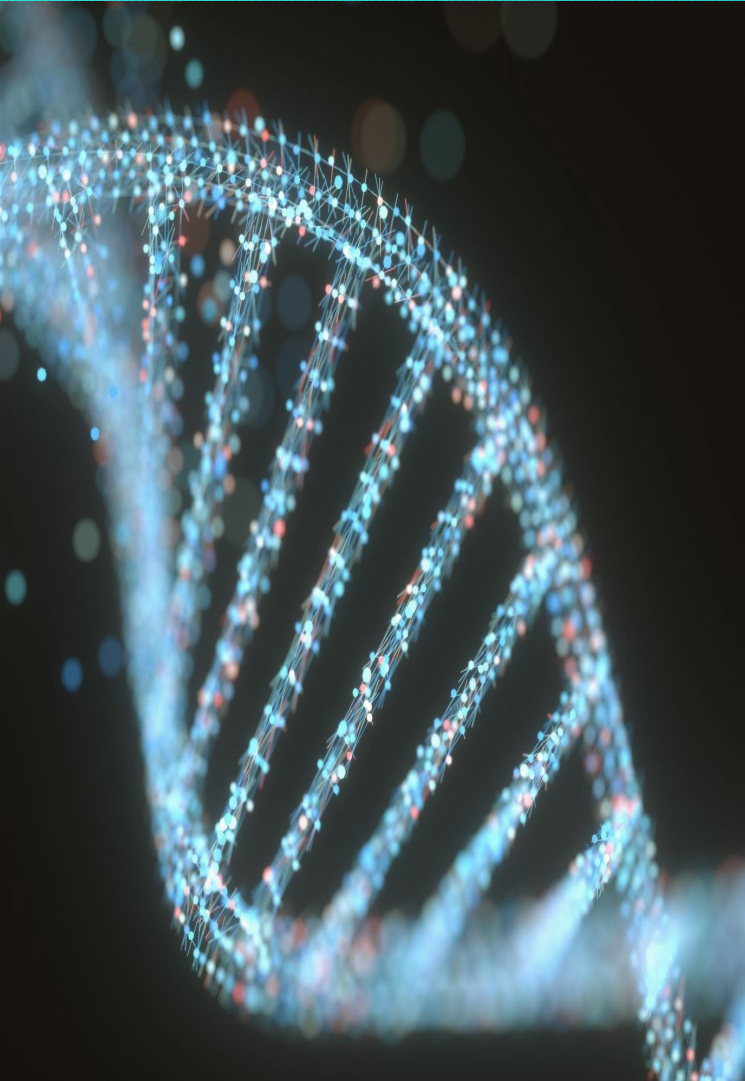


Overview of Pharmacoeconomic issues
related to pharmacogenomics –
Anthony Morreale, Pharm.D



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The Journal of Precision Medicine

Improving Patient Outcomes Through the Integration of Pharmacogenomic Testing into Comprehensive Medication Management Care Models

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ARTICLE

<https://www.thejournalofprecisionmedicine.com/wp-content/uploads/improving-patient-outcomes-integration-pharmacogenomic-testing.pdf>

Reference: Journal of Precision Medicine September 2021

Challenges - Traditional PE Analysis Applied to PGx

Table 3. Categories of pharmacoeconomic analysis

Method	Description	Comments
Cost Minimization Analysis (CMA)	Finds the program with the lowest cost among those of equal benefit	Although simple, this approach is hard to apply to PGx, since it includes only limited costs. It is justified when alternatives of comparable programs or therapies produce clinically equivalent results.
Cost Effectiveness Analysis (CEA)	The results of CEA are expressed by a cost/effectiveness ratio. Effectiveness is measured as higher survival, lower incidence of adverse reactions.	Although CEA is the most common analysis, it is difficult to establish comparisons between studies of different diseases (for instance, asthma and hypertension), due to differences in the measurement of primary effectiveness.
Cost Utility Analysis (CUA)	Considers the relationship between costs of a treatment and its benefits to the health-related quality of life of the patient, as well as the risks of adverse drug reactions. CUA is applicable in studies aimed at comparing different treatments, mainly focused on chronic patients.	Despite being an improvement over CEA, as it introduces the patient's level of satisfaction with the treatment, it is still difficult to measure some utilities from different sectors, such as health costs in relation to education.
Cost Benefit Analysis (CBA)	CBA is used to compare positive and negative consequences of alternative uses of resources, and it has a monetary unit as a measure of outcome.	Its use is more focused on macroeconomic issues, given that it is very difficult in clinical practice to convert subjective outcomes, such as quality of life, satisfaction, or pain intensity in monetary units. This type of instrument evaluates the economic viability of social projects.

Adapted from Areda et al., 2011. Pharmacoeconomy: An indispensable tool for the rationalization of health costs. *Braz. J. Pharm. Sci.*, 47:231 and Venturini & Johnson, 2002. Introduction to pharmacoeconomic principles and application in pharmacy practice. *Calif. J. Health Syst. Pharm.*, 14:6.

Value of pharmacogenomic: integrated CMM care models

- Has been demonstrated to improve patient access to healthcare but is not equal in all practice areas⁶²
- Has show improvement in clinical outcomes in certain populations (e.g., Programs of All Inclusive Care for the Elderly, PACE). ^{62,64-68}
- Is known to decrease cost and cost-avoidance benefits have demonstrated promising results.^{14, 61}
- Bain et al. found a mean cost avoidance of \$1,983 per actionable drug-gene pair.¹⁴
- Another study found that pharmacists using a pharmacogenomics tool designed to analyze cumulative drug-gene interaction helped predict the magnitude of drug-level changes and provided more meaningful recommendations to providers.⁶¹

Reference: *Journal of Precision Medicine* September 2021 References: 14, 61-68

Other Referenced Cost Effectiveness Statements

- **Multigene tests are superior to single gene tests**, given their increased cost effectiveness.⁶⁹
- In other cases, pharmacogenomic testing guides clinicians to **reduce total medication costs and improve patient outcomes** by reducing risks associated with unsafe medications.⁷⁰
- In one study, pharmacogenomic testing **decreased the probability of death from suicide** compared to patients who received standard care for certain mental health conditions.⁶⁴
- Actionable PGx variants are common - studies consistently show that **nearly all patients carry at least one actionable pharmacogenomic variant**,^{69,71} and that nearly **one in five medications in the United States have a labeled pharmacogenomic recommendation** based on those variants.⁷²
- **Preemptive pharmacogenomic testing has been associated with reduced ADEs**,⁷³ it is advisable to incorporate preemptive testing into CMM care models.

PGx Minimizes ADR's

> [Pharmacogenomics J.](#) 2016 Apr;16(2):129-36. doi: 10.1038/tpj.2015.39. Epub 2015 May 19.

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions

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Affiliations + expand

PMID: 25987241 DOI: [10.1038/tpj.2015.39](#)

Abstract

We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US\$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of \$43,165 (95% confidence interval (CI) is (\$42,769,\$43,561)) per additional LY and \$53,680 per additional QALY (95% CI is (\$53,182,\$54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing.

Markov-based Monte Carlo simulation of ADR events in the life time of a patient

One time genetic test had ICER of \$43,165 per life year saved and \$53,680 per QALY

Cost Per Death Prevention

ORIGINAL RESEARCH article

Front. Pharmacol., 28 June
2022

Sec. Pharmacogenetics and
Pharmacogenomics

<https://doi.org/10.3389/fphar.2022.918493>

Cost-Effectiveness of Pharmacogenomics-Guided Prescribing to Prevent Gene-Drug- Related Deaths: A Decision-Analytic Model



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Dutch Study - Decision-analytic model to quantify the number and cost per gene- drug-related death prevented, 1-year perspective. The modeled intervention is a single gene PGx-test for CYP2C19, DPYD, TPMT or UGT1A1.

Results: For 148,128 patients initiating one of seven drugs in a given year, costs for PGx- testing, interpretation, and drugs would increase by €21.4 million. Of these drug initiators, 35,762 (24.1%) would require an alternative dose or drug. **PGx-guided prescribing would relatively reduce gene-drug related mortality by 10.6% (range per DGI: 8.1-14.5%) and prevent 419 (0.3% of initiators) deaths a year. Cost-effectiveness is estimated at €51,000 per prevented gene-drug-related death**

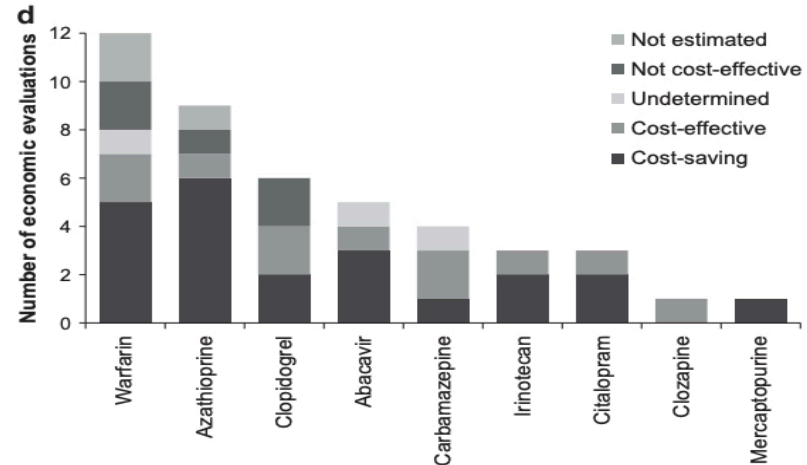
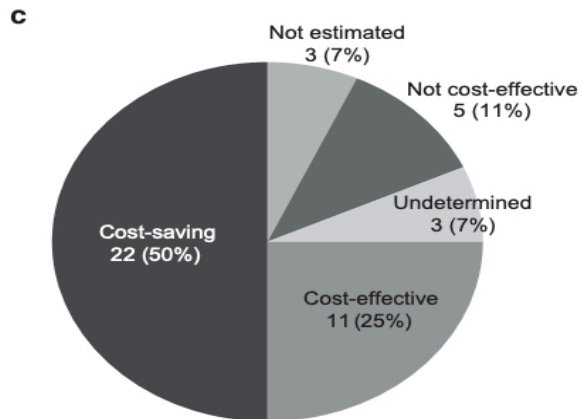
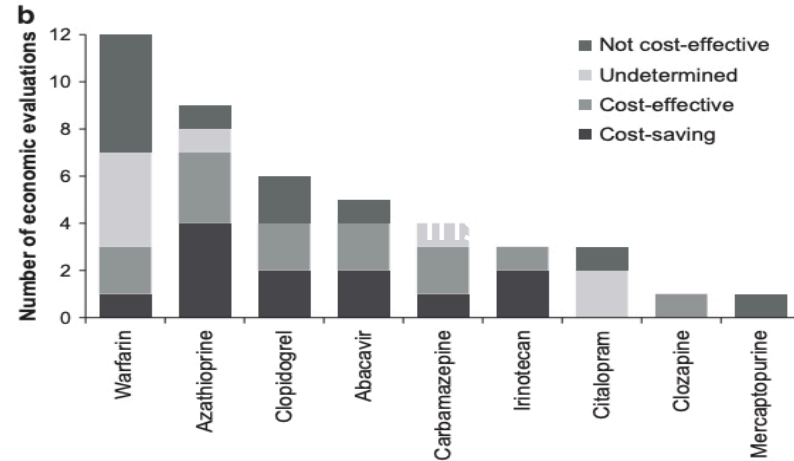
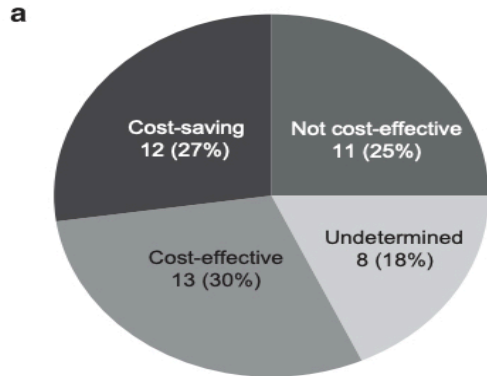
Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet?

- Reviewed economic evaluations for PGx associations listed in the US Food and Drug Administration (FDA) Table of Pharmacogenomic Biomarkers in Drug Labeling.
- Determined the proportion of evaluations that found PGx-guided treatment to be cost-effective or dominant over the alternative strategies, and estimated the impact on this proportion of removing the cost of genetic testing.
- Of the 137 PGx associations in the FDA table, 44 economic evaluations, relating to 10 drugs, were identified.
- **57% drew conclusions in favor of PGx testing, of which 30% were cost-effective and 27% were dominant (cost-saving).**
- If genetic information was freely available, **75% of economic evaluations would support PGx-guided treatment, of which 25% would be cost-effective and 50% would be dominant.**
- PGx-guided treatment can be a cost-effective and even a cost-saving strategy. Having genetic information readily available in the clinical health record is a realistic future.

Cost Effectiveness Meta-Analysis

Cost-effectiveness of pharmacogenetic testing
M Verbelen *et al*

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Legend

Cost-saving/dominant
PGx was more effective at lower cost

Cost-effective
PGx was more effective at acceptable additional cost

Undetermined
Reviewed study did not reach unequivocal conclusion

Not cost-effective
PGx was not cost-effective

Not estimated
Study did not report enough detail to estimate impact on conclusion

Figure 3. Conclusions of reviewed economic evaluations regarding cost-effectiveness of PGx testing strategy (a) overall and (b) by drug, and estimated conclusions in scenario of no extra cost for genetic information (c) overall and (d) by drug. PGx, pharmacogenetics-guided treatment.

Challenges with PGx PE evaluation

Identifying PGx testing cost

- Laboratory Cost (internal) - highly volume dependent
 - Phlebotomy
 - Processing Costs - supplies and employee time
 - Equipment
- Laboratory Cost vs charges - Contracted
- Interpretation Costs
- Implementation Costs - Informatics, Decision Support, maintenance

Is PGx Cost Effective

- Loaded Question - it is like asking are drugs cost effective!
- It depends highly on:
 - Patient Population being tested
 - Cost and Availability of testing
 - Risk of the Medication being given
 - Severity of event being avoided
 - Availability of test results in relation to medication administration and

Is Pre-emptive Multi-gene Testing More Cost Effective - PE considerations

- Cost of pre-emptive panel vs single gene testing for cause
- Rapidity of test results
- Time horizon for analysis - over time panels can be used over and over with each new medication a patient may have
- Number of Medications a patient is taking - the more the better the odds of utility
- Number of co-morbidities
- Severity of events prevented
- Avoidance of ineffective therapy resulting in hospitalizations, ER or clinic visits

Factors in favor of pre-emptive testing

- In most situations turnaround time of reactive tests is approximately 7-10 days
- This delay in turnaround time prohibits the prescriber from efficiently using the results from pharmacogenomic testing to initiate appropriate therapy.
- With consented, preemptive testing, the prescriber and the clinical pharmacist have direct access to the results during the assessment and prescribing process.
- Patient convenience is optimized as it decreases the demand on the pharmacogenomic laboratory and offers more sufficient time for reporting and result interpretation.

How does PGx Testing Compare to other routine tests

“When I was a clinician on the heme wards, we ordered CBC with diff four times a day for leukemia patients as routine surveillance. The hospital where I worked quoted me a cost of nearly \$200 per test. So, one lifetime PGx panel is less than one day of monitoring leukemic blood counts on a heme ward” (J Bates)

Points include

- As in all scientific endeavors there needs to be a control or comparator group. We have figured out how to do this with lab testing and benefits.
- Keep in mind that most of the lab tests we repeatedly perform, and most results are negative and no actions are taken over and over again. What is the value except avoiding misadventures!
- PGx on the other hand is always “positive” in that it informs us of an important demographic of patients that will stay relatively constant over time. Once identified as a being CPY2D6 rapid metabolizer you will always be one!
- Another great example is if we pre-emptively know the PGx of a mental health patient we can pay off the tests 10 times over by avoiding the wrong drug selection up front and all the time and follow-up visits of tweaking their meds

Low Hanging Fruit

- Poor outcomes without testing (relative contraindication):
 - CYP2C19 and clopidogrel
 - TPMT and thiopurines
 - DPYD and fluoropyrimidines
- Department of Defense PGx internally developed laboratory program focuses on mental health medicines
 - CYP2D6
 - CYP2C19
- Provider requested HLA testing (see chart)
- Potential ROI (i.e., cost savings) for polypharmacy/deprescribing workflow using multigene panel
- Potentially high volume impact for drug-gene pairs:
 - SLCO1B1 and statins
 - CYP2D6 and opioids

Drug	Gene
Abacavir	HLA-B*57:01
Allopurinol	HLA-B*58:01
Carbamazepine	HLA-B*15:02, HLA-A*31:01
Fosphenytoin	HLA-B*15:02
Oxcarbazepine	HLA-B*15:02
Phenytoin	HLA-B*15:02

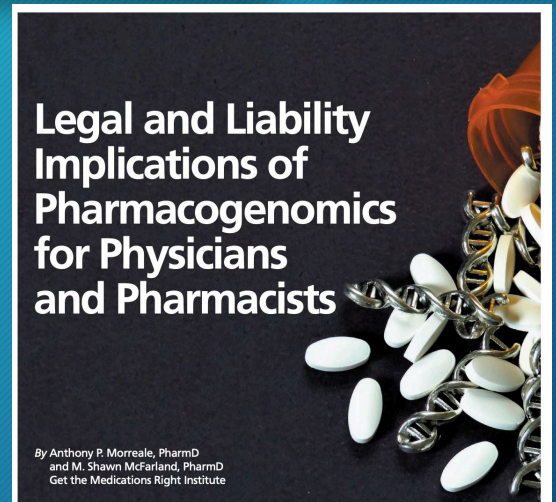
Medico-Legal Considerations

Questions & Issues

- Will legal actions drive adoption like it did with CT scans and other diagnostics?
- When is a standard of care achieved - FDA, CPIC, Volume of Use, law suits, disciplinary actions?
- What is the Cost of not testing - when do you become defensive?
- What are the risk of ignoring or misinterpreting PGx test results when available?

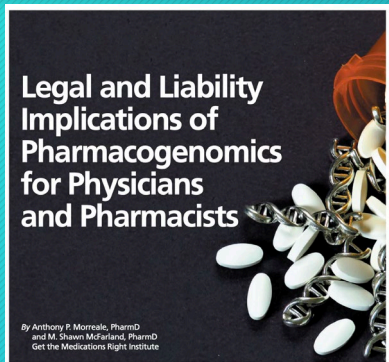
Trends

- More Patients have PGx tests already and with a rapidly declining price of testing it will not be long before everyone has pre-emptive testing in their EMR
- PGx testing now available direct to consumers (eg: 23&Me)
- FDA - more than 350 therapeutic products have [FDA-designated PGx labeling](#), including many common medications for depression and blood clots.



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Legal Quotes



Physicians have the responsibility to diagnose, treat, and inform patients of the risks and benefits of the proposed treatment and the fiduciary obligation towards their patients to act in their best interest utilizing the most current accepted and evidence-based practices. As a result, physicians face challenges to stay up to date on the latest developments in PGx-indicated medication use, especially given the accelerating volume of pharmacogenomic research.”

If a patient suffers an adverse drug reaction or ineffective treatment, and damages are incurred, the major legal hurdle is establishing a standard of care that may have been breached, and the “novelty” of PGx testing won’t be a strong defense

As with any newer technology or evidence, adoption is often slow so many clinicians and lawyers rest their case on the percentage of medical experts who might be utilizing the technology regardless of the strength of the evidence that it should be quickly incorporated into practice. This defense will be eroded as PGx is more commonly incorporated into care.”

Will Reimbursement mitigate or obviate the need for Pharmacoeconomic Assessments?

- Reimbursement Mechanisms for PGx testing remains inconsistent but it is improving.
- Current Procedural Terminology (CPT®) codes have been developed to facilitate billing and coverage of some single gene tests.⁷⁴
- Some large commercial payers have introduced new coverage policies for multigene panels, specifically for antidepressants and antipsychotics.⁷⁵
- Significant new local coverage determinations (LCDs) that include both single and panel-based tests were promulgated for Medicare beneficiaries through the MoDx program which was designed to establish coverage and reimbursement for molecular diagnostic tests .⁷⁶
- Testing for more than 50 actionable gene/drug pairs included in CPIC guidelines and/ or FDA labeling is covered for patients in the 28 states impacted.⁷⁶

Will Reimbursement mitigate or obviate the need for PE?

- Reimbursement is often determined by the insurer based on their own analyses of available evidence supporting the clinical utility of testing.
- There is also significant variability among insurers, which creates apprehension and hesitancy among providers who are ordering the test. While CPT® codes are now available for pharmacogenomic testing, documentation of testing and results in medical records is inconsistent.⁷⁷
- The major medical insurance industry has been largely resistant to advocacy and other efforts to standardize evidence evaluation, clinical utility determination, and documentation for pharmacogenomic testing.
- While pre-emptive pharmacogenomic testing is preferable to reactionary single-gene testing, many insurers remain hesitant to cover panel-based testing as compared with single-gene tests despite the clear benefit of panel-based testing.⁷⁸
- Finally, because it is an emerging science, many clinicians are unfamiliar with the billing logistics for pharmacogenomic testing and may have difficulties navigating this process.

Conclusion- PE of PGx

- There is a growing body of evidence that supports the clinical and economic benefits of PGx.
- However there are significant challenges to PGx PE modeling that are not easily overcome.
- The economics of PGx testing and application are changing quickly as are result of other forces including:
 - Rapidly falling cost of testing
 - Improved reimbursement for testing and interpretation
 - FDA, CPIC and other guidelines which essentially establish a standard of care
 - Expanding Medico-Legal Liability costs