Rapid Synthesis

Examining the Coverage of Pharmacogenetic Tests and Use of Pharmacogenetic Information at the Population Level

15 September 2017

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Rapid Synthesis:
Examining the Coverage of Pharmacogenetic Tests and Use of Pharmacogenetic Information at the Population Level
30-day response

15 September 2017

McMaster Health Forum

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Timeline

Rapid syntheses can be requested in a three-, 10- or 30-business-day timeframe. This synthesis was prepared over a 30-business-day timeframe. An overview of what can be provided and what cannot be provided in each of the different timelines is provided on the McMaster Health Forum's Rapid Response program webpage (https://www.mcmasterforum.org/find-evidence/rapid-response).

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Conflict of interest

The authors declare that they have no professional or commercial interests relevant to the rapid synthesis. The funder played no role in the identification, selection, assessment, synthesis or presentation of the research evidence profiled in the rapid synthesis.

Merit review

The rapid synthesis was reviewed by a small number of policymakers, stakeholders and researchers in order to ensure its scientific rigour and system relevance.

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KEY MESSAGES

Questions

- What pharmacogenetic tests are publicly available in comparator jurisdictions and for what conditions?
- What does the evidence say about the cost-effectiveness of using population-based genetic screening to inform pharmacological decisions?

Why the issue is important

- Rapid technological advances in pharmacogenetics and pharmacogenomics hold promise for advancing the field of personalized medicine.
- While the use of genetic information is increasingly viewed as a valuable tool in clinical care, opportunities to use it at a population level are now being explored.
- Yet, concerns remain about the high costs of some pharmacogenetic tests, the costs of drug therapies that result from such tests, and whether they represent good value for money from a system perspective.
- With the potential for harnessing genetic information to inform policy and coverage decisions regarding drugs, it is timely to take stock of what is known about the coverage of pharmacogenetic tests and their cost-effectiveness.

What we found

- We identified a total of 12 documents including six systematic reviews, one protocol for a systematic review, four non-systematic literature reviews, and one primary study.
- In addition, we undertook a scan of 16 comparator jurisdictions (each Canadian province other than British Columbia which is where the synthesis was requested from, Australia, New Zealand, the United Kingdom, and four large HMOs – Athem, Blue Cross Blue Shield, Cigna and United Healthcare – in the United States) to, where possible, identify what pharmacogenetic tests are publicly provided, for whom, and how they are paid for.
- While some information was found on what individual pharmacogenetic tests are publicly provided across jurisdictions for select conditions, we found limited information on the use of pharmacogenetic data aggregated at a population level to make drug coverage and policy decisions.
- One non-systematic review noted that the majority of cost-effectiveness analyses are calculated on an individual basis, and are not population-based.
- Seven systematic reviews found mixed levels of cost-effectiveness of pharmacogenetic tests.
- One of the older medium-quality reviews identified factors found to be determinants of cost-effective tests, which included: test characteristics (e.g., sensitivity and specificity); population characteristics (e.g., size of population being tested); mutation characteristics (e.g., prevalence and penetrance); and disease characteristics (e.g., severity and costs of outcomes and treatments).
- One non-systematic review examined challenges to implement pharmacogenetic tests. There is little uptake by patients of genetic testing that predicts risk of rare diseases due to various concerns (e.g., cost, lack of effective treatment options, privacy and discrimination concerns), but there is a strong patient demand for testing that is directly related to key treatment decisions, such as testing for the purpose of prescribing drug therapy based on genetic variation of the disease.
- The same non-systematic review revealed that providers also face implementation challenges regarding the costs, benefits and risks of genetic-testing technologies (e.g., understanding the availability and effectiveness of various tests, how tests will alter patient management, deciding the appropriate level of counselling for an informed consent for tests, and justifying testing or not testing certain racial or ethnic groups where prevalence of the genetic variant is low).

QUESTIONS

- What pharmacogenetic screening tests are publicly available in comparator jurisdictions and for what conditions?
- What does the evidence say about the cost-effectiveness of using population-based genetic screening to inform pharmacological decisions?

WHY THE ISSUE IS IMPORTANT

Rapid technological advances in pharmacogenetics and pharmacogenomics hold promise for advancing the field of personalized medicine. Pharmacogenetics refers to the role of genetic variation in a response to a drug. Such variation can be inherited through the germline or be acquired (e.g., in a tumour). Pharmacogenetics is generally used to refer to a specific DNA mutation or coding variant rather than changes across the entire genome.(1) Pharmacogenetics is a sub-category of pharmacogenomics, which refers to the way in which a component of the genome reacts to a drug. The terms pharmacogenetics and pharmacogenomics are often used interchangeably.(1)

The capacity to identify genetic factors influencing drug absorption, metabolism and action at the receptor level could result in:

- individualized therapy;
- greater drug effectiveness;
- lower toxicity profiles in a given population;
- a reduction in morbidity and mortality (through increased drug safety and fewer adverse drug reactions); and
- cost-saving opportunities (through increased drug effectiveness).(1)

Box 1: Background to the rapid synthesis

This rapid synthesis mobilizes both global and local research evidence about a question submitted to the McMaster Health Forum's Rapid Response program. Whenever possible, the rapid synthesis summarizes research evidence drawn from systematic reviews of the research literature and occasionally from single research studies. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select and appraise research studies, and to synthesize data from the included studies. The rapid synthesis does not contain recommendations, which would have required the authors to make judgments based on their personal values and preferences.

Rapid syntheses can be requested in a three-, 10- or 30-business-day timeframe. An overview of what can be provided and what cannot be provided in each of these timelines is provided on the McMaster Health Forum's Rapid Response program webpage (https://www.mcmasterforum.org/find-evidence/rapid-response).

This rapid synthesis was prepared over a 30-business-day timeframe and involved four steps:

1) submission of a question from a health system policymaker or stakeholder (in this case, the Ministry of Health of British Columbia);
2) identifying, selecting, appraising and synthesizing relevant research evidence about the question;
3) drafting the rapid synthesis in such a way as to present concisely and in accessible language the research evidence; and
4) finalizing the rapid synthesis based on the input of at least two merit reviewers.

There is a growing number of drugs that are now labelled with pharmacogenetics information. The U.S. Food and Drug Administration (FDA) listed more than 200 FDA-approved drugs with pharmacogenomic information in their labelling (e.g., adverse reactions, use in specific populations, drug interactions, contraindications, warnings and precautions) in many therapeutic areas (e.g., anesthesiology, cardiology, dental, dermatology, endocrinology, gastroenterology, gynecology, hematology, infectious diseases, neurology, oncology, psychiatry, rheumatology).(2) We provide the full list in Appendix 3. The labelling for some drugs, but not all, includes specific actions to be taken based on the biomarker information collected. In addition, there is a growing number of pharmacogenetic tests available, with the NIH Genetic Testing Registry identifying 45 pharmacogenetic tests for 168 conditions.(3)

Many companies have begun to bring these tests to the Canadian market.(4-9) While some companies offer tests that can be directly ordered by patients (via a direct-to-consumer approach), others require tests to be ordered by a clinician. Several initiatives are also underway to make these tests available through community pharmacies across the country, such as the recent partnership between the B.C. Pharmacy Association and the industry.(10)

While the use of genetic information is increasingly viewed as a valuable tool in clinical care, a narrative literature review examining the potential connections between pharmacogenomics and public health concluded that "what was previously considered a tool for personalized medicine is now paving the path towards 'populationized' medicine."(11)

Harnessing pharmacogenetic information at the population level could help guide policy and coverage decisions regarding existing, new and emerging drugs. Expected benefits include, but are not limited to:

- using public funds more efficiently (e.g., decreasing healthcare spending and improving resource allocation);(11)
- improving the widespread use of effective and safe drug treatments (in a context where therapeutic indices may vary across populations, some countries may question the effectiveness of drug treatments within their own populations in comparison to study populations);(11)
- improving capacity to screen for disease predispositions and treatment responsiveness;(12) and
- ensuring equitable access to (and distribution of) healthcare resources for disadvantaged populations who may receive sub-optimal drug treatments and experience dangerous side effects.(11)

Nevertheless, some of these potential benefits are being debated. For instance, concerns remain about the high costs of some pharmacogenetic tests, the costs of drug therapies that result from such tests, and whether pharmacogenetic tests actually represent good value for money from a system perspective.(13)

With the potential for harnessing genetic information to inform policy and coverage decisions regarding drugs, it is timely to take stock of what is known about the coverage of pharmacogenetic tests and their cost-effectiveness.

WHAT WE FOUND

We identified a total of 12 relevant documents by searching four databases (Health Systems Evidence, Health Evidence, PubMed and EMBASE), with the search strategy for these databases detailed in Box 2. As mentioned above, literature was included when it directly addressed one of the two questions posed for this rapid synthesis. Among the documents, we found seven systematic reviews, one protocol for a systematic review, three non-systematic literature reviews, and one primary study that were deemed relevant to this rapid synthesis. In addition, we undertook a scan of government websites and stakeholder websites from 16 comparator jurisdictions that were identified by the requestor. These included each Canadian province (other than British Columbia which is where the synthesis was requested from), Australia, New Zealand, the United Kingdom, and four of the largest HMOs in the United States (Athem, Blue Cross Blue Shield, Cigna and United Healthcare). For these jurisdictions, we identified (where possible) what pharmacogenetic tests are publicly provided, for whom, and how they are paid for. To conduct the scan, we purposefully sampled websites from each of the jurisdictions. This included reviewing the websites of the government agency responsible for health in each jurisdiction, as well as key agencies or organizations involved in providing insurance for or delivering genetic-testing services in each jurisdiction to identify the schedule of benefits. We provide more details about each review and single study in Appendix 1 and 2, respectively.

What pharmacogenetic screening tests are publicly available at a population-level in comparator jurisdictions and for what conditions?

Our jurisdictional scan yielded no information about phamacogenetic tests that are publicly covered at the population level for select conditions across the jurisdictions reviewed. However, in reviewing the literature, we did find one primary study that examined coverage policies for individual pharmacogenetic tests among six U.S. insurance companies, and we detail the findings in Table 1.(14) This study reveals that coverage policies for specific pharmacogenetic tests varied greatly across insurance companies, and that the majority of tests were deemed experimental/investigational and therefore not eligible for coverage.(14)

Box 2: Identification, selection and synthesis of research evidence

For the first question, we undertook a purposeful sampling of websites of the government and agencies involved in genetic testing in each of the jurisdictions.

For the second question, we identified systematic reviews and economic evaluations about the cost-effectiveness of using population-level genetic information to inform pharmaceutical decisions. We conducted searches in July 2017 in Health Systems Evidence (www.healthsystemsevidence.org), Health Evidence, PubMed and EMBASE. We used the following search strategy: (population-based genetic screening OR pharmacogenetics OR pharmacogenomics) AND (resource allocation OR coverage decisions OR insurance coverage OR policy making OR rationing OR framework OR criteria OR national health programs OR insur* OR public* fund OR public* finance* OR public* coverage) AND (cost-effectiveness OR economic evaluations OR costing studies).

The results from the searches were assessed by one reviewer for inclusion. A document was included if it fit within the scope of the questions posed for the rapid synthesis.

For each systematic review we included in the synthesis, we documented the focus of the review, key findings, last year the literature was searched (as an indicator of how recently it was conducted), methodological quality using the AMSTAR quality appraisal tool (see the Appendix for more detail), and the proportion of the included studies that were conducted in Canada. For primary research (if included), we documented the focus of the study, methods used, a description of the sample, the jurisdiction(s) studied, key features of the intervention, and key findings. Note that the methodological quality of primary studies and non-systematic reviews was not appraised due to the shortened timeframe required to conduct a rapid synthesis. We then used this extracted information to develop a synthesis of the key findings from the included reviews and primary studies.

Table 1. Coverage policies for pharmacogenetic tests by insurers as of 2012 (table adapted from Hresko & Haga 2012)(14)

Test	Drug indication	Insurer coverage					
		Aetna	Independence BCBS	Cigna	Humana	United Health	BCBS
Apo E	Lipid lowering medications	No	-	No	-	-	-
BRAF	Cetuximab pantimumab	-	No	-	-	-	-
Caris TargetNOW molecular profiling	Cancer therapy	No	-	-	No	-	-
CYP2C19	Clopidogrel	Yes	Yes	No	No	-	-
CYP2C19	Proton pump inhibitors	No	No	-	No	-	-
VKORC 1	Warfarin	No	No	No	No	-	-
CYP2D6	Tamoxifen	No	No	No	No	-	No
CYP2D6	Tetrabenezine	Yes	-	-	Yes	-	-
CYP2D6	Donepezil	No	-	-	-	-	-
CYP2C9	Proton pump inhibitors	-	-	-	No	-	-
CYP450	SSRIs	No	-	No	No	-	-
DPDY	5-Fluorouracil	No	-	-	No	-	No
EGFR	Erlotinib	Yes	No	-	Yes	-	Yes
ERCC1	Cisplatin, carboplatin, and oxaloplatin	-	-	-	No	-	-
HLA-B*1502	Cabamazepine	Yes (in Asian patients)	-	-	Yes (in Asian patients)	-	-
HLA-B*5701	Abacavir	Yes	-	Yes	Yes	-	-
IL28B	Interferon therapy for Hepatitis C	No	-	-	-	-	-
KIF6	Statin	-	No	-	-	-	-
KRAS	Erlotinib	Yes	No	-	No	-	-
MGMT Methylation	Temozolomide	-	-	-	No	-	-
MTHFR	Antifolate chemotherapy	No	-	-	-	-	-
Rs3798220	Aspirin	No	-	-	-	-	-
TPMT	Mercaptopurine, azathipurine	Yes	Yes	Yes	Yes	-	-
Thymidylate Synthase	5-Fluorouracil	No	-	-	-	-	No
Urovysion	Follow-up treatment for bladder cancer	Yes	-	-	-	-	-
UTG1A1	Irinotecan	No	-	No	No	-	-
Whole Genome/Whole Exome/ Genome-wide Association study	Pharmacogenetics	-	-	-	No	-	-

* Indicates that no information was found on the coverage of this test

In addition, we found one non-systematic review which described how relatively few pharmacogenetic tests (either at an individual or population-based level) are actually available for use in clinical practice, and even when tests are available, there has been slow adoption of these tests to inform clinical decision-making in practice.(1)

What does the evidence say about the cost-effectiveness of using population-based genetic screening to inform pharmacological decisions?

We found six systematic reviews, one systematic review in progress, and four non-systematic reviews with relevance to the cost-effectiveness of pharmacogenetic tests. One non-systematic review noted that the use of pharmacogenetic data aggregated at the population level is still in its infancy.(11) In addition, the majority of cost-effectiveness analyses are calculated on an individual basis, and are not population-based. Yet, the review revealed that some countries are exploring how to use population-level genetic information to inform policy and coverage decisions regarding pharmaceuticals. For example, Germany has been investigating the cost-saving benefit of pharmacogenomics. Also, Greece and Poland are working towards pharmacogenomics implementation in their national health formularies. Applying population-based genetic information to inform policy and coverage decisions is also gaining traction in low- and middle-income countries, such as Ghana, through the PharmacoGenetics for Every Nation Initiative that aims to evaluate the use of pharmacogenetics to enhance global drug-use policy.(11)

Beyond these broad considerations, we found that relatively few cost-effectiveness analyses have been performed. While crucial to informing decisions about reimbursement for routine pharmacogenetic tests, the limited number of available analyses may be driven by difficulties in conducting cost-effectiveness or cost-utility analyses in this area. Specifically, analyses in this area are made difficult because of limited data addressing how often pharmacogenetic testing actually prevents clinically significant adverse drug reactions.(1) This challenge may be exacerbated by a lack of studies using robust methodologies to assess the cost-effectiveness of pharmacogenetic tests, which precludes meaningful comparison across studies even when the same drug and marker are being considered.(13) The validity of existing cost-effectiveness analyses may also be limited since the price of pharmacogenetic tests is likely to drop continuously over the next few years.(1)

Across the systematic reviews that we identified, we found mixed levels of cost-effectiveness of pharmacogenetic tests. One older high-quality systematic review was unable to determine the cost-effectiveness or cost-utility of pharmacogenetic tests due to methodological limitations of the literature (e.g., reliability limitations of the Quality of Health Economic Studies instrument used, and the clinical validity and utility of pharmacogenetic tests not being derived from systematic evidence assessments).(15) That review found that while 10 of the 16 studies included in the review found pharmacogenetic tests (the majority of which assessed their application for thromboembolic-related diseases) had high clinical validity (defined as "how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest"), only two were found to have high clinical utility (defined as "how likely the test is to significantly improve patient outcomes").(15) The review also revealed that only two tests were found to have both clinical validity and utility (HER-2 and HLA-B 5701), while the majority of tests had unclear clinical utility and were limited by either a lack of studies or conflicting findings.(15)

One older medium-quality review found that among patients with high risk of adverse outcomes to proposed drug treatments, pharmacogenetic screening was more cost-effective than no screening.(16) These findings resonated with another older medium-quality review examining the findings from 11 studies which found that the majority of studies (seven out of 11) reported that the pharmacogenetic tests were relatively cost-effective (e.g., < US$50,000 per quality adjusted life year gained or that the pharmacogenetic strategy dominated the alternative). The pharmacogenetic tests that were cost-effective focused on deep vein thrombosis (n=3), rheumatoid arthritis or systemic lupus erythematosus (n=2), drug-resistant HIV (n=1) and chronic hepatitis C virus (n=1). However, two studies reported that a pharmacogenetic strategy was not cost-effective (chronic hepatitis C virus and factor V Leiden), and two others reported equivocal results (deep vein thrombosis and metastatic breast cancer).(17)

A more recent medium-quality systematic review examining 80 studies revealed the application of most pharmacogenetic tests to be a cost-effective or cost-saving strategy. Yet, a minority of studies evaluated the intrinsic value of the pharmacogenetic tests (i.e., the economic value of using a pharmacogenetic test as compared to no testing), while the majority compared a pharmacogenetic test treatment in combination with

an alternative treatment.(18)

Another more recent and medium-quality review examined pharmacogenetic tests that aim to prevent or reduce the incidence of adverse drug reactions.(13) Findings from 47 studies revealed robust evidence of the cost-effectiveness of pharmacogenetic tests prior to treatment with abacavir, allopurinol, carbamazepine, clopidogrel and irinotecan. Existing evidence is inconclusive with respect to: pharmacogenetic tests prior to taking 6-mercaptoputine, or azathioprine, or undergoing cisplatin treatment; informing genotype-guided dosing of coumarin derivatives; prior to methotrexate treatment; and prior to oral contraception. Pharmacogenetic tests prior to prescribing aminoglycosides is not cost-effective.

A recent non-systematic review examined cost-effectiveness and cost-utility based on 84 studies of 'individualized medicine' (including pharmacogenetic tests to stratify patients by response or by risk of adverse effects to drug treatments).(19) It revealed mixed findings and the authors concluded that: "(individualized medicine) neither seems to display superior cost-effectiveness than other types of medical interventions nor to be economically inferior."(19) Findings differed according to test type. For instance, genetic tests for disease prognosis or screening appeared to be more favourable than tests to stratify patients by response or by risk of adverse effects (but results were not significant).(19)

One of the older medium-quality reviews also identified key factors that can drive the cost-effectiveness of pharmacogenetic tests, and these included:

- test characteristics (e.g., sensitivity and specificity);
- population characteristics (e.g., size of population being tested);
- mutation characteristics (e.g., prevalence and penetrance); and
- disease characteristics (e.g., severity and costs of outcomes and treatments).(17)

One older medium-quality systematic review and one recent protocol for a systematic review proposed that the following key elements be included in future economic evaluations of pharmacogenetic tests:

- marker prevalence;
- population ethnicity;
- the strength of the relationship between genetic information and clinical outcomes;
- pharmacogenetic treatment effects;
- cost of data collection and analysis;
- estimates of uptake by patients and clinicians;
- consequences of false-positive and false-negative test results;
- cost of genetic counselling associated with the test; and
- test failures and/or repeated testing.(20-21)

Lastly, one non-systematic review outlined key issues for patients, providers and insurance companies for implementing genetic tests. The non-systematic review found that:

- there is little uptake by patients of genetic testing that predicts risk of rare diseases due to various concerns (e.g., cost, lack of effective treatment options available for those testing positive, privacy and discrimination concerns, limited predictive value, and negative impact on quality of life), but there is strong patient demand for genetic testing that directly relates to key treatment decisions;
- healthcare providers face several challenges regarding the costs, benefits and risks of genetic-testing technologies (e.g., understanding the availability and effectiveness of various genetic tests, how genetic tests will alter patient management, deciding the appropriate level of counselling for an informed consent for genetic tests, and justifying testing or not testing certain racial or ethnic groups where prevalence of the genetic variant is low).; and
- health insurance companies acknowledge that pharmacogenomic testing for individuals is relatively cheap, but may represent a significant cost at the population level.(22)

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APPENDICES

The following tables provide detailed information about the systematic reviews and primary studies identified in the rapid synthesis. The ensuing information was extracted from the following sources:

- systematic reviews - the focus of the review, key findings, last year the literature was searched, the proportion of studies conducted in Canada and the proportion of studies focused on pharmacogenetic tests; and
- primary studies (in this case, economic evaluations and costing studies) - the focus of the study, methods used, study sample, jurisdiction studied, key features of the intervention and the study findings (based on the outcomes reported in the study).

For the appendix table providing details about the systematic reviews, the fourth column presents a rating of the overall quality of each review. The quality of each review has been assessed using AMSTAR (A MeaSurement Tool to Assess Reviews), which rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial or governance arrangements within health systems. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered "high scores." A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8).

All of the information provided in the appendix tables was taken into account by the authors in describing the findings in the rapid synthesis.

Appendix 1: Summary of findings from systematic reviews about pharmacogenetic testing

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
Systematic review	Economic evaluation of pharmacogenetics and pharmacogenomics screening tests (18)	This review provided an update of the existing literature. Thirty-eight new studies were found that investigated the cost-effectiveness of pharmacogenetics and pharmacogenomics (PGx) screening tests, and the results of these studies were combined with 42 studies from previous reviews. Cost-utility analysis was the technique most commonly applied (68%), followed by cost-effectiveness analysis (25%) and cost-minimization analysis (6%). It was found that some studies assessed the intrinsic value of pharmacogenomic tests. However, the majority of the newer studies (i.e., since 2010) utilized a pharmacogenomics strategy in combination with a drug and compared this combination with another drug, and thus the intrinsic value of the pharmacogenomics was not evaluated. There were considerable differences found between the costs of the PGx tests, with tests generally costing less in newer studies. This was likely due to technological advancements of the genetic tests. Twenty-one out of the 80 studies concluded PGx testing resulted in clinical benefits and was cost-effective. From 2010 onwards, most studies concluded that PGx testing was cost-effective. Additionally, several studies from 2010 to 2014 provided specific conditions at which genetic testing might become cost-effective, such as specific patient populations or diseases. Due to the imperfect capability of PGx tests to differentiate between carriers of a genetic variant, some patients might be misclassified and receive sub-optimal treatment. The majority of the newly included papers discussed their limitations and uncertainties. The most common one discussed was the lack of solid clinical evidence. Therefore, many studies had to make assumptions and use experts' opinions. Another common limitation was the time in which test results became available for clinical decision-making. Most studies assumed the rest results were immediately available. However, the review noted that this is an unrealistic assumption, and only one of 38 studies mentioned this assumption as a limitation. Lastly, the majority of studies (71%) were rated as high quality using the Quality of Health Economics Studies instrument.	2014	5/9 (AMSTAR rating from McMaster Health Forum)	Not reported in detail

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
Systematic review	Provide a systematic and critical review of economic evaluations of pharmacogenetic tests (15)	The review included 34 economic evaluation studies that investigated pharmacogenomics. The most common disease category was thromboembolic disease, which accounted for nine of the studies. Thomboembolic diseases and cancer were also the most common diseases evaluated in recently published studies. The two most common biomarkers investigated were thiopurine methyltransferase and cytochrome P450 2C9. The average overall quality of these studies, assessed using the Quality of Health Economics Studies, was higher in more recently published studies. All of the studies were either cost-effectiveness or cost-utility studies, where the cost-utility studies had higher quality scores than cost-effectiveness studies (83.2 versus 60.1). The results of these studies were highly variable, from the screen-and-treat intervention dominating to being unlikely to be cost-effective. The authors also assessed the clinical validity and clinical utility of the genetic tests. Clinical validity was defined as how consistently and accurately the test detected or predicted the outcomes of interest, whereas clinical utility was defined as how likely the test was to significantly improve patient outcomes. Ten of 16 biomarkers evaluated were estimated to have clinical validity, one biomarker was estimated to have no clinical validity, and the rest were unclear. The majority of the biomarkers had an unclear clinical utility. Only two biomarkers were assessed to have clinical utility, two were likely to have utility, and one did not have any clinical utility. In total, only two biomarkers were found to have both clinical validity and utility (HER-2 and HLA-B*5701). Additionally, one biomarker (alpha-adducin Gly460Trp) was found to have neither clinical validity or utility despite having a favourable conclusion in the cost-effectiveness study.	2009	8/9 (AMSTAR rating from McMaster Health Forum)	Not reported in detail
Systematic review	Identify and comment on the parameters influencing the cost-effectiveness of pharmacogenomic tests (20)	The review included 15 pharmacoeconomic evaluations and investigated various topics, including the components related to the test, the model, health outcomes, costs and incremental cost-effectiveness ratio (ICER). The review identified components specific to pharmacogenomic tests that should be included in pharmacoeconomic evaluations as marker prevalence, population ethnicity, pharmacogenomics treatment effect, and cost of genomic data collection and analysis. The majority of the economic evaluations did not consider analytical or clinical sensitivity. These studies focused on clinical utility instead, even when pharmacogenetic tests were medical devices that frequently underwent product modification. Similarly, the studies that considered false positives and negatives did not clearly assess and outline their impact on disease risks and costs. Additionally, only a few studies gave information on	Not reported in detail	4/9 (AMSTAR rating from McMaster Health Forum)	Not reported in detail

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
		performances and detailed costs of the tests. Several studies that were included in this review also did not consider the identifier prevalence in the target population, or clearly refer to a specific ethnicity. This causes potential biases and limits the transferability of test performance and treatment response across different populations. Due to limited data available on pharmacogenomic tests and drugs that may benefit from pharmacogenomic tests, modelling techniques were required. The studies reviewed had different modelling choices, such as type and number of comparators or risk assumptions. This could in part explain the important differences in ICERs found. Half of the studies used a time horizon of two years or less. Although many consequences of testing may be encountered in the short term, they may influence long-term outcomes. Thus, lifetime horizons were recommended by the authors.			
Systematic review	Review the content of and adherence to pharmacoeconomic guidelines of recent analyses performed in the field of pharmacogenetics and pharmacogenomics(16)	The review included 20 studies that covered a variety of healthcare issues. Most of the studies concluded that genetic screening is cost-effective and often dominated existing non-screening strategies. This was primarily due to the fact that the patient groups under study had a high risk of a severe outcome to treatment, or the treatment itself had high costs. In these cases, a screening method would have high probabilities of being cost-effective or cost-saving, as screening costs are relatively low and one-off. Only three studies concluded that screening had a potentially less favourable outcome than non-screening. The relation between a patient's genotype and treatment response is part of the genotype-phenotype association. A person's phenotype depends on the genotype as well as many environmental factors that can change over time, with potential confounding of a clear association. The review noted it is important to provide a sufficiently evidence-based rationale for the association between genotype and drug effectiveness or toxicity. However, several studies in the review failed to provide adequate evidence-based data for an association between genotype and phenotype. For example, some analyses based their assumptions on only a small group of individuals.	2007	4/9 (AMSTAR rating from McMaster Health Forum)	Not reported in detail
Systematic review	Review the cost-effectiveness of pharmacogenomics interventions (17)	The review included 11 cost-effectiveness analyses of pharmacogenomics (PGx) interventions. The most commonly investigated diseases were deep vein thrombosis treated by anticoagulation therapy (n=4), cancer (n=3), and viral infections	2004	5/9 (AMSTAR rating from McMaster Health Forum)	Not reported in detail

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
		(n=3). Seven studies concluded that the PGx-based strategy was relatively cost-effective. Two studies reported that the PGx-based strategy was relatively not cost-effective, and two studies reported that the cost-effectiveness varied depending on the strategy or assumptions. The review also illustrated factors that had a significant impact on the cost-effectiveness of the PGx-based strategies. Some of these factors included prevalence of the genetic mutation, disease characteristics, severity of outcomes, treatment costs and length, and accuracy of the genetic test.			
Systematic review	Review economic evaluations of pharmacogenetic tests that aim to prevent or reduce the incidence of adverse drug reactions (13)	A total of 47 papers met the inclusion criteria. Most of the studies showed that testing leads to an improved health outcome, but at an increased cost. Most high-quality studies found that genotyping prior to using abacavir, allopurinol, carbamazepine, clopidogrel and irinotecan was either dominant, cost-saving, or cost-effective across a variety of populations. Evidence on the cost-effectiveness of genotyping prior to usage of 6-MP, azathioprine, warfarin, oral contraceptives or phenprocoumon was mixed. Evidence supporting the cost-effectiveness of genetic testing prior to the usage of cisplatin, methotrexate, SSRIs, and *HLA-A*31:01* before carbamazepine was weak, being based mostly on single studies. Often, the clinical and cost-effectiveness of pharmacogenetic testing varied across populations due to differences in genotype prevalence. Though the quality of reporting in included studies was generally high, it should be noted that most of the evidence supporting the effectiveness of pharmacogenetic testing was not based on randomized controlled trials. Furthermore, there was substantial variation in populations, countries, perspectives, analysis and methods among the included studies.	2015	7/10 (AMSTAR rating from McMaster Health Forum)	5/47
Protocol for a systematic review	Investigate test-related evidence used to inform decision models developed for the economic evaluation of genetic tests (21)	Pharmacogenetic and pharmacogenomic tests are often economically evaluated with decision models. However, decision models often require a lot of evidence, and previous research has found that the evidence used in this field is diverse and of uncertain quality. Thus, this systematic review has four specific objectives: determine what test-related evidence is being included in model-based economic evaluations of pharmacogenomic tests; determine how the evidence is being identified; determine the quality of evidence; and determine the general quality of model-based economic evaluation. Included studies will include economic evaluations of pharmacogenomic tests used for predicting treatment response. The investigators will search several scientific databases, reports from health-technology-assessment	Still in progress at the time of publishing	No rating tool available for this type of document	Still in progress at the time of publishing

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
		agencies, and the online records of several government agencies from England, Australia and Canada. Study quality will be assessed with a modified version of a previously published checklist.			
Non-systematic review	Review the cost-effectiveness of individualized medicine compared to treatment without genetic stratification (19)	The review included 84 studies examining cost-effectiveness from a payer, societal and service-provider perspective. The included studies covered a variety of medical conditions, with cancer being the most frequent (46%). These studies focused on breast cancer and colorectal cancer. Following cancer, the most frequently cited condition included in the studies were diseases of the circulatory system such as vein thrombosis and atrial fibrillation. Studies also varied greatly on the genes that tests examined. The studies included four categories of genetic tests: 1) tests used to distinguish patients who respond from patients who do not respond to a specific treatment; 2) tests used to identify patients who could experience side effects given a treatment; 3) tests used to screen for a certain disease or genetic mutation in an asymptomatic population; and 4) studies used to gain information on a prognosis of a specific disease. Of the included studies, 53 that focused on individualized medicine were within the acceptable ICER threshold. Of the remaining studies, six showed favourability (dominance) towards the individualized medicine strategy, 21 were equivalent between individualized medicine and non-genetically guided care, and four found that individualized medicine was not a favourable option (dominated) from a cost perspective. While the cost-effectiveness of individualized medicine was found to differ, the review concluded that these differences were not significant. The results of the studies were largely driven by early breast cancer tests, which were isolated and compared to adjuvant therapy. All but two were found to be dominant and below the QALY threshold. This was largely a result of increased life expectancy and reduced costs from unnecessary chemotherapy. Tests used to screen for certain diseases found similar results, whereby all but two were found dominant and below the QALY threshold, with this being largely attributable to treatment effects incurred earlier or the use of preventive interventions whereby fewer adverse events occurred. Of the studies assessing genetic tests to identify patients who had	2013	No rating tool available for this type of document	0/84

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
		experienced adverse effects to specific treatments, six studies reported ICERs high than the threshold. Studies included tests for stratification of responders and non-responders, and nine of the studies reported ICERs higher than the QALY threshold. Cost-effectiveness was also different according to the stated perspective, with studies using a societal perspective having a higher QALY than those conducted from a payer's perspective. Overall, the evidence on cost-effectiveness can be considered mixed, however it falls on average just below the threshold of $US 22,000/QALY gained that has been determined following a systematic review of 30 years of cost-utility analyses.			
Non-systematic review	Investigate the potential impact of genetic testing and pharmacogenomics on healthcare delivery and costs (22)	The review assessed the potential impact of genetic testing and pharmacogenomics on healthcare delivery and costs. Three examples of genetic tests that serve different purposes were examined: 1) genetic testing for the purpose of predicting future disease risk based on an inherited mutation in an individual; 2) genetic testing for the purpose of prescribing drug therapy based on genetic variation of the disease; and 3) genetic testing for the purpose of prescribing drug therapy based on genetic variation of the individual. The key issues in implementing genetic testing were outlined from the perspectives of various stakeholders. <u>Patients</u> There is little uptake of genetic testing that predicts risk of rare diseases due to concerns about cost, lack of effective treatment options available for those testing positive, privacy and discrimination concerns, limited predictive value, and negative impact on quality of life. However, there appeared to be a strong patient demand for testing that is directly related to key treatment decisions, such as testing for the purpose of prescribing drug therapy based on genetic variation of the disease. <u>Providers</u> Providers face several challenges regarding the costs, benefits and risks of genetic-testing technologies. These challenges include understanding the availability and effectiveness of various genetic tests, how genetic tests will alter patient management, deciding the appropriate level of counselling an informed consent for genetic tests, and justifying testing or not testing certain racial or ethnic groups where prevalence of the genetic variant is low. <u>Insurers</u>	Not reported in detail	No rating tool available for this type of document	Not reported in detail

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
		Typically, insurance companies have not universally covered testing for risk prediction. In contrast, there is usually high coverage on genetic testing for the purpose of prescribing drug therapy based on genetic variation of the disease. Treating for relatively rare and highly penetrant gene mutations is expensive on an individual level, but modest on a health-plan level. On the other hand, testing for more common mutations and for targeting drug therapies is relatively less expensive on an individual level, but will apply to a much larger population and the total costs may be substantial. Thus, the authors noted it is critical that insurers have necessary cost and outcome data to evaluate genomic technologies. <u>Industry</u> Pharmaceutical companies have a mixed interest in genomic technologies. Genomics will likely provide several new drug targets and enable drug development. However, more targeted drugs may lead to decreased market share and fewer blockbuster drugs. In contrast, the diagnostic industry has a clearer incentive to use genetic information. Genetic information will likely increase the market for diagnostics as genetic tests will be required for risk prediction and to stratify patients regardless of whether they receive an intervention. <u>Government</u> In the United States, commercial testing is rapidly advancing which is causing concerns about accessibility, price and quality. Unless there is government intervention, this commercialization will cause industry and economic incentives to play a relatively large role in determining the overall impact of genomic technologies.			
Non-systematic review	Provide a practical overview of the field of pharmacogenomics (1)	Genetic factors can influence a patient's response to pharmaceutical therapies by affecting drug metabolism, therapeutic efficacy, and the likelihood of adverse effects. By identifying genetic variations within a patient, genetic tests increase drug safety and reduce drug costs. In recent years, there has been increased interest and research in examining the potential role of genetic tests in individualized therapy. Additionally, the U.S. Food and Drug Administration has updated approximately 10% of drug labels to include information on pharmacogenomics issues applicable to specific drugs. Despite this, genetic tests are not routinely used. Implementation barriers	2017	No rating tool available for this type of document	Not reported in detail

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
		include a deficit of prospective randomized trials and cost-effectiveness analyses, ethical concerns, and the lack of education and awareness among patients and healthcare providers. Debate persists on whether, and the extent to which, pharmacogenomic testing will be integrated into clinical practice.			
Non-systematic review	Examine how pharmacogenomics can be used beneficially in public health (11)	This narrative literature review examined 27 articles about how pharmacogenomics and public health can constructively intersect, with a specific focus on resource-poor settings. The benefits of including pharmacogenomics in policy decisions can be realized on multiple levels of society, including local health benefits, resource allocation, increased scientific collaboration and the marketability of scientific knowledge. The implementation of pharmacogenomics into national healthcare plans has the potential to make healthcare more cost-effective by ensuring the best treatment of individuals, the proper prescription of medication, and identification of sub-populations at risk of disease and adverse drug reactions. Further studies should aim to assess the public's and stakeholders' views on incorporating this technology into national healthcare plans.	Not reported in detail	No rating tool available for this type of document	Not reported in detail

Appendix 2: Summary of findings from primary studies about pharmacogenetic testing

Focus of study	Methods	Publication date	Sample description	Jurisdiction(s) studied	Key features of the intervention(s)	Key findings
Evaluation of insurance coverage policies for personalized medicine (14)	An analysis of single coverage determination policies of companies that insured nationally, along with a review of health technology assessments of genomic and pharmacogenetic tests conducted by the Centers for Disease Control and Blue Cross Blue Shield	2012	Forty-one coverage policies of the largest U.S. insurers for 49 unique tests (22 disease diagnosis, prognosis, or risk assessment tests, 27 pharmacogenetic tests)	U.S.	No intervention	Generally, insurers agreed on their coverage policies for genomic tests. Most of the tests were deemed investigational and not medically necessary, and only 25% of tests reviewed by major insurers were covered. Some coverage policies included background information or justifications for their policy decisions. Generally, tests that were not covered lacked evidence from prospective, randomized clinical trials. For tests with a strong association between genotype and the interested outcome, the lack of evidence of clinical utility was mentioned to justify the decision not to cover the test. There were no coverage policies that mentioned evidence of cost-effectiveness. Only five tests had different coverage policies among insurers. In these cases, insurers either examined different data, or reached different conclusions from analyses of similar sets of data. FDA test approval did not appear to heavily influence coverage decisions. However, the inclusion of pharmacogenetic test information in drug package inserts were found to be an important factor. To promote uptake and coverage of tests, the authors suggest multiple approaches, including improving physician and patient awareness of tests, and expanding data collection efforts outside of traditional clinical trial study designs.

Appendix 3. FDA-approved drugs with pharmacogenomics information in their labelling (2)

Therapeutic Area*	Drug	Biomarker	Labeling Sections
Anesthesiology	Codeine	CYP2D6	Boxed warning, warnings and precautions, use in specific populations, patient counselling information
	Desflurane	Not specified	Contraindications
	Isoflurane	Not specified	Contraindications
	Lidocaine and Prilocaine (1)	Not specified	Warnings and precautions
	Lidocaine and Prilocaine (2)	G6PD	Warnings and precautions, clinical pharmacology
	Sevoflurane	RYR1	Warnings
	Tramadol	CYP2D6	Clinical pharmacology
Cardiology	Carvedilol	CYP2D6	Drug interactions, clinical pharmacology
	Clopidogrel	CYP2C19	Boxed warning, warnings and precautions, clinical pharmacology
	Hydralazine	NAT1, NAT2	Clinical pharmacology
	Isosorbide Dinitrate	CYB5R1, CYB5R2, CYB5R3, CYB5R4	Overdosage
	Isosorbide Mononitrate	CYB5R1, CYB5R2, CYB5R3, CYB5R4	Overdosage
	Metoprolol	CYP2D6	Drug interactions, clinical pharmacology
	Nebivolol	CYP2D6	Dosage and administration, clinical pharmacology
	Prasugrel (1)	CYP2C19	Use in specific populations, clinical pharmacology, clinical studies
	Prasugrel (2)	CYP2C9	Use in specific populations, clinical pharmacology, clinical studies
	Prasugrel (3)	CYP3A5	Use in specific populations, clinical pharmacology, clinical Studies
	Prasugrel (4)	CYP2B6	Use in specific populations, clinical pharmacology, clinical studies
	Propafenone	CYP2D6	Dosage and administration, warnings and precautions, drug interactions, clinical pharmacology
	Propranolol	CYP2D6	Clinical pharmacology
	Quinidine	CYP2D6	Precautions
	Ticagrelor	CYP2C19	Clinical pharmacology
Dental	Cevimeline	CYP2D6	Precautions

Therapeutic Area*	Drug	Biomarker	Labeling Sections
Dermatology	Dapsone (1)	G6PD	Warnings and precautions, use in specific populations
	Dapsone (2)	Not specified	Warnings and precautions
	Fluorouracil (1)	DPYD	Contraindications, warnings
Dermatology and Gastroenterology	Ustekinumab	IL12A, IL12B, IL23A	Warnings and precautions
Endocrinology	Alirocumab	Not specified	Indications and usage, adverse reactions, clinical studies
	Chlorpropamide	G6PD	Precautions
	Evolocumab	Not specified	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical studies
	Glimepiride	G6PD	Warnings and precautions, adverse reactions
	Glipizide	G6PD	Precautions
	Glyburide	G6PD	Precautions
	Lomitapide	Not specified	Boxed warning, indication and usage, warnings and precautions, adverse reactions, clinical studies
	Mipomersen	Not specified	Boxed warning, indications and usage, warnings and precautions, adverse reactions, use in specific populations, clinical studies
	Rosuvastatin	SLCO1B1	Clinical pharmacology
Gastroenterology	Ascorbic Acid, PEG-3350, Potassium Chloride, Sodium Ascorbate, Sodium Chloride, and Sodium Sulfate	G6PD	Warnings and precautions
	Dexlansoprazole	CYP2C19	Drug interactions, clinical pharmacology
	Dronabinol	CYP2C9	Use in specific populations, clinical pharmacology
	Esomeprazole	CYP2C19	Drug interactions, clinical pharmacology
	Lansoprazole	CYP2C19	Drug interactions, clinical pharmacology
	Metoclopramide (1)	CYB5R1, CYB5R2, CYB5R3, CYB5R4	Precautions, overdosage
	Metoclopramide (2)	G6PD	Precautions, overdosage
	Omeprazole	CYP2C19	Drug interactions, clinical pharmacology
	Ondansetron	CYP2D6	Clinical pharmacology

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Palonosetron	CYP2D6	Clinical pharmacology
	Pantoprazole	CYP2C19	Clinical pharmacology
	Rabeprazole	CYP2C19	Clinical pharmacology
	Sulfasalazine	G6PD	Precautions
Gynecology	Drospirenone and Ethinyl Estradiol	CYP2C19	Clinical pharmacology
	Flibanserin (1)	CYP2C9	Clinical pharmacology
	Flibanserin (2)	CYP2C19	Adverse reactions, use in specific populations, clinical pharmacology
	Flibanserin (3)	CYP2D6	Clinical pharmacology
Hematology	Eltrombopag (1)	F5 (Factor V Leiden)	Warnings and precautions
	Eltrombopag (2)	SERPINC1 (Antithrombin III)	Warnings and precautions
	Lenalidomide	del (5q)	Boxed warning, indications and usage, adverse reactions, use in specific populations, clinical studies
	Methylene Blue	G6PD	Contraindications, warnings and precautions
	Succimer	G6PD	Clinical pharmacology
	Warfarin (1)	CYP2C9	Dosage and administration, drug interactions, clinical pharmacology
	Warfarin (2)	VKORC1	Dosage and administration, clinical pharmacology
	Warfarin (3)	PROS1	Warnings and precautions
	Warfarin (4)	PROC	Warnings and precautions
Inborn Errors of Metabolism	Carglumic Acid	NAGS	Indications and usage, warnings and precautions, use in specific populations, clinical pharmacology, clinical studies
	Eliglustat	CYP2D6	Indications and usage, dosage and administration, contraindications, warnings and precautions, drug interactions, use in specific populations, clinical pharmacology, clinical studies
	Elosulfase	GALNS	Indications and usage, warnings and precautions, use in specific populations, clinical pharmacology, clinical studies
	Parathyroid Hormone	CASR	Indications and usage, clinical studies
Infectious Diseases	Abacavir	HLA-B*57:01	Boxed warning, dosage and administration, contraindications, warnings and precautions
	Boceprevir	IFNL3 (IL28B)	Clinical pharmacology
	Chloroquine	G6PD	Precautions
	Daclatasvir	IFNL3 (IL28B)	Clinical studies

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Dapsone (3)	G6PD	Precautions, adverse reactions, overdosage
	Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir	IFNL3 (IL28B)	Clinical studies
	Dolutegravir	UGT1A1	Clinical pharmacology
	Efavirenz	CYP2B6	Clinical pharmacology
	Elbasvir and Grazoprevir	IFNL3 (IL28B)	Clinical studies
	Erythromycin and Sulfisoxazole	G6PD	Precautions
	Isoniazid, Pyrazinamide, and Rifampin	NAT1, NAT2	Clinical pharmacology
	Ledipasvir and Sofosbuvir	IFNL3 (IL28B)	Clinical studies
	Mafenide	G6PD	Warnings, adverse reactions
	Nalidixic Acid	G6PD	Precautions, adverse reactions
	Nitrofurantoin	G6PD	Warnings, adverse reactions
	Ombitasvir, Paritaprevir, and Ritonavir	IFNL3 (IL28B)	Clinical studies
	Peginterferon Alfa-2b	IFNL3 (IL28B)	Clinical pharmacology
	Primaquine (1)	G6PD	Contraindications, warnings, precautions, adverse reactions, overdosage
	Primaquine (2)	CYB5R1, CYB5R2, CYB5R3, CYB5R4	Precautions, adverse reactions
	Quinine Sulfate (1)	G6PD	Contraindications
	Quinine Sulfate (2)	CYP2D6	Drug interactions
	Simeprevir	IFNL3 (IL28B)	Clinical pharmacology, clinical studies
	Sofosbuvir	IFNL3 (IL28B)	Clinical studies
	Sofosbuvir and Velpatasvir	IFNL3 (IL28B)	Clinical studies
	Sulfamethoxazole and Trimethoprim	G6PD	Precautions
	Telaprevir	IFNL3 (IL28B)	Clinical pharmacology, clinical studies
	Voriconazole	CYP2C19	Clinical pharmacology
Neurology	Brivaracetam	CYP2C19	Clinical pharmacology

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Carbamazepine (1)	HLA-B*15:02	Boxed warning, warnings, precautions
	Carbamazepine (2)	HLA-A*31:01	Warnings
	Clobazam	CYP2C19	Dosage and administration, use in specific populations, clinical pharmacology
	Dextromethorphan and Quinidine	CYP2D6	Warnings and precautions, clinical pharmacology
	Diazepam	CYP2C19	Clinical pharmacology
	Eteplirsen	DMD	Indications and usage, adverse reactions, use in specific populations, clinical studies
	Galantamine	CYP2D6	Clinical pharmacology
	Lacosamide	CYP2C19	Clinical pharmacology
	Oxcarbazepine	HLA-B*15:02	Warnings and precautions
	Phenytoin (1)	CYP2C9	Clinical pharmacology
	Phenytoin (2)	CYP2C19	Clinical pharmacology
	Phenytoin (3)	HLA-B*15:02	Warnings
	Tetrabenazine	CYP2D6	Dosage and administration, warnings and precautions, use in specific populations, clinical pharmacology
	Valproic Acid (1)	POLG	Boxed warning, contraindications, warnings and precautions
	Valproic Acid (2)	ABL2, ASL, ASS1, CPS1, NAGS, OTC	Contraindications, warnings and precautions
Oncology	Ado-Trastuzumab Emtansine	ERBB2 (HER2)	Indications and usage, warnings and precautions, adverse reactions, clinical pharmacology, clinical studies
	Afatinib	EGFR	Indications and usage, dosage and administration, adverse reactions, clinical studies
	Alectinib	ALK	Indications and usage, adverse reactions, clinical pharmacology, clinical studies
	Anastrozole	ESR1, PGR	Indications and usage, adverse reactions, drug interactions, clinical studies
	Arsenic Trioxide	PML-RARA	Indications and usage
	Atezolizumab	CD274 (PD-L1)	Adverse reactions, clinical pharmacology, clinical studies
	Belinostat	UGT1A1	Dosage and administration, clinical pharmacology
	Blinatumomab	BCR-ABL1 (Philadelphia chromosome)	Indications and usage, clinical studies
	Bosutinib	BCR-ABL1 (Philadelphia chromosome)	Indications and usage, adverse reactions, use in specific populations, clinical studies
	Brentuximab Vedotin	ALK	Clinical studies

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Busulfan	BCR-ABL1 (Philadelphia chromosome)	Clinical studies
	Cabozantinib	RET	Clinical studies
	Capecitabine	DPYD	Warnings and precautions, patient counselling information
	Ceritinib	ALK	Indications and usage, adverse reactions, clinical pharmacology, clinical studies
	Cetuximab (1)	EGFR	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, clinical studies
	Cetuximab (2)	KRAS, NRAS (RAS)	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, clinical studies
	Cisplatin	TPMT	Adverse reactions
	Cobimetinib	BRAF	Indications and usage, dosage and administration, adverse reactions, clinical studies
	Crizotinib (1)	ALK	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical pharmacology, clinical studies
	Crizotinib (2)	ROS1	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical studies
	Dabrafenib (1)	BRAF	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, clinical pharmacology, clinical studies, patient counselling information
	Dabrafenib (2)	G6PD	Warnings and precautions, adverse reactions, patient counselling information
	Dabrafenib (3)	HRAS, KRAS, NRAS (RAS)	Dosage and administration, warnings and precautions
	Dasatinib	BCR-ABL1 (Philadelphia chromosome); T315I mutation	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, clinical studies
	Denileukin Diftitox	IL2RA (CD25 antigen)	Indications and usage, warnings and precautions, clinical studies
	Dinutuximab	MYCN	Clinical studies
	Erlotinib	EGFR	Indications and usage, dosage and administration, adverse reactions, clinical studies
	Everolimus (1)	ERBB2 (HER2)	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, drug interactions, use in specific populations, clinical studies
	Everolimus (2)	ESR1	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, drug interactions, use in specific populations, clinical studies
	Exemestane	ESR1, PGR	Indications and usage, dosage and administration, clinical studies
	Fluorouracil (2)	DPYD	Warnings and precautions, patient counselling information
	Fulvestrant (1)	ERBB2 (HER2)	Indications and usage, adverse reactions, clinical studies
	Fulvestrant (2)	ESR1, PGR	Indications and usage, adverse reactions, clinical pharmacology, clinical studies
	Gefitinib	EGFR	Indications and usage, dosage and administration, clinical studies

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Ibrutinib	del (17p)	Indications and usage, clinical studies
	Imatinib (1)	KIT	Indications and usage, dosage and administration, clinical studies
	Imatinib (2)	BCR-ABL1 (Philadelphia chromosome)	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, use in specific populations, clinical pharmacology, clinical studies
	Imatinib (3)	PDGFRB	Indications and usage, dosage and administration, clinical studies
	Imatinib (4)	FIP1L1-PDGFRA	Indications and usage, dosage and administration, clinical studies
	Irinotecan	UGT1A1	Dosage and administration, warnings and precautions, clinical pharmacology
	Lapatinib (1)	ERBB2 (HER2)	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical studies
	Lapatinib (2)	ESR1, PGR	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical studies
	Lapatinib (3)	HLA-DQA1*02:01, HLA-DRB1*07:01	Clinical pharmacology
	Letrozole	ESR1, PGR	Indications and usage, adverse reactions, clinical studies
	Mercaptopurine	TPMT	Dosage and administration, warnings, precautions, adverse reactions, clinical pharmacology
	Nilotinib (1)	BCR-ABL1 (Philadelphia chromosome)	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, use in specific populations, clinical studies
	Nilotinib (2)	UGT1A1	Clinical pharmacology
	Nivolumab	BRAF	Indications and usage, adverse reactions, clinical studies
	Obinutuzumab	MS4A1 (CD20 antigen)	Clinical studies
	Olaparib	BRCA1, BRCA2	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, clinical studies
	Olaratumab	PDGFRA	Clinical studies
	Omacetaxine	BCR-ABL1 (Philadelphia chromosome)	Clinical studies
	Osimertinib	EGFR	Indications and usage, dosage and administration, adverse reactions, clinical studies
	Palbociclib (1)	ESR1	Indications and usage, adverse reactions, clinical studies
	Palbociclib (2)	ERBB2 (HER2)	Indications and usage, adverse reactions, clinical studies
	Panitumumab (1)	EGFR	Adverse reactions, clinical pharmacology, clinical studies
	Panitumumab (2)	KRAS, NRAS (RAS)	Indications and usage, dosage and administration, warnings and precautions, adverse reactions, clinical studies
	Pazopanib (1)	UGT1A1	Clinical pharmacology
	Pazopanib (2)	HLA-B*57:01	Clinical pharmacology

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Pembrolizumab (1)	BRAF	Clinical studies
	Pembrolizumab (2)	CD274 (PD-L1)	Indications and usage, dosage and administration, clinical studies
	Pertuzumab (1)	ERBB2 (HER2)	Indications and usage, warnings and precautions, adverse reactions, clinical pharmacology, clinical studies
	Pertuzumab (2)	ESR1, PGR	Clinical studies
	Ponatinib	BCR-ABL1 (Philadelphia chromosome); T315I mutation	Indications and usage, warnings and precautions, adverse reactions, use in specific populations, clinical studies
	Rasburicase (1)	G6PD	Boxed warning, contraindications, warnings and precautions
	Rasburicase (2)	CYB5R1, CYB5R2, CYB5R3, CYB5R4	Boxed warning, contraindications, warnings and precautions
	Rituximab	MS4A1 (CD20 antigen)	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical studies
	Rucaparib (1)	BRCA1, BRCA2	Indications and usage, dosage and administration, adverse reactions, use in specific populations, clinical studies
	Rucaparib (2)	CYP2D6	Clinical pharmacology
	Rucaparib (3)	CYP1A2	Clinical pharmacology
	Tamoxifen (1)	ESR1, PGR	Indications and usage, precautions, adverse reactions, clinical studies
	Tamoxifen (2)	F5 (Factor V Leiden)	Warnings
	Tamoxifen (3)	F2 (Prothrombin)	Warnings
	Thioguanine	TPMT	Dosage and administration, warnings, precautions
	Trametinib	BRAF	Indications and usage, dosage and administration, adverse reactions, clinical pharmacology, clinical studies, patient counselling information
	Trastuzumab (1)	ERBB2 (HER2)	Indications and usage, warnings and precautions, clinical pharmacology, clinical studies
	Trastuzumab (2)	ESR1, PGR	Clinical studies
	Tretinoin	PML-RARA	Indications and usage, warnings, clinical pharmacology
	Vemurafenib (1)	BRAF	Indications and usage, dosage and administration, warnings and precautions, clinical pharmacology, clinical Studies, patient counselling information
	Vemurafenib (2)	NRAS	Warnings and precautions, adverse reactions
	Venetoclax	del (17p)	Indications and usage, dosage and administration, use in specific populations, clinical studies
Psychiatry	Amitriptyline	CYP2D6	Precautions
	Aripiprazole	CYP2D6	Dosage and administration, use in specific populations, clinical pharmacology
	Aripiprazole Lauroxil	CYP2D6	Dosage and administration, use in specific populations, clinical pharmacology

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Atomoxetine	CYP2D6	Dosage and administration, warnings and precautions, adverse reactions, drug interactions, clinical pharmacology
	Brexpiprazole	CYP2D6	Dosage and administration, use in specific populations, clinical pharmacology
	Citalopram (1)	CYP2C19	Dosage and administration, warnings, clinical pharmacology
	Citalopram (2)	CYP2D6	Clinical pharmacology
	Clomipramine	CYP2D6	Precautions
	Clozapine	CYP2D6	Dosage and administration, use in specific populations, clinical pharmacology
	Desipramine	CYP2D6	Precautions
	Doxepin (1)	CYP2D6	Clinical pharmacology
	Doxepin (2)	CYP2C19	Clinical pharmacology
	Duloxetine	CYP2D6	Drug interactions
	Escitalopram (1)	CYP2D6	Drug interactions
	Escitalopram (2)	CYP2C19	Adverse reactions
	Fluoxetine	CYP2D6	Precautions, clinical pharmacology
	Fluvoxamine	CYP2D6	Drug interactions
	Iloperidone	CYP2D6	Dosage and administration, warnings and precautions, drug interactions, clinical pharmacology
	Imipramine	CYP2D6	Precautions
	Modafinil	CYP2D6	Clinical pharmacology
	Nefazodone	CYP2D6	Precautions
	Nortriptyline	CYP2D6	Precautions
	Paroxetine	CYP2D6	Drug interactions
	Perphenazine	CYP2D6	Precautions, clinical pharmacology
	Pimozide	CYP2D6	Dosage and administration, precautions
	Protriptyline	CYP2D6	Precautions
	Risperidone	CYP2D6	Drug interactions, clinical pharmacology
	Thioridazine	CYP2D6	Contraindications, warnings, precautions
	Trimipramine	CYP2D6	Precautions

Therapeutic Area*	Drug	Biomarker	Labeling Sections
	Venlafaxine	CYP2D6	Precautions
	Vortioxetine	CYP2D6	Dosage and administration, clinical pharmacology
Pulmonary	Arformoterol (1)	UGT1A1	Clinical pharmacology
	Arformoterol (2)	CYP2D6	Clinical pharmacology
	Indacaterol	UGT1A1	Clinical pharmacology
	Ivacaftor	CFTR	Indications and usage, adverse reactions, use in specific populations, clinical pharmacology, clinical studies
	Ivacaftor and Lumacaftor	CFTR	Indications and usage, adverse reactions, use in specific populations, clinical studies
Rheumatology	Azathioprine	TPMT	Dosage and administration, warnings, precautions, drug interactions, adverse reactions, clinical pharmacology
	Carisoprodol	CYP2C19	Use in specific populations, clinical pharmacology
	Celecoxib	CYP2C9	Dosage and administration, use in specific Populations, clinical pharmacology
	Flurbiprofen	CYP2C9	Clinical pharmacology
	Lesinurad	CYP2C9	Drug Interactions, Clinical Pharmacology
	Pegloticase	G6PD	Boxed warning, contraindications, warnings and precautions, patient counselling information
	Piroxicam	CYP2C9	Clinical pharmacology
Toxicology	Sodium Nitrite	G6PD	Warnings and precautions
Transplantation	Mycophenolic Acid	HPRT1	Warnings and precautions
Urology	Darifenacin	CYP2D6	Clinical pharmacology
	Fesoterodine	CYP2D6	Drug interactions, clinical pharmacology
	Tolterodine	CYP2D6	Precautions, clinical pharmacology

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