藥物基因檢測的實證與資訊平台

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仿單中的藥物基因體學生物標誌新知

- http://www.cde.org.tw/Content/Files/Knowledge/81a0e7d2-dda3-4cec-8856-86c422145e8e.pdf

當代醫藥法規
RegMed News

仿單中的藥物基因體學生物標誌新知

王蓉君[1] 高純琇[2]

前言

新英格蘭醫學雜誌期刊 (The New England Journal of Medicine) 於今 2011 年 3 月 24 日刊出由台灣研究團隊所證實，用藥前實施基因篩檢可以有效預防卡巴氮平(Carbamazepine)所引起的嚴重副作用 "史蒂文生氏強生症候群/毒性表皮溶解症(SJS/TEN)" 之論文[1]；為了減少國人嚴重藥物副作用的發生，健保局近期修正 Carbamazepine 全民健康保險藥品給付規定，並於今年 8 月 1 日開始實施，要求醫師對於新病人處方藥物 Carbamazepine 之前，應先確認病人之 HLA-B*1502 基因檢測結果[2]。

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結語

藥物基因體學生物標誌的進展，使得現今的臨床醫學邁入了個人化醫療(personalized medicine)的時代；藥物基因體學研究的新知，充份揭露於藥物仿單之中，生物標誌於今所扮演的角色，包括可以協助臨床醫師辨識病人對於治療藥物是否具有療效反應、避免嚴重副作用的產生、協助病人選擇最適當的藥物及劑量等，除了提升研發新藥的療效之外，同時也可以降低藥害事件發生率，預期可將現行的事後救濟邁向事前預防的新階段。同時，藥物基因體學的進步和新知識也間接帶動醫療產業的進展，促成醫療檢驗方法、多標的陣列平台基因診斷試劑、生物晶片和諸多醫療器材研發的新興市場。

Clinical study design and quality of evidence
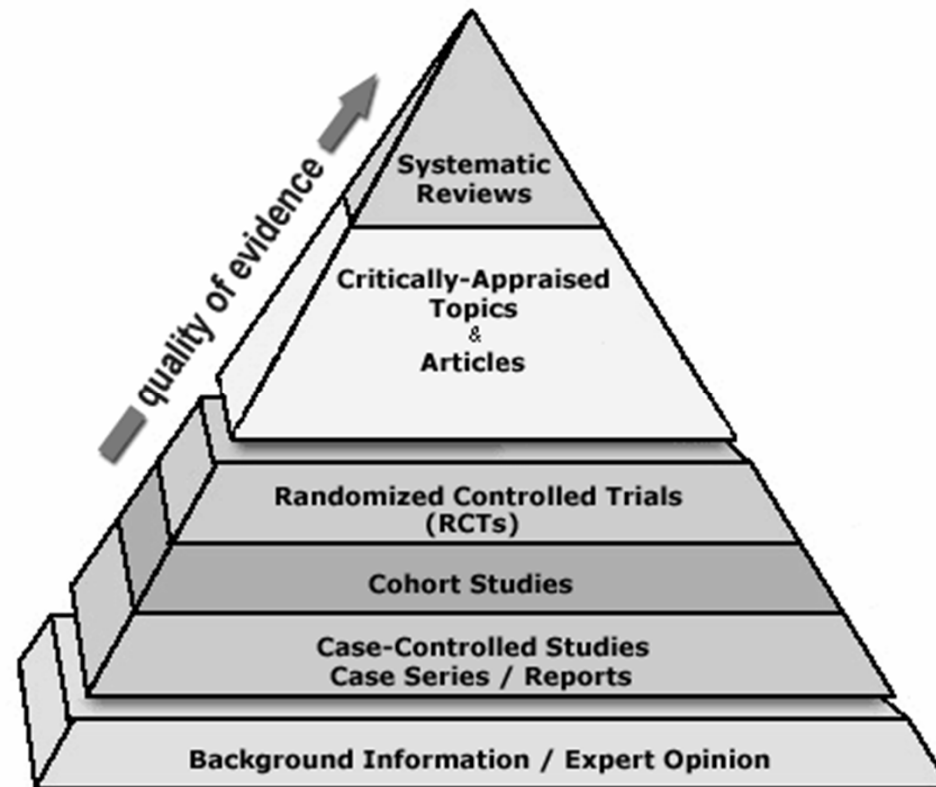
藥物基因檢測實際上到臨床應用可能遇到的問題

並非所有PGx的結果都能直接應用在臨床上，可能影響的因素包含:
○**信度問題**
　○檢測結果是否能準確預測與藥物相關的表現
○**效度問題(actionable)**
　○臨床上是否可以真的接受，進而改變治療策略及影響臨床結果

Medical Genetics Summaries

Medical Genetics Summaries is a growing collection of summaries which describe the impact that specific sequence variations have on health. The summaries review genetic variants that underlie inherited conditions, affect the risk of developing a disease in the future, or influence how an individual may respond to a specific drug.

https://www.ncbi.nlm.nih.gov/pubmed/28520340

Pharmacogenomics Knowledge Base (PharmGKB)

Knowledge resource that collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses

Drug-gene pairs are assigned a level of evidence based on multiple criteria, including replication, statistical significance and study size – Level 1A/1B (highest) to Level 4 (lowest, preliminary)

Clinical Pharmacogenetics Implementation Consortium (CPIC)

Started as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN) in 2009

To implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

- Creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines
- Follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal

Clinical Pharmacogenetics Implementation Consortium (CPIC)

CPIC assigns CPIC levels to genes/drugs with
- (1) PharmGKB Clinical Annotation Levels of Evidence of 1A, 1B, 2A and 2B
- (2) a PharmGKB PGx level for FDA-approved drug labels of "actionable pgx", "genetic testing recommended", or "genetic testing required"
- (3) based on nomination to CPIC for consideration.

Clinical Annotation Levels of Evidence (Pharm GKB)
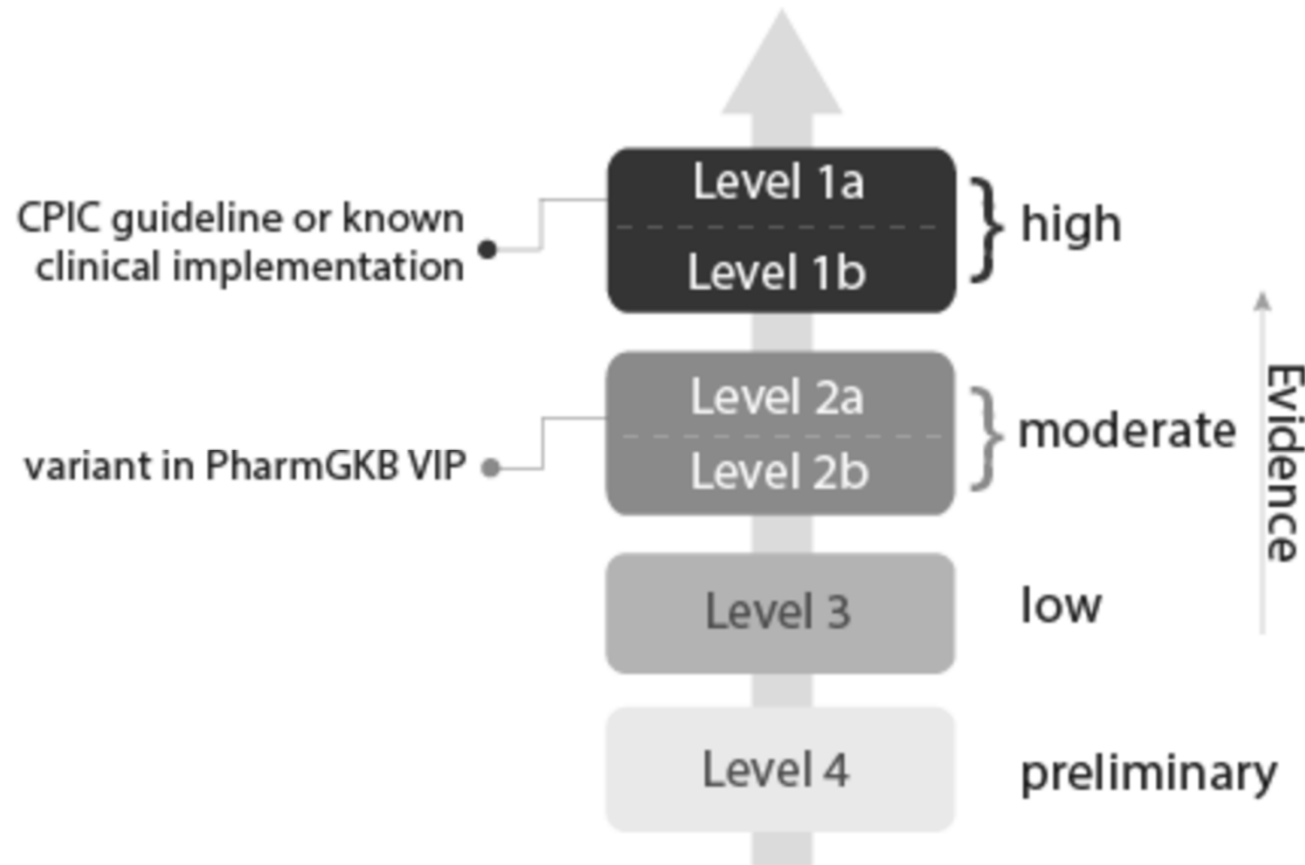
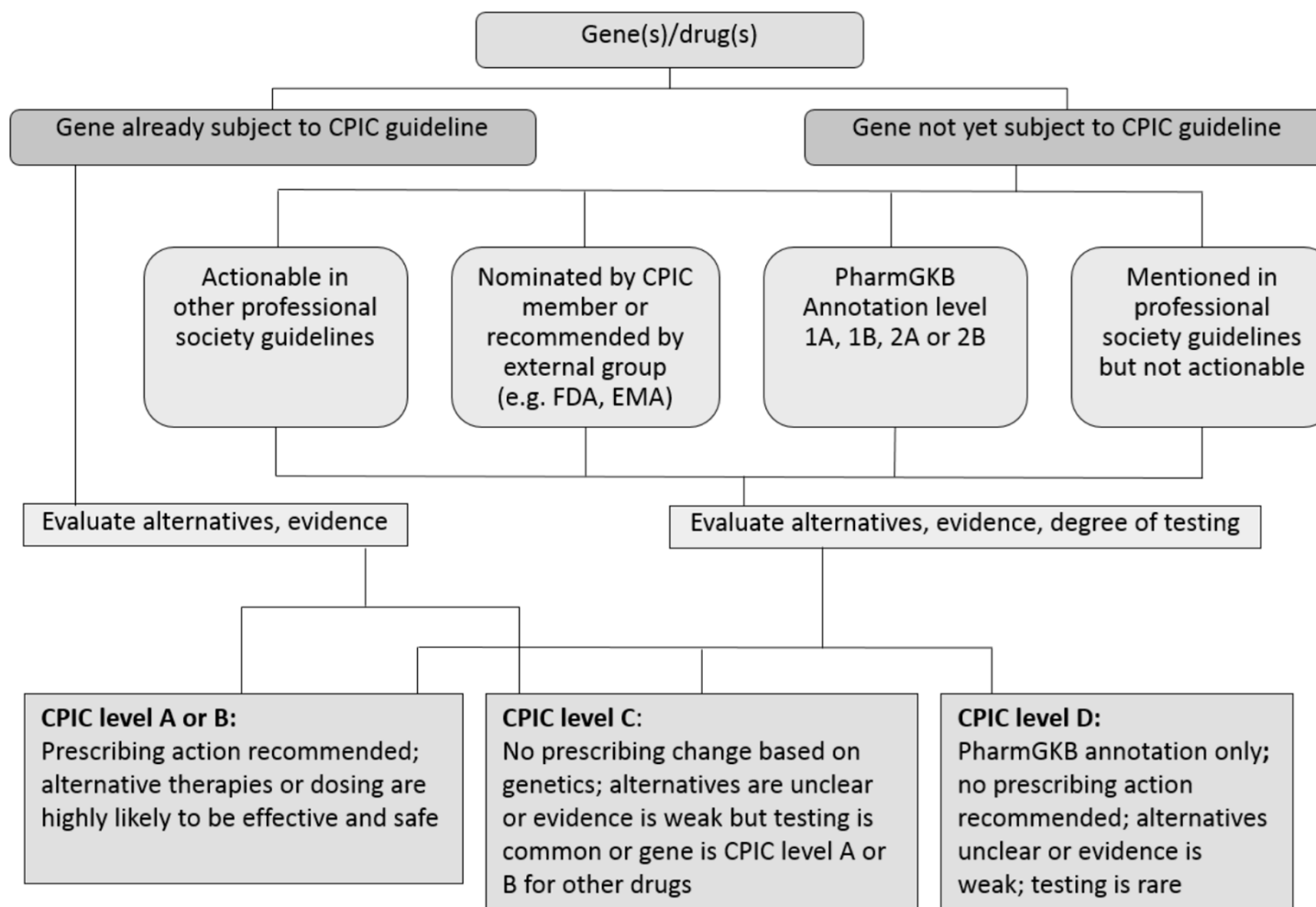# PharmGKB PGx level for FDA-approved drug labels

PGx Level

Testing required The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients. PharmGKB considers labels that state the variant is an indication for the drug, as implying a test requirement. If the label states a test "should be" performed, this is also interpreted as a requirement.

Testing recommended The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended before using this drug. This recommendation may only be for a particular subset of patients. PharmGKB considers labels that say testing "should be considered" to be recommending testing.

Actionable PGx The label does not discuss genetic or other testing for gene/protein/chromosomal variants, but does contain information about changes in efficacy, dosage or toxicity due to such variants. The label may mention contraindication of the drug in a particular subset of patients but does not require or recommend gene, protein or chromosomal testing.

Informative PGx The label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response.

Considerations for Assignment of CPIC Level for Genes/Drugs

Gene(s)/drug(s)

Gene already subject to CPIC guideline | Gene not yet subject to CPIC guideline

Actionable in other professional society guidelines

Nominated by CPIC member or recommended by external group (e.g. FDA, EMA)

PharmGKB Annotation level 1A, 1B, 2A or 2B

Mentioned in professional society guidelines but not actionable

Evaluate alternatives, evidence

Evaluate alternatives, evidence, degree of testing

CPIC level A or B:
Prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe

CPIC level C:
No prescribing change based on genetics; alternatives are unclear or evidence is weak but testing is common or gene is CPIC level A or B for other drugs

CPIC level D:
PharmGKB annotation only; no prescribing action recommended; alternatives unclear or evidence is weak; testing is rare

Level Definitions for CPIC Genes/Drugs

CPIC LEVEL	CLINICAL CONTEXT	LEVEL OF EVIDENCE	STRENGTH OF RECOMMENDATION
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	Evidence levels can vary	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary	No prescribing actions are recommended.

Over 35 Medications with CPIC Guidelines

Cardiology

- Clopidogrel – **CYP2C19**
- Simvastatin – *SLCO1B1*
- Warfarin – **CYP2C9** and *VKORC1*

Infectious disease

- Abacavir – *HLA-B*57:01*
- Atazanavir – *UGT1A1*
- PEG-interferon – *IL28B*

Neurology

- Carbamazepine – *HLA-B*15:02*
- Phenytion – **CYP2C9**, *HLA-B*15:02*

Oncology

- Thiopurines – *TPMT*
- Capecitabine/5-FU – *DPYD*
- Rasburicase - *G6PD*

Pain management

- Codeine – **CYP2D6**
- Tramadol – **CYP2D6**
- Tricyclic antidepressants – **CYP2C19, CYP2D6**

Psychiatry

- Tricyclic antidepressants – **CYP2C19, CYP2D6**
- Selective serotonin reuptake inhibitors– **CYP2C19, CYP2D6**

Rheumatology

- Thiopurines – *TPMT*
- Allopurinol – *HLA-B*58:01*

Solid organ transplant

- Tacrolimus – *CYP3A5*

Respiratory

- Ivacaftor - *CFTR*

Figure 1. Current drug-gene pairs with Clinical Pharmacogenetics Implementation Consortium guidelines grouped by disease state. The genes in bold (*CYP2C19, CYP2C9, CYP2D6*) are the backbone genes for a general pharmacogenomics implementation initiative.

Vo et al. Pharmacotherapy 2017; 37:1014-1022.

Elements of CPIC Guidelines

Introduction

• Literature review process

• Gene(s):

– Background

– Genetic test interpretation

– Available genetic test options

– Incidental findings

– Other considerations

• Drug(s):

– Background

– Linking genetic variability to variability in drug-related phenotypes

– Dosage and/or therapeutic recommendations

– Recommendations for incidental findings

– Other considerations

• Potential benefits and risks for the patient

• Caveats: appropriate use and/or potential misuse of genetic tests

• Disclaimer

• Assignment of likely phenotypes based on genotypes

• Recommended prescribing of drug(s) by phenotype

Other Databases or evidence

- Dutch Pharmacogenetics Working Group (DPWG)

  – https://www.pharmgkb.org/page/dpwg

- Professional society guidelines for certain gene-drug pairs. Examples:

  – Canadian Pharmacogenomics Network for Drug Safety (e.g., carbamazepine)

  – Antiretroviral Guidelines (abacavir)

  – American College of Rheumatology (allopurinol)

- Clinical Genome Resource (ClinGen)

CPIC guideline example
CYP2D6 and codeine Therapy
https://www.youtube.com/watch?v=Rv0Rb7w1u2A

Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (*CYP2D6*) diplotypes

Likely phenotype[a]	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN
Extensive metabolizer (~77–92% of patients)	1.0–2.0[b]	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10
Intermediate metabolizer (~2–11% of patients)	0.5[b]	An individual carrying one reduced-function and one nonfunctional allele	*4/*10, *5/*41
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6

[a]The frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See **Supplementary Data** online for estimates of phenotype frequencies among different ethnic/geographic groups. [b]Note that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and those with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.[12]

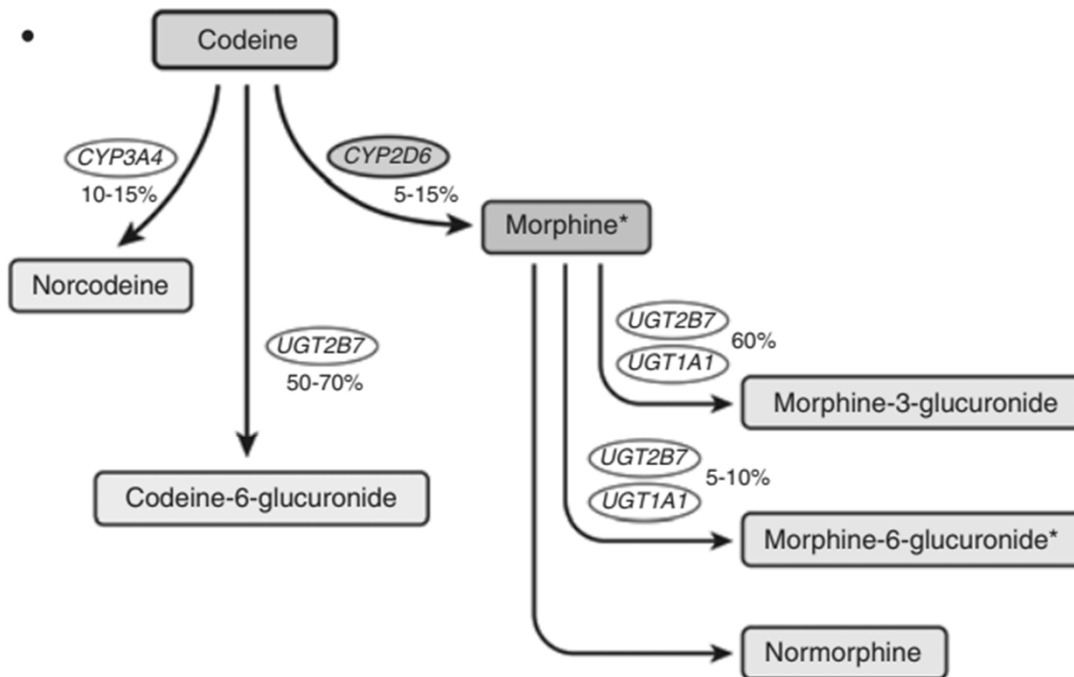# CPIC guideline example
CYP2D6 and codeineTherapy

Figure 1 Codeine metabolism pathway in an individual with cytochrome P450 2D6 (CYP2D6) extensive metabolism. Asterisks (*) denote active metabolites.

CPIC guideline example
CYP2D6 and codeine Therapy

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

[a]Rating scheme is described in **Supplementary Data** online. [b]There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable.[18,20,21] [c]Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.

Prevalence of CYP2C9, 2C19, 2D6 genotyping & Drug, drug, gene interactions

Table 1. Definitions of clinical impact categories for drug interactions.

Clinical impact	Definition
Major interaction	Contraindicated combination Conditionally contraindicated combination Significant interactions likely to require action >200% increase in AUC predicted >90% reduction in AUC predicted
Substantial interaction	Interactions that may need monitoring and/or dose adjustments of affected medications 75–200% increase in AUC predicted 60–90% reduction in AUC predicted
Moderate interaction	Possible interactions 25–75% increase in AUC predicted 25–60% reduction in AUC predicted
No interaction or minimal interaction	No clinically significant interaction expected <25% change in AUC predicted

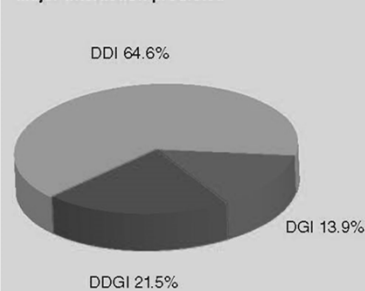**Table 2. Drug and gene interaction types.**

Type of interaction	Definition
DDI	An interaction solely caused by drug response to a coadministered drug (both pharmacokinetic and pharmacodynamic)
DGI	An interaction solely caused by drug response to CYP450 genetics
DDGI	An interaction that is a cumulative effect of both a DDI and DGI

DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.

Table 3. Total number of potential significant and major interactions.

	Potentially substantial or major interaction	Potentially major interaction
Number of patients	501	321
Number of interactions (total)	1053	525
Number of interactions per patient	2.1	1.6
Number of DDIs	696 (66.1%)	339 (64.6%)
Number of DGIs	155 (14.7%)	73 (13.9%)
Number of DDGIs	202 (19.2%)	113 (21.5)

DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.
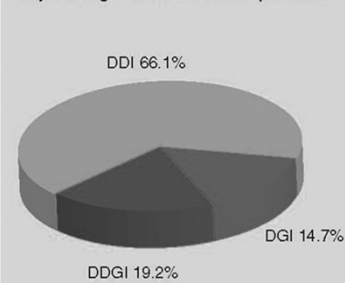

Figure 2. Frequency of drug–drug, drug–gene and drug–drug–gene interactions predicted.
DDI: Drug–drug interaction; DDGI: Drug–drug–gene interaction; DGI: Drug–gene interaction.

Major interaction predicted: DDI 64.6%, DGI 13.9%, DDGI 21.5%

Major or significant interaction predicted: DDI 66.1%, DGI 14.7%, DDGI 19.2%

Table 6. Allele frequency for CYP2D6, CYP2C19 and CYP2C9.

CYP2D6 Allele	n (%)	CYP2C19 Allele	n (%)	CYP2C9 Allele	n (%)
*1	952 (41.8)	*1	1490 (65.3)	*1	1873 (82.2)
*2	86 (3.8)	*2	340 (14.9)	*2	235 (10.3)
*2A	438 (19.2)	*3	3 (0.1)	*3	139 (6.1)
*3	31 (1.4)	*4	5 (0.2)	*5	5 (0.2)
*4	354 (15.6)	*6	1 (0.0)	*6	1 (0.0)
*5	76 (3.3)	*8	7 (0.3)	*8	14 (0.6)
*6	20 (0.9)	*17	436 (19.1)	*11	9 (0.4)
*8	1 (0.0)			Unknown†	2 (0.1)
*9	56 (2.5)				
*10	58 (2.5)				
*17	49 (2.2)				
*41	153 (6.7)				
Unknown†	2 (0.1)				
Duplications	66 (2.8)‡				
Grand total	2276 (100.0)		2282 (100.0)		2278 (100.0)

†The combination of variants were unusual and an allele designation was not available at analysis.
‡Percentage for duplications based on number of patients and not number of alleles. Duplications not counted towards allele grand total.

Table 7. Phenotype frequency for CYP2D6, CYP2C19 and CYP2C9.

CYP2D6 Phenotype	n (%)	CYP2C19 Phenotype	n (%)	CYP2C9 Phenotype	n (%)
Extensive metabolizer	634 (55.6)	Extensive metabolizer	494 (43.3)	Extensive metabolizer	780 (68.5)
Intermediate metabolizer†	405 (35.5)	Intermediate metabolizer	302 (26.5)	Intermediate metabolizer	315 (27.7)
Poor metabolizer	52 (4.6)	Poor metabolizer	27 (2.4)	Poor metabolizer	44 (3.9)
Ultrarapid metabolizer‡	49 (4.3)	Rapid metabolizer	267 (23.4)		
		Ultrarapid metabolizer	51 (4.5)		
Grand allele total	1140		1141		1139

†Twelve individuals' CYP2D6 phenotypes had two possible phenotypes: CYP2D6 intermediate metabolizer or CYP2D6 extensive metabolizer. In these scenarios, the individual was classified as the worst-case scenario phenotype, CYP2D6 intermediate metabolizer.
‡Nine individuals' CYP2D6 phenotypes had two possible phenotypes: CYP2D6 ultrarapid metabolizer or CYP2D6 extensive metabolizer. In these scenarios, the individual was classified as the worst-case scenario phenotype, CYP2D6 ultrarapid metabolizer.

Variant frequency differ from population to population

CYP2C19 allele	East Asian Allele Frequency	South/Central Asian Allele Frequency	Caucasian Allele frequency (European & North American)	African American Allele frequency	American Allele frequency
*1	57.60	48.50	62.10	57.00	67/00
*2	29.30	33.10	14.60	18.30	13.10
*3	8.60	1.60	0.60	0.30	0.30
*4A	0.10	0.00	0.30	0.00	0.03
*5	0.00	0.00	0.00	0.00	0.00
*6	0.00	0.00	0.10	0.00	0.00
*7	0.00	0.00	0.00	0.00	0.00
*8	0.00	0.00	0.30	0.20	0.10
*9	0.00		0.00	1.10	0.10
*10	0.00		0.00	0.40	0.10
*12	0.00		0.00	0.20	0.00
*13	0.00		0.10	1.20	0.40
*14	0.00		0.00	0.00	0.00
*15	0.20		0.20	1.40	0.40
*17	1.60		21.30	20.10	16.30
*35	0.00		0.00	0.80	2.10

https://www.pharmgkb.org/page/cyp2c19RefMaterials

Different PGx testing has different coverage…
Take 2C19 as the example

Gene	PGX1	PGX2	PGX3	PGX4	PGX5
CYP2C19	*2,*3,*4,*4B, *10,*17	*2,*3,*4,*4B, *5,*6,*7,*8,* 9,*10,*17	*2,*3,*4,*5,* 7,*8,*17	*2,*3,*4,*6,* 8,*9,*17	*2,*3,*17

Which one is better?

Is it necessary to conduct PGx RCTs?

- Compare genotype-guided dosing/drug selection versus is still conventional for dosing/drug selection

- Prospective RCT in PGx are not common

- Expense, feasibility, rare adverse events among RCTs

- It is still controversial to conduct prospective PGx RCTs to demonstrate clinical utility…

Example of RCT for PGx Testing

BMC Psychiatry

RESEARCH ARTICLE   Open Access

CrossMark

Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial

Víctor Pérez[1,2], Ariana Salavert[3], Jordi Espadaler[3], Miquel Tuson[3], Jerónimo Saiz-Ruiz[1,4], Cristina Sáez-Navarro[1,5], Julio Bobes[1,6], Enrique Baca-García[1,7,8,9], Eduard Vieta[1,10], José M. Olivares[11], Roberto Rodriguez-Jimenez[1,12], José M. Villagrán[13], Josep Gascón[14], Josep Cañete-Crespillo[15], Montse Solé[1,5], Pilar A. Saiz[1,6], Ángela Ibáñez[1,4], Javier de Diego-Adeliño[1,16], AB-GEN Collaborative Group and José M. Menchón[1,17,18*]
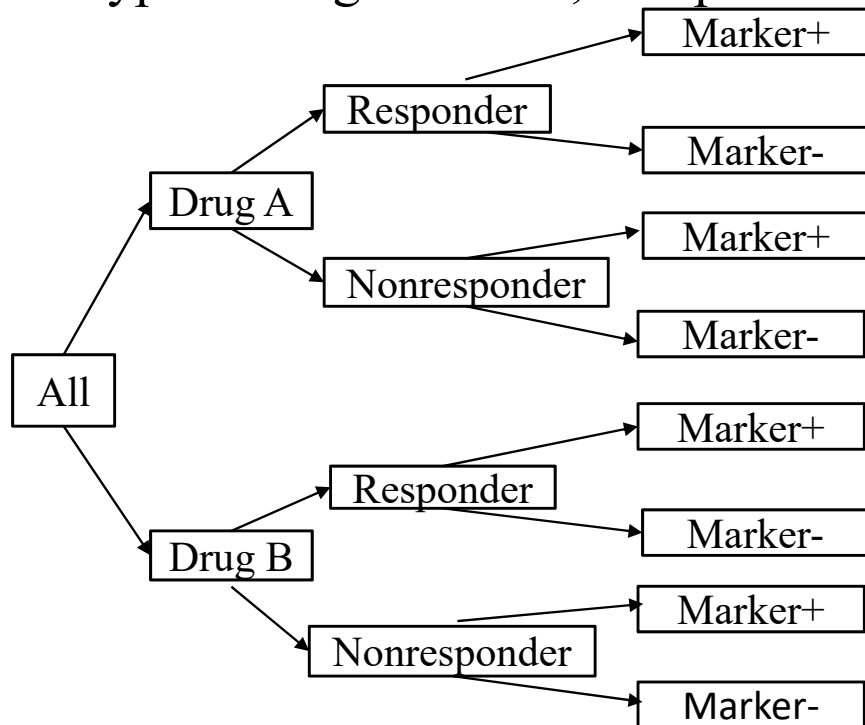
Abstract

Background: A 12-week, double-blind, parallel, multi-center randomized controlled trial in 316 adult patients with major depressive disorder (MDD) was conducted to evaluate the effectiveness of pharmacogenetic (PGx) testing for drug therapy guidance.

Methods: Patients with a CGI-S ≥ 4 and requiring antidepressant medication de novo or changes in their medication regime were recruited at 18 Spanish public hospitals, genotyped with a commercial PGx panel (Neuropharmagen®), and randomized to PGx-guided treatment (n = 155) or treatment as usual (TAU, control group, n = 161), using a computer-generated random list that locked or unlocked psychiatrist access to the results of the PGx panel depending on group allocation. The primary endpoint was the proportion of patients achieving a sustained response (Patient

Conclusion:PGx-guided treatment resulted in significant improvement of MDD patient's response at 12 weeks, dependent on the number of previously failed medication trials, but not on sustained response during the study period. Burden of side effects was also significantly reduced.
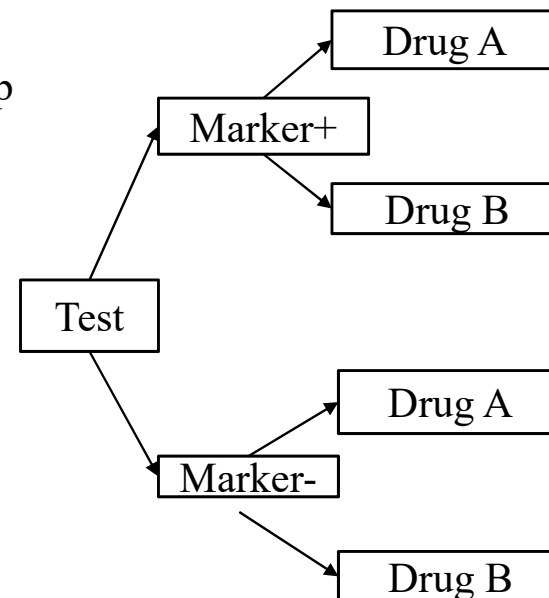
Pharmacogenomics trial design (I)

Retrospective: for marker unknown, hypothesis generation, independent validation

Prospective stratified (I): base on a prior hypothesis, enrichment, balance treatment assignment

All → Drug A → Responder → Marker+ / Marker-

All → Drug A → Nonresponder → Marker+ / Marker-

All → Drug B → Responder → Marker+ / Marker-

All → Drug B → Nonresponder → Marker+ / Marker-

But:
Unbalanced group
Reduced power
Missing data

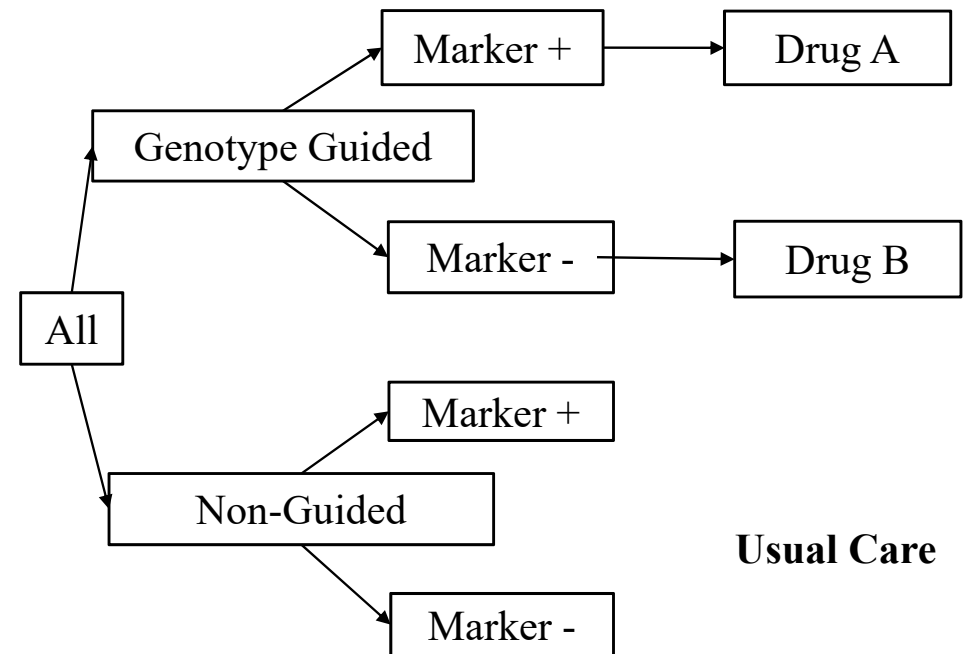Test → Marker+ → Drug A / Drug B

Test → Marker- → Drug A / Drug B

But:
Need to a prior hypothesis of variant

Pharmacogenomics trial design (II)

Prospective stratified (I): unknown intervention
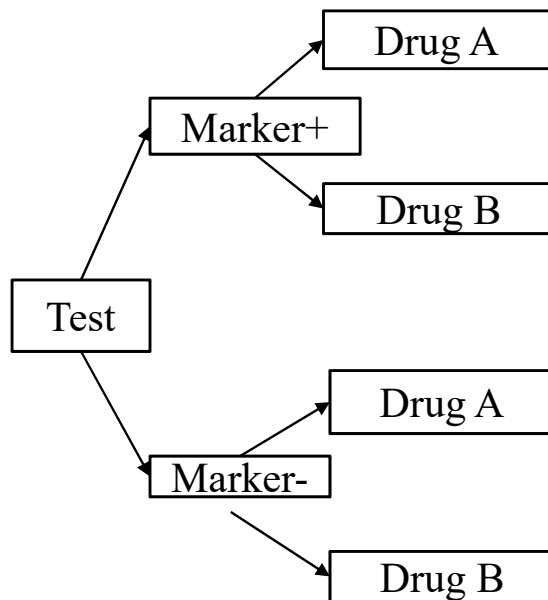
Prospective clinical practice/intervention
: Good for clinical practice

藥物基因檢測的實證與資訊平台練習

Pharmacogenomics Knowledge Base (PharmGKB)
https://www.pharmgkb.org/
Clinical Pharmacogenetics Implementation Consortium (CPIC)
https://cpicpgx.org/
FDA biomarker list
https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm
PharmVar
www.pharmvar.org
dbSNP
https://www.ncbi.nlm.nih.gov/projects/SNP/
Genetic testing registry
https://www.ncbi.nlm.nih.gov/gtr

請大家上去查Clopidogrel, Codeine等

●**Drugs@FDA (**https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) SANOFI AVENTIS

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020839

●台灣仿單

●Pharm GKB

●CPIC guideline

●FDA biomarker list

Clopidogrel 之CYP2C19 *2/*2 的phenotype?

適用哪一種病人族群