

藥物基因體臨床應用與發展

Pharmacogenomics

From Standard Dose to Personalized Care

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The Pharmacogenomics Society of Taiwan (PGST)

Data integration: Hai-Ling Liang, RPh.
Date: 19 Dec 2025

Current Position

Associate Professor, Dept. Clinical Pharmacy (Chair), School of Pharmacy, TMU

Professional Service

Expert Advisory Committee (PK part) , Center for Drug Evaluation (CDE)

Council Board, The Pharmacogenomics Society of Taiwan (PGST)

Committee Board, Education Development, TSHP

Reviewer Board, Continuing Education Review Board, TSHP

Committee Member and Executive Secretary, Taichung Tzu Chi Hospital Research Ethic Committee (IRB)

Former Executive Secretary, Taichung Tzu Chi Hospital BioBank Committee (EGC)

Education & Training

B.Sc. in Pharmacy (2003) Taipei Medical University, Taipei, TAIWAN

Ph.D. in Pharm Sci (2012) EMSOP, Rutgers University, NJ, USA

Pharmacogenomics/ Epigenomics
Pharmacokinetics and Pharmacodynamics

Research Associate, Clinical PKPD Dept, NIBR, Novartis, E. Hanover, NJ

Clinical PKPD data analysis

Postdoctoral Fellow, Mount Sinai Medical Center, New York, NY, U.S.A.

Genomic imprinting, reprogramming and epigenetic modifications
Genomic data analysis

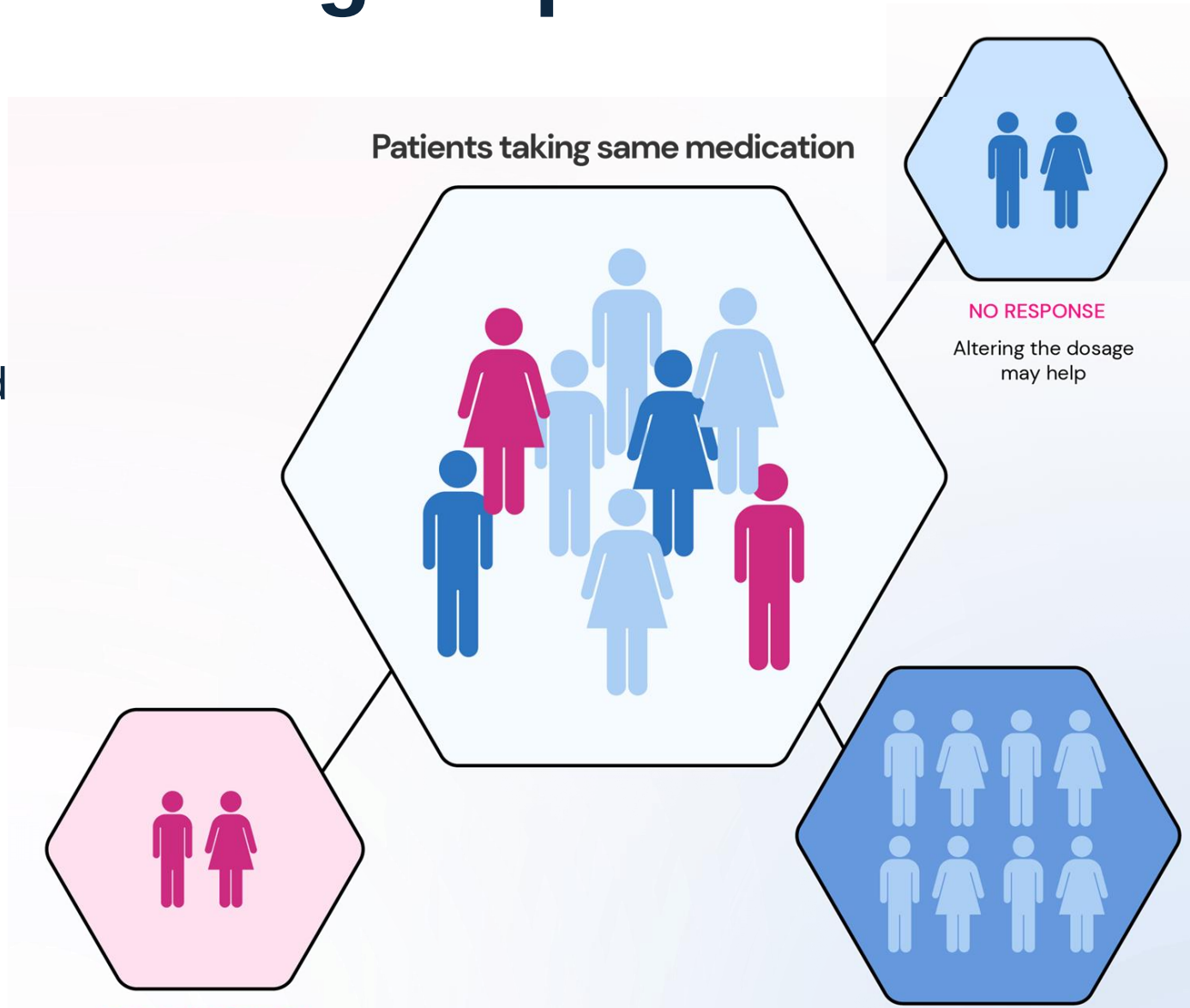
Postdoctoral Fellow, Cancer New Drug Development Ctr, TMU

Genomic and mtDNA database analysis for epigenomic study

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Individual differences in drug response

- The same prescription can be therapeutic for one patient, ineffective for another, and toxic for a third.
- This variability isn’t random; it’s rooted in our individual genetic makeup.



https://www.xcode.life/research/genomic-medicine-future/

台灣藥物基因體學會 臺灣臨床藥學會

藥物基因體學之
臨床藥事服務
應用指引

Guidelines for the Application of Pharmacogenomics in Clinical Pharmacy Services - Taiwan Version

總 編 輯：吳明芬 吳天元 張偉嶠

執行編輯：廖怡茹

合編：王郁青 吳俊男 沈玫秋 周宛萱 林英琦 姜紹青 徐幸愉 張惠華 許茜甯 郭俊男 陳寬軒 黃織芬 顏志和 蘇慧真

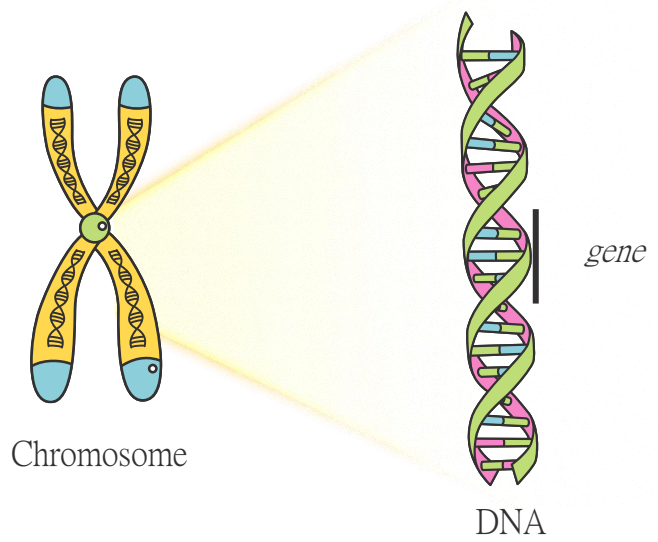


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緣起:

台灣各大醫學中心逐步提升精準醫療以及基因體相關服務



2023	2024/03/16 臺中榮民總醫院	2025/09
臺灣臨床藥學會 張豫立理事長 台灣藥物基因體學會 張偉崎理事長 共同發起	第一次工作小組會議 TSHP & PGST 共同擔任召集人 TSHP: 10位全國醫學中心代表 PGST: 6位 全國藥學系代表	正式出版

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目標

- 藥物與基因之相互作用
- 藥物基因諮詢
- 臨床藥學服務
- 臨床治療劑量調整

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基因變異與藥物相關性之表現型與基因型(1)

CYP2D6可依等為基因與copy number variant的數目計算Activity score，再將其表現型分為超快速代謝 (Activity score >2.25)、正常代謝 (1.25≤ Activity score ≤2.25)、中速代謝 (0< Activity score <1.25)與慢速代謝（Activity score 0），根據CPIC指引資料，**0.82%的東亞族群為超快速代謝者**，54%為正常代謝者，38%為中速代謝者，0.79%為慢速代謝者，相較於歐美族群有較少的超快速代謝者與慢速代謝者。

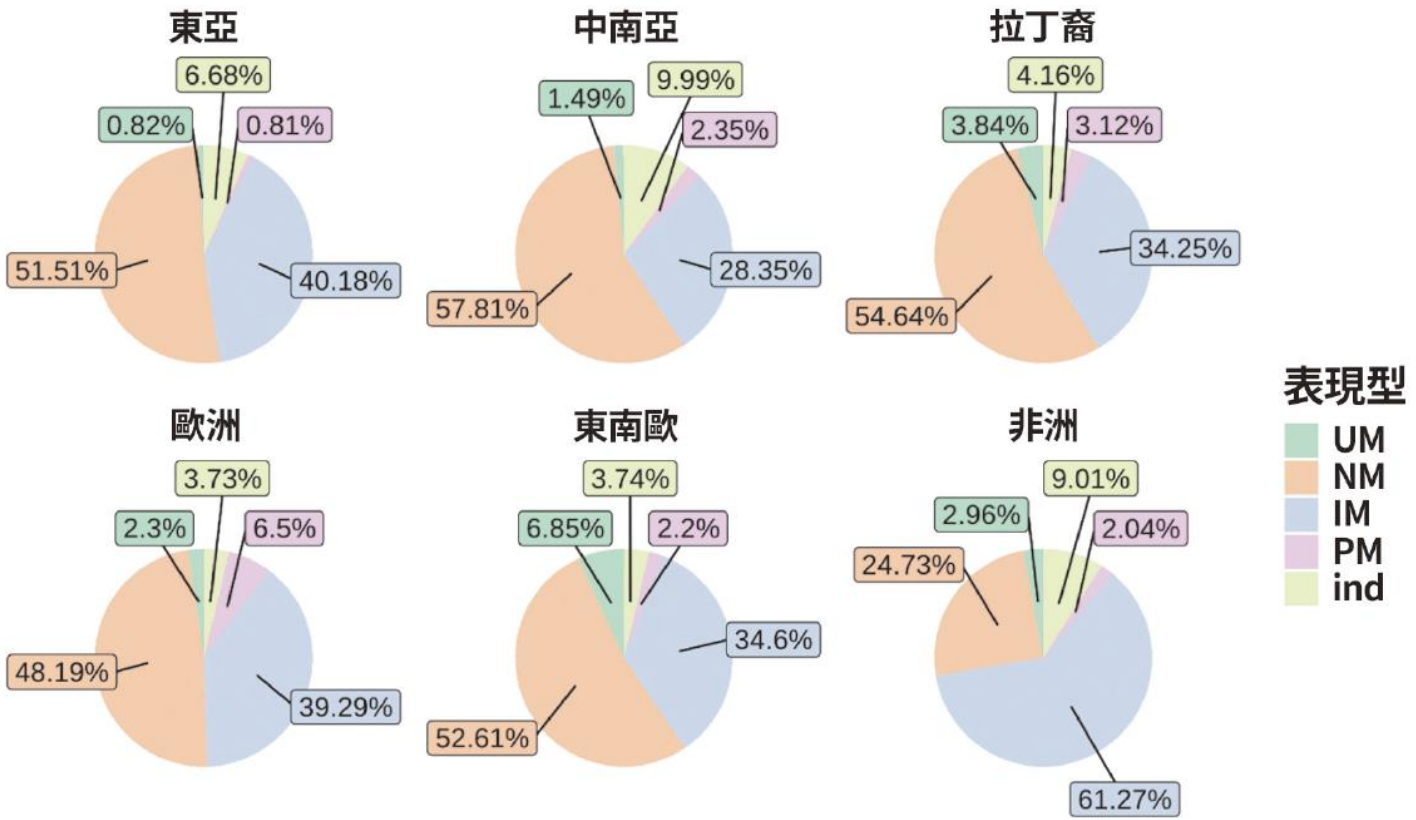


圖 6. *CYP2D6* 表現型各族群頻率分布

基因變異與藥物相關性之表現型與基因型(2)

CYP2C9依等位基因不同分別被定義為

1. 無功能0分如CYP2C9*3、*6和*13
2. 功能減少定義為0.5分如CYP2C9*2、*5、*8和*11
3. 功能正常則定義為1分如CYP2C9*1

這些值加總可以得到每個 diplotype的activity score (AS)，AS為0或0.5的個體為慢速代謝者，AS為1或1.5的為中速代謝者，AS為2的為正常代謝者，最廣泛研究的變異是 CYP2C9*2（rs1799853）和 CYP2C9*3（rs1057910），根據CPIC指引資料，CYP2C9**的在東亞族群中，正常代謝者占83.8%，**中速代謝者且AS為1.5者占5.3%，中速代謝者且AS為1者占9.9%，慢速代謝者占0.6%。

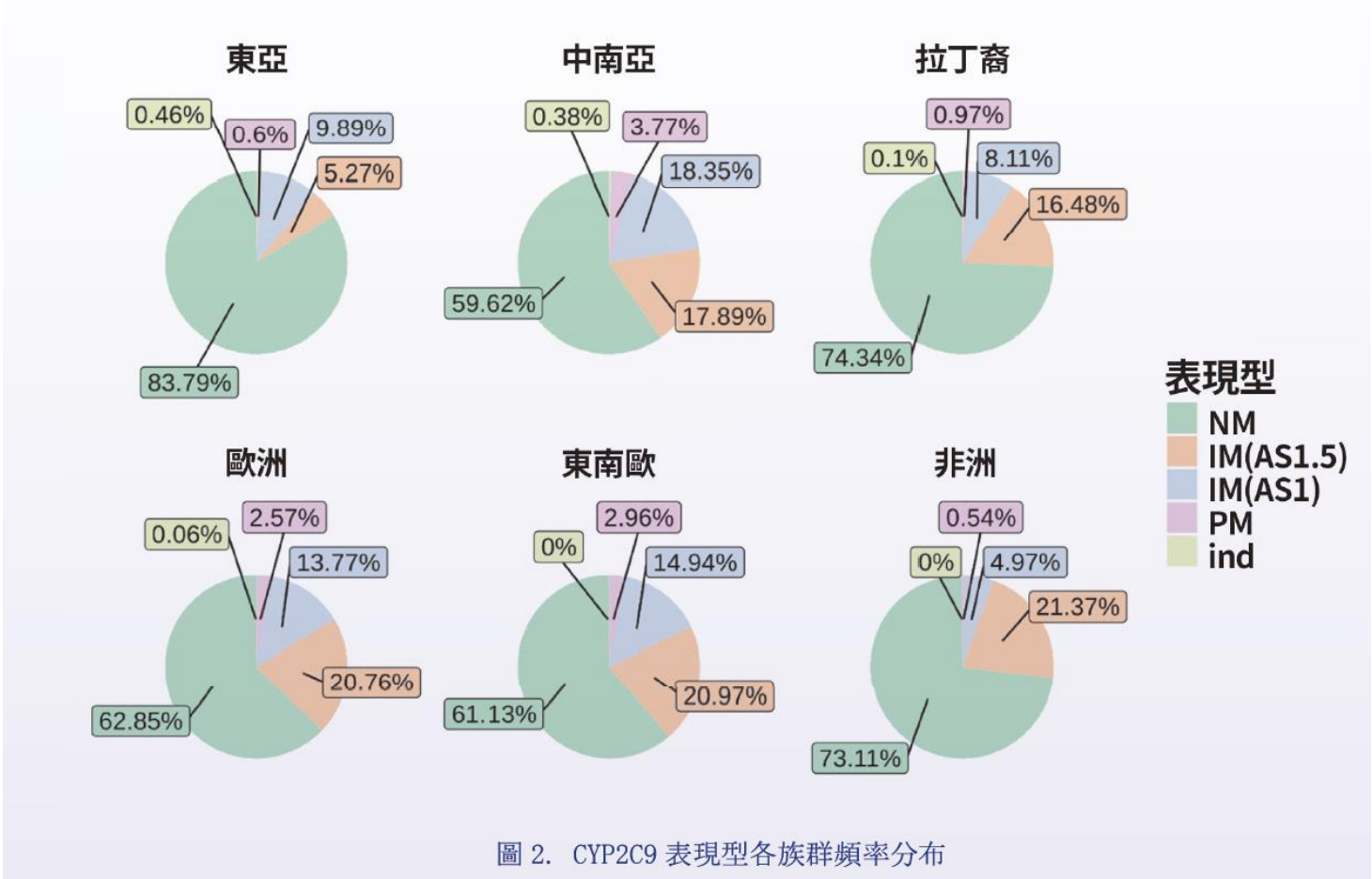


圖 2. CYP2C9 表現型各族群頻率分布

藥品-基因組合選擇 (germline mutation)

01 全國各大醫學中心之精準醫療服務品項

全國各醫學中心之檢測以及服務品項:　包括臺大醫院、臺北榮民總醫院、臺中榮民總醫院、中國醫藥大學附設醫院、中山醫學大學附設醫院、奇美醫院、高雄長庚醫院、高雄醫學大學附設醫院等

02 藥品種類

心血管治療藥品、身心科治療藥品、免疫相關藥品、抗微生物藥品、癌症藥品、HLA與藥物不良反應相關藥品等

03 藥物基因體學常用參考文獻

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) 、US FDA、DPWG

04 可應用性與實證強度

CPIC level A或FDA PGx Assn 1

重要藥物基因組合共152項(36組)



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藥品與基因組合

01 肝臟代謝酵素

- CYP2C19 & CYP2D6 與 SSRI/ TCA/ 其他身心科相關藥品
- CYP2C19 與 PPI/ Clopidogrel/ 其他藥品
- CYP2C9/ CYP4F2/ VKORC1 與 warfarin
- CYP2C9 與 NSAIDs
- CYP2C9 & CYP2D6 與止吐藥

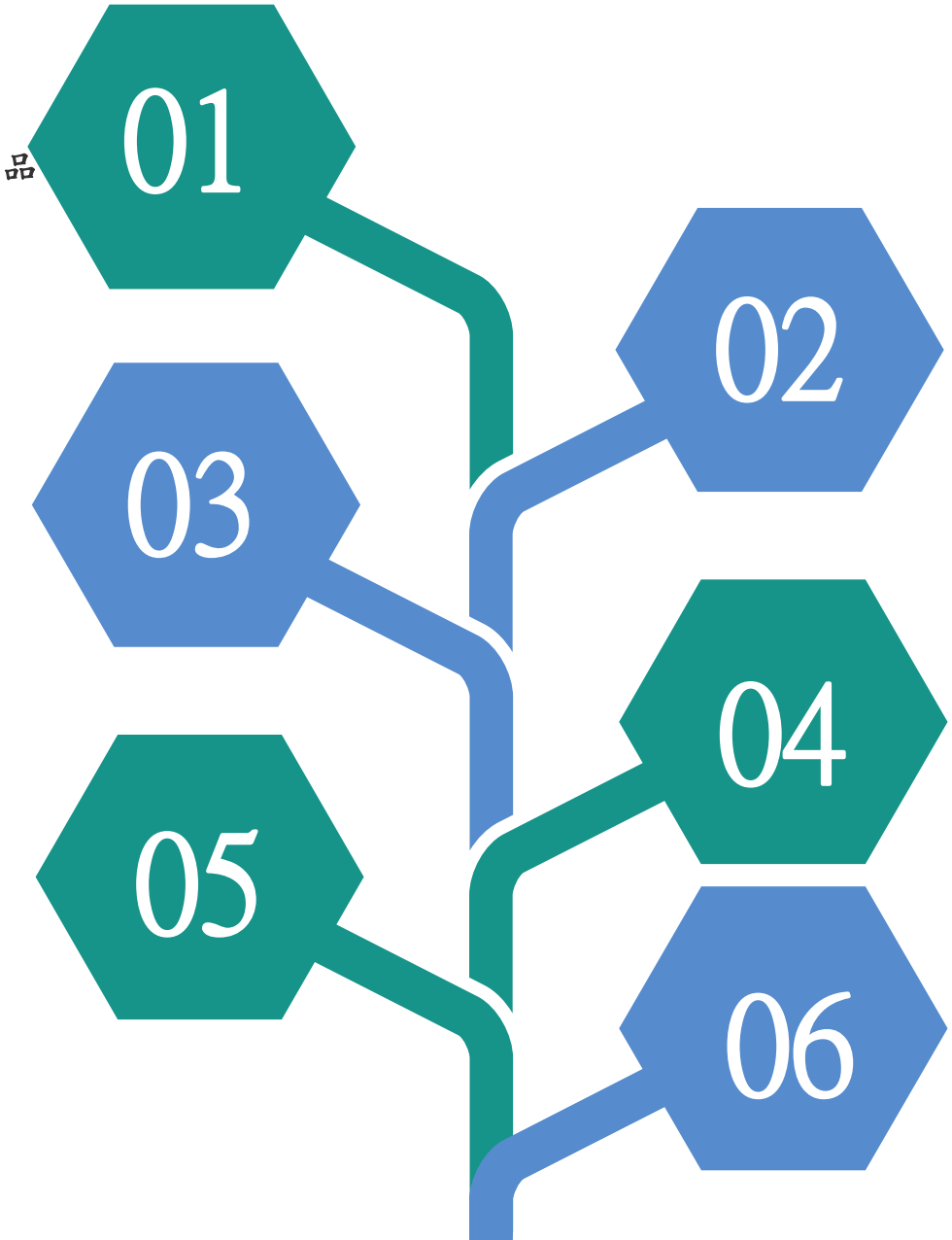
02 TPMT & UGT1A1 Phase II metabolized enzymes

03 G6PD and Adverse Drug Reaction

04 HLA and Adverse Drug Reaction

05 SLCO1B1, ABCG2 transporters

06 MT-RNR1 耳毒性與aminoglycosides



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藥品個論



藥品簡介

藥品分類、臨床適應症、藥品主要作用機轉及副作用



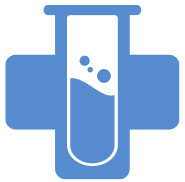
藥品與基因

基因變異與藥物相關之表現型與基因型



臨床治療劑量建議

基因型與表現型與劑量調整



病人使用時的潛在利益與風險

基因檢測可帶來辨識病人的潛在效益或風險

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- **臨床劑量與藥物治療建議**

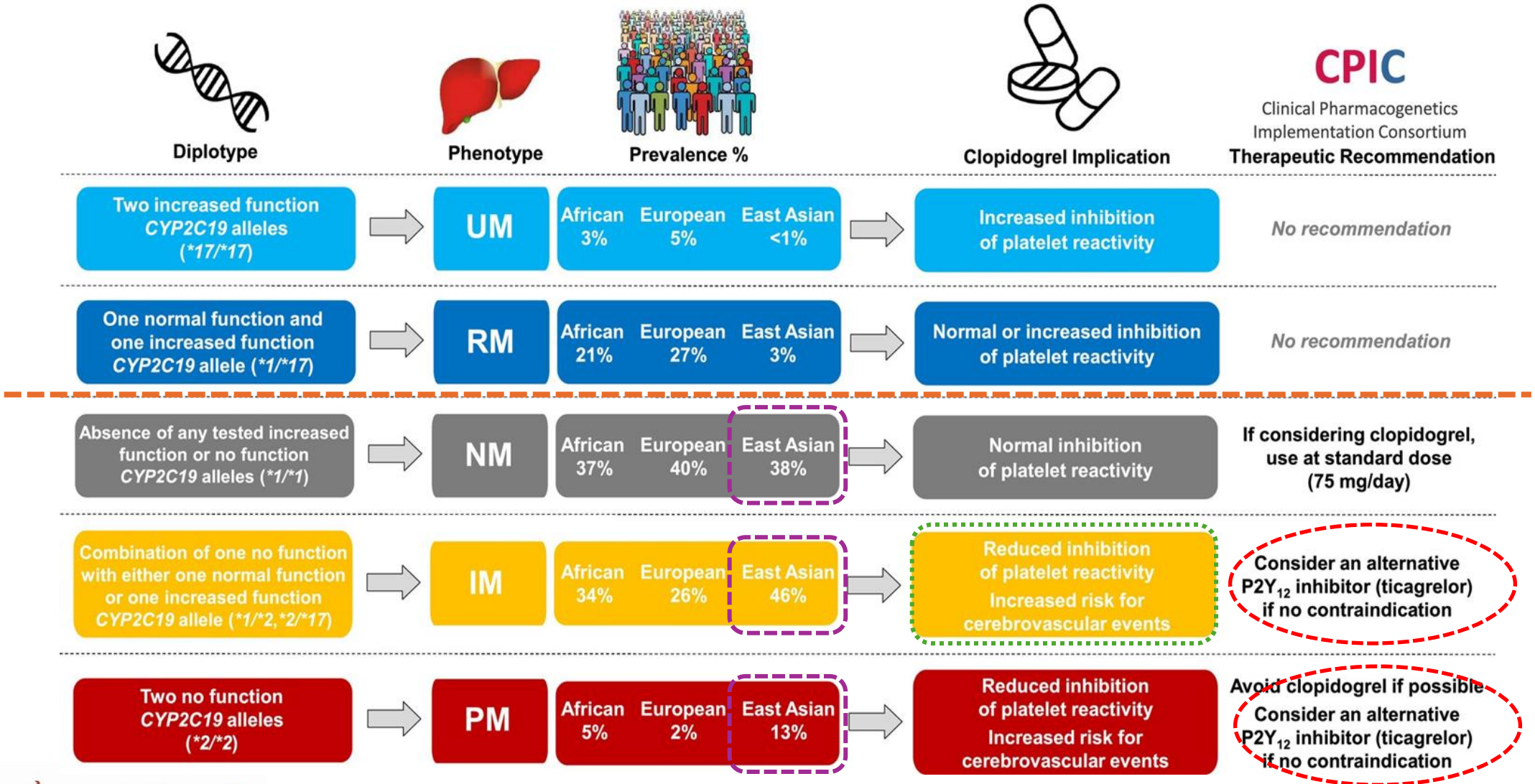
✓ 臨床劑量調整、藥物治療建議

Genotype /Phenotype	Description	Frequency of Asian Population

Phenotype	Description	Frequency	Drug	Recommendation	Major Reference Main References
CYP2C9 NM AS=2	正常代謝	83.8%	Celecoxib Flurbiprofen	使用一般起始劑量	CPIC (Level A)
CYP2C9 IM AS=1.5	輕微減少代謝	5.3%	Celecoxib Flurbiprofen	使用一般起始劑量	CPIC (Level A)
CYP2C9 IM AS=1	中度減少代謝，增加藥物血中濃度	9.9%	Celecoxib Flurbiprofen	使用一般起始劑量的最低劑量，建議密切監測潛在的不良反應，例如血壓變化和腎功能損害。	CPIC (Level A)
CYP2C9 PM AS=0.5/0	顯著減少代謝和延長半衰期，增加藥物血中濃度	0.6%	Celecoxib Flurbiprofen	以一般起始劑量的 25–50% 開始治療，並根據患者的臨床反應逐漸調整劑量，最高可達建議劑量的 25–50% 至少需要 8 天的治療時間才能達到 steady state，應達 steady state 才可上調藥品劑量。 建議密切監測潛在的不良反應，例如血壓變化和腎功能損害。 可以考慮使用不依賴 CYP2C9 代謝或不被 CYP2C9 基因型影響的替代藥物。	CPIC (Level A) FDA：Table of Pharmacogenetic Associations (Section 1)
CYP2C9 NM AS=2	正常代謝	83.8%	Meloxicam	使用一般起始劑量	CPIC (Level A)
CYP2C9 IM AS=1.5	輕微減少代謝	5.3%	Meloxicam	使用一般起始劑量	CPIC (Level A)
CYP2C9 IM AS=1	中度減少代謝，增加藥物血中濃度	9.9%	Meloxicam	以一般起始劑量的 50% 開始治療，並根據患者的臨床反應逐漸調整劑量，最高可達建議劑量的 50%。 至少需要 7 天的治療時間才能達到 steady state，應達 steady state 才可上調藥品劑量。 建議密切監測潛在的不良反應，例如血壓變化和腎功能損害。 可以考慮使用不依賴 CYP2C9 代謝或不被 CYP2C9 基因型影響的替代藥物。	CPIC (Level A)
CYP2C9 PM AS=0.5/0	顯著減少代謝和延長半衰期，增加藥物血中濃度	0.6%	Meloxicam	考慮使用不依賴 CYP2C9 代謝或不被 CYP2C9 基因型影響的替代藥物 若有使用需求須減量使用並密切監測副作用 。	CPIC (Level A) FDA：Table of Pharmacogenetic Associations (Section 1)

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Clopidogrel & CYP2C19 ➡ Ticagrelor ?

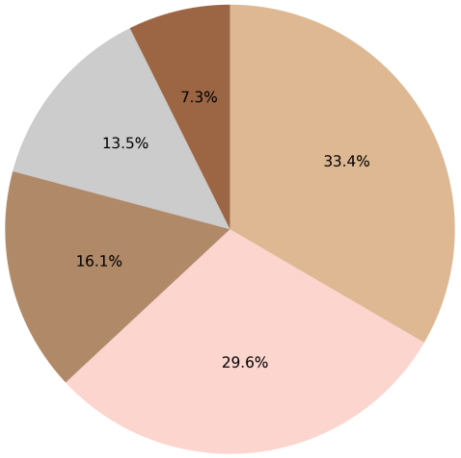


Tunehag, K.R., Pearce, A.F., Fox, L.P., Stouffer, G.A., Solander, S. and Lee, C.R. (2025), CYP2C19 Genotype-Guided Antiplatelet Therapy and Clinical Outcomes in Patients Undergoing a Neurointerventional Procedure. Clin Transl Sci, 18: e70131. https://doi.org/10.1111/cts.70131

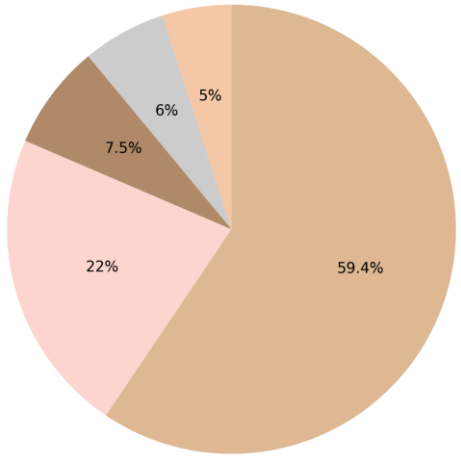
CYP2D6 gene polymorphism

Likely phenotype	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1-20% of patients)[a]	> 2.0	An individual carrying duplications of functional alleles	*(*1/*1)xN, (*1/*2)xN, (*2/*2)xN*[b]
Normal metabolizer (~72-88% of patients)	1.0-2.0[c]	An individual carrying two normal function alleles or two decreased function alleles or one normal and no function allele or one normal function and decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0 −2.0.	**1/*1, *1/*2, *2/*2, *1/*9, *1/*41, *41/*41, *1/*5, *1/*4*
Intermediate metabolizer (~1-13% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*41, *5/*9, *4/*10*
Poor metabolizer (~1-10% of patients)	0	An individual carrying only no function alleles	**4/*4, (*4/*4)xN, *3/*4, *5/*5, *5/*6*

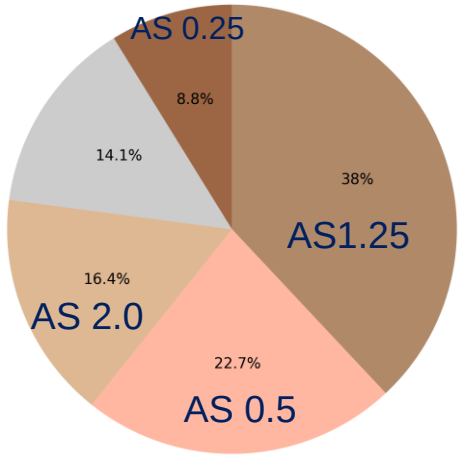
European



American



East Asian



Activity Score

2.0 — 33.4%
1.0 — 29.6%
1.25 — 16.1%
Others — 13.5%
0.25 — 7.3%

2.0 — 59.4%
1.0 — 22%
1.25 — 7.5%
Others — 6%
3.0 — 5%

1.25 — 38%
0.5 — 22.7%
2.0 — 16.4%
Others — 14.1%
0.25 — 8.8%

Clinical Applications

More about precision medicine

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Ongoing Project

- TMU x TMUH
  - PGx precision dosing- Beyond Lifelong Medication: Personalized Strategies for Safer Sedative-Hypnotic Use
- TMU x WFH
  - PKPD modeling & simulation + PGx to predict MDR-TB patient dosing

TMUH PGx project

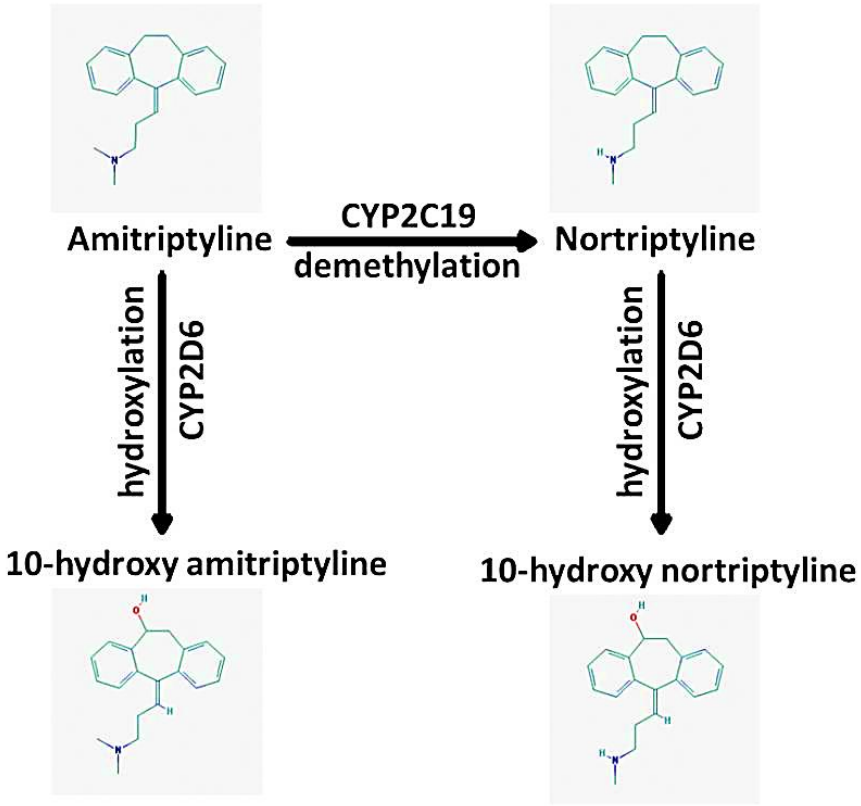
Personalized Strategies for Safer Sedative-Hypnotic Use

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Individualized & Precision dosing

- Genomic testing (16 genes including drug metabolic and response)
- According to genes testing, choose sedative-hypnotic medicine
- Optimizing sedative-hypnotic medicine dosing

Tricyclic Antidepressants (TCAs) with CYP2D6 and CYP2C19 gene polymorphism



- CYP2D6 and CYP2C19 polymorphisms affect the exposure, efficacy and safety of tricyclic antidepressants (TCAs).
- Some drugs being affected by CYP2D6 only (e.g., nortriptyline and desipramine)
- Others by both polymorphic enzymes (e.g., amitriptyline, clomipramine, doxepin, imipramine, and trimipramine).

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44. doi: 10.1002/cpt.597. Epub 2017 Feb 13. PMID: 27997040; PMCID: PMC5478479.

Dosing Recommendations for TCAs based on CYP2D6 Phenotype

Phenotype	Implication	Therapeutic recommendation[a,b]	Classification of recommendation for amitriptyline and nortripyline[c]	Classification of recommendation for other TCAs[c,d]
CYP2D6 ultrarapid metabolizer	Increased metabolism of TCAs to less active compounds compared to normal metabolizers Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers).[e] Utilize therapeutic drug monitoring to guide dose adjustments.	Strong	Optional
CYP2D6 normal metabolizer	Normal metabolism of TCAs	Initiate therapy with recommended starting dose.[f]	Strong	Strong
CYP2D6 intermediate metabolizer	Reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	Consider a 25% reduction of recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Moderate	Optional
CYP2D6 poor metabolizer	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Strong	Optional

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44. doi: 10.1002/cpt.597. Epub 2017 Feb 13. PMID: 27997040; PMCID: PMC5478479.

Dosing Recommendations for TCAs, clomipramine, doxepin, imipramine, and trimipramine based on CYP2C19 Phenotype

Phenotype	Implication	Therapeutic recommendation[a,b]	Classification of recommendation for amitriptyline[c]	Classification of recommendation for other tertiary amine TCAs[c,d]
CYP2C19 ultrarapid metabolizer and CYP2C19 rapid metabolizer	Increased metabolism of tertiary amines compared to normal metabolizers Greater conversion of tertiary amines to secondary amines may affect response or side effects	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. If a tertiary amine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.[e]	Optional	Optional
CYP2C19 normal metabolizer	Normal metabolism of tertiary amines	Initiate therapy with recommended starting dose.[f]	Strong	Strong
CYP2C19 intermediate metabolizer	Reduced metabolism of tertiary amines compared to normal metabolizers	Initiate therapy with recommended starting dose.[f]	Strong	Optional
CYP2C19 poor metabolizer	Greatly reduced metabolism of tertiary amines compared to normal metabolizers Decreased conversion of tertiary amines to secondary amines may affect response or side effects	Avoid tertiary amine use due to potential for sub-optimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include the secondary amines nortriptyline and desipramine. For tertiary amines, consider a 50% reduction of the recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Moderate	Optional

Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, Bishop JR, Kharasch ED, Skaar TC, Gaedigk A, Dunnenberger HM, Klein TE, Caudle KE, Stingl JC. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44. doi: 10.1002/cpt.597. Epub 2017 Feb 13. PMID: 27997040; PMCID: PMC5478479.

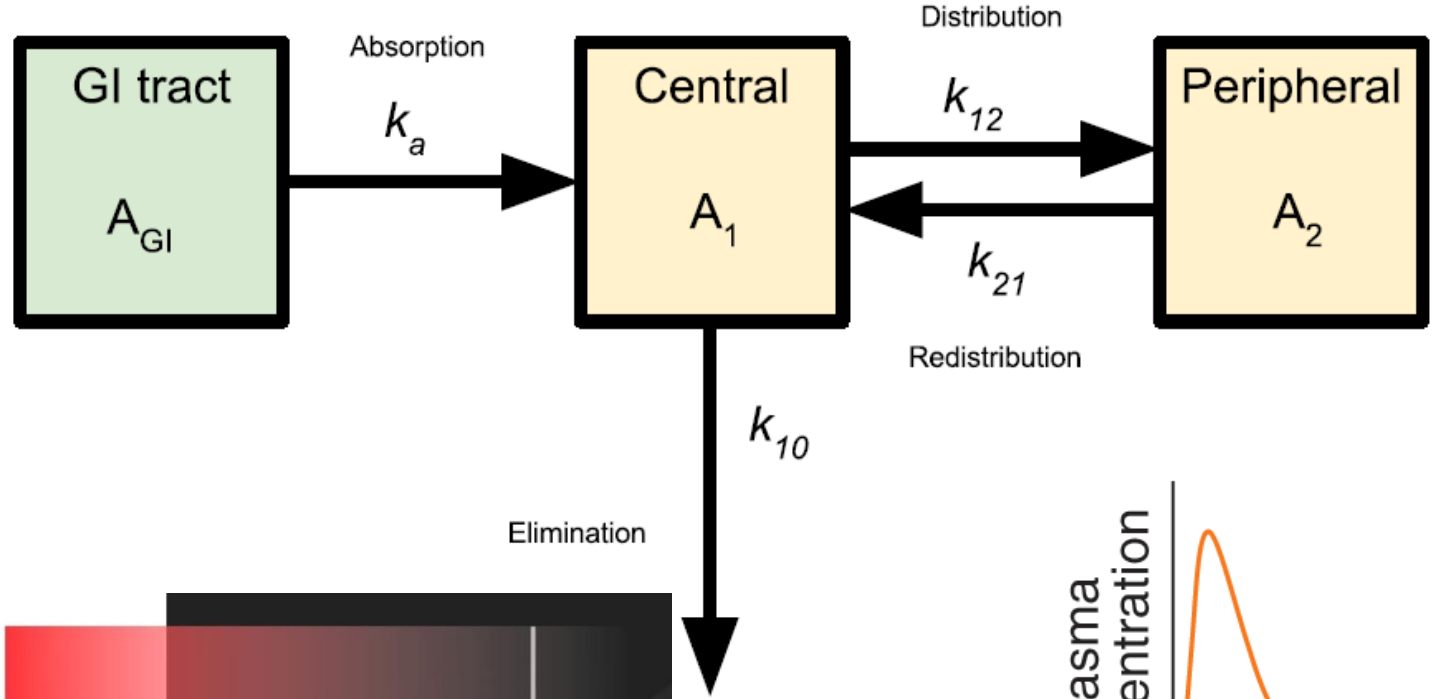
Dosing Recommendations for amitriptyline based on both CYP2D6 and CYP2C19 Phenotypes

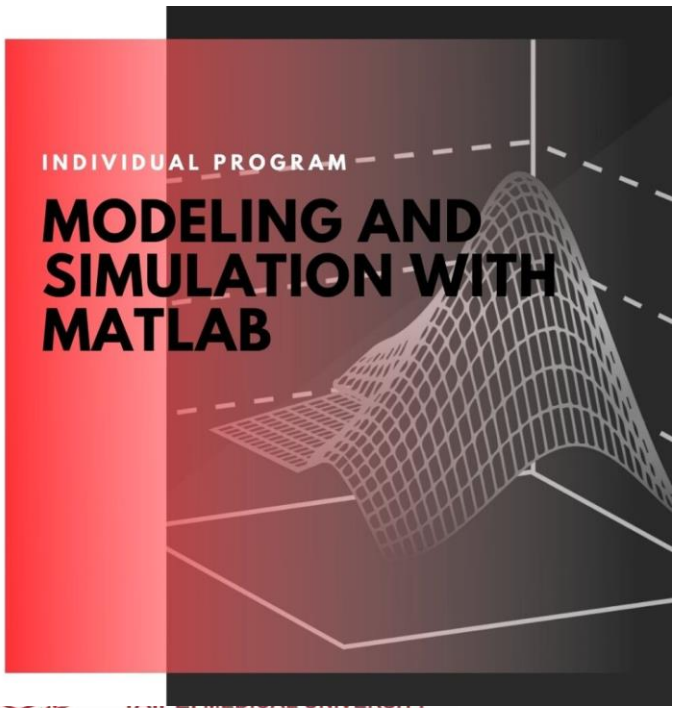
Phenotype	CYP2D6 ultrarapid metabolizer	CYP2D6 normal metabolizer	CYP2D6 intermediate metabolizer	CYP2D6 poor metabolizer
CYP2C19 ultrarapid or rapid metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional	Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional
CYP2C19 normal metabolizer	Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers)[f,g] Classification of recommendation[d]: Strong	Initiate therapy with recommended starting dose[h] Classification of recommendation[d]: Strong	Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Strong
CYP2C19 intermediate metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Initiate therapy with recommended starting dose[h] Classification of recommendation[d]: Strong	Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Optional	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Optional
CYP2C19 poor metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional

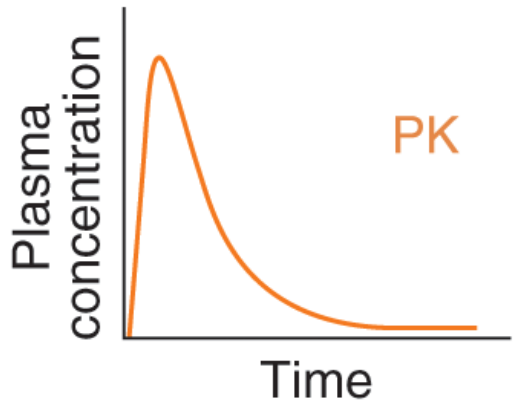
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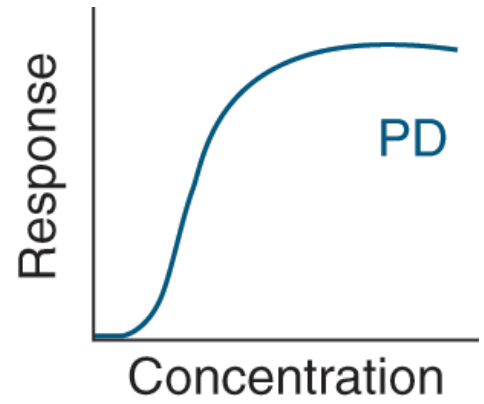
PKPD modeling & simulation
Plus Pharmacogenomics

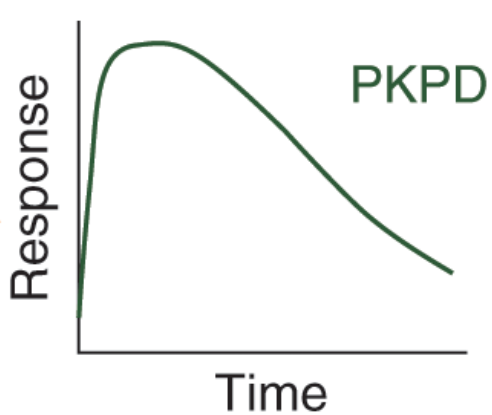
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GI tract
A_{GI}
Absorption
k_a
Central
A_1
Distribution
k_{12}
k_{21}
Peripheral
A_2
Redistribution
k_{10}
Elimination


INDIVIDUAL PROGRAM
MODELING AND SIMULATION WITH MATLAB


Plasma concentration
PK
Time


Response
PD
Concentration


Response
PKPD
Time

PKPD modeling & simulation

- Quantify and predict the relationship between the dose of a drug, the concentration of that drug in the body over time, and the resulting biological effect

$$\text{Dose} \xrightarrow{\text{PK}} \text{Concentration}(C) \xrightarrow{\text{PD}} \text{Effect}(E)$$

- “Modeling” is fitting equations to observed data to understand the past. (Estimation)
- "Simulation" is using those equations to predict the future. (Prediction)
- FDA and EMA highly value M&S (often called Model-Informed Drug Development or MIDD) because it saves time, money, and reduces risk to patients.

Benefit of Modeling and Simulation

Benefit	Description
Dose Optimization	Helps select the exact dose that maximizes efficacy while minimizing toxicity before starting large Phase 3 trials.
Special Populations	Allows prediction of dosing for groups often excluded from early trials, such as children (pediatrics), the elderly, or those with organ impairment.
Go/No-Go Decisions	Helps companies decide early if a drug is unlikely to work, saving billions in failed trials.
Trial Design	Helps determine how many patients are needed and how often to sample their blood in a clinical trial.

Linezolid Population PK Model Validation

Random Effects

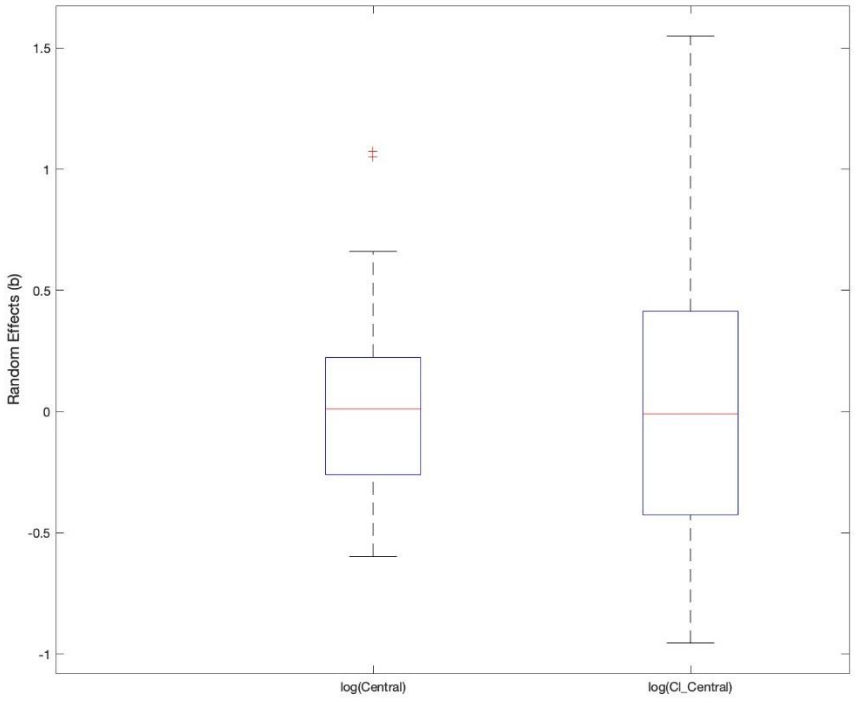


Figure 5. Boxplot of interindividual variability in random effects for model parameters (Central: volume of distribution, Cl_Central: clearance)

Model Validation with External Dataset

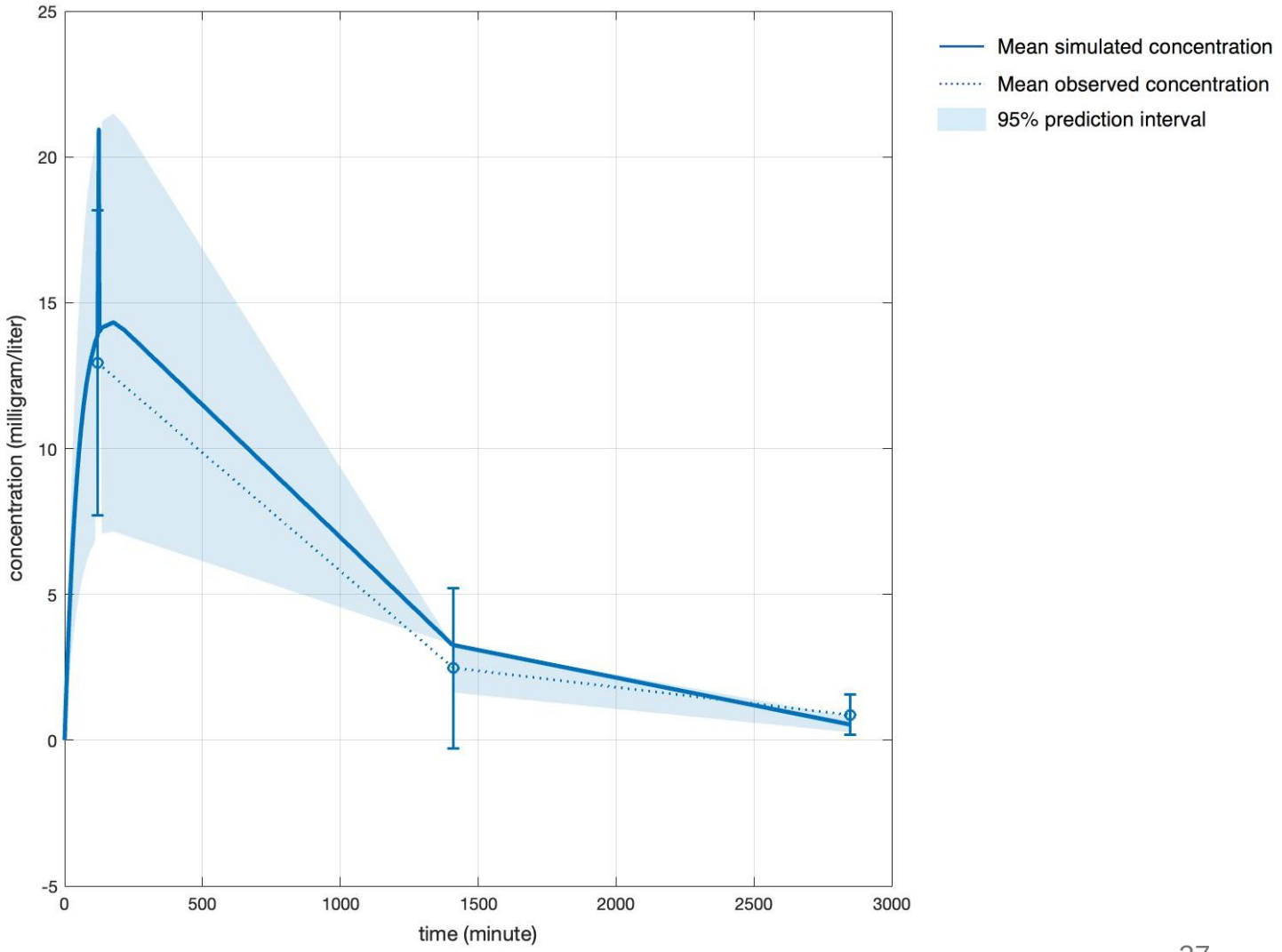
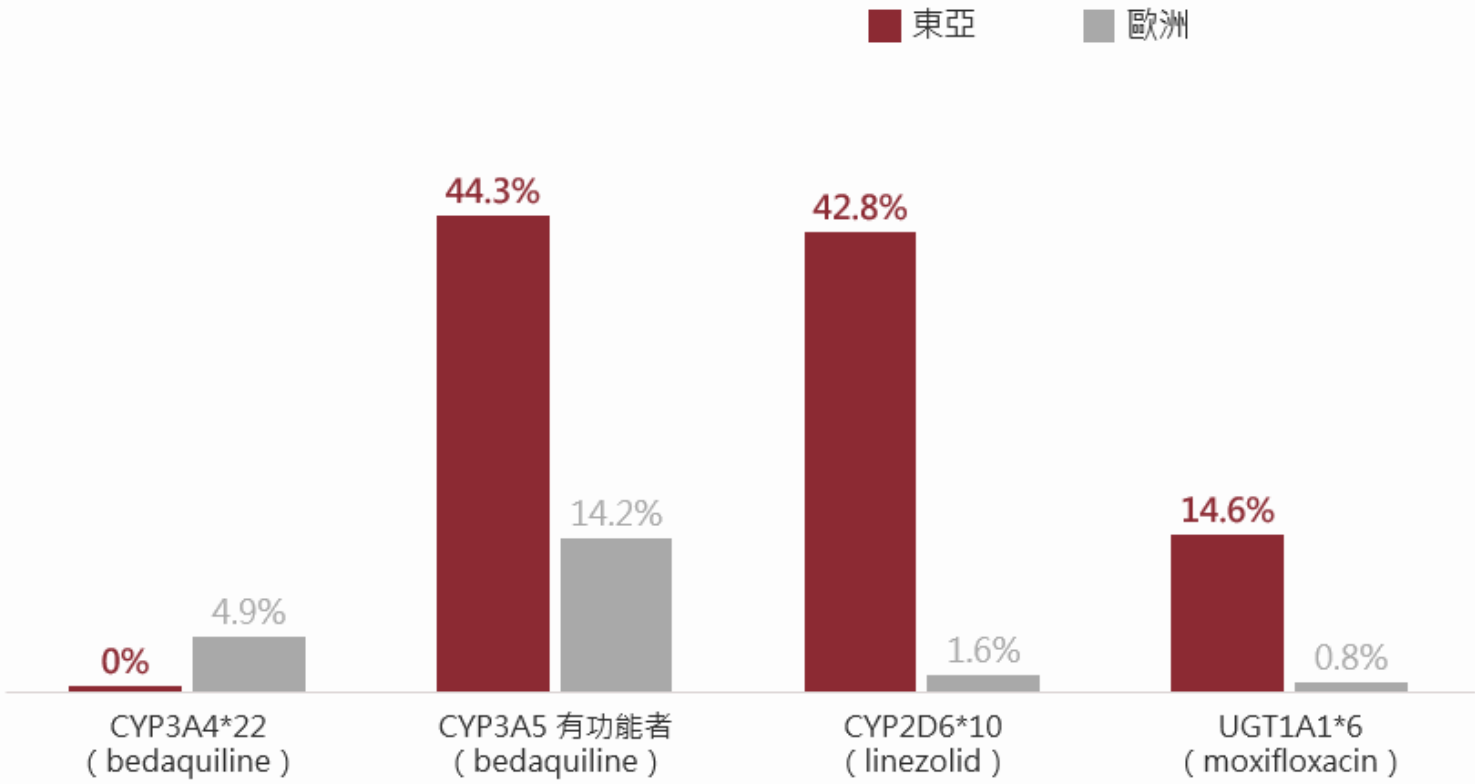


Figure 6. Visual Predictive Check (VPC) for External Validation

標的藥物之代謝酵素與亞洲人基因型



% (等位基因頻率；CYP3A5 為帶有可作用型之比例)

本計畫檢測基因

bedaquiline
CYP3A4、CYP3A5、CYP2B6、CYP2C19

linezolid
CYP4F2、CYP3A5、CYP2D6

moxifloxacin
UGT1A1

CYP3A5 台灣本土資料 (兩個獨立世代)

臺大醫院 3,562 人 (Lin 2026)
有功能者 48.7% | *3 為 71.2%

台灣人體生物資料庫 1,017 人 (Hsu 2024)
*3 為 73.2%

→ 與 CPIC 東亞推估 (*3 74.6%) 一致

國外的基因結論不能直接套用 → 需要本土資料

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表 1-10 *CYP3A5* 表現型及東亞帶因率對照表

表現型（phenotype）	東亞帶因率	雙倍型（diplotype）範例
一般代謝者 (normal metabolizers， NM)	6.4%	*1/*1
可能中速代謝者 (possible intermediate metabolizer)	0%	*1/*8、*1/*9
中速代謝者 (intermediate metabolizers， IM)	37.8%	*1/*3、*1/*6、*1/*7
慢速代謝者 (poor metabolizer， PM)	55.7%	*3/*3、*3/*6、*6/*7
代謝狀態不明者 (indeterminate metabolizer)	0%	*8/*9、*3/*8、*3/*9

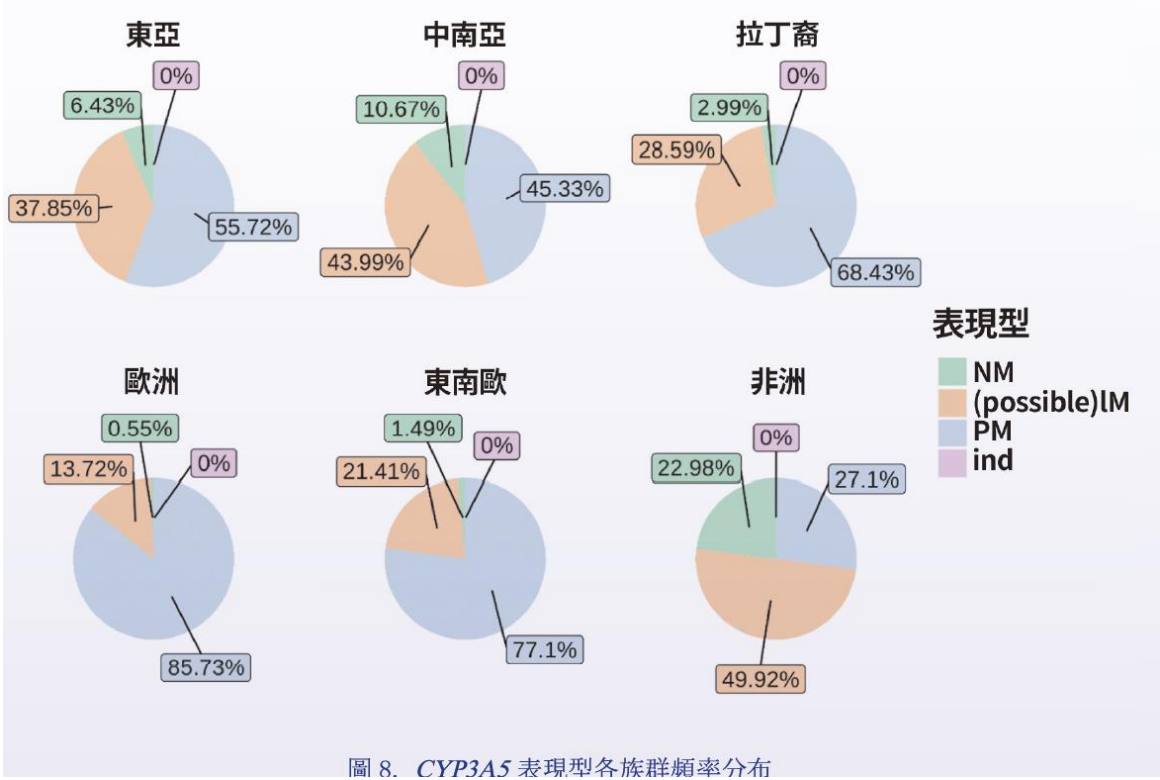


圖 8. *CYP3A5* 表現型各族群頻率分布

CYP3A5 gene polymorphism

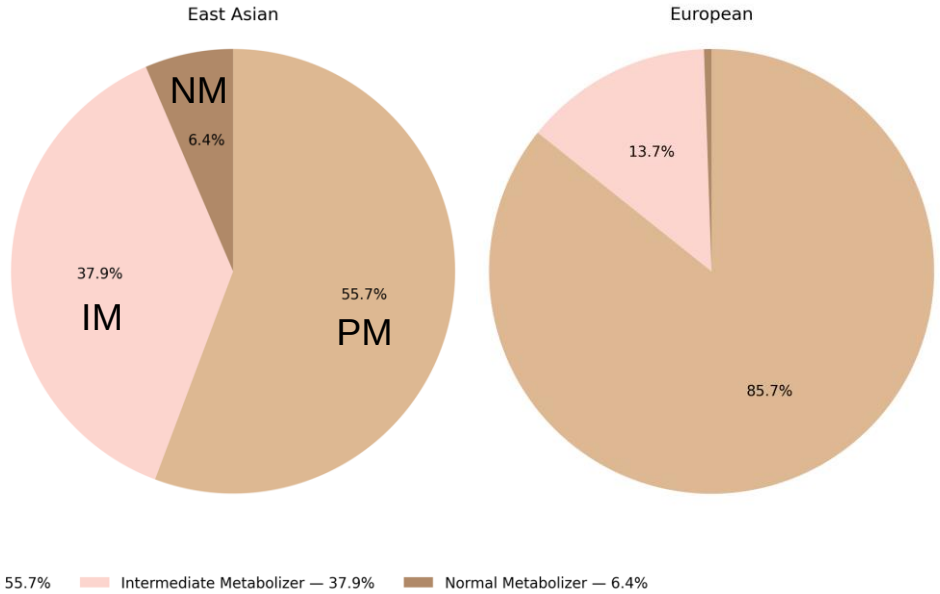
Table 1 Assignment of likely metabolism phenotypes based on *CYP3A5* diplotypes

Likely phenotype	Genotypes	Examples of diplotypes[a]
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one nonfunctional allele	*1/*3, *1/*6, *1/*7
Poor metabolizer (CYP3A5 nonexpresser)	An individual carrying two nonfunctional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7

[a]Additional rare variants, such as *CYP3A5*2*, *8, and *9 may be found, which are of unknown functional significance. However, if a copy of *1 is present, expected phenotype would be intermediate metabolizer.

39 Heart transplant + 24 Renal transplant recipients (NTUH study)

CYP3A5 genotype	Tacrolimus trough/ daily dose (ng/mL per mg/d)	P-value
*3/*3 (n=36)	3.7 ± 2.0	P < 0.001
*1/*1, *1/*3 (n=27)	1.6 ± 0.8	



Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, Wang D, Vinks AA, He Y, Swen JJ, Leeder JS, van Schaik R, Thummel KE, Klein TE, Caudle KE, MacPhee IA. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015 Jul;98(1):19-24. doi: 10.1002/cpt.113. Epub 2015 Jun 3. PMID: 25801146; PMCID: PMC4481158.

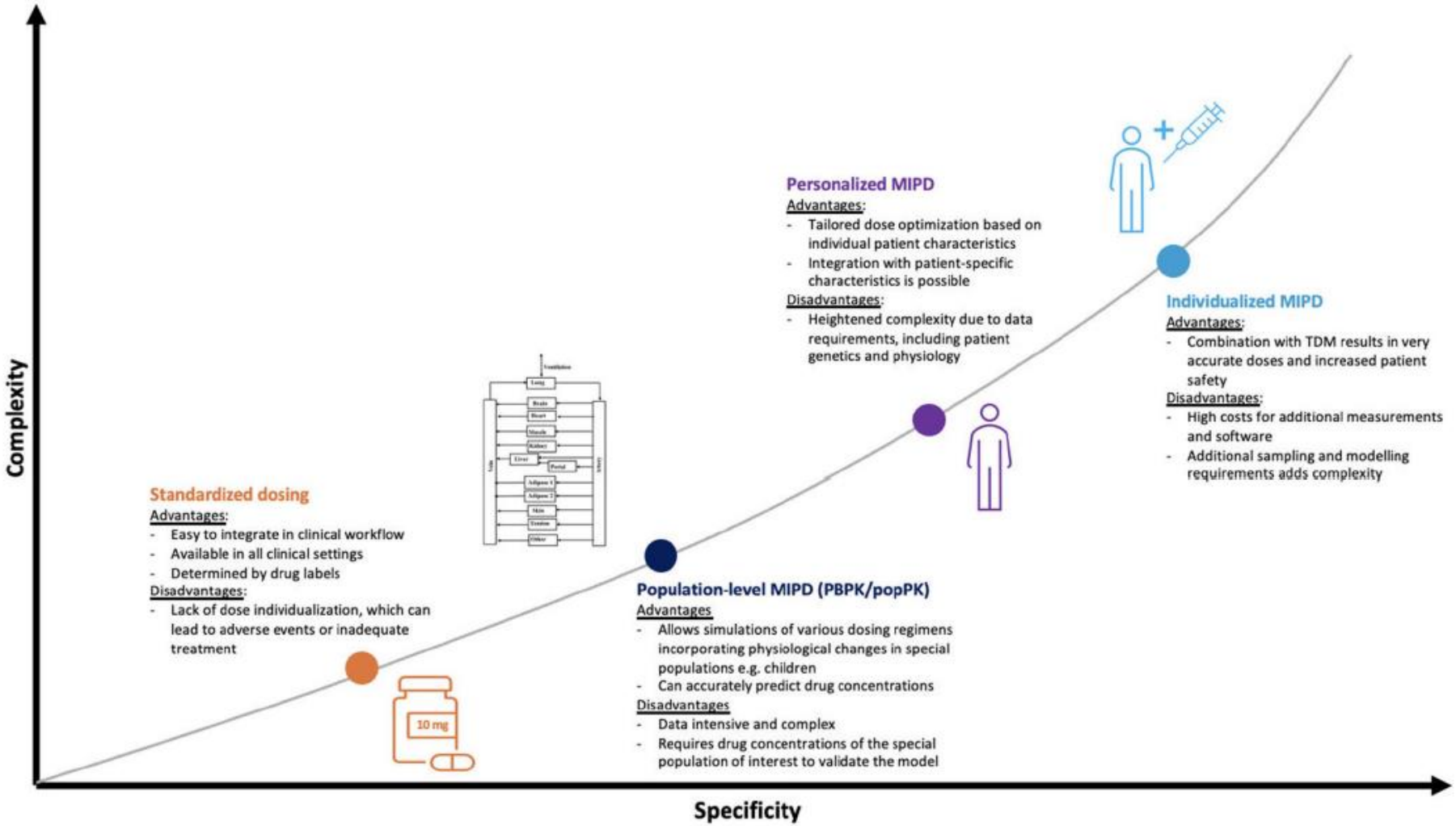
CYP3A5 Normal or Intermediate Metabolizer: Increase Tacrolimus Starting Dose

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

[a]Typically, with other CYP enzymes, an extensive metabolizer would be classified as a "normal" metabolizer, and, therefore, the drug dose would not change based on the patient's genotype. However, in the case of CYP3A5 and tacrolimus, a CYP3A5 expresser (i.e., CYP3A5 extensive metabolizer or intermediate metabolizer) would require a higher recommended starting dose and the CYP3A5 nonexpresser (i.e., poor metabolizer) would require the standard recommended starting dose. [b]This recommendation includes the use of tacrolimus in kidney, heart, lung, and hematopoietic stem cell transplant patients, and liver transplant patients in which the donor and recipient genotypes are identical. [c]Rating scheme is described in **Supplementary Data** online. [d]Further dose adjustments or selection of alternative therapy may be necessary because of other clinical factors (e.g., medication interactions, or hepatic function).

Birdwell KA, Decker B, Barbarino JM, Peterson JF, Stein CM, Sadee W, Wang D, Vinks AA, He Y, Swen JJ, Leeder JS, van Schaik R, Thummel KE, Klein TE, Caudle KE, MacPhee IA. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015 Jul;98(1):19-24. doi: 10.1002/cpt.113. Epub 2015 Jun 3. PMID: 25801146; PMCID: PMC4481158.



SPECIFICITY ↑ · COMPLEXITY ↑

- **Standardized**
  Label dose for everyone;
  no individualization
- **Population-level**
  popPK / PBPK
  → fixed doses for a group
- **Personalized**
  A priori: covariates such as genotype set the start dose
- **Individualized**
  A posteriori:
  TDM + Bayesian updating

PGx Testing Applications
In Clinical Medication Decision-making

- Why is Pharmacoeconomics (PE) necessary?
- Perspectives of Cost-effectiveness analysis (CEA).
- From PE to Health Technology Assessment (HTA).
- Current challenges and future vision.

Effectiveness of Single Allele Test

Classification	Outcome measurement	Example
Improvement of clinical events	Relative risk reduction (RRR) for ADR, mortality, treatment failure.	• Genetic testing can reduce the incidence of ADR from 5% to 1%. • CYP2C19-guided antiplatelet drugs can reduce treatment failure rate by 10%.
Avoid the use of medical resources	AE related health services uses (hospitalization days, outpatient visit)	• Can avoid hospitalization or prolonged hospitalization due to SJS/ HTN.
Survival time and health assessment	Quality-adjusted life years (QALY)	• HLB-B*58:01-guided therapy group show an average increase of 0.05 in QALY.

Perspectives of CEA: Uncertainty

4. Implementation Factors:

- Detection accessibility and reporting time.
- Clinical staff education and interpretation skills.
- Insurance payment policies and indications.
- Patient acceptance and ethical considerations.
- Uptake (If too few people use it, even the best product will be ineffective.)

1. Clinical Factors:

- The strength of the association between gene and drugs
- Severity of clinical consequences (metabolic activity score)
- Prevalence of variant genes in populations (e.g., HLA-B*1502, Asian > European)
- Feasibility of alternative treatment options
- Strength of clinical evidence (RCT or large study)

3. Decision Making:

- ICER < Decision-maker's willingness to pay threshold (λ, WTP)*
- Budget impact analysis
- Equitable access to healthcare

*UK NICE (Government): £20,000-30,000/QALY
WHO recommends (Government or insurers): 1-3 GDP/QALY per capita.

2. Economic Factors:

- Testing costs (from single- to multi-gene modules, becoming increasingly cheaper)
- Detection timing (pre-emptive/ reactive) and scope
- Differences in healthcare spending and QALY: ICER (△Cost/ △QALY)

PGx Resources

PHARMGKB

ClinPGx

CPIC®
Clinical Pharmacogenetics Implementation Consortium

KNMP DPWG

PharmVar
Pharmacogene Variation Consortium

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Thank you for attention.

Q&A

