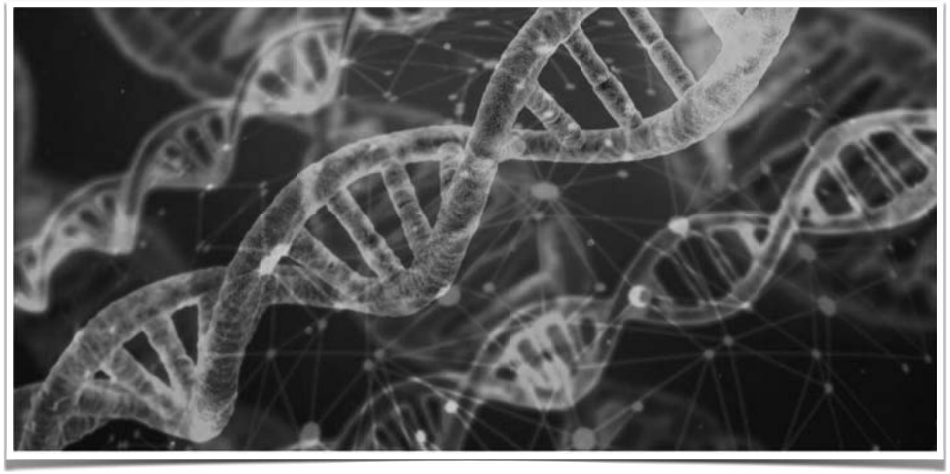


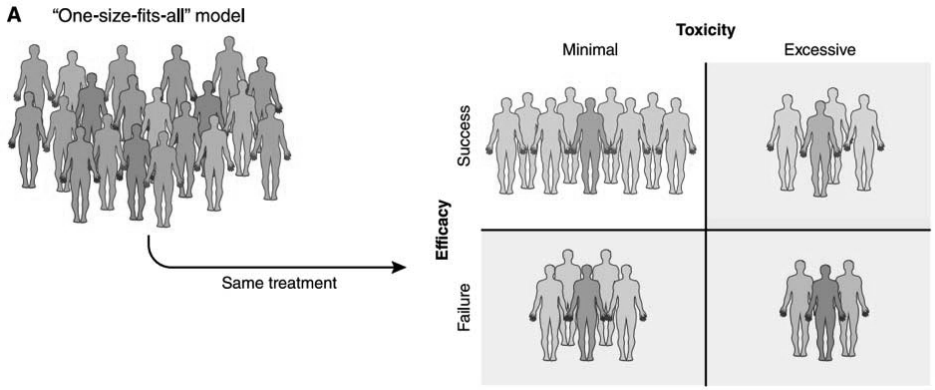
藥物基因檢測介紹與藥師角色

吳尚樺藥師 2019.5.4

藥物？基因？檢測？？

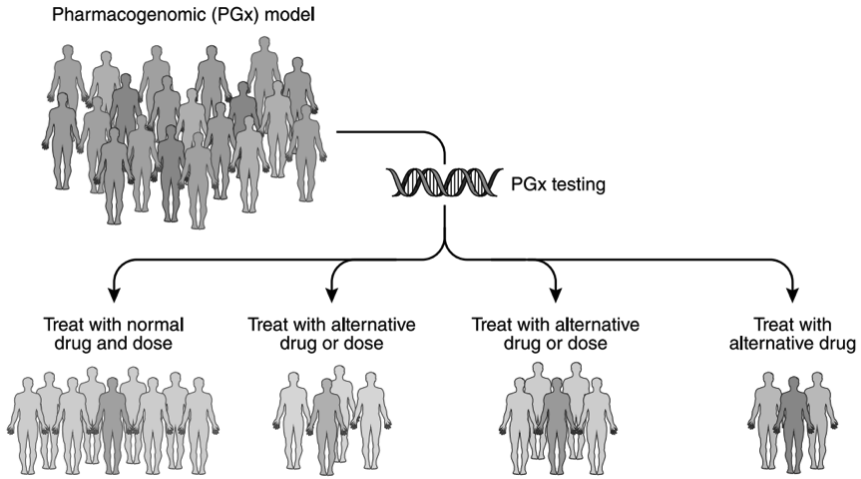
- **Pharmacogenomic testing (PGx)**
  - 結合藥理學與藥物基因體學
  - 用來實現精準醫療的工具
  - 透過檢測與藥物相關的基因，選擇適合的藥物、劑量
  - 確保最佳療效且將副作用降到最低

一般我們用藥的情況是這樣子



Clin J Am Soc Nephrol. 2018 Oct 8;13(10):1561-1571.

透過藥物基因檢測可能變成這樣子



Clin J Am Soc Nephrol. 2018 Oct 8;13(10):1561-1571.

藥物基因檢測在臨床上的意義

- 藥物基因檢測提供醫療人員資訊輔助臨床藥物使用的決策
- 藥物基因檢測不是萬能，仍須考量其他影響因子如：
  - 性別、身高、體重、年齡、肝腎功能、疾病
  - 是否吸菸、是否喝咖啡、其他藥物及保健食品的併用
  - 是否正確用藥？服藥順從性的評估

溫故知新：藥物基因學的名詞介紹

- Genome, Chromosome, Gene, Nucleotide
- Gene Expression
  - DNA—Transcription—RNA—Translation—Protein
- Gene Structure
  - Promoter, Exon, Intron, 5'UTR, 3'UTR
- Genetic Variation
  - Polymorphism, Mutation
- Allele
  - SNP, Homozygous alleles / Heterozygous alleles
- Genotype and Phenotype

藥物基因變異影響藥物反應

- 每個人對於藥物的反應不同，很高比例可能跟藥物基因變異有關
- 藥物基因的變異依照藥物的不同，估計對於藥物的反應有20%-95%的影響
- 這些影響藥物的變異主要發生在基因編碼Drug metabolism enzymes & transporters (the ADME genes), Drug Target, or HLA alleles 的位置
  - Regulatory region: affecting level of expression
  - Coding region: affecting the function of gene
    - 影響藥物濃度高低、增加或減少藥物作用、引發藥物不良反應

Mukerjee, G., et al., User considerations in assessing pharmacogenomic tests and their clinical support tools. npj Genomic Medicine, 2018. **3**(1): p. 26.

藥物基因檢測？癌症藥物檢測？

- Germline variation

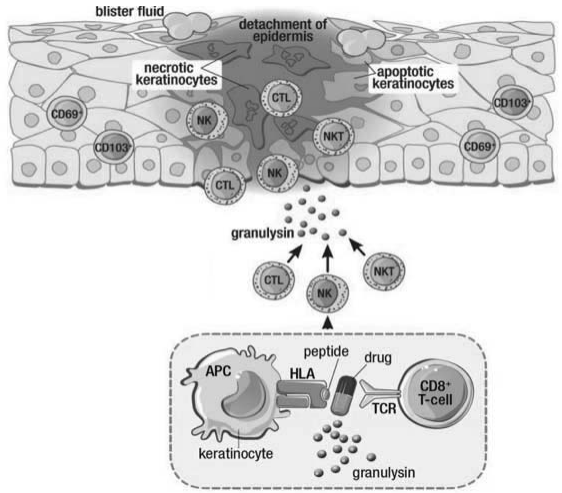
通常只需要檢測一次

  - Drug hypersensitivity：HLA-B*1502 / Carbamazepine
  - PK genes：CYP2C19 / Clopidogrel
  - PD genes：VKORC1 / Warfarin
  - Disease：LDLR (Cause Familial hypercholesterolemia/PCSK9)
- Somatic mutations

可能隨著病情改變需要進行多次檢測

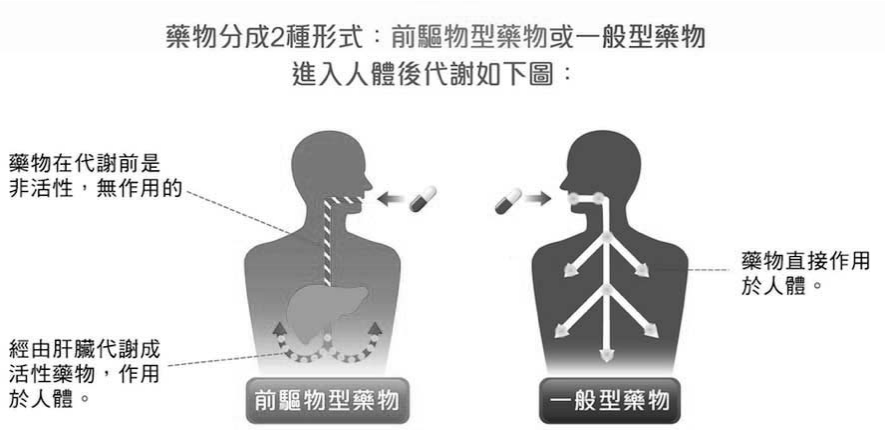
  - HER2, EFGR, ALK, KRAS to choose optimize Cancer therapy

HUMAN LEUKOCYTE ANTIGENS AND DRUG-INDUCED HYPERSENSITIVITY REACTIONS

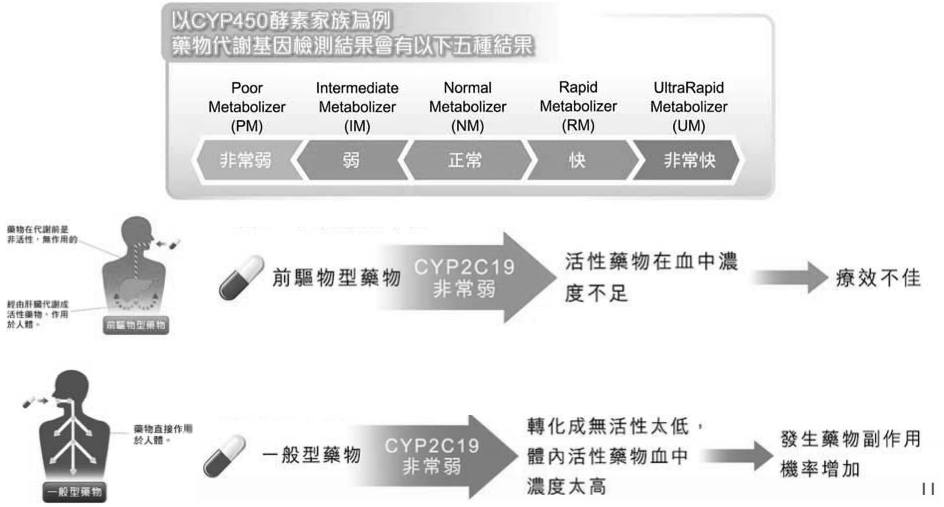


Peter et al., The Journal of Allergy and Clinical Immunology: In Practice, 5(3), 547–563. 2017

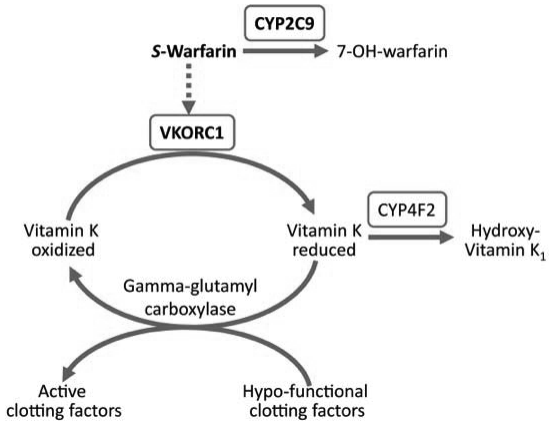
透過檢測CYP能力預測血中濃度



透過檢測CYP能力預測血中濃度



檢測藥物作用關鍵基因-WARFARIN



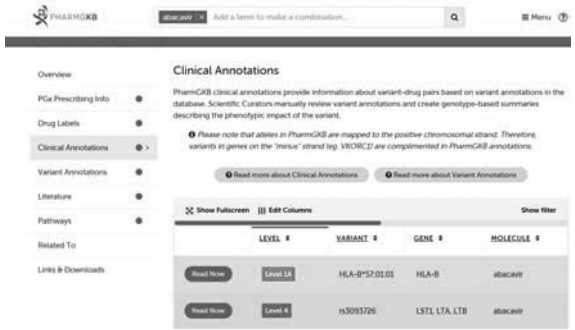
Johnson, J.A., & Cavallari, L. H. (2013). Pharmacogenetics and cardiovascular disease--implications for personalized medicine. Pharmacological reviews, 65(3), 987–1009. doi:10.1124/pr.112.007252

最直接的資訊來源-仿單

- FDA目前已有兩百多種藥品仿單提供藥物基因相關資訊
  - Warfarin
    - 起始劑量可參考CYP2C9及VKORC1檢測結果
  - Citalopram
    - CYP2C19 Poor Metabolizer的用量建議一天不超過20mg
  - Mercaptopurine(6-MP)
    - Homozygous deficiency in either TPMT or NUDT15 - typically require 10% or less of the standard dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency.
    - Heterozygous deficiency in TPMT and/or NUDT15 . Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on tolerability

藥物基因檢測的實證-PHARM GKB

- Pharmacogenomics (PGx) knowledge resource
- The impact of human genetic variation on drug responses



https://www.pharmgkb.org/

藥物基因檢測的實證-PHARM GKB

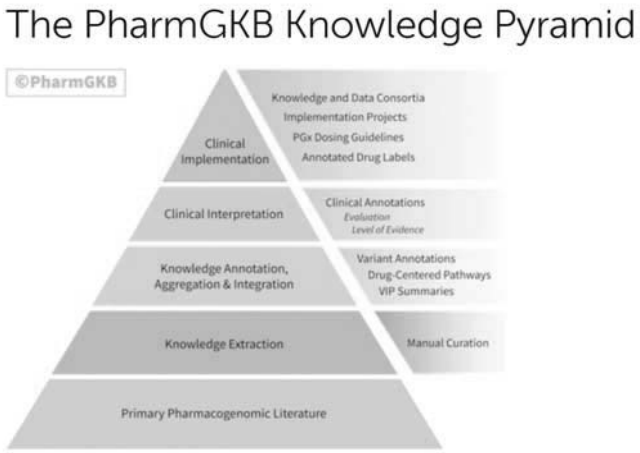
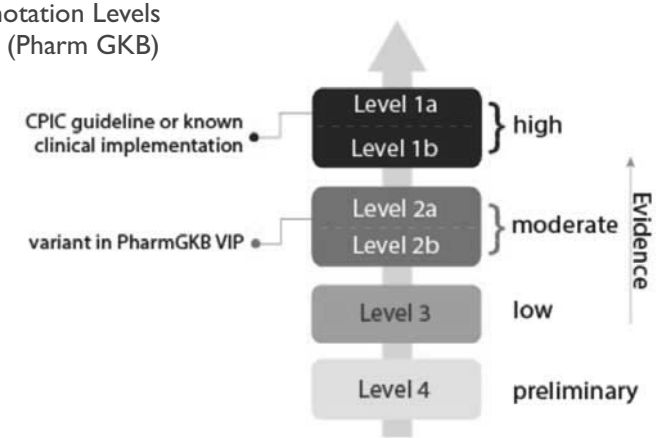


Figure 1: The PharmGKB Knowledge Pyramid.

https://www.pharmgkb.org/

藥物基因檢測的實證-PHARM GKB

- Clinical Annotation Levels of Evidence (Pharm GKB)



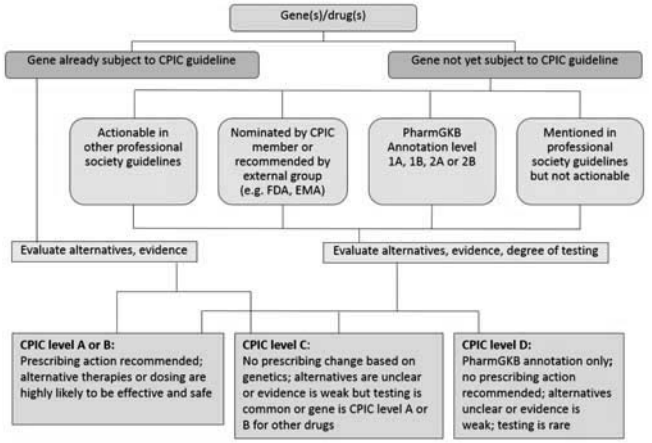
https://www.pharmgkb.org/

藥物基因檢測的實證-CPIC

- Started as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN) in 2009
  - Overcome the barrier to implementation of pharmacogenetic testing in the clinic
  - The difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs
- CPIC guideline
  - 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

藥物基因檢測的實證-CPIC

Considerations for Assignment of CPIC Level for Genes/Drugs



藥物基因檢測的實證-CPIC

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.

藥物基因檢測的實證-CPIC

Clinical Pharmacogenetics Implementation Consortium Guideline for *HLA* Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update

Elizabeth J. Phillips[1], Chonlaphat Sukasem[2,3], Michelle Whirl-Carrillo[4], Daniel J. Müller[5,6], Henry M. Dunnenberger[7], Wasun Chantratita[8,9], Barry Goldspiel[10], Yuan-Tsong Chen[11,12], Bruce C. Carleton[13], Alfred L. George Jr.[14], Taisei Mushiroda[15], Teri Klein[4], Roseann S. Gammal[16,17] and Munir Pirmohamed[18]

Table 1 Assignment of *HLA-B* and *HLA-A* genotypes

Genotype	Definition	Examples of diplotypes
*HLA-B*15:02* negative	Homozygous for an allele other than *HLA-B*15:02*	$*X^a/*X^a$
*HLA-B*15:02* positive	Heterozygous or homozygous variant	$*15:02/*X^a$, $*15:02/*15:02$
*HLA-A*31:01* negative	Homozygous for an allele other than *HLA-A*31:01*	$*Y^b/*Y^b$
*HLA-A*31:01* positive	Heterozygous or homozygous variant	$*31:01/*Y^b$, $*31:01/*31:01$

[a]Where *X = any *HLA-B* allele other than *HLA-B*15:02*. [b]Where *Y = any *HLA-A* allele other than *HLA-A*31:01*.

藥物基因檢測的實證-CPIC

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative and *HLA-A*31:01* positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naive and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent.
		If patient is carbamazepine-naive and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction.	Optional	N/A
		The latency period for cutaneous adverse drug reactions is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

藥物基因檢測的實證-CPIC

*HLA-B*15:02* positive[c] and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	Greater risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naïve, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

DRESS, drug reaction with eosinophilia and systemic symptoms; MPE, maculopapular exanthema; N/A, not applicable; SJS = Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]If only *HLA-B*15:02* was tested, assume *HLA-A*31:01* is negative and vice versa. [b]*HLA-B*15:02* has a 100% negative predictive value for carbamazepine-induced SJS/TEN, and its use is currently recommended to guide use of carbamazepine and oxcarbazepine only. Because there is a much weaker association and less than 100% negative predictive value of *HLA-B*15:02* for SJS/TEN associated with other aromatic anticonvulsants, using these drugs instead of carbamazepine or oxcarbazepine in the setting of a negative *HLA-B*15:02* test in Southeast Asians will not result in prevention of anticonvulsant-associated SJS/TEN.[40] [c]In addition to *HLA-B*15:02*, risk for carbamazepine-induced SJS/TEN has been reported in association with the most common B75 serotype alleles in Southeast Asia, *HLA-B*15:08*, *HLA-B*15:11*, and *HLA-B*15:21*. Although not described, the possibility of carbamazepine-induced SJS/TEN in association with less frequently carried B75 serotype alleles, such as *HLA-B*15:30* and *HLA-B*15:31*, should also be considered. [d]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.

藥師在藥物基因檢測扮演的角色

- **ASHP Statement on the Pharmacist's Role in Clinical Pharmacogenomics**
  - **Recommending or scheduling pharmacogenomic testing** to aid in the process of drug and dosage selection.
  - **Designing a patient-specific drug and dosage regimen** based on the patient's **pharmacogenomic profile** that also considers the **pharmacokinetic and pharmacodynamics properties of the drug.**
    - These factors should be combined in the regimen design along with other pertinent patient-specific factors such as comorbidities, other drug therapy, demographics, and laboratory data to optimize patient outcomes.

Am J Health Syst Pharm. 2015 Apr 1;72(7):579-81.

藥師在藥物基因檢測扮演的角色

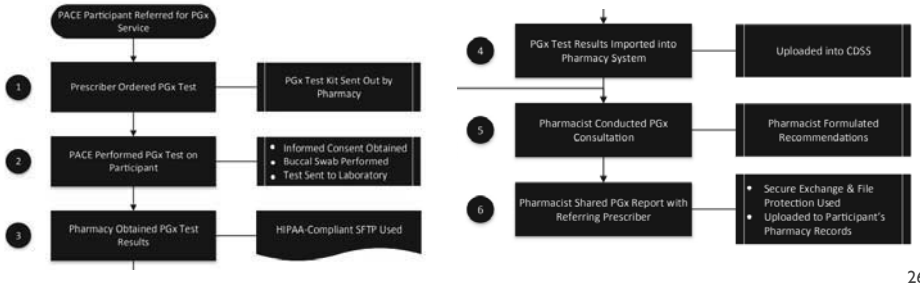
- **ASHP Statement on the Pharmacist's Role in Clinical Pharmacogenomics (Cont.)**
  - Educating patients, pharmacists, and other health care professionals about **pharmacogenomic principles and appropriate indications for clinical pharmacogenomics testing**, including the cost-effective use of pharmacogenomics testing.
  - Communicating pharmacogenomic-specific drug therapy recommendations to the health care team, including **documentation of interpretation of results in the patient's health record.**

Am J Health Syst Pharm. 2015 Apr 1;72(7):579-81.

應用藥物基因檢測進行藥事照護

Implementation of a pharmacist-led pharmacogenomics service for the Program of All-Inclusive Care for the Elderly (PHARM-GENOME-PACE)

- Individuals 55 years of age and older enrolled in PACE who underwent PGx testing as part of their medical care (n = 296).



Journal of the American Pharmacists Association, 58(3), 281–289.e1.

應用藥物基因檢測進行藥事照護

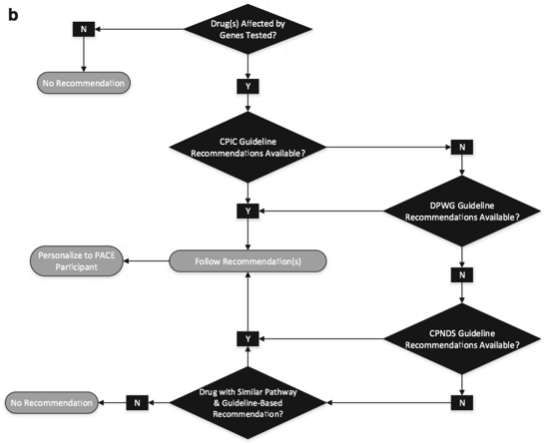


Figure 1. continued

Journal of the American Pharmacists Association, 58(3), 281–289.e1.

CHALLENGES AND SOLUTIONS ASSOCIATED WITH IMPLEMENTING A PGX SERVICE FOR PACE -HEALTH CARE RELATED

- **A lack of systems interoperability for health exchange information**
  - Pharmacists communicated PGx test results and consultations with prescribers directly by
    - transmitting documents through secure HIPAA-compliant servers (i.e., encrypted e-mails)
    - indirectly by uploading documents to participants' pharmacy records, which were readily accessible to prescribers.

Journal of the American Pharmacists Association, 58(3), 281–289.e1.

CHALLENGES AND SOLUTIONS ASSOCIATED WITH IMPLEMENTING A PGX SERVICE FOR PACE -HEALTH CARE RELATED

- **Pharmacists had limited access to participants' medical EHR.**
  - Pharmacists based their recommendations primarily on available pharmacy data, which always included participants' complete drug regimens, PGx test results, and drug-related allergies.
  - When medical data (e.g., height and weight, serum creatinine)were available, pharmacists used these additional data to inform their recommendations.

Journal of the American Pharmacists Association, 58(3), 281–289.e1.

CHALLENGES AND SOLUTIONS ASSOCIATED WITH IMPLEMENTING A PGX SERVICE FOR PACE -HEALTH PROFESSIONAL RELATED

- **We experienced knowledge and competency gaps among health professionals, particularly prescribers.**
  - As an organization, we provided educational sessions (e.g., webinars) to prescribers on various topics in the field of PGx.
  - As a service, we used a select group of pharmacists with extensive education and training in PGx, and pharmacists were readily available to prescribers for one-on-one telephone consultations.

ROLES OF PHARMACISTS LEADING A PGX SERVICE FOR PACE

- **Operational**
  - Developed processes for PACE prescribers to order PGx tests
  - Designed templates for PACE pharmacists to perform PGx consultations for PACE prescribers
  - Established processes for PACE pharmacists to communicate PGx test results and consultations to PACE prescribers
  - Created processes for PACE pharmacists to document PGx test results and consultations in participants' pharmacy records

ROLES OF PHARMACISTS LEADING A PGX SERVICE FOR PACE

- **Clinical Recommended PGx testing for select PACE participants**
  - Interpreted PGx test results for PACE prescribers
  - Provided recommendations to PACE prescribers to guide optimal drug selection and dosing based on PGx test results
  - Collaborated with PACE prescribers to design participant-individualized drug regimens
  - Contributed to the on-going evaluation of PGx biomedical literature and formulation of PGx reference library
  - Aided in developing CDSS to guide PACE pharmacists and prescribers on applying PGx-specific data to drug decision making

Journal of the American Pharmacists Association, 58(3), 281–289.e1.

ROLES OF PHARMACISTS LEADING A PGX SERVICE FOR PACE

- **Educational**
  - Advocated for appropriate PGx testing in PACE
  - Educated and provided information on the clinical application of PGx to PACE prescribers and fellow health professionals

Table 4
Distribution of pharmacists' recommendations and prescribers' acceptances

Recommendation category	Frequency of category, n (%)[a]	
	Recommendation	Acceptance
Continue drug (no change)	208 (47.7%)	208 (100%)
Consider drug dose adjustment[b]	49 (11.2%)	49 (100%)
Consider drug regimen change[b]	101 (23.2%)	101 (100%)
Implement drug dose adjustment or drug regimen change	78 (17.9%)	30 (38.5%)
Total	436 (100%)	388 (89.0%)

[a] Ten recommendations were excluded owing to inability to follow up on and determine the prescriber's response.
[b] These types of recommendations always included suggestions for monitoring.

Journal of the American Pharmacists Association, 58(3), 281–289.e1.