1. *Customizing Value-based Methods to Prioritize Implementation of Pharmacogenomic Clinical Decision Support for Learning Health Systems*

Principal Investigator:

Emily Beth Devine, PhD, PharmD, MBA

Co-investigators

Patrick Mathias, MD, PhD[2,3]
David L. Veenstra, PharmD, PhD[1]
Peter Tarczy/Hornoch, MD, PhD[3]
Brian Shirts, MD, PhD[2,3]
Shangqing (Joyce) Jiang, MPh, PhD student research assistant[1]
Nathaniel Hendrix, PharmD, PhD, Post-doctoral researcher[1,4]
Yilin Chin, MPH, PhD student research assistant[1]

Participants

Brian Shirts, University of Washington
Dan Malone, University of Utah
Ann Moyer, Mayo Clinic
Firas Wehbe, Northwestern University
Luke Rasmussen, Northwestern University
Wade Schulz, Yale University

Consultant

Dan Malone, PharmD, PhD, Professor[5]

Organization

[1]The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, School of Pharmacy, University of Washington
[2]Department of Laboratory Medicine, University of Washington
[3]Precision Medicine Informatics Group, School of Medicine, University of Washington
[4]Harvard TH Chan, School of Public Health, Harvard University (formerly The CHOICE Institute)
[5]Skaggs Research Institute, School of Pharmacy, University of Utah

Inclusive Dates of the Project

September 1, 2019 through October 31, 2021

Federal Project Officer

Roland Gamache

Acknowledgment:

AHRQ PA-17-246 (R21): Health Information Technology to Improve Healthcare Quality and Outcomes

Grant number: 5R21HS026544-02

2. Structured Abstract

Purpose

To assist Learning Health Systems (LHSs) in making informed value decisions about the implementation of a pharmacogenomics clinical decision support (PGx-CDS) alert program.

Scope

We created a customizable cost-effectiveness model to estimate the value of the program (**Aim 1**), adopted it to an online platform, creating a publicly available, web-based tool. (**Aim 2**).

Methods

Our model compared clinical and economic value of developing and implementing a program versus no program (**Aim 1**). We modeled CYP2C19-clopidogrel for acute coronary syndrome and CYP2C9/ CYP4F2/ VKORC1-warfarin for atrial fibrillation. We obtained input parameters from the published literature and our own retrospective database analysis of commercial claims. We beta-tested our web-based, interactive tool with LHS users (**Aim 2**).

Results

In our base case, over 20 years: 1) 3,169 alerts fired; 2) 16 major clinical events and 6 deaths were avoided (ACS), 2 clinical events and 0.9 deaths were avoided (AF). The incremental cost-effectiveness ratio (ICER) was $39,477 per quality adjusted life year gained. (**Aim 1**) We beta-tested the web version of our model with six experts from five LHSs. The feedback was overwhelmingly positive; the tool required minimum modification prior to public posting. (**Aim 2**)

Key Words

PGx-CDs program, economic evaluation, cardiovascular diseases

3. Purpose (Objectives of the study)

The objective of this research project was to assist Learning Health Systems (LHSs) make informed decisions about the implementation of pharmacogenomics clinical decision support (PGx-CDS) alerts specific to their populations that consider trade-offs between the cost of implementation and the potential clinical benefit to patients. In **Aim 1**, we created a framework for estimating the value of PGx-CDS alerts. In **Aim 2**, we adapted this framework to an online platform, creating a publicly available, web-based tool that enables customized estimates of the value of PGx-CDS alerts specific to each LHS. We piloted and improved the tool by collaborating with stakeholder-colleagues in LHSs.

The name of our project is *PhaRmacogEnomics Clinical Support Economic Value* (PRECISE-VALUE).

4. Scope

Background

Pharmacogenomics (PGx) offers significant potential to improve drug outcomes.[1,2] The Clinical Pharmacogenomics Implementation Consortium (CPIC) has published 25 guidelines for 20 pharmacogenes and 61 drugs.[3] The prevalence of variants and the life-long relevance of germline biomarkers have motivated clinician-researchers to implement preemptive genotyping programs.[4-6] However, barriers exist that result in low incorporation of PGx testing into routine clinical practice.[7-9] First, germline genomic testing will frequently be performed well before a decision needs to be made, often compromising the availability of that information when needed.[10] In addition, incorporating PGx information into current workflows is challenging.[11] Finally, most clinicians lack the training to readily interpret genomic test results.[11-13]

Clinical decision support (CDS) alerts, embedded in electronic health records (EHRs), promise to be a viable solution to these challenges.[14,15] CDS programs help provide clinical knowledge and patient-level information to aid decision-making at the point of care. For example, CDS programs can prompt with reminders for screening procedures and fire alerts to draw attention to important and relevant medical history. Ideally, the CDS program can reduce clinicians' mental workload, smooth clinical workflow and improve patients' health outcomes.[16,17]

However, CDS has not been universally adopted, especially in the context of PGx testing. A potential concern is around the uncertain value of such a CDS program and the economic burden to health systems. The effectiveness of CDS tools in guiding clinical management using genetic information remains largely inconsistent.[18,19] Additionally, because the CDS program involves advanced technologies and requires sufficient informatics equipment and the accompanying workforce,[17] the financial considerations are of importance to health systems.[20,21]

Context

We aimed to assess the clinical utility and economic value of developing and implementing a CDS alert program in the context of PGx testing, by developing a cost-utility model from the perspective of a LHS, compared to no alert program. (**Aim 1**) We then adapted the model to a web-based, online platform that we beta-tested with LHS user-experts. The model is publicly available on our university website. The PRECISE Value interactive web application is available here: https://uwchoice.shinyapps.io/precise_value/. (**Aim 2**)

Settings

We developed a cost-effectiveness model for a hypothetical cohort of 500,000 health-system members to compare a CDS alert program to no alert program **(Figure 1)**. We based our model in the disease areas of acute coronary syndrome (ACS) and atrial fibrillation (AF) in which the value of PGx testing has been most widely studied.[22-30]

Participants

As **Aim 1** was a modeling study, there were no participants. **Aim 2** was a beta-test of the web-based, online version of our model. For this aim, six colleagues from five health systems beta-tested the model and provided helpful feedback to facilitate model improvement.

Incidence, Prevalence

See *Probabilities* section below under 'Methods/Data Sources/Collection'.

5. Methods

Study Design (Aim 1)

To develop the model we followed the guidelines put forth by the Second Panel on Cost-Effectiveness in Health and Medicine.[31] We created a model that employed an annual, cross-sectional approach. We did not follow the hypothetical cohort of patients over time, but rather, looked at a sequential cross-sectional average, testing a certain proportion of patients each year within each strategy. We reasoned that this cross-sectional approach would reflect real-world implementation of PGx testing, as membership in a health system is dynamic and therefore any health system-wide decision would necessarily be implemented repeatedly to ensure newly eligible members have the same opportunity to benefit from the decision. Because our model estimated the value of a CDS alert program, and not PGx testing, in both strategies the same proportion of people aged between 55 and 65 would receive pre-emptive PGx testing each year.

A proportion of individuals in each strategy who underwent PGx testing were identified as a pharmacogene carrier for ACS, based on their race/ethnicity status. Carriers who were later diagnosed with ACS were at risk of inappropriately receiving clopidogrel. With the CDS alert program, an alert was fired to notify the provider of the carrier status and suggest an alternative prescription for ticagrelor. Patients would gain benefit if a provider followed the

alert's suggestion. The pathway is the same for AF except that patients would gain benefit if the dosing of warfarin is adjusted based on PGx information. The hypothetical cohort consisted of 500,000 individuals between the ages of 18 and 100 years. The age and race/ethnicity (European, African, and Asian) distribution followed that of the US general population in 2020.[32]

To examine the robustness of the economic value to input parameters, we performed a one-way sensitivity analysis (OWSA) on all parameters. We further performed a probabilistic sensitivity analysis (PSA) by varying all parameters using plausible ranges in 5,000 Monte Carlo simulations.[33] We also identified three plausible scenarios (high, medium, and low PGx testing). In the high-testing scenario, all individuals aged between 45 and 75 years would undergo PGx testing at the beginning of the alerting program. In the medium-testing scenario, individuals aged between 55 and 65 years would have 30% chance of undergoing PGx testing every year. In the low-testing scenario, individuals aged between 55 and 65 years would have 1% chance of undergoing PGx testing every year. We applied an annual 3% discount rate to the investment.[31] The model was built in R version 3.6.3.

Study Design (Aim 2)

The PRECISE Value application is based on the decision analytic model described above. The purpose of the tool is to quickly communicate the cost effectiveness of developing and implementing a PGx-CDS testing program. This goal is to allow administrative and informatics leaders to assess whether the investments in CDS to alert providers about PGx testing results are likely to be cost effective for their population and in their practice setting. Implementing the decision analytic model in the R statistical programming language allows for public dissemination using the shiny and shinydashboard packages, which allow for model inputs to be changed with immediate reactivity of model outputs.

Data Sources/Collection (Aim 1)

Our sources of data were the existing literature and a retrospective claims database analysis that we conducted expressly for this study.

Model assumptions: We assumed that the CDS alert program was in place at the beginning of the study, and PGx testing results were able to be embedded into CDS alert program with no delay. Based on experts' opinion, we assumed the CDS alert program lasted for 20 years. In addition, we assumed that each year, 20% of individuals in a health system between the ages of 55 and 65 would receive preemptive PGx testing to reflect a plausible, non-selective preemptive PGx screening strategy. This uptake rate was assumed to be constant over 20 years. The probability of undergoing PGx testing over 20 years for each individual was capped at 100%. Moreover, we assumed that providers might still look for PGx results even in the absence of an alert program, reasoning that they might have received sufficient education about PGx testing or had prior experience with PGx testing.

Probabilities: To develop our model, we obtained estimates of pharmacogenes and risks of clinical events from the published literature.[34-42] We estimated lifetime risk of an incident prescription by age group from 18 to 100 years, using the IBM MarketScan® Research Databases 2015-2019, consisting of the Commercial Claims and Encounters Database and Medicare Supplemental and Coordination of Benefits Database.[43]

Provider behavior: We estimated alert fatigue from the existing literature.[44-51]

Costs: We incorporated a one-time start-up cost to reflect the financial burden of CDS alert infrastructure establishment, obtained from our previous empirical work.[52] We also incorporated an annual maintenance cost of the alert system in years 2 through 20, estimated as 20% of establishment costs.[52] We adjusted all costs to 2021 US dollars by applying the general Consumer Price Index (CPI), as the medical component-CPI was not fully applicable to the costs of developing and maintaining a CDS alert program.[53]

Outcomes: We modeled three outcomes. First, we modeled one implementation outcome: cost per alert fired. We then modeled clinical outcomes: adverse events and deaths caused or averted. Finally, we modeled the traditional economic outcome: cost per quality-adjusted life year gained (cost per QALY gained).[54,55]

Data Sources/Collection (Aim 2)

To gather feedback on the tool, we interviewed six subject matter experts who are involved with PGx and/or informatics efforts at five health systems. These individuals were selected based upon ongoing engagement with PGx-CDS work at their home institution. Experts were asked to navigate to the web application and talk through their interactions with the tool, based on our introduction of its rationale. Formal tasks were not assigned; users were asked to provide any feedback regarding utility or expected scenarios for utilizing the application. This part of our study was approved by the University of Washington Institutional Review Board under exempt status.

Interventions (both aims)

The intervention was the PGx-CDS alert program. We compared this to the strategy of no PGx-CDS alert program.

Measures (both aims)

As above, we modeled three outcomes. First, we modeled one implementation outcome: cost per alert fired. We then modeled clinical outcomes: adverse events and deaths averted. Finally, we modeled the traditional economic outcome: cost per quality-adjusted life year gained (cost per QALY gained) and presented the incremental cost-effectiveness ratio (ICER).[54,55]

Limitations (Aim 1)

Our study has a several strengths. We based our cost evaluations on our prior work that examined real-world cost estimates of developing and implementing CDS alerts for PGx testing.[52] Additionally, we conducted database analyses using the IBM MarketScan® Research Databases 2015-2019,[43] to generate real-world estimates of incident prescription use of clopidogrel for ACS, and warfarin for AF. Importantly, the real-world estimates of incident warfarin use during 2015 to 2019 reflect the decreased use of warfarin due to introduction of direct-acting oral anticoagulants (DOACs). Moreover, we incorporated alert fatigue to mimic the real-world acceptance rate of CDS alerts, based on estimates from the literature.[44-51] We performed a systematic literature review to identify outcomes of PGx testing compared to no PGx testing that were most aligned with our study setting.

Our study also has a few limitations. The idea of PGx-CDS alerts is simplified. We did not focus on factors such as visual design, and timing and frequency of alerts, which may affect the usability of alerts.[17] Moreover, we only used alerts to guide prescribing based on PGx results. However, a CDS program virtually can be configured with other types of supports that help deliver PGx results and guide prescribing.[56] Additionally, we assumed that PGx test results were embedded into CDS alerts with no delay, and thus, we did not account for waiting time for obtaining PGx results. Furthermore, clinical benefits for patients prescribed with warfarin for AF were based on population-level average estimates. Although we believed this would be the best approach based on current evidence from randomized controlled trials, it is likely that heterogeneity exists, which we did not address in our model. Moreover, we acknowledge that specifying that 20% of individuals would receive PGx testing every year was a crude and optimistic assumption. Thus, we performed scenario analyses where the proportion of patients who received PGx testing varied from 1% to 100% and found that even with 10% of individuals receiving PGx testing every year, the ICER of $71,874.10 per QALY gained was still below the WTP threshold of $100,000 per QALY gained. However, we encourage health systems to use their own estimates to assess the ICER. Lastly, we modeled the incident prescription of clopidogrel and warfarin, and therefore did not consider alerts for refills. In addition, clopidogrel or warfarin were modeled separately, and thus the same patient would not trigger multiple alerts for multiple drugs. Incorporation of alerts fired for refills and the possibility that the same patient may require multiple drugs would likely change the implementation outcomes. Future work may enrich the model by accounting for these complex set-ups and examine the change in the outcomes.

6. Results

Principal Findings (Aim 1)

In total, 3,169 alerts would be fired. The CDS alert program would help avoid 16 major clinical events and 6 deaths for ACS; and 2 clinical events and 0.9 deaths for AF. The ICER was $39,477/QALY. A PGx-CDS alert program was cost-effective, under a willingness-to-pay threshold of $100,000/QALY gained, compared to no alert program.

Principal Findings (Aim 2)

The PRECISE Value interactive web application is available here: https://uwchoice.shinyapps.io/precise_value/. We beta-tested the RShiny version of our model with six colleagues from five institutions listed above. Our participants were those who are working in the field. They see the value of the decision model that compares pharmacogenomic testing with versus without CDS alerts. Their feedback was overwhelmingly positive; each suggested the tool may be useful to LHSs. They consistently stated that the app required minimal changes to improve understanding and usability. We have incorporated all their suggestions into the version of the tool that is currently posted on our website.

Outcomes (Aim 1)

Implementation outcomes: The model predicted that 3,169 PGx-CDS alerts would fire, including 1,721 alerts for clopidogrel for patients with ACS, and 1,448 for warfarin for patients with AF, over 20 years. This corresponded to 0.003 alerts per person in the PGx-CDS alert program. On average, the total cost was $420/alert fired, consisting of a medical cost of $395/alert fired, and an informatics cost $24/alert fired. The PGx-CDS alert program costs the health system just under $3 per person, over 20 years.

Clinical outcomes: On average, 105 alerts were needed to fire for clopidogrel use for ACS to avert one major non-fatal clinical event, 287 alerts were needed to avert one cardiovascular death, and 3,019 alerts had to fire to prevent one additional bleeding event. The CDS alert program helped to reduce the number of major non-fatal clinical events by 16.32 and the number of cardiovascular deaths by 5.99. However, it also resulted in additional 0.57 bleeding events. Similarly, 739 and 1,664 alerts would be needed to fire for warfarin use for AF to avert one clinical event and one death, respectively. In addition, the CDS alert program decreased the number of clinical events and deaths by 1.96 and 0.87, respectively.

Economic outcomes: The incremental cost was $1,330,375, and the incremental QALYs gained were 33.7 comparing a CDS program to no CDS program. The ICER was estimated as $39,477 per QALY gained.

Sensitivity analyses: Five parameters that were most influential on the ICER were the QALYs and costs of PGx testing for ACS compared to no PGx testing, number of hours needed to develop the CDS system, and the probability that providers' change treatment**.** The probabilities that the PGx-CDS was cost-effective were 71.8%, 98.3%, and 99.5% under $50,000/QALY, $100,000/QALY and $150,000/QALY willingness to pay (WTP) thresholds, respectively. **(Figures 2 and 3)**

Scenario analyses: A total 6,670 alerts, would be fired in the high testing scenario. The estimated ICER was $38,095 per QALY gained. In a medium testing scenario, a total 3,485 alerts fired, resulting in an ICER of $39,196 per QALY gained. In the low testing scenario, only 228 alerts were fired and the ICER was $71,874 per QALY gained.

Outcomes (Aim 2)

The user interface reserves a sidebar to manipulate inputs to the model that impact implementation outcomes such as population size, proportions of race in the population, duration of screening, and age range for screening, among other variables. The inputs dynamically update the output seen on a summary page, which include cost per alert fired (an implementation outcome), adverse events and deaths caused or averted (clinical outcomes), an ICER (economic value outcome), and the medical and information technology costs of implementation. To review the data in more detail, there are additional tabs a user can navigate to and see more specific details related to the implementation, clinical and economic outcomes, and costs expected with and without PGx-CDS alert program. In addition, a data dictionary for variables and outcomes as well as a general cost effectiveness primer are provided.

User feedback acknowledged that the tool was generally intuitive and easy to use and accomplished the stated goals of modeling important outcomes related to costs, and the economic value of developing and implementing a CDS alert program given a specified population. Experts suggested a variety of improvements that may be made to the application but were beyond the scope for the current application development, including: the addition of more genes and drugs, the ability to import past data of observed adverse drug events or more general demographic data from electronic health records, and the explicit modeling of cost over time (as opposed to showing summary numbers).

Discussion (both aims)

We found that 3,169 alerts would be fired with a PGx-CDS alert program, and each alert would cost on average $420. Alerts would help reduce clinical events and deaths for both ACS and AF. The estimated ICER of $39,477 per QALY gained was below the WTP threshold of $100,000 per QALY gained, suggesting that a CDS alert program was cost-effective compared to no alert program. The value of the CDS alert program was most sensitive to the cost and benefits of PGx testing, costs of developing and maintaining a PGx-CDS alert program and providers' behavior in following the alerted prescribing recommendation. A PGx-CDS alert program was cost-effective at 98% of the time based on a WTP threshold of $100,000/QALY, given PGx testing was performed 20% per year in a population aged between 55 and 65 years, for 20 years.

Conclusions (both aims)

Our model demonstrates a PGx-CDS alert program helps reduce clinical events and is cost-effective, compared to no alert program, for patients with ACS and AF. Future studies should explore the cutoff value of PGx testing to realize good value for money spent on a CDS alert program.

Significance (both aims)

Our study is the first to provide a structured and scientific approach to answer three key questions – "What are the implementation outcomes, clinical impacts, and the economic value of a CDS alert program in the context of PGx compared to no alert program?"

Implications (both aims)

Our study has a few implications. First, the results that a PGx-CDS alert program has clinical utility for patients in improving health outcomes emphasizes the importance of establishing a CDS infrastructure in delivering PGx information and guide prescribing.[18,19] However, the clinical utility of such a program first relies on the value of PGx testing and whether information is utilized in clinical practice. This demonstrates the power of CDS infrastructure in distributing crucial information and supporting clinical decision-making.[56] The interplay of PGx testing and a CDS alert program to guide prescribing suggests a wholistic approach in clinical practice to improve health outcomes.

Second, our results that a PGx-CDS alert program is cost-effective suggest that CDS investment provides good value for money, which addresses a common economic concern in adopting CDS alert programs in health systems.[20,21] However, establishing a CDS alert program that is cost-effective, as our results suggest, is not to be construed as cost-saving. Rather, cost-effectiveness using commonly accepted willingness to pay thresholds indicates that implementation of a program is worth the money spent on the investment, in terms of the clinical benefits gained. The incremental cost consists of costs of using ticagrelor for ACS, a more expensive drug than clopidogrel, which will increase financial burden to payers and patients, and the financial investment in CDS. To promote adoption of a PGx-CDS alert program, decision-makers should consider budget impacts and cost implications for payers and patients, along with the value information of a PGx-CDS alerts, as we provide here.[20,21]

Third, our results highlight the impact of the scale-up of PGx testing on the cost and value of a PGx-CDS alert program. In our scenario analyses, as the PGx testing rate increases, the cost of developing and implementing the CDS alert program per alert fired decreases significantly, from $339 per alert to $11 per alert, and the value of a PGx-CDS alert program increases too, from $71,874 per QALY gained to $38,095 per QALY gained. Although the PGx-CDS alert program remains cost-effective even in a low-testing scenario, the scale of PGx testing is a key factor in determining the value of the CDS alert program. Decision makers should incorporate the current uptake of PGx testing within their system first and

deliberate the possibility of expanding PGx testing for members to best realize the power of a CDS alert program.

Fourth, our modeling approach has implications for designing the scope of a CDS alert program. More than 100 pharmacogenes have the highest level of clinical evidence in corresponding disease areas, and are considered actionable.[3] A recent study found that many drugs with actionable pharmacogenes were commonly dispensed in practice.[5]This evidence suggests that incorporating a broad list of genes, drugs, and diseases when designing a PGx-CDS alert program should be considered. In addition, because of the decreasing costs of PGx testing, the marginal cost of testing an additional gene is decreasing, and thus a comprehensive PGx-CDS program can potentially bring economies of scale and influence system-level practice. Although our model only included clopidogrel-ACS and warfarin-AF for which there are the largest bodies of evidence in support of PGx testing, they may serve as a prototype that allows for adding multiple genes, drugs, and diseases in the future, which could potentially alter the value of a PGx-CDS alert. However, although a CDS alert program is promising and capable of delivering a broad range of PGx test information, the value of developing a CDS alert program varies by costs and clinical benefits of PGx testing in different diseases. With the modeling approach, presenting tradeoff between costs and effectiveness helps rationalize investments in CDS alerts. Future studies should explore the cutoff for value of PGx testing to realize good value for money spent on developing a CDS alert program.

Lastly, our study findings can be particularly relevant for LHSs, in which science, informatics, incentives and culture are aligned and new knowledge is integrated into delivery. The wholistic approach where testing and informatics are integrated in advancing precision medicine encourages different functions in a LHS to collaborate together, and promotes efforts in learning their own patients' genetic information, providers' behavior, and PGx testing patterns. The learning will, in return, help guide their own decision-making in developing a PGx-CDS alert program in LHSs and eventually make the workflow in LHSs more efficient and cohesive.

7. List of Publications and Products (Bibliography of Outputs) from the study.

Internal Presentations

1) Jiang S, Mathias PC, Hendrix N, Shirts BH, Tarczy-Hornoch P, Malone D, Veenstra DL, Devine B. The University of Washington Precision Medicine Informatics Group. September 2019.
2) Jiang S, Mathias PC, Hendrix N, Shirts BH, Tarczy-Hornoch P, Malone D, Veenstra DL, Devine B. The University of Washington Precision Medicine Informatics Group. January 2020.
3) Jiang S, Mathias PC, Hendrix N, Shirts BH, Tarczy-Hornoch P, Malone D, Veenstra DL, Devine B. The University of Washington Precision Medicine Informatics Group. February 2021.

National Presentations:

Jiang S, Mathias PC, Hendrix N, Shirts BH, Tarczy-Hornoch P, Malone D, Veenstra DL, Devine B. Implementation of Pharmacogenomic clinical decision support for health systems: a cost-utility analysis. ISPOR-the Professional Society for Health Economics and Outcomes Research, International Meeting, May 2021 (virtual poster)

Publications:

1) Jiang S, Mathias PC, Hendrix N, Shirts BH, Tarczy-Hornoch P, Malone D, Veenstra DL, Devine B. *Implementation of Pharmacogenomic clinical decision support for health systems: a cost-utility analysis. The Pharmacogenomics Journal.* 2022;22(3):188’197. doi: 10.1038-s41397-022-00275-7. Epub 2022 Apr 1.
2) Mathias PC, Jiang S, Hendrix N, Shirts BH, Tarczy-Hornoch P, Veenstra DL, Devine B. *A graphical model to estimate the value of a pharmacogenomic clinical decision support alert program for Learning Health Systems*. (submitted as a software article to *BMC Medical Informatics and Decision Making*, April 2022).
3) We leveraged this project to write and edit a textbook on Pharmacogenomics Clinical Decision Support. Clinical Decision Support for Pharmacogenomic Precision Medicine. Foundations and Implementation. Eds: Devine B, Boyce RD, Wiisanen K. Elsevier Academic Press, ISBN 978-0-12-824453-1, June 24, 2022.

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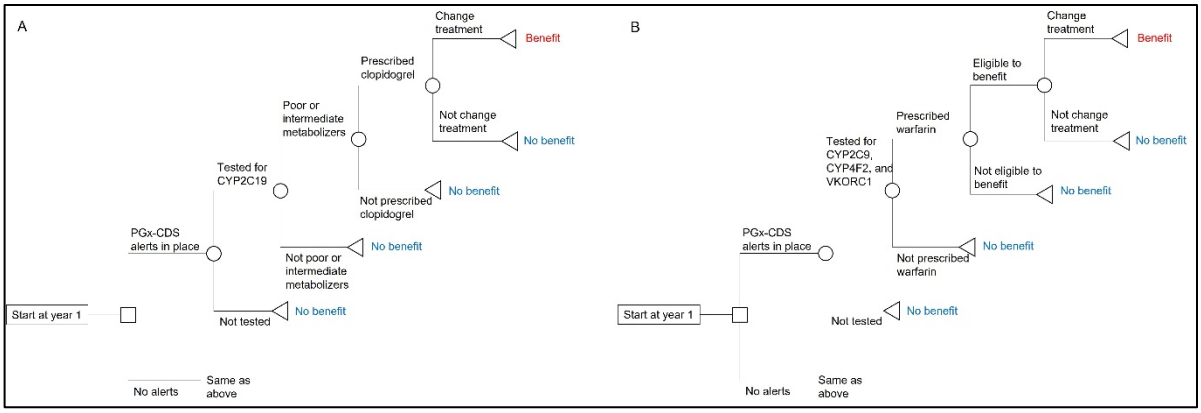

Figure 1: cost-effectiveness (cost-utility model comparing the strategy of implementation of PGx-CDS alerts versus no alerts)

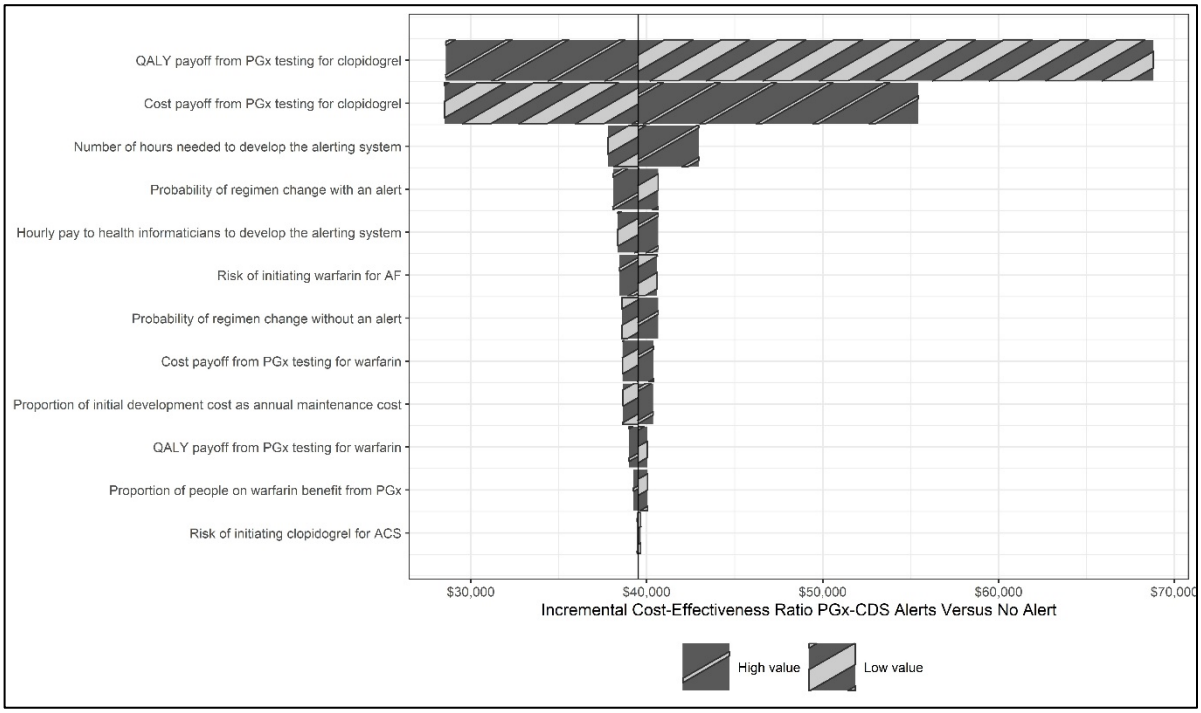

Figure 2: One-way sensitivity analysis of model

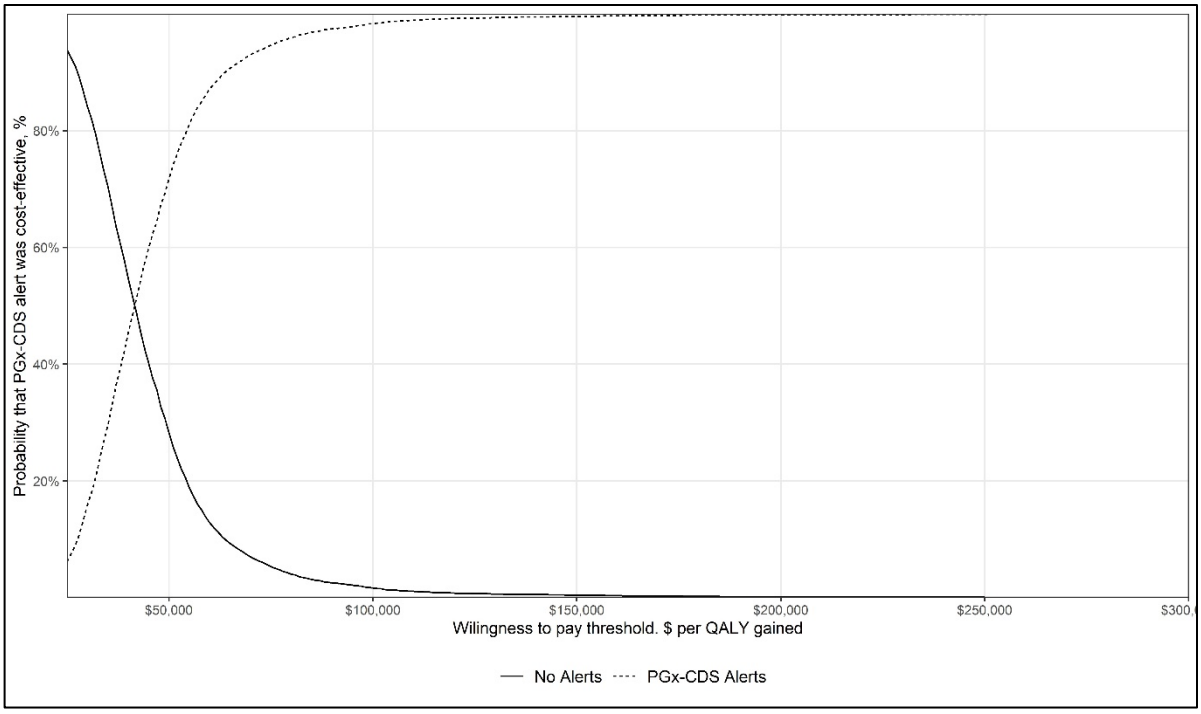

Figure 3: Cost-effectiveness acceptability curve