PE (56%)	1015	4 weeks	%TTR	CYP2C9*2, *3 VKORC1	VKORC1: 11% CYP2C9*2 and *3: 1%	45.2% vs 45% p = 0.91	Not before the 1st dose for 55% of patients	Clinical dosing algorithm
Gage (GIFT) (82)	2017	91% European	Hip or knee arthroplasty	1650	30 and 60 days	Composite (major bleeding, INR≥4, VT, death)	CYP2C9*2,*3 CYP4F2	NA	RR 0.73 (0.56-0.95) p = 0.02	NA	NA

AF: atrial fibrillation, DVT: Deep-vein thrombosis, PE: pulmonary embolism. %TTR: percentage time in therapeutic range. NA: Not applicable

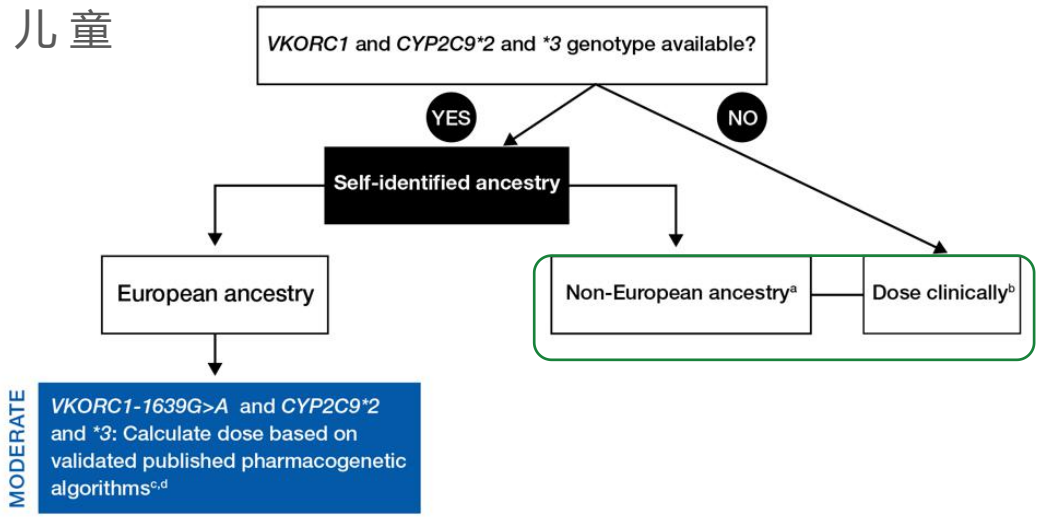
Davila-Fajardo CL, et al., Genes. 2019

CPIC, DPWG, CPNDS 指南建议基因检测指导华法林剂量调整

成人



儿童



Warfarindosing.org

Gage, IWPC 算法

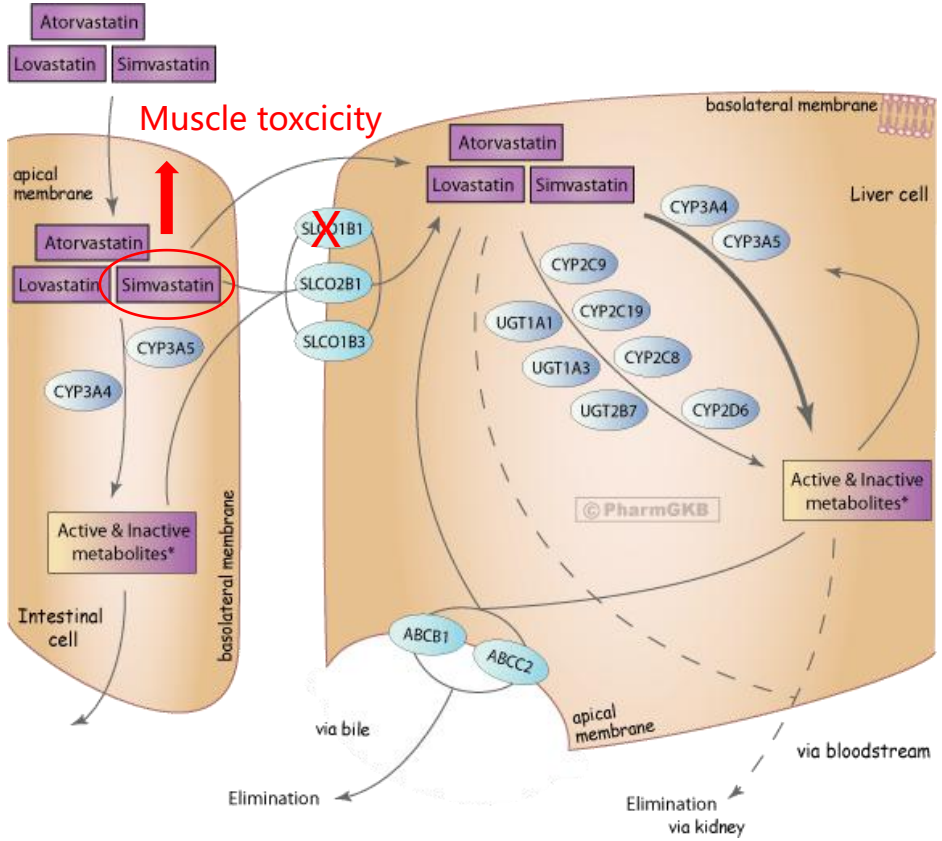
Johnson JA, et al., Clin Pharmacol Ther. 2017

Gage BF, et al., Clin Pharmacol Ther. 2008

International Warfarin Pharmacogenetics Consortium, N Engl J Med. 2009

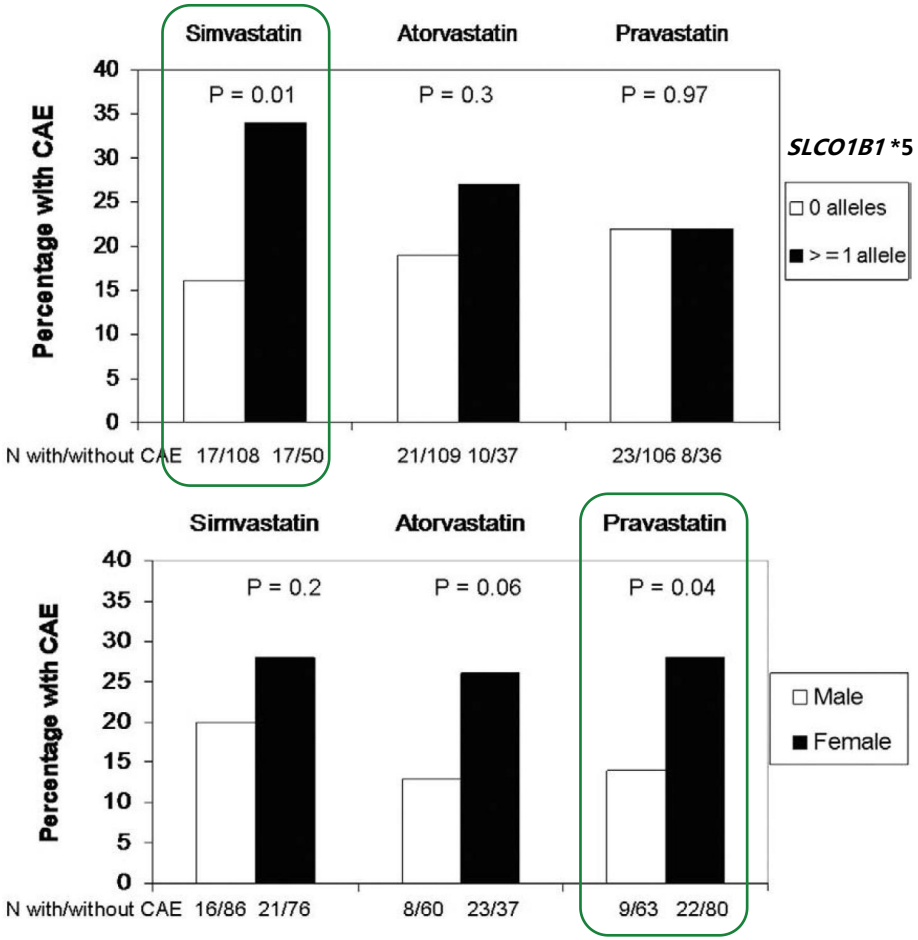
PGx最新研究进展 | 心血管疾病

药物	基因	PGx指南
氯吡格雷	*CYP2C19*	CPIC, DPWG
华法林	*CYP2C9, VKORC1, CYP4F2*	CPIC, DPWG, CPNDS
➡ 辛伐他汀	*SLCO1B1*	CPIC, DPWG



*SLCO1B1**5 与肌肉病变不良反应风险相关

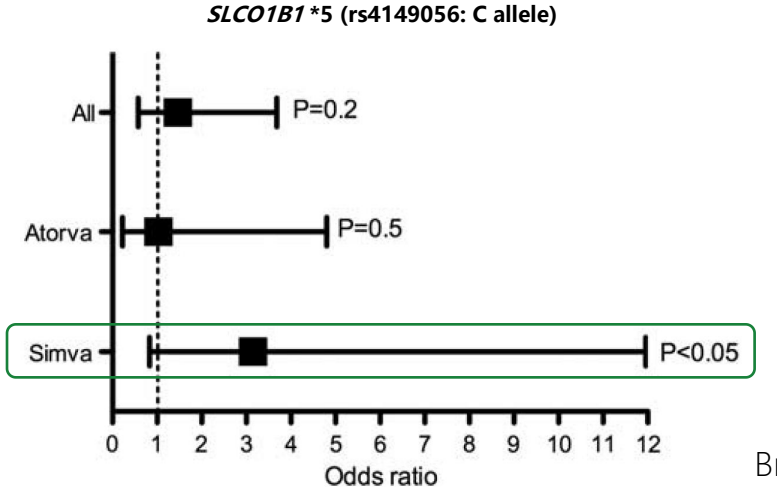
STRENGTH study (n=452: 99 cases+353 controls)



Brunham study (n=108: 25 cases+83 controls)

Table 2 Association between rs4149056 genotype and myopathy

Statin-type	*Cases*			*Controls*			*C allele frequency*		
	T/T	*T/C*	*C/C*	*T/T*	*T/C*	*C/C*	*Cases*	*Controls*	P *value*
All	15	8	2	57	20	6	0.24	0.19	0.21
Simva	5	6	1	27	10	2	0.33	0.18	0.042
Atorva	7	2	1	24	7	3	0.20	0.19	0.48



Voora D, et al., J Am Coll Cardiol. 2009
Brunham LR, et al., Pharmacogenomics J. 2012

CPIC和DPWG指南建议检测*SLCO1B1*指导辛伐他汀用药方案

PGx指南	基因多态性	风险描述	治疗建议
CPIC	rs4149056: TT	肌肉病变风险较低	按适应症指南选择药物剂量常规使用
	rs4149056: CT	肌肉病变风险适中	降低剂量或选择替代药物（例如：普伐他汀、瑞舒伐他汀），并常规监测肌酸激酶
	rs4149056: CC	肌肉病变风险较高	降低剂量或选择替代药物（例如：普伐他汀、瑞舒伐他汀），并常规监测肌酸激酶
DPWG	rs4149056: CT	肝细胞摄取减少，血药浓度和肌肉病变风险升高	1. 选择替代药物（例如：普伐他汀、瑞舒伐他汀、氟伐他汀） 2. 若无替代药物则最大剂量不超过40 mg/d，并在出现肌肉症状时及时就医
	rs4149056: CC	肝细胞摄取减少，血药浓度和肌肉病变风险升高	选择替代药物（例如：普伐他汀、瑞舒伐他汀、氟伐他汀），并考虑他汀诱导肌肉病变的其他风险因子

CPIC 2014 update: Ramsey LB, et al., Clin Pharmacol Ther. 2014

DPWG 2018 update

PGx精准用药欧美趋势 | One test, more treatments

Mayo Clinic	时效性检测 (Reactive)	预判性检测 (Preemptive)
检测时机	用药时	用药前 / 出生时
检测目的	指导当前特定用药 / 剂量	指导未来用药相关处方
检测基因	1 个或几个基因	多基因 Panel / 全基因组
结果参考	可能不再参考	多次参考
检测时效	要求高 / 越快越好	要求不高 / 随用随取
检测项目	华法林 CYP2C9 / VKORC1 氯吡格雷 CYP2C19 他汀类降血脂药 SLCO1B1 / APOE	高血压用药 Panel 精神用药 Panel 冠心病联合用药 Panel 心血管用药 Panel CPIC 指南用药 Panel 综合型 FDA 标签用药 Panel 全基因组用药 Panel

Ann MM, Pedro JC, Expert Review of Pharmacoeconomics & Outcomes Research, 2017

先声诊断 Simcere

先 声 诊 断：用 精 准 医 疗 帮 助 每 个 人

Live longer, live better

公司简介

- 先声诊断是中国领先的医药集团先声控股旗下**精准医疗解决方案提供商**
- 致力于在人类健康的重大挑战领域创造**精准、全面、快捷、可及**的诊断产品和服务体系

临床解决方案

面向医务工作者和医疗机构

通过整合多种领先的分子检测平台和生物信息学分析能力，在肿瘤、中枢神经系统、感染、药物基因组学、自身免疫疾病等治疗领域提供精准医疗的决策基础

个人检验服务

面向患者和健康人群

通过深度整合科技、数据及制造能力
提供基于自采样、寄样的专业医学检验服务
以创新的服务模式提升公共医疗的质量、效率和体验

合作伙伴

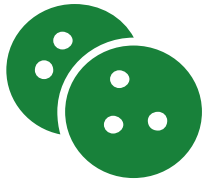
- 先声诊断与美国Agena达成战略合作，共同开拓核酸质谱平台MassARRAY在中国伴随诊断和药物基因组学领域的产业化应用
- **独家权益**：MassARRAY机器 + 药物基因组学PGX试剂盒的NMPA注册及销售
- **其它权益**：肿瘤、液体活检、甲基化及病原体耐药试剂盒的NMPA注册及销售

- 先声诊断与罗氏诊断达成战略合作，共同致力于**新一代测序产品**的开发与应用，为更多终端用户提供高品质的检测结果，满足转化医学精准治疗的细致需求
- 借助罗氏诊断产品开发能力，**完善先声的分子诊断产品线**，为临床诊断提供更加符合未来发展的解决方案

- 先声诊断与安捷伦达成战略合作
- 双方将发挥各自的优势，紧密合作，共同推动精准医疗发展，帮助科学家和医生应对人类健康的重大挑战

检验服务

先声诊断 Simcere



肿瘤

- 覆盖**实体瘤**和**血液肿瘤**伴随诊断服务 - 患者全生命周期管理式诊断
- 遗传/易感检测
- 早期筛查
- 分子分型/用药指导
- 预后评估
- 实时动态监控

中枢神经

- 针对**脑部肿瘤**诊疗产品，对不同基因型的患者提供差异化治疗方案
- 针对6大**神经系统自身免疫性疾病**，进行自身抗体的全面检测，提供疑难疾病的综合诊断

感染病原体

- 提供**感染病原体**快速分析和诊断的全套解决方案
- 用药/耐药/药敏监测
- 急重症/复杂感染检测
- 普检
- 初筛
- 家庭自检

药物基因组

- 指导临床选择**最佳治疗药物**和**最适剂量**提高药物疗效、避免不良反应、改善预后、节约医疗成本，实现个体化治疗
- 对FDA批准、CPIC推荐并在国内上市的药物基本全覆盖

检验服务 | 药物基因组

先声诊断 - 国内该技术平台在药物基因组领域产品类型最丰富的公司

药物不良反应频发

- 2017年全国药品不良反应事件报告约**143万份**
- 药物不良反应已成为我国居民死亡的**第四大原因**

遗传是个体化差异首要原因

- 约**60%**的药物反应个体化差异是遗传因素决定的

用药检测是重要解决方法

- ✓ 评估药物疗效和毒副作用，选择合适药物
- ✓ 调整用药剂量，减少过度治疗或治疗不足
- ✓ 避免药物不良反应发生

基于MassARRAY®平台的药物基因组检测组合

心脑血管疾病个体化用药检测	降脂药物个体化用药检测
降压药物个体化用药检测	抗血栓药物个体化用药检测
神经与精神疾病个体化用药检测	儿童安全用药检测

产品 | 心脑血管疾病个体化用药检测

全面： 6大类心脑血管疾病+46种常见药物+19个基因+25个多态性位点

专业： 基于国内外最新权威指南和数据库

细致： 3个小套餐–降脂药、降压药和抗血栓药

	药物标签					PGx指南			
	FDA	HCSC	PMDA	EMA	Swissmedic	CPIC	DPWG	CPNDS	中国卫计委
氯沙坦									*CYP2C9*
依那普利 卡托普利 福辛普利 赖诺普利									*ACE*
美托洛尔 卡维地洛	*CYP2D6*	*CYP2D6*					*CYP2D6*		*CYP2D6, ADRB1*
辛伐他汀						*SLCO1B1*	*SLCO1B1*		*SLCO1B1*
瑞舒伐他汀	*SLCO1B1*								
阿托伐他汀							*SLCO1B1*		*SLCO1B1*
普伐他汀	*APOE*								*APOE*
匹伐他汀									*SLCO1B1*
氯吡格雷	*CYP2C19*	*CYP2C19*	*CYP2C19*	*CYP2C19*		*CYP2C19*	*CYP2C19*		*CYP2C19*
华法林	*CYP2C9, VKORC1*	*CYP2C9, VKORC1*				*CYP2C9, CYP4F2, VKORC1*	*CYP2C9, VKORC1*	*CYP2C9, VKORC1*	*CYP2C9, CYP4F2, VKORC1*
苯丙香豆素							*CYP2C9, VKORC1*		
醋硝香豆素					*CYP2C9*		*CYP2C9, VKORC1*		
氟卡尼							*CYP2D6*		
普罗帕酮	*CYP2D6*	*CYP2D6*					*CYP2D6*		
硝酸甘油									*ALDH2*

产品 | 神经与精神疾病个体化用药检测

全面： 5大类神经与精神疾病 + 52种常见药物 + 23个基因 + 30个多态性位点

专业： 基于国内外最新权威指南和数据库

细致： 3个小套餐 - 抗癫痫药、抗抑郁与焦虑药、抗精神病药

	药物标签				PGx指南			
	FDA	HCSC	PMDA	EMA	CPIC	DPWG	CPNDS	中国卫计委
卡马西平	*HLA-B, HLA-A*	*HLA-B, HLA-A*	*HLA-B, HLA-A*		*HLA-B, HLA-A*		*HLA-B, HLA-A*	*HLA-B*
奥卡西平	*HLA-B*				*HLA-B*			
苯妥英	*HLA-B, CYP2C9*	*HLA-B*			*HLA-B, CYP2C9*	*CYP2C9*		*HLA-B, CYP2C9*
氯巴占	*CYP2C19*							
丙戊酸	*POLG*	*POLG*						
地西泮	*CYP2C19*							
西酞普兰	*CYP2C19*	*CYP2C19*			*CYP2C19*	*CYP2C19*		
艾司西酞普兰	*CYP2C19*		*CYP2C19*		*CYP2C19*	*CYP2C19*		
氟西汀	*CYP2D6*							
氟伏沙明	*CYP2D6*				*CYP2D6*			
丙咪嗪	*CYP2D6*				*CYP2C19, CYP2D6*	*CYP2C19, CYP2D6*		*CYP2D6*
氯丙咪嗪	*CYP2D6*				*CYP2C19, CYP2D6*	*CYP2D6*		*CYP2D6*
舍曲林					*CYP2C19*	*CYP2C19*		
阿米替林	*CYP2D6*				*CYP2C19, CYP2D6*	*CYP2D6*		*CYP2C19, CYP2D6*
地昔帕明	*CYP2D6*				*CYP2D6*			*CYP2D6*
去甲替林	*CYP2D6*	*CYP2D6*			*CYP2D6*	*CYP2D6*		*CYP2D6*
帕罗西汀	*CYP2D6*				*CYP2D6*	*CYP2D6*		
文拉法辛	*CYP2D6*					*CYP2D6*		
多塞平	*CYP2C19, CYP2D6*				*CYP2C19, CYP2D6*	*CYP2D6*		
普罗替林	*CYP2D6*							
曲米帕明	*CYP2D6*				*CYP2C19, CYP2D6*			
沃替西汀	*CYP2D6*	*CYP2D6*		*CYP2D6*				
度洛西汀	*CYP2D6*			*CYP2D6*				
氟哌啶醇						*CYP2D6*		
阿立哌唑	*CYP2D6*	*CYP2D6*		*CYP2D6*		*CYP2D6*		
氯氮平	*CYP2D6*							
奥氮平	*CYP2D6*			*CYP2D6*				
利培酮	*CYP2D6*	*CYP2D6*						
奋乃静	*CYP2D6*		*CYP2D6*					
珠氯噻醇						*CYP2D6*		
硫利达嗪	*CYP2D6*							
阿托莫西汀	*CYP2D6*	*CYP2D6*	*CYP2D6*		*CYP2D6*	*CYP2D6*		

产品 | 风湿免疫疾病个体化用药检测

全面： 4大类风湿免疫疾病+19种常见药物+29个基因+41个多态性位点

专业： 基于国内外最新权威指南和数据库

细致： 3个小套餐-改善病情的抗风湿药、生物制剂和抗痛风药

	药物标签			PGx指南			
	FDA	HCSC	PMDA	CPIC	DPWG	ACR	中国卫计委
硫唑嘌呤	*NUDT15, TPMT*	*TPMT*	*TPMT*	*NUDT15, TPMT*	*TPMT*		*TPMT*
他克莫司				*CYP3A5*	*CYP3A5*		*CYP3A5*
羟氯喹	*G6PD*						
柳氮磺吡啶	*G6PD, NAT2*	*G6PD*	*G6PD*				
别嘌呤醇			*HLA-B*	*HLA-B*		*HLA-B*	*HLA-B*

产品 | 儿童安全用药检测

全面：9大疾病领域+140种儿童常用药物+33个基因+50个多态性位点

专业：基于国内外最新权威指南和数据库

细致：2种端口–面向临床、争对患者

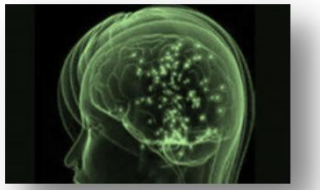
适用人群	人群特征	检测意义
患病儿童	发热疼痛患者 哮喘咳嗽患者 神经与精神病患者 心脑血管疾病患者 感染病患者 糖尿病患者 消化系统疾病患者 麻醉病人 免疫化疗患者	**精准用药**：从剂量、药效、不良反应等多方面给予个性化用药提示，改善患者疗效并减少或避免严重副作用
健康儿童	关注用药风险儿童 曾有过药物不良反应史的儿童 家族成员中有过药物不良反应史的儿童	**风险评估**：评估儿童用药风险 **指导安全用药**：根据风险评估结果，选择合适药物，有效规避潜在用药不当风险

平台 | MassARRAY核酸飞行时间质谱

MassARRAY临床应用



药物基因组全线产品　脑胶质瘤精准检测　泛癌种化疗用药



遗传性耳聋检测　营养元素基因检测　叶酸代谢基因检测

更多出生缺陷及遗传领域临床应用开发中

先声诊断与Agena达成战略合作

Agena授权了合作开发及NMPA注册权益

平台 | MassARRAY技术平台优势

MassARRAY 系统将质谱分析、高灵敏度和稳定性的
化学试剂与先进的数据分析软件相结合
以满足基因组学实验室的检测设计、验证和性能需求

高灵活性

简化了在实验室中设计
和实施开展新测试项目的流程

PCR反应条件均一化
检测试剂通用化
位点探针设计便捷

高精准度

MassARRAY ®核酸质谱仪检测技
术灵敏度高，检测结果准确

FDA将其特许作为第二代测序仪
illumina MiSeqDx 的验证平台

高通量性

在单个反应孔中实现
高度多重性的能力（高达40重）

可通宵运行，最大程度提高通量

高性价比

检测成本有明显的价格优势

无需荧光标记、低成本定量分析

多功能性

可检测SNP/Indel基因分型、
基因融合、染色体结构变异、
DNA甲基化、CNV等各类已知
变异

全自动化

从检测到结果报告全程8小时

无需生信分析
点样及质谱飞行过程全自动化
最大程度降低污染风险

一站式解决方案 | 精准医学中心战略合作

打包第三方检验服务

按相应政策法规为医院提供符合质量规范的临检服务及医学支持

技术供应商

基础项目本地化/人才培养/PCR实验室建设等

区域检验中心（暨国重分中心）建设

国家重点实验室联手打造集约化区域检验中心，提升临检与科研发展水平

Thank You

先声诊断 Simcere

PGx临床获益性研究 | 经济性vs有效性

别嘌呤醇、卡马西平、华法林和氯吡格雷在临床进行基因检测经济有效

	参考研究	适应症	标记物人群频率	有效性	经济性
阿巴卡韦 HLA-B*57:01 ADR: 过敏	Hughes et al. 2004	HIV	UK: 3.7%	Test: 1.9% ADR; No test: 3.7% ADR	$490/ADR avoided for testing
	Schackman et al. 2008	HIV	USA: 5.7%	Test: 0% ADR, No test: 2.73% ADR	Test dominates other strategies
	Kapoor et al. 2014	HIV	Han Chinese 1.1%	Test vs No test: Improve quality of life	Not cost-effective for testing
	Calatravaa et al. 2010	HIV	Spain: 5.6%	Test: 4.25% ADR; No test: 7.8% ADR	$630/ADR avoided for testing
别嘌呤醇 HLA-B*58:01 ADR: 过敏	Park et al. 2015	Gout	Korea: 12.2%	Test: 0% ADR, No test: 2.19% ADR	Test dominates other strategies
卡马西平 HLA-B*15:02, HLA-A*31:01 ADR: SJS, TEN	Dong et al. 2012	Epilepsy	Singapore: 14.87%	Test vs No test: Improve quality of life	Test dominates valproate
华法林 CYP2C9*2, *3, VKORC1 ADR: 出血	Leey et al. 2009	AF	USA: NA	Test vs No test: reduce major bleeding	Test dominates other strategies
	You et al. 2009	Anticoagulation	USA: NA	Test vs No test: reduce ADR	$170192/ADR averted for testing
	Schalekamp et al. 2006	Thromboembolic	Netherlands: 36%	Test: 4.6% ADR, No test: 5.1% ADR	$4233/ADR averted for testing
	You et al. 2012	AF	USA: NA	Test vs No test: Improve quality of life	Test dominates standard care
	You et al. 2004	Thromboembolic	USA: 36%	Test: 9.58% ADR, No test: 10.48% ADR	$5778/ADR averted for testing
氯吡格雷 CYP2C19 ADR: 主要心血管不良反应	Lala et al. 2012	ACS	USA: 27.1%	Test vs No test: Improve quality of life	Test dominates other strategies
	Panattoni et al. 2012	ACS	Asian 29%	Test vs No test: Improve quality of life	Test dominates prasugrel
	Reese et al. 2012	ACS, MI, stroke	USA: 27%	Test vs No test: Improve quality of life	Test dominates other strategies
	Sorich et al. 2013	ACS	Australia: 28.2%	Test vs No test: Improve quality of life	Test dominates ticagrelor