Technology Assessment Program
Office of Patient Care Services

Bibliography*: Pharmacogenomic Testing

*Selected, quality filtered, not subject to external review

Policy issue: To support oversight of clinical quality and safety programs within VA, the Associate Deputy Under Secretary for Health for Quality and Safety requested evidence on the clinical use of pharmacogenomic testing in the VA population. Of primary interest were pharmacogenomic testing for: Cytochrome P450 polymorphisms; UGT1A1 polymorphisms in Irinotecan toxicity; and dihydropyrimidine dehydrogenase (DPD) polymorphisms in fluoropyrimidine toxicity.

This request was handled by the VA Technology Assessment Advisory Group (TAAG) within the Office of Patient Care Services (OPCS), which was created to deliver evidence-based recommendations for use of new technologies in VA in a timely manner. As part of this process, the VA Technology Assessment Program (VATAP) was charged with providing the best available evidence on a topic within a two-week time period to help support guidance for acquisition and use of pharmacogenomic testing in VA.

This bibliographic report will rely on evidence from available health technology assessments (HTA[1]) and systematic reviews to address the following questions:

- *What pharmacogenomic tests are available commercially?*
- *For which clinical conditions should each pharmacogenomic test be applied?*
- *What is the quality of evidence for their usefulness?*

Background: The success of the Human Genome Project[2] and the introduction of new technologies, which make it possible to analyze multiple genes on a large scale simultaneously, are providing new opportunities for health promotion and disease prevention.[3] Pharmacogenomics is a young field that studies the relationship between variants in a large collection of genes and variable drug effects:[4]

> *"Although the concept of pharmacogenetics, 1 allele at a time, was first proposed over a century ago, the more recent term "pharmacogenomic" captures the essence of contemporary work in this field. In addition to studying single allelic variants with large clinical effects, investigators are beginning to explore much larger sets of genes, including pathways up to the whole genome[5], and how variations in these pathways may affect drug response."*

Roden (2006) describes two processes in which genetic factors can underlie the generation of clinical drug reaction: 1) delivery to and removal from target sites in plasma on cell surfaces or within cells (pharmacokinetics), and; 2) interaction with the targets to generate a cellular effect that is translated to clinical effect (pharmacodynamics). Applying such knowledge may permit drugs to be tailored and adapted to each person's own genetic makeup, thereby improving efficacy and safety of drug therapy.

[1] Health Technology Assessment (HTA) is a multidisciplinary field of policy analysis that systematically studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.
[2] http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml accessed December 21, 2007.
[3] CDC Fact Sheet: Translating Genomics into Public Health Practice. www.cdc.gov/genomics
[4] Roden DM, Altman RB, Benowitz NL, et al. Pharmacogenomics: Challenges and Opportunities. An Intern Med 2006;145:749-57.
[5] The genome is all of the genetic information possessed by an organism.

Roden further summarized the scientific challenges in pharmacogenomics that progress from basic science knowledge to public health practice:

- Establishing that drug responses are inherited genetically;
- Defining candidate genes;
- Defining drug responses;
- Managing data, including uniform representation of phenotypic[6] data;
- Demonstrating reproducibility;
- Conducting statistical analysis of associations;
- Evaluating very large sets of polymorphisms[7] in large numbers of patients;
- Moving to practice.

Translating pharmacogenomic research into practice: As new pharmacogenomic testing becomes available, health care decision makers need timely and reliable information on evidence of efficacy and cost-effectiveness to determine their clinical potential within the context of a coordinated approach for effectively translating genomic applications into clinical practice and health policy. One such effort in the US is the Evaluation of Genomic Applications in Practice and Prevention (EGAPP). EGAPP is an initiative launched in 2004 by the CDC National Office of Public Health Genomics to support a coordinated, systematic process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the US.[8]

The EGAPP Working Group was established in 2005 to support the development of this process by: 1) prioritizing and selecting tests for consideration; 2) reviewing CDC-commissioned evidence reports and other contextual factors; 3) highlighting critical knowledge gaps; and 4) providing guidance on appropriate use of genetic tests in specific clinical scenarios.

EGAPP applies the ACCE model process in its analytic framework to guide evidence-based recommendations for clinical use.[9] ACCE takes its name from the four components of evaluation—**A**nalytic validity, **C**linical validity, **C**linical utility and associated **E**thical, legal and social implications. The evaluation process begins once the clinical disorder, the type of testing, and the setting in which testing would take place have been clearly established.[10] An important output of this process is the identification of knowledge gaps.

Internationally, evidence-based efforts that employ HTA in translating genomic knowledge into clinical policy are taking place within and across country borders (Dr. Karen Facey: personal communication, December 24, 2008). For example, evidence-based frameworks have been developed to support the integration of genetic services in the Canadian provinces of Ontario[11] and Alberta[12] and in the Spanish province of Andalucía.[13] Public Health Genomics European Network (PHGEN) is a network of European Union members and other international collaborators funded by the European Commission to serve as an "*…'early detection unit' for*

[6] The observable characteristics of an organism.
[7] A genetic (DNA) variant that appears in at least 1% of a given population.
[8] http://www.egappreviews.org/about.htm accessed December 17, 2008.
[9] http://www.cdc.gov/genomics/gtesting/ACCE.htm , accessed December 19, 2007.
[10] http://www.cdc.gov/genomics/gtesting/ACCE.htm accessed December 17, 2007.
[11] Giacomini M, Miller F, Browman G. Confronting the "gray zones" of technology assessment: evaluating genetic testing services for public insurance coverage in Canada. International Jour of Tech Assess in Health Care. 2003:19(2);301-16.
[12] http://www.ihe.ca/documents/hta/genetic_cancer_risk_assessment_technologies.pdf accessed January 4, 2008.
[13] http://www.juntadeandalucia.es/salud/contenidos/aetsa/pdf/Framework_Genetic_testing_def.pdf accessed January 8, 2008.

horizon scanning, fact finding, and monitoring of the integration of genome-based knowledge into public health."[14] The United Kingdom Genetic Testing Network[15] and EuroGentest[16] were created to coordinate and harmonize genetics practices in Europe.

Common themes among these organizations are dimensions and frameworks that take into account ACCE core criteria regarding the quality of scientific information about test performance, clinical utility and safety, as well as the social, ethical, economic and organizational implications for health services provisions within their jurisdictions. Frameworks applying ACCE criteria allow policy makers to have access to up-to-date and reliable information for decision making.

Systematic review

Synthesizing available information through rigorous systematic review is an important component of the EGAPP initiative, and the ACCE model process provides a sound framework with which to guide the systematic review.[17] The conclusions and recommendations of a systematic review are based on the quality and content of the evidence, thus allowing medical literature to be used effectively in guiding medical decisions. The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes where they receive the highest level designation.[18,19]

The ACCE framework lists several key questions to address in a systematic review of pharmacogenomics testing that establish test performance and value added and identify ethical, legal and social issues:[20]

- (Overarching question) Does the test lead to improvement in outcomes, or are testing results useful in medical, personal, or public health decision making?
- Analytic validity—How well does the genetic test accurately and reliably measure the genotype of interest?
- Clinical validity—How well does the genetic test detect or predict the disorder of interest (eg. drug efficacy or drug reactions)?
  - What factors affect this association (eg. race/ethnicity, diet or other medications)?
- Clinical utility—What elements need to be considered when evaluating the risks and benefits associated with the test's introduction into routine practice?
  - How does the test influence management decisions by patients and providers that could improve or worsen outcomes?
  - Does use of the test lead to improved clinical outcomes compared to not testing?
  - Are the test results useful in medical, personal or public health decisionmaking?
  - What are the harms associated with the test and subsequent management decisions?

[14] http://www.phgen.nrw.de/typo3/fileadmin/downloads/flyer_phgen_2007.pdf accessed January 4, 2008.
[15] http://www.ukgtn.nhs.uk/gtn/UKGTN-information/What-is-the-UKGTN.html accessed January 4, 2008.
[16] http://www.eurogentest.org/ accessed January 4, 2008.
[17] Gudgeon JM, S. WM, McClain MR, E. PG, Gudgeon JM. Rapid ACCE: Experience with a rapid and structured approach for evaluating gene-based testing. Genetics in Medicine 2007;9(7):473-8.
[18] Cook, DJ, Guyatt GH, Laupaucis A, Sackett DL, Goldberg RJ. Clinical recommendations using levels of evidence for antithrombotic agents. *Chest.*1995 Oct;108(4 Suppl):227S-230S.
[19] Guyatt, GH, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. *Journal of the American Medical Association.*1995;274(22):1800-4.
[20] Matchar DB, Thakur ME, Grossman I, et al. Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake inhibitors (SSRIs). Evidence Report/Technology Assessment No. 146. (prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025). AHRQ Publication no. 07-E002. Rockville, MD: Agency for Healthcare Research and Quality. November 2006.

Regulation of pharmacogenomic testing: Several governmental organizations have functions relevant to pharmacogenomics regulation in the US, including: [21]

- Health and Human Services (HHS) Secretary's Advisory Committee on Genetics, Health, and Society, which advises the Department of HHS on genomics policy;
- Center for Medicare and Medicaid Services (CMS), which regulates all laboratory testing in the US through the Clinical Laboratory Improvement Amendments (CLIA), and;
- US Food and Drug Administration, which regulates drugs and diagnostic tests in its mandate to protect public health and safety.

In general, FDA focuses on test accuracy, while CLIA address laboratory quality. One of the challenges to regulating pharmacogenomic testing is that pharmacogenomics involves both drugs and diagnostic tests, which are regulated differently by FDA. Regulators such as FDA are developing guidance on a process for joint or simultaneous review.

Another challenge is to align methods currently used to evaluate product safety and efficacy and to manufacture products with current scientific knowledge in molecular medicine. The FDA Critical Path Initiative was developed to apply new scientific knowledge from molecular medicine to improve and modernize the efficiency of medical product development.[22] Public-private partnerships such as the Biomarkers Consortium managed by the Foundation for the National Institutes of Health have been created to gather evidence used in research and regulatory approval processes related to molecular medicine advances.[23]

With regard to testing, presently FDA provides guidance for use of pharmacogenomic tests, although FDA approval of pharmacogenomic assays is not required for clinical use. [24] The regulatory route to market for any new *in vitro* diagnostic test is determined largely by the risk associated with use of the device and by precedent from review of similar devices. Benefits of FDA regulation in pharmacogenomic testing include clear definition of claims for the device (as stated in labeling), requirement for manufacturer's adherence to a Quality System for the device, and reporting of problems with the device for appropriate action.

FDA provides a public listing of valid genomic biomarkers in the context of FDA-approved drug labels with links to pharmacogenomic data.[25] While most drug labels in the list require no immediate recommendation for action (eg. for genomic testing), a few labels recommend or require genomic testing specifying the use of these markers for assisting therapeutic decisions.

Methods: In December 2007, VATAP conducted literature searches and made direct inquiries to HTA colleagues to identify the best available evidence for this report, focusing on existing systematic reviews and HTAs. Emphasis on systematic reviews and HTAs provides an indicator of applications where current scientific activity is concentrated and which have the greatest probability of being translated to clinical practice.

[21] Phillips KA and Bebber SL. Regulatory Perspectives on Pharmacogenomics: A Review of the Literature on Key Issues Faced by the United States Food and Drug Administration. Medical Care Research and Review. June 2006;63(3):301-26.
[22] http://www.fda.gov/oc/initiatives/criticalpath/faq2.html accessed January 8, 2008.
[23] http://www.biomarkersconsortium.org/index.php?option=com_content&task=section&id=5&Itemid=39 accessed January 7, 2008.
[24] http://www.fda.gov/Cder/guidance/6400fnl.pdf accessed December 19, 2007.
[25] http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm accessed December 17, 2007.

Search strategies/Inclusion criteria
To find the most recent systematic reviews and HTAs on pharmacogenomics testing published in English that would address the questions of validity and utility in adult populations, VATAP conducted searches in the HTA database (www.inahta.org) and the Cochrane Library databases for completed systematic reviews published through December 2007 and supplemented the searches with a query on December 14, 2007 to the listserv of members of the International Network of Agencies for HTA (INAHTA; www.inahta.org) for updated work.

In December 2007, multiple searches were then conducted to identify literature published since 1997 (a cutoff that represents the recent emergence of this field). The Cochrane Library® via the Wiley web-based system, plus PubMed®, EMBASE®, and Current Contents® via Dialog were searched using an array of controlled vocabulary, MeSH, and free text words and phrases for gene, genetics, genome, pharmacogenetics, and pharmacogenomics. The search results were filtered for controlled studies, randomized trials, meta-analyses, systematic reviews, guidelines, methods reviews, plus related synonyms. In all, 285 references were captured in the searches.

Studies meeting the following criteria were included in this report:
- adult, human subjects
- published in English
- subject matter covered polymorphisms of Cytochrome P450, UGT1A1 in Irinotecan toxicity, and dihydropyrimidine dehydrogenase (DPD) in fluoropyrimidine toxicity.

Meeting abstracts, animal studies and systematic reviews or HTAs superseded by more recent ones on the same subject were excluded.

One author (Adams) selected citations for full-text retrieval, reviewed all articles, and prepared this overview.

Results: Electronic inquires of HTA colleagues and searching identified six systematic reviews, including one AHRQ (2007) review in progress, and three scoping reports of pharmacogenomic testing applications (See Table 1). While these scoping reports are not formal systematic reviews, they represent comprehensive compilations of existing literature on the specific pharmacogenomic applications of interest where systematic reviews presently do no exist. Table 1 also lists the FDA Testing Requirement for each topic, where available.

Guidelines: In December 2007, a search for guidelines in pharmacogenomics using the VATAP IMPROVE Intranet portal (vaww.va.gov/vatap/Improve/guidelines.htm) and the terms "pharmacogenomic" or "genomic" in the following databases was conducted:

- VA DOD Guidelines:
- US National Guideline Clearinghouse:
- CMA InfoBase:
- UK Guidelines:
- NICE.

11 citations were found and are listed below. All addressed indications for warfarin and included the FDA update to the labeling for Coumadin that included pharmacogenomics

information explaining that people's genetic makeup may influence how they respond to the drug.

Blondin MM. Prevention of deep vein thrombosis. Iowa City (IA): University of Iowa Gerontological Nursing Research Center, Research Dissemination Core; 2006 Feb. 40 p. [79 references]

Finnish Medical Society Duodecim. Systemic diseases in pregnancy. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2006 Aug 30 [Various].

Harrington RA, Becker RC, Ezekowitz M, Meade TW, O'Connor CM, Vorchheimer DA, Guyatt GH. Antithrombotic therapy for coronary artery disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):513S-48S. [164 references]

Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):311S-37S. [179 references]

Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, Pauker SG. Antithrombotic therapy in valvular heart disease--native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):457S-82S. [234 references]

Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, Taubert KA. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/Am Stroke Assoc. Circulation 2003 Sep 9;108(10):1278-90.

Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):429S-56S. [199 references]

Finnish Medical Society Duodecim. Deep vein thrombosis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2006 Apr 27 [Various].

American College of Cardiology Foundation (ACCF), American Heart Association (AHA). ACC/AHA guideline update on perioperative cardiovascular evaluation for noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to Update the 1996 Guidelines). Bethesda (MD): American College of Cardiology Foundation; 2002. 58 p. [390 references]

Fleisher LA, Beckman JA, Freeman WK, Brown KA, Froeclich JB, Calkins H, Kasper EK, Chaikof E, Kersten JR, Fleischmann KE, Riegel B. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation on noncardiac surgery: focused update on perioperative beta-blocker therapy. A report of the American College of Cardiology/American Heart Association Task Force on Practice [trunc]. J Am Coll Cardiol 2006;47:1-12. [25 references]

Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2002 Oct. 47 p. (SIGN publication; no. 62). [214 references]

Conclusions/Discussion: Focusing on the clinical utility of commercially available pharmacogenomic testing of polymorphisms of Cytochrome P450, UGT1A1 in Irinotecan toxicity, and dihydropyrimidine dehydrogenase (DPD) in fluoropyrimidine toxicity, the questions VATAP sought to address based on evidence from available systematic reviews and scoping reports are as follows:

1. What pharmacogenomic tests are available commercially?

The FDA-approved tests identified in this report are:

- CYP450 AmpliChip® (Roche Molecular Diagnostics, Pleasanton, CA);
- Invader® UGT1A1 Molecular Assay (Third Wave Technologies, Madison WI);
- Warfarin Target Dose Safety Test (Genelex Corp., Seattle, WA);
- PGxPredict: WARFARIN™ (Clinical Data, Inc., New Haven, CT);
- Warfarin DoseAdvise (Kimball Genetics, Inc. , Denver, CO);
- Verigene System (Nanosphere Inc., Northbrook, IL).

2. For which clinical conditions should each pharmacogenomic test be applied?
3. What is the quality of evidence for their usefulness?

The clinical conditions for which each of the commercially available pharmacogenomic tests listed above have been rigorously reviewed or comprehensively catalogued are organized in Table 1, according to: mental health disorders; neoplasms; cardiovascular disorders; and other (pain management).

- The strongest evidence for use of pharmacogenomic testing supports using genotyping to aid in the determination of warfarin dosage along with existing tools such as routine monitoring of the International Normalized Ratio (INR) by a physician. This is based on evidence supporting comparable analytic validity (diagnostic test performance) to that of most genomic tests and evidence supporting a relationship between the genomic variant(s) and the final warfarin dose. Specifically, the American College of Medical Genetics recommends that: *"…C9 and VKORC1 genotypes can reasonably be used as part of diagnostic efforts to determine the cause of an unusually low maintenance dose of warfarin or an unusually high INR during standard dosing."*[26] However, significant knowledge gaps regarding clinical utility and the balance between harm, benefit and cost must be resolved before this testing becomes the standard of care for all patients undergoing anticoagulation with warfarin.

- None of the existing reviews supported using pharmacogenomic testing alone for routine clinical use. However, although completion of the AHRQ systematic review of Irinotecan for colorectal cancer is still pending, FDA has recommended UGT1A1 testing in patients planned for treatment with Irinotecan to identify individuals who are homozygous for the UGT1A*28 allele. Patient with this mutation are at increased risk for neutropenia following initiation of treatment, and a reduced initial dose should be considered.

[26] http://www.acmg.net/AM/Template.cfm?Section=News_Releases&Template=/CM/HTMLDisplay.cfm&ContentID=2336 accessed December 18, 2007.

- For all of the clinical applications reviewed in this report, evidence linking the use of pharmacogenomic testing to improvements in clinical outcomes and clarifying the risks and benefits associated with use of these tests is needed in order to determine the clinical utility of pharmacogenomic testing.

Table 1. Systematic Reviews and Scoping Reports of Pharmacogenomics Testing in Adult Populations

Note: CCOHTA 2006 is presented in both the mental health disorders and cardiovascular disorders sections.

Source for FDA testing requirement: http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm accessed December 17, 2007.

	Results of Literature Reviews					FDA Testing Requirement in Approved Drug Labels
Citation	**Manufacturer**	**Drug**	**Gene variants**	**Predicted phenotypes**	**Findings**	
Mental health disorders						
Arranz 2007 (scoping report of PGX of schizophrenia)	Not specified	Antipsychotics	Various but primarily CYP450 genes	Drug metabolizer status: • Poor metabolizers • Intermediate metabolizers, • Extensive metabolizers • Ultra-rapid metabolizers Prediction of treatment response Prediction of side effects	• *"The most significant results are the association between drug metabolic PMs, mainly in cytochrome P450 genes, with variations in drug metabolic rates and side effects."* • Results suggest an association between response phenotypes and PMs in dopamine and serotonin receptor genes, probably reflecting the strong affinities that most antipsychotics display for these receptors, and between the influence of a 5-HT2C PM (-759-T/C) and antipsychotic-induced weight gain. • *"These developments can be considered as successes, but the objectives of bringing pharmacogenetic and pharmacogenomic research in psychiatric clinical practice are far from being realized."*	None- Information only
AHRQ 2006 (for CDC EGAPP)	CYP450 AmpliChip® Roche Molecular Diagnostics Pleasanton, CA	SSRIs for non-psychotic depression	CYP2D6 CYP2C19 CYP2C9 Others: CYP2C8 CYP1A1	Poor metabolizers Intermediate metabolizers, Extensive metabolizers Ultra-rapid metabolizers	• Evidence is insufficient to demonstrate improved outcomes, or whether testing results are useful in medical, personal, or public health decisionmaking • EGAPP recommendation[27]: There was insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. • EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.	None- Information only

[27] Genetics in Medicine:Volume 9(12)December 2007pp 819-825. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. **[EGAPP Recommendation Statement].** Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group.

	Results of Literature Reviews					FDA Testing Requirement in Approved Drug Labels
Citation	**Manufacturer**	**Drug**	**Gene variants**	**Predicted phenotypes**	**Findings**	
	Invader® UGT1A1 Molecular Assay Third Wave Technologies, Madison WI	SSRIs for non-psychotic depression	UGT1A1		• Based on one study included in the review • Insufficient evidence	Not stated
CCOHTA 2006	CYP450 AmpliChip® Roche Molecular Diagnostics Pleasanton, CA	For CYP2D6: unspecified antidepressants, antipsychotics, antiarrythmics, beta-blockers, and narcotics For CYP2C19: Proton pump inhibitors, diazepam, select anticonvulsants, anti infectives	CYP2D6 CYP2C19	For CYP2D6: • Poor metabolizers • Intermediate metabolizers, • Extensive metabolizers • Ultra-rapid metabolizers For CYP2C19: • Poor metabolizers, • Extensive metabolizers	• No published studies show that patient outcomes can be predicted or altered by knowledge of DME status in the absence of other confounding variables • Prospective studies are needed to assess the benefits and potential risks of the test in guiding drug selection and dose adjustment. Until then, DME test results can only supplement other tools for therapeutic decision making with routine monitoring by a physician	None- Information only
Neoplasms						
AHRQ 2007 (for CDC EGAPP)	Invader® UGT1A1 Molecular Assay Third Wave Technologies, Madison WI	Irinotecan for colorectal cancer	UGT1A1		Results pending, slated for completion end 2007	Test recommended
BCBS TEC 2007 (scoping report- PGX of cancer-candidate genes)	Not specified	Irinotecan for colorectal cancer	UGT1A1		Results pending, EGAPP review slated for completion end 2007	Test recommended
	Not specified	5-FU for various cancers	DPYD*2A	DPD deficiency/5-FU toxicity	• BSBC TEC cited ASCO recommendations[28]: Little empirical evidence supports DPD alone as a prognostic marker." • Data were judged insufficient for use in patient management. • Note: Studies that include DPD in multigene profiles to improve prediction of response to 5-FU are preliminary and have not demonstrated value in improving management decisions or patient outcomes.	None- Information only

[28] Locker GY, Hamilton S, Harris J. ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer. J Clin Oncol 2006;24(33):5313-27.

	Results of Literature Reviews					FDA Testing Requirement in Approved Drug Labels
Citation	**Manufacturer**	**Drug**	**Gene variants**	**Predicted phenotypes**	**Findings**	
	Not specified	Tamoxifen	CYP2D6	Poor metabolizers Intermediate metabolizers	• Research suggested that patients with reduced CYP2D6 metabolism had a significantly shorter time to recurrence • Additional studies of outcomes of increased dose tamoxifen or its alternatives evaluated by CYP2D6 patient genotype, in addition to cost-effectiveness analyses, would help determine the utility of pretreatment CYP2D6 genotyping.	None- Information only
Cardiovascular therapy						
CADTH 2007	Warfarin Target Dose Safety Test Genelex Corp. Seattle, WA PGxPredict: WARFARIN™ Clinical Data, Inc. New Haven, CT Warfarin DoseAdvise Kimball Genetics, Inc. Denver, CO Verigene System Nanosphere Inc. Northbrook, IL	Warfarin	CYP2C9 VKORC1	Variability in dosing and response	• Although studies have shown that genetic polymorphisms in CYP2C9 and VKORC1 affect warfarin dosing, no RCTs have linked the use of pharmacogenetic testing to improvements in clinical outcomes. • Pharmacogenetic testing should be used in addition to routine INR monitoring • Prospective studies are needed to determine whether PGX testing improves patient outcomes, identify which subgroups of patients may benefit, and clarify the risks and costs associated with the use of these tests. • Several RCTs are currently evaluating the impact of PGX on dosing accuracy, time to achieve and maintain target INR, incidence of bleeding or thromboembolic events, and monitoring requirements.	None—information only Note: product label for warfarin updated in August 2007 to include genetic variants in CYP2C9 and VKORC1
McClain 2006 for American College of Medical Genetics (ACMG)	Not specified	Warfarin	CYP2C9 VKORC1	Variability in dosing and response	• Analytic validity: the test itself is as accurate as most genetic tests • Clinical validity: there is strong evidence to support the relationship between the genetic variant(s) and the final dose of warfarin in patients. • CYP2C9 and VKORC1 genotypes can reasonably be used as part of diagnostic efforts to determine the cause of an unusually low maintenance dose of warfarin or an unusually high INR during standard dosing • Clinical utility: there are still significant knowledge gaps in the balance between harm, benefit and cost, which should be resolved before employing genetic testing into standard care for all patients undergoing anticoagulation with warfarin. There are also insufficient data	None—information only Note: product label for warfarin updated in August 2007 to include consideration of genetic variants in CYP2C9 and VKORC1 in dosing, but genetic testing is not required and specific dosing recommendations have not changed

	Results of Literature Reviews					FDA Testing Requirement in Approved Drug Labels
Citation	**Manufacturer**	**Drug**	**Gene variants**	**Predicted phenotypes**	**Findings**	
					about the impact of this testing on adverse events.	
CCOHTA 2006	CYP450 AmpliChip® Roche Molecular Diagnostics Pleasanton, CA	For CYP2D6: unspecified antidepressants, antipsychotics, antiarrythmics, beta-blockers, and narcotics For CYP2C19: Proton pump inhibitors, diazepam, select anticonvulsants, anti infectives	CYP2D6 CYP2C19	For CYP2D6: Poor metabolizers Intermediate metabolizers, Extensive metabolizers Ultra-rapid metabolizers For CYP2C19: Poor metabolizers, extensive metabolizers	• No published studies show that patient outcomes can be predicted or altered by knowledge of DME status in the absence of other confounding variables • Prospective studies are needed to assess the benefits and potential risks of the test in guiding drug selection and dose adjustment. Until then, DME test results can only supplement other tools for therapeutic decision making with routine monitoring by a physician	None- Information only
Arnett 2006 (scoping report of PGX of anti-hypertensives)	Not specified	Antihypertensives: • Diuretics • Beta (β) blockers • Renin-angiotensin-aldosterone system drugs	Various tabulated in report including: CYP2D6 in β blockers CYP450 2C9 in multiple drug classes	Varied	• Of the > 40 studies that have investigated associations between genetic PMs and response to antihypertensive drugs, ACE inhibitors and β blockers have been most frequently studied, followed by angiotensin II blockers, diuretics, adrenergic alpha-agonists, and calcium channel blockers. • Renin-angiotensin-aldosterone system genes have been the most widely studied, with the ACE I/D variant being typed in about one-half of all hypertension pharmacogenetic studies. In total, 160 possible gene PM-drug interactions have been explored, with about one-quarter of these showing that genes predict drug response. • However, findings are disparate and conflicting, and the discovery of clinically relevant antihypertensive drug-response genes remains elusive.	None—information only
Other applications						
Fishbain 2004	Not specified	Pain medicines	CYP1A2 CYP2D6 CYP2C9 CYP3A4 CYP3A5	Poor metabolizers Intermediate metabolizers, Extensive metabolizers Ultra-rapid metabolizers	• Genomic testing for enzymes of drug metabolism has significant potential for improving the efficacy of drug treatment and reducing adverse drug reaction, but the value of the genotyping information has not yet been determined.	None—information only for CYP2D6 and CYP2C9 variants Other variants not

	Results of Literature Reviews					FDA Testing Requirement in Approved Drug Labels
Citation	**Manufacturer**	**Drug**	**Gene variants**	**Predicted phenotypes**	**Findings**	
					• Therefore, this technology may be premature for routine use with every patient pretreatment. • Only a few genetic PMs in drug metabolism have clinical drug relevance. For the vast majority of drugs, the clinical consequences of gene PMs have not yet been determined. Thus, genomic testing may not be cost effective at the present time, if one is not using or planning to use a drug previously determined to be the subject of drug PM.	stated

ACE, angiotensin converting-enzyme
DME, drug metabolizing enzyme
EGFR, Epidermal Growth Factor Receptor
INR, International Normalized Ratio
PGX, pharmacogenomics
PM, polymorphism
SSRI, selective serotonin reuptake inhibitor

END REFERENCES

Systematic reviews and scoping reports included in report

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