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Implementation of clinical pharmacogenetic testing

Soo-Youn Lee

Department of Laboratory Medicine & Genetics,
Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Potentially useful genomic markers of drug response have been suggested, and we have a number of pharmacogenetic tests available for predicting toxicity or efficacy. However, clinical translation of pharmacogenetics predictor is not always guaranteed, even for a marker with promising evidence of its role in drug response. We need high-quality clinical studies on which to base practical recommendations for our decision making for the diagnosis and personalized treatment for each patient. Many clinical trials using various omics technologies are underway to identify potential biomarkers and to confirm and validate their clinical utility in a variety of disease conditions.

As there are many factors influencing therapeutic outcome, there will be no single pharmacogenetic marker that will completely predict drug response. Comprehensive analysis of multiple candidate genes and high-throughput technologies would help us more precise prediction of drug response. Both germline and somatic mutations should be considered to select candidate genes in cancer pharmacogenomics. Also, drug response is largely determined by non-genetic factors such as patient compliance, drug interactions, immunity, nutrition, and various disease states including liver or renal dysfunction. The pharmacokinetic assessment may be helpful for the evaluation of patients with an unusual drug response and for the maintenance of continuous stability during the whole treatment period.

Unfortunately, at the moment, there is a considerable gap between our knowledge and clinical application of pharmacogenomics. For the application of pharmacogenetic testing in the real clinical setting, validation of the clinical usefulness of the genomic predictors in well-designed large-scale prospective clinical trials and the development of standardized guidelines are warranted. At Samsung medical center, we have been trying to implement pharmacogenetic tests in our routine clinical practice. Here I am going to share some of my experiences on the clinical pharmacogenomics and to address the challenges and issues that clinicians and laboratories face in the clinical setting.

Pharmacogenetics (PGx) testing

- Pharmacokinetics vs. Pharmacodynamics
- Genotyping vs. Phenotyping
- Retropective vs. Prospective

Clinical relevance of PGx test

- Large inter-individual variability in response
- Narrow therapeutic index
- Rare but severe, irreversible adverse events
- Difficulty predicting response or adverse effects
- Drug resistance

- Long-term treatment
- Expensive regimen

Application of PGx in clinical practice (from **NACB guideline)**

- Define requirements for clinical use
- Define interface between PGx and TDM
- Formulate guidelines for clinical laboarotory
- Provide guidance to IVD companies
- Provide payers and regulators recommendations

Clinical laboratory service considerations (from **NACB guideline)**

- What level of certification should be required for clinical laboratories & personnel performing PGx tests?
- What should be the primary test-result output?
- What criteria should be used to establish which genetic variants of a locus should be included for diagnostics purposes?
- Evidence to demonstrate cost effectiveness before recommending clinical use of PGx tests

Role of clinical laboratory (from **NACB guideline)**

- Establishing genetic profiling strategies to maximize sensitivity and specificity of predicting phenotype
- Developing methods to reduce testing cost and technical difficulty
- Providing availability of testing
- Educating the end-users of PGx test results
- Overcoming perceived barriers to genotyping

Ethical considerations (from **CLSI guideline)**

- Not have the same potential ethical, social, and legal implications as does heritable disease testing
- Improvement of the selection & delivery of medications
- As an extension of TDM
- PGx testing alone cannot predict a patients' phenotype with certainty.
- Environmental factors may have effects that are as great as or greater than those of PGx.

Candidate genes/drugs (from **PharmGKB)**

Gene	Drug	Category	LOE*	Guideline and reference
ANKK1	Antipsychotics	Toxicity/ADR	1B	Mol Psychiatry. 2007;12:794.
BCR/ABL1	Imatinib, Dasatinib, Nilotinib, Bosutinib	Efficacy	-	CLSI, Clinical chemistry textbook, Eur J Clin Pharmacol. 2013;69:S17.
BRAF	Vemurafenib Cetuximab	Efficacy	-	N Engl J Med. 2011;364:2507., J Clin Oncol. 2008;26:5705.
CFTR	Ivacaftor	Efficacy	1A	J Cyst Fibros. 2013 (In press)
COMT	Cisplatin	Toxicity/ADR	1B	Nat Genet. 2009;41:1345.

CYP2C19	Clopidogrel	Dosage, Efficacy, Toxicity/ADR	1A	CPIC (High), DPWG (3, 4)
CYP2C9	Warfarin	Dosage, Toxicity/ADR	1A	NACB (A-II), CLSI, CPIC (High)
CYP2D6	Antidepressants, Tamoxifen, Atomoxetine	Dosage, Efficacy, Toxicity/ADR	1A/2A	NACB (B-III; tamoxifen, atomoxetine), CPIC (High, Moderate; antidepressants), DPWG (3, 4)
CYP3A5	Tacrolimus	Dosage	1B	DPWG (4)
CYP4F2	Acenocoumarol	Dosage	1B	J Thromb Haemost. 2013;11:1200
DPYD	Pyrimidine analogues	Toxicity/ADR	1B	CPIC (Weak, Moderate, High), DPWG (3)
EGFR	Erlotinib, Gefitinib	Efficacy	1B	J Thorac Oncol. 2012;7:1490.
EML4/ALK	Crizotinib	Efficacy	-	N Engl J Med. 2010;363:1734.
ERBB2	HER2/neu Inhibitor	Efficacy	3	NACB (B-II)
ESR1	Exemestane	Efficacy	-	Eur J Clin Pharmacol. 2013;69:S17. Breast Cancer Res Treat. 2013;138:807.
FIP1L1/ PDGFRA	Imatinib	Efficacy	-	Haematologica. 2007;92:1173.
FLOT1	Carbamazepine	Toxicity/ADR	1B	Epilepsia. 2008;49:2087.
G6PD	Dapsone	Toxicity/ADR	1B	Pharmacogenet Genomics. 2012;22:219.
GRIK4	Citalopram	Efficacy	1B	Am J Psychiatry. 2007;164:1181.
GSTA1	Anti-cancer drug	Toxicity/ADR	3	Clinical chemistry textbook Pharmacogenomics. 2012;13:171.
GSTM1	Isoniazid	Toxicity/ADR	3	Clinical chemistry textbook J Clin Pharm Ther. 2012;37:712.
GSTM3	Anti-cancer drug	Toxicity/ADR	3	Pharmacogenomics J. 2010;10:54.
GSTP1	Anti-cancer drug	Efficacy, Toxicity/ADR	2A/3	Clinical chemistry textbook J Clin Oncol. 2010;28:3227.
GSTT1	Thalidomide	Toxicity/ADR	3	Leuk Res. 2011;35:1178.
HLA-B	Abacavir, Allopurinol	Toxicity/ADR	1A	NACB (A-II ; abacavir), CPIC (High)
IFNL3	Peginterferon	Efficacy	1A/1B	J Viral Hepat. 2013;20:e107.
c-KIT	Imatinib	Efficacy	-	CLSI, Clinical chemistry textbook, Proc Natl Acad Sci USA. 2009;106:1542.
KRAS	EGFR inhibitor	Efficacy	3	CLSI, Clinical chemistry textbook, Cancer Res. 2006;66:3992.
MTHFR	Methotrexate	Toxicity/ADR	1B	Pharmacogenomics. 2013;14:305.
NAT2	Isoniazid	Toxicity/ADR	2B/3	Clinical chemistry textbook J Toxicol Sci. 2008;33:187.
PDGFRB	Imatinib	Efficacy	-	Blood. 2007;109:61.
PML/RARA	Arsenic Trioxide	Efficacy	-	CLSI, Clinical chemistry textbook, Eur J Clin Pharmacol. 2013;69:S17.
SLCO1B1	Simvastatin	Toxicity/ADR	1A	CPIC (High)
TMEM43	Cisplatin	Toxicity/ADR	1B	Pharmacogenomics. 2010;11:1377.
TPMT	Purine analogues	Toxicity/ADR	1A	NACB (A-I), CPIC (High), DPWG (4)
UGT1A1	Irinotecan	Toxicity/ADR	2A, 3, 4	NACB (A-II), DPWG (3)
VKORC1	Warfarin	Dosage	1A/1B	NACB (A-II), CLSI, CPIC (High)

References

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- NACB Laboratory Medicine Practice Guideline : Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice.
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