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Clinical Pharmacogenetic Testing and Application: 2024 Updated Guidelines by the Korean Society for Laboratory Medicine

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In the era of precision medicine, pharmacogenetics has substantial potential for addressing inter-individual variability in drug responses. Although pharmacogenetics has been a research focus for many years, resulting in the establishment of several formal guidelines, its clinical implementation remains limited to several gene–drug combinations in most countries, including Korea. The main causes of delayed implementation are technical challenges in genotyping and knowledge gaps among healthcare providers; therefore, clinical laboratories play a critical role in the timely implementation of pharmacogenetics. This paper presents an update of the Clinical Pharmacogenetic Testing and Application guidelines issued by the Korean Society for Laboratory Medicine and aims to provide the necessary information for clinical laboratories planning to implement or expand their pharmacogenetic testing. Current knowledge regarding nomenclature, gene–drug relationships, genotyping technologies, testing strategies, methods for clinically relevant information delivery, QC, and reimbursements has been curated and described in this guideline.

Key Words: Clinical laboratory, Guideline, Korea, Pharmacogenetics, Pharmacogenetic testing

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SCOPE AND PURPOSE OF THE GUIDELINE

This revised guideline is an update of the Clinical Pharmacogenetic Testing and Application guidelines [1–3] issued by the Korean Society for Laboratory Medicine (KSLM) in 2016. The current guideline was developed by professionals within the society to reflect changes in the academic and medical fields until 2024. We incorporated recent advances in pharmacogenetic testing technology, changes in clinical fields and laboratory environments, and new evidence on pharmacogenetic testing to facilitate the practical application of the latest pharmacogenetic knowledge in clinical settings.

Recently, various international consortia and expert groups have made practical joint recommendations based on the integration of databases and consensus guidelines [4]. However, testing laboratory environments and clinical practices vary by country, and the frequency of specific genetic variants differs by ethnicity. Therefore, the spectrum of recommended pharmacogenetic tests also varies, implying a need for updated domestic clinical guidelines that reflect recent evidence and criteria for the effective utilization of pharmacogenetic testing.

This guideline aims to provide principles and recommendations based on the latest insights to ensure that clinical laboratories currently performing or planning to implement pharmacogenetic testing can perform these tests effectively and apply them appropriately in clinical practice. The guideline includes updates on the nomenclature for pharmacogenetic testing, evidence supporting clinically useful test items, and strategies for applying clinical pharmacogenetic testing.

This guideline includes changes from the previous version, presenting updates on nomenclature, the latest evidence for target gene–drug combinations, and an explanation of current genetic testing methods, including next-generation sequencing (NGS). In addition, the guideline describes strategies for preemptive testing and integration into clinical decision-making systems, which were not covered in the previous version. The current guideline also includes detailed updates on domestic and international external quality assessment programs and reference materials. Finally, the guideline has been revised to reflect recent changes in domestic accreditation programs and the latest information on healthcare reimbursement costs.

We publish an English version of the guideline for more readers to understand, with the translated Korean language version of this article simultaneously published in Laboratory Medicine Online. The pharmacogenetic tests discussed in these guidelines are limited to the clinical tests performed at medical institutions.

OVERVIEW OF CLINICAL PHARMACOGENETIC TESTS

The basic concepts and terminologies for pharmacogenetic tests can be found in the previous guidelines [1, 2]. This section focuses on the interpretative process. The general process of interpreting clinical pharmacogenetic tests is shown in Fig. 1. The first step is to detect genetic variants using molecular diagnostic methods. The next step is to determine a diplotype consisting of the two haplotypes. Phenotypes are derived from diplotypes. When describing phenotypes, the use of standardized terms based on the functional category of the genes is recommended [5]. For drug-metabolizing enzymes, such as *CYP2C9* and *CYP2C19*, the use of terms such as “ultrarapid metabolizer,” “rapid metabolizer,” “normal metabolizer,” “intermediate metabolizer,” and “poor metabolizer” in decreasing order of enzyme activity, is recommended. For drug transporters, such as *SLCO1B1*, terms such as “increased function,” “normal function,” “de-

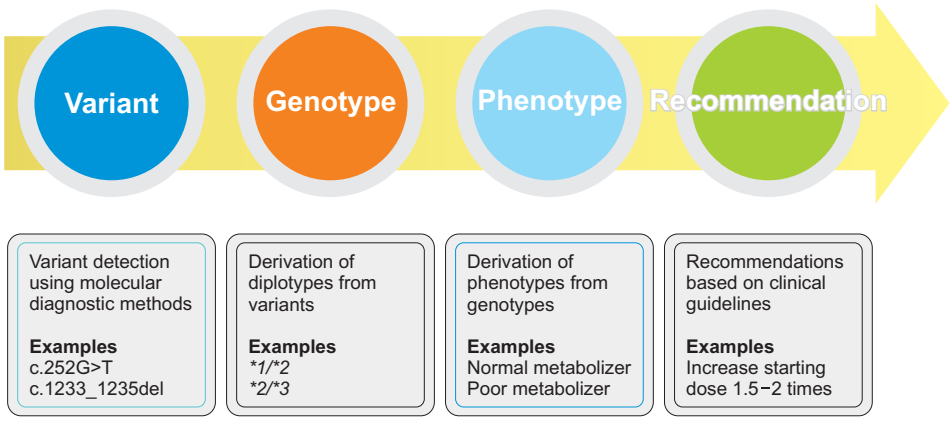

Fig. 1. General process of pharmacogenetic test interpretation.

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creased function," and "poor function" are recommended. "Positive" and "negative" can be used to describe high-risk genotypes, such as *HLA-B*15:02*. In the final step, clinical recommendations are established based on the phenotypes. Diplotype–phenotype relationships and clinical recommendations can be obtained from authorized guidelines, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC, https://cpicpgx.org/guidelines/) [6–17] and the Dutch Pharmacogenetics Working Group (DPWG, https://www.pharmgkb.org/page/dpwgMapping) guidelines [18–25].

Various genetic biomarkers are used to determine the eligibility of chemotherapeutic agents for cancer treatment. Typical examples include somatic variants in oncogenes such as *EGFR*, *BRAF*, and *ERBB2*, which are used to predict responses to targeted agents. Although this category of biomarkers has been considered in the previous guidelines, in the present version, the scope is limited to genes for which germline variants have been investigated for inborn variability in drug responses.

TARGET GENES AND DRUG COMBINATIONS

Since the first publication of the clinical pharmacogenetic testing guidelines by the KSLM [1–3], various target gene–drug pairs have been comprehensively evaluated for clinical utility. PharmGKB (https://www.pharmgkb.org/) [26] and CPIC (https://cpicpgx.org/) [27] are widely used pharmacogenetic databases for systematical evaluation of accumulated evidence. They offer objective gene–drug combinations based on reviews of international guidelines and the literature, curated by experts, and presented in a web-based format. Table 1 summarizes the gene–drug combinations with sufficient clinical evidence based on the two databases. These combinations correspond to CPIC A (final/provisional) and B (final) ratings and PharmGKB Levels 1A and 1B, respectively, indicating sufficient clinical evidence to assist in dosage adjustments, efficacy, metabolic/pharmacokinetic changes, and toxicity prediction through pharmacogenetic testing. Clinical laboratories can use Table 1 to introduce pharmacogenetic tests that meet the requirements of their healthcare institutions. Gene–drug combinations with currently insufficient evidence are listed in Supplemental Data Table S1. These combinations may be introduced into clinical testing as evidence accumulates in forthcoming clinical and experimental studies.

In addition to the CPIC and PharmGKB databases, professional sources, such as drug labels from the U.S. Food and Drug Administration (FDA) with PharmGKB annotation for drug pharmacogenetics (PGx) levels [28] and recommendations from national or disease-specific expert groups, such as DPWG, provide drug–gene information. However, the terms and evidence presented in the different guidelines vary, and new information and recommendations are continuously emerging. Therefore, when considering the introduction of specific pharmacogenetic tests in clinical practice, clinical pathologists should comprehensively review various sources and the latest information.

LABORATORY METHODS

Currently available pharmacogenetic testing methods and examples of platforms are listed in Table 2. The methods can be classified into two main categories: targeted genotyping and sequencing. In targeted genotyping, the genotypes to be evaluated are pre-defined and typically limited to the more common variants. Common methods include real-time PCR, microarray, and single-base extension. In contrast, sequencing allows for the detection of all variants within the genomic region analyzed. Sanger sequencing is the most widely used sequencing method; however, the use of NGS is increasing because of its ability to analyze multiple genes simultaneously. Long-read sequencing is also gaining attention in pharmacogenetics, particularly for genes with complex structures, such as *CYP2D6* [29–31]. Structural complexities in *CYP2D6*, caused by pseudogenes, copy number variants (CNVs), and hybrid genes, have posed challenges to its clinical implementation. Long-read sequencing is expected to overcome these limitations. CNVs can also be analyzed using methods such as real-time PCR, microarrays, and NGS. More accurate approaches for CNV detection include multiplex ligation-dependent probe amplification and long-range PCR, which can be used to confirm CNVs identified using other methods. For a deeper understanding of the structure of *CYP2D6* and the strategies used to analyze it, we highly recommend the tutorial on structural variants recently published by the Pharmacogene Variation Consortium (PharmVar; https://www.pharmvar.org/) [29].

CLINICAL APPLICATION STRATEGIES

Clinical laboratory test results are critical for patient care and should, therefore, be appropriate, accurate, and reliable. However, various factors, ranging from systematic or random errors to clerical mistakes in genotyping or interpretation, can compromise the quality of the results, potentially placing patients at risk. Therefore, risk management is essential at each stage. Genotypes are inherent and remain unchanged throughout life;

Table 1. Pharmacogenetic target gene–drug pairs with concordantly strong levels of evidence according to the CPIC and PharmGKB databases

Gene	Drugs	Category	CPIC level (status)	PharmGKB LOE	FDA Label*	Publications (PMIDs)
ABCG2	Rosuvastatin	Metabolism/PK, toxicity	A (final)	1A		35152405
CACNA1S	Desflurane, enflurane, isoflurane, sevoflurane, succinylcholine	Toxicity	A (final)	1A	Actionable PGx	30499100
	Halothane, methoxyflurane	Toxicity	A (final)	1A		30499100
CFTR	Ivacaftor	Efficacy	A (final)	1A	Testing required	24598717
CYP2B6	Efavirenz	Metabolism/PK, toxicity	A (final)	1A	Actionable PGx	31006110
	Sertraline	Metabolism/PK	B (final)	1A		37032427
CYP2C19	Amitriptyline	Metabolism/PK	A (final)	1A		23486447; 27997040
	Citalopram, escitalopram	Metabolism/PK, toxicity	A (final)	1A	Actionable PGx	25974703; 37032427
	Clomipramine, imipramine, trimipramine	Metabolism/PK	B (final)	1A		23486447; 27997040
	Clopidogrel	Efficacy, metabolism/PK, toxicity	A (final)	1A	Actionable PGx	21716271; 23698643; 35034351
	Dexlansoprazole	Metabolism/PK	B (final)	1A	Actionable PGx	32770672
	Doxepin	Metabolism/PK	B (final)	1A	Actionable PGx	23486447; 27997040
	Lansoprazole	Efficacy, metabolism/PK	A (final)	1A		32770672
	Lornoxicam	Metabolism/PK	A (final)	1A		32189324
	Omeprazole, pantoprazole	Efficacy, metabolism/PK	A (final)	1A	Actionable PGx	32770672
	Sertraline	Metabolism/PK	A (final)	1A		25974703; 37032427
	Voriconazole	Metabolism/PK	A (final)	1A	Actionable PGx	27981572
CYP2C9	Celecoxib, flurbiprofen, meloxicam, piroxicam	Metabolism/PK	A (final)	1A	Actionable PGx	32189324
	Fluvastatin	Metabolism/PK, toxicity	A (final)	1A		35152405
	Ibuprofen, lornoxicam, tenoxicam	Metabolism/PK	A (final)	1A		32189324
	Phenytoin	Metabolism/PK, toxicity	A (final)	1A	Actionable PGx	25099164; 32779747
	Siponimod	Metabolism/PK	A (provisional)	1A	Testing required	29273968
	Warfarin	Dosage, toxicity	A (final)	1A	Actionable PGx	21900891; 28198005
CYP2D6	Amitriptyline, nortriptyline	Metabolism/PK, toxicity	A (final)	1A	Actionable PGx	23486447; 27997040
	Atomoxetine	Metabolism/PK, toxicity	A (final)	1A	Actionable PGx	30801677
	Clomipramine, desipramine, doxepin, fluvoxamine, imipramine, trimipramine	Dosage, metabolism/PK, toxicity	B (final)	1A	Actionable PGx	23486447; 27997040
	Codeine	Efficacy, metabolism/PK, toxicity	A (final)	1A	Actionable PGx	22205192; 24458010; 33387367
	Hydrocodone	Efficacy, metabolism/PK	B (final)	1A		33387367
	Ondansetron	Efficacy	A (final)	1A	Informative PGx	28002639
	Paroxetine	Metabolism/PK	A (final)	1A		25974703; 37032427
	Tamoxifen	Efficacy, metabolism/PK	A (final)	1A	Actionable PGx	29385237
	Tramadol	Efficacy, metabolism/PK, toxicity	A (final)	1A	Actionable PGx	33387367
	Tropisetron	Efficacy, metabolism/PK	A (final)	1A		28002639
	Venlafaxine	Metabolism/PK, toxicity	B (final)	1A	Actionable PGx	37032427
	Vortioxetine	Metabolism/PK	A (final)	1A	Actionable PGx	37032427
CYP3A5	Tacrolimus	Dosage, metabolism/PK	A (final)	1A		25801146

(Continued to the next page)

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Table 1. Continued

Gene	Drugs	Category	CPIC level (status)	PharmGKB LOE	FDA Label*	Publications (PMIDs)
CYP4F2	Warfarin	Dosage	A (final)	1A		21900891; 28198005
DPYD	Capecitabine	Toxicity	A (final)	1A	Testing recommended	23988873; 29152729
	Fluorouracil	Toxicity, other	A (final)	1A	Actionable PGx	23988873; 29152729
G6PD	Rasburicase	Toxicity	A (final)	1A	Testing required	24787449; 36049896
HLA-A	Carbamazepine (*31:01)	Toxicity	A (final)	1A	Actionable PGx	23695185; 29392710
HLA-B	Abacavir (*57:01)	Toxicity	A (final)	1A	Testing required	24561393; 22378157
	Allopurinol (*58:01)	Toxicity	A (final)	1A	Testing recommended	23232549; 26094938
	Carbamazepine (*15:02, *15:11), oxcarbazepine (*15:02)	Toxicity	A (final)	1A	Testing recommended	23695185; 29392710
	Phenytoin (*15:02)	Toxicity	A (final)	1A	Actionable PGx	25099164; 32779747
IFNL3	Peginterferon alfa-2a	Efficacy	A (final)	1B		24096968
	Peginterferon alfa-2b	Efficacy	A (final)	1B	Actionable PGx	24096968
IFNL4	Peginterferon alfa-2a, peginterferon alfa-2b	Efficacy	A (final)	1B		23291588; 24205831; 24748394
MT-RNR1	Amikacin, gentamicin, streptomycin, tobramycin	Toxicity	A (final)	1A	Actionable PGx	34032273
	Dibekacin, kanamycin, netilmicin, ribostamycin	Toxicity	A (final)	1A		34032273
NAT2	Isoniazid	Toxicity	C† (provisional)	1B		18330759; 18421452; 20392357
NUDT15	Azathioprine, mercaptopurine	Dosage, toxicity	A (final)	1A	Testing recommended	21270794; 23422873; 30447069
RYR1	Desflurane, enflurane, isoflurane, sevoflurane, succinylcholine	Toxicity	A (final)	1A	Actionable PGx	30499100
	Halothane, methoxyflurane	Toxicity	A (final)	1A		30499100
SLCO1B1	Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin	Metabolism/PK, toxicity	A (final)	1A		35152405
	Rosuvastatin	Metabolism/PK, toxicity	A (final)	1A	Actionable PGx	35152405
	Simvastatin	Metabolism/PK, toxicity	A (final)	1A		22617227; 24918167; 35152405
TPMT	Azathioprine, mercaptopurine, thioguanine	Dosage, metabolism/PK, toxicity	A (final)	1A	Testing recommended	21270794; 23422873; 30447069
UGT1A1	Atazanavir	Toxicity	A (final)	1A		26417955
	Irinotecan	Dosage, toxicity	A (provisional)	1A/1B	Testing recommended	28502040; 36443464
VKORC1	Warfarin	Dosage, toxicity	A (final)	1A	Actionable PGx	21900891; 28198005

(https://cpicpgx.org/ and https://www.pharmgkb.org/ assessed on Aug 1st 2024)
*PharmGKB provides "drug label PGx level" based on FDA drug labels, for which criteria and detailed explanations are provided in [28].
†Validity of *NAT2*-isoniazid pair as PGx target was confirmed by the authors despite current Level C provisional annotation by the CPIC.
Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; LOE, level of evidence; PGx, pharmacogenetics; PK, pharmacokinetics; PMID, PubMed identifier.

Table 2. Methods for pharmacogenetic testing

Methods	Possible target variants	Short variants* detection	CNV detection	Available platforms
Real-time PCR	Pre-defined variants†	Accurate	Possible for targeted regions	TaqMan (Thermo Fisher Scientific, Waltham, MA, USA)
Microarray	Pre-defined variants†	Accurate	Possible for targeted regions	PharmacoScan (Thermo Fisher Scientific)
Single-base extension	Pre-defined variants†	Accurate	Not available	Agena (Agena Bioscience, San Diego, CA, USA) (detection by mass spectrometry) SPMed (SPMED, Busan, Korea) (detection by capillary electrophoresis)
Sanger sequencing	All variants in the target range	Accurate	Not available	Laboratory-developed tests
NGS	All variants in the target range	Accurate	Possible	MiSeq, NextSeq, NovaSeq (Illumina, San Diego, CA, USA) Ion Torrent S5, Genexus (Thermo Fisher Scientific)
Long-read sequencing	All variants in the target range	Less accurate	Possible	PacBio (Pacific Bioscience, Menlo Park, CA, USA) Nanopore (Oxford Nanopore, Oxford, UK)

*Single nucleotide variants and indel variants not longer than 50 bp.
†A set of variants targeted in the design of the test.
Abbreviations: CNV, copy number variant; NGS, next-generation sequencing.

therefore, an error in testing can lead to a lifelong misinterpretation of results. Moreover, incorrect interpretation and dosage adjustments may increase the risks of toxicity and treatment failure. Therefore, clinical laboratories must implement quality improvement plans to mitigate potential risks and ensure the safe and effective application of pharmacogenetic testing in clinical practice.

Pharmacogenetic testing can be performed either retrospectively to identify genetic predispositions in patients who have exhibited adverse reactions to conventional drug treatments or prospectively to predict therapeutic responses and side effects before initiating treatment, enabling safe and effective dosing.

The indications, conditions, and points of consideration for clinical pharmacogenetic testing are summarized in Table 3. The major purpose of pharmacogenetic testing is to predict treatment failure or the risk of drug toxicity, helping clinicians select appropriate medications and determine optimal dosing regimens. Clinical pharmacogenetic testing is particularly valuable when supported by solid scientific evidence and demonstrated clinical relevance and when the results can guide the selection of alternative medications or dose adjustments. The presence of standardized guidelines further enhances its usability as a clinical tool.

When interpreting genotyping results, considering factors such as age, weight, disease status, detailed medication history of the drug and co-administered drugs, various other test findings, drug or metabolite concentrations, clinical therapeutic responses, and side effects is essential. This comprehensive approach helps to determine the most appropriate drug and dosage for each patient. The test report should be carefully designed to effectively communicate the pharmacogenetic test results with clinicians. The report should clearly explain the results and minimize the use of specialized or technical jargon to facilitate smooth communication between laboratory specialists and clinicians. The final report should include a summary of test result interpretation, along with a context-based analysis that considers the clinical information provided by the requesting physician. This approach ensures that the report is both clinically relevant and easily understandable, helping guide appropriate treatment decisions. The contents that should be included in a pharmacogenetic test report are summarized in Table 4.

Clinical laboratories can develop effective clinical application strategies tailored to specific situations within healthcare institutions by accurately understanding and assessing the advantages and disadvantages of preemptive testing, clinical decision support systems (CDSSs), and harmonization with therapeutic drug monitoring (TDM). To accomplish successful clinical application strategies, clinical pathologists with professional knowledge of both laboratory testing and clinical pharmacology/genomics encompassing laboratory medicine should take full responsibility and control of pharmacogenetic testing.

Preemptive testing

Preemptive pharmacogenetic testing is a proactive test performed before the initiation of drug therapy to predict therapeutic responses and potential side effects, allowing for safe and effective dosing. While this generally refers to checking results before drug administration, it can also include testing in the gen-

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Table 3. Consideration points for clinical pharmacogenetic testing

Characteristics of drugs for which clinical pharmacogenetic testing may be considered [43]	
Significant inter-individual variability in drug response	
Narrow therapeutic range	
Potential for severe adverse effects	
Development of treatment resistance	
Need for long-term treatment	
High cost of the medication	
Consideration points for clinical pharmacogenetic testing	
Correlation between genotype and phenotype (predictive power for drug response)	The degree of correlation between genetic variants and drug response outcomes should be well established.
Clear and sufficient evidence of clinical utility	There must be robust evidence supporting the clinical usefulness of pharmacogenetic testing, such as large-scale studies, randomized controlled trials, and meta-analyses.
Standardized guidelines for drug selection and dosage adjustment based on pharmacogenetic profiles	There should be clear, standardized guidelines on how to use pharmacogenomic information to select drugs and adjust dosages.
Genotypic and phenotypic variability by ethnicity or race	Information on the types and distribution of alleles and genotypes across different ethnic or racial groups should be available.
Technical feasibility and analytical capability of testing methods	The ease of use, expected analytical performance, and cost of testing should be considered.
Comprehensive interpretation by experts	The ability to provide thorough result interpretation should be supported by adequate knowledge and experience in various fields, such as medicine, clinical pharmacology, clinical genetics, and laboratory medicine.
Turnaround time for results	The time required to obtain test results should align with the clinical indications and requirements of the healthcare environment.
Cost-effectiveness	The clinical utility of the test should justify its cost, with a favorable balance between test expenses and the benefits gained.

eral population, regardless of the presence of disease or the possibility of drug administration. Considering the risks of adverse drug reactions, treatment failure, and associated costs, preemptive pharmacogenetic testing using NGS-based multidrug gene tests has been identified as a cost-effective strategy [32, 33].

Clinically significant and actionable variants are frequently observed in the general population [34]. With the aging and extended life expectancy of the general population, individuals are more likely to be prescribed drugs that are targets of pharmacogenetic testing, and the prescription frequency for related drugs tends to increase in Korea [35]. Therefore, a preemptive pharmacogenetic testing strategy is expected to be useful. Multitarget gene analysis in preemptive testing is anticipated to be cost-effective and to aid in preventing severe side effects of drugs.

Considerations for preemptive testing include the selection of target genes and analytical methods, result interpretation and reporting, legal and ethical issues, training of relevant healthcare providers, and issues related to fees and healthcare reimbursements [36]. Recent studies evaluating the clinical utility of preemptive pharmacogenetic testing through randomized clinical trials in several European countries reported that genotype-based treatment strategies using 12-drug–gene panels reduced the incidence of drug side effects by 6.7%–7.1% [37, 38]. However, some preemptive strategies for anticoagulant-related pharmacogenetic testing did not decrease major cardiovascular side effects [39], indicating the need for a careful review of focused applications and testing strategies.

Integration into CDSSs

To effectively adjust drug dosages and select alternative medications based on pharmacogenetic test results, practical solutions must be developed to overcome the complexity of CDSSs, from genetic testing results to actual drug adjustment processes. In addition to the Pharmacogenomics Clinical Annotation Tool [40], developed by PharmGKB and PGRN, bioinformatics tools for integrating and applying pharmacogenetic test results into CDSSs include FARMAPRICE, GeneSight, RIGHT, PREDICT, and PG4KDS [41, 42].

Although the content presented by the CDSS platforms varies,

Table 4. Elements to include in the pharmacogenetic testing result report

Category	Elements
Test request information	Reason for test request or test indication Clinical diagnosis or relevant clinical information Medication history Demographic data (e.g., age, sex, ethnicity)
Test information	Type of specimen Names of the gene(s) analyzed Regions of target gene(s) included in the test (target alleles and/or variants) Test method: Assay principle Indicate whether a laboratory-developed or commercially available kit was used, and whether the test was performed within the laboratory or by a referral laboratory Test limitations: Mention whether there are clinically significant genotypes that the test method cannot detect Note any specific characteristics or limitations based on the test method
Test results	Types of detected genetic variants, corresponding alleles, and genotype results: Describe genetic variants using standard nomenclature Indicate whether the patient is heterozygous or homozygous for the variant Provide the type of variant discovered Relevant reference literature: when available, include allele frequency data in the target population/ethnicity Description of expected phenotype: phenotype conversion
Interpretation and recommendation	Brief explanation of important drugs associated with the target gene Discussion of the relevance of the results to the test indication Description of the drug response related to the variants identified (e.g., sensitivity or resistance to chemotherapy) If applicable, any cautions related to result interpretation If applicable, recommendations for additional testing Clinical application considerations, such as dose adjustment or the use of alternative drugs based on genotype Citation of the appropriate references and publications associated with interpretation and recommendation
Additional elements required in the final report format	Interpretation and (electronic) signature of the laboratory director on the final report Name and address of the laboratory, patient name, unique patient identifier, and date of birth (or age) Include the name of the requesting physician and the affiliated institution; for requests from different institutions, add the name or contact information of the requesting organization Date of specimen receipt and date of result report
Name of the testing personnel and (electronic) signature of the laboratory director who interpreted the results	For tests referred from other laboratories, documentation must indicate the referral along with the (electronic) signature of the laboratory director from the requesting institution

they commonly provide alert messages, recommendations for alternative drugs or dosage adjustments, and evidence levels. Implementing a CDSS is an effective strategy for enhancing the activation and clinical utility of pharmacogenetic testing. Establishing core information delivery systems, setting appropriate information limits, and continuously checking and updating the CDSS using the latest databases are necessary prerequisites.

Comprehensive application of pharmacogenetic testing in combination with TDM

Pharmacogenetic testing is crucial for predicting drug metabolism or responsiveness; however, it cannot replace the clinical evaluation of drug responses or TDM. Therefore, pharmacogenetic testing and TDM are complementary. Pharmacogenetic testing typically provides information that can help assess the appropriateness and risks of a drug before starting treatment, whereas TDM, which includes drug concentration measurements, is essential during the treatment process after the drug or dosage has been selected. The half-life of drug elimination can vary depending on the genotype, and the duration until the steady-state concentration is reached may be prolonged or shortened. Genotype affecting drug receptor sensitivity may alter drug responsiveness, and the therapeutic range might have to be adjusted for the given genotype. Therefore, considering the genotype is necessary for the optimization of TDM in clinical practice.

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TDM provides valuable information from a pharmacokinetic perspective, as it evaluates changes in drug concentration over time, and from a pharmacodynamic perspective, as it assesses the relationship between the drug concentration and its effect. The relationship between the genotype and phenotype is not always perfect or predictable. TDM helps identify influencing factors beyond the genotype, such as co-administered drugs or liver function. TDM can also aid in understanding patient compliance and the causes of drug resistance. Furthermore, because pharmacogenetic tests do not screen for all variants or may detect novel variants, the measurement of drug concentrations and metabolites can complement pharmacogenetic testing.

QUALITY MANAGEMENT (QM) AND ACCREDITATION

QM

Laboratories performing pharmacogenetic testing should have in-house QM programs. The QM program should cover general issues, such as sample collection, identification, preparation, assay validation, and sample storage. Considering the importance of databases for pharmacogenetic testing, a database management plan should be implemented. Data on allele definition, allele functionality, diplotype–phenotype relationship, and allele frequency of the major pharmacogenes can be downloaded from the CPIC or PharmGKB website. In addition, clinical guidelines published by the CPIC and DPWG should be used in test report generation [5–24]. As the above databases and guidelines are frequently updated, laboratory databases should be updated at least once every six months.

Result accumulation and a review of the distribution of the reported genotypes in each laboratory are recommended. The distribution should be compared with known genotype frequencies. When the distribution deviates from that of the population group, the potential causes of bias should be investigated.

Reference materials for validation and QC can be purchased from the Get-RM project of the Coriell Institute (https://www.coriell.org/1/NIGMS/Additional-Resources/Pharmacogenetics). The consensus genotypes of the materials can be found in the articles provided on the website; however, they may not reflect an updated database. In such cases, the latest publications can be searched for true genotypes.

External quality assessment

Laboratories should participate in proficiency testing for each item. An alternative program must be prepared in the absence of proficiency testing for a specific item. In Korea, a pharmacogenetic testing program is provided by the Korean Association of External Quality Assessment Service (https://keqas.org/). The genotyping of six genes, including *CYP2C19*, *CYP2C9*, *VKORC1*, *CYP2D6*, *TPMT*, and *NUDT15*, can be evaluated using this program. Internationally, the College of American Pathologists (CAP) provides three pharmacogenetic programs in which laboratories can participate: PGX (*CYP2C19*, *CYP2C9*, *CYP2B6*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *SLCO1B1*, and *VKORC1*), PGX1 (*IL28B*, *COMT*, *G6PD*, and *OPRM1*), and PGX3 (*DPYD*, *NUDT15*, *TPMT*, and *UGT1A1*) (https://www.cap.org/laboratory-improvement/proficiency-testing). Additionally, the European Molecular Genetics Quality Network provides a pharmacogenetic program that evaluates *DPYD* and *UGT1A1* genotyping (https://www.emqn.org/).

Laboratory accreditation

Participation in laboratory accreditation programs can drive improvements in laboratory QM systems. CAP is a global organization of board-certified pathologists that aims to foster excellence in laboratory medicine and pathology (https://www.cap.org/). CAP accreditation can be achieved by inspection every 2 years by a CAP-assigned inspection team that determines compliance with specific laboratory standards regarding QM systems and safety measures.

In Korea, two accreditation programs are available: the Outstanding Laboratory Accreditation Program (OLAP) of the Laboratory Medicine Foundation (https://www.lmf.or.kr/) and the Korea Institute of Genetic Testing Evaluation (KIGTE) (http://www.kigte.org/). The OLAP, performed as a peer-review by a team of laboratory medicine specialists, investigates the statuses of internal/external QC, facilities, equipment, personnel, and environment. Two categories of laboratory pharmacogenetic tests must be evaluated: laboratory management and molecular diagnostics. KIGTE accreditation is mandatory for laboratories performing any type of genetic testing, including pharmacogenetic testing. However, clinical laboratories in medical institutions that have achieved OLAP accreditation can be exempted from KIGTE accreditation.

REIMBURSEMENT

Pharmacogenetic tests covered by the National Health Insurance Service (NHIS) in Korea are listed in Table 5 (https://repository.hira.or.kr/handle/2019.oak/3201). For items covered by the NHIS, following the general rule for genetic tests, pharma-

Table 5. Pharmacogenetic tests covered in the Korean healthcare reimbursement system

Sector	EDI code	Method name	Gene name
HLA typing	D8413	Nucleic acid amplification	*HLA-B*58:01*
	D8414	Sequencing	*HLA-B*58:01*
Hereditary genetic tests	C5801	PCR-hybridization	*CYP2C9*
			*MTHFR**
			TPMT
			VKORC1
			CYP2C19
			NUDT15
	C1581	PCR-hybridization (multiple genes)	*CYP2C9*, *VKORC1*
	C5802	PCR-restriction fragment length polymorphism	*MTHFR**
	C5806	Sequencing (≤ 10 reactions)	*CYP2C9*
			CYP2C19
			TPMT
			UGT1A1
			VKORC1
			NUDT15
	C5807	Sequencing (10 < reactions ≤ 20)	*UGT1A1*
			CYP2C9
			CYP2C19
			CYP2D6
			TPMT
	C5808	Sequencing (20 < reactions ≤ 40)	*G6PD*
	C5809	Sequencing (40 < reactions ≤ 80)	*CFTR*

**MTHFR* testing is only reimbursable for diagnostic investigations in patients with homocysteinemia (methylenetetrahydrofolate reductase deficiency), not for pharmacogenetic investigations in patients undergoing methotrexate treatment. Sequencing tests for *CYP2C9*, *CYP2C19*, *TPMT*, and *UGT1A1* are divided into two groups based on the number of sequencing reactions: those with ≤10 reactions and those with >10 but <20 reactions.
Abbreviation: EDI, electronic data exchange.

cogenetic tests that guide therapeutic decisions or predict critical side effects are reimbursable. Additionally, gene-specific rules exist for *HLA-B*58:01* and *TPMT*. Nucleic acid amplification tests and sequencing of *HLA-B*58:01* are reimbursable when used before allopurinol treatment for hyperuricemia (uric acid level ≥9 mg/dL) in a patient with chronic kidney disease. Otherwise, only the first nucleic acid amplification test performed before allopurinol treatment is reimbursed. Although *TPMT* tests are fully reimbursable when used for patients with symptoms of adverse drug reactions to thiopurines, 80% deductibility is applied when used to predict the drug response before treatment. *MTHFR*, *G6PD*, and *CFTR* are established pharmacogenes; however, they also are causative genes of the inherited diseases homocystinuria, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and cystic fibrosis, respectively. Tests for *MTHFR* are reimbursable only when used to diagnose inherited diseases, not when used as a pharmacogenetic test. In contrast, tests for *G6PD* and *CFTR* are reimbursable for both indications.

The reimbursement criteria were determined based on both clinical indications and test methods. The diagnostic methods covered by the NHIS of Korea include nucleic acid amplification-based methods, such as real-time PCR and sequencing. For sequencing codes, the insurance fee is determined based on the number of sequencifng reactions. Notably, either of the two codes, for ≤10 and ≤20 reactions, can be used for *CYP2C9*, *CYP2C19*, *TPMT*, and *UGT1A1*, according to the number of targeted exons.

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CONCLUSION

This guideline provides practical information on clinical pharmacogenetic testing and its application, covering updates on nomenclature, target gene–drug combinations, laboratory methods for pharmacogenetic testing, strategies for efficient clinical application, QM and accreditation programs, and current reimbursement issues. Clinical pathologists have a pivotal role in ensuring the reliability and professionalism of clinical pharmacogenetic testing. Appropriate application of clinical pharmacogenetic testing is an essential prerequisite for precision medicine. We suggest clinical practice guidelines for the clinical application, interpretation, and reporting of clinically useful pharmacogenetic tests with updated evidence and the current status.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3343/alm.2024.0572

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AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

None declared.

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