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Health Policy Analysis

Are There Different Evidence Thresholds for Genomic Versus Clinical Precision Medicine? A Value of Information-Based Framework Applied to Antiplatelet Drug Therapy

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ABSTRACT

Background: The threshold of sufficient evidence for adoption of clinically- and genomically-guided precision medicine (PM) has been unclear.

Objective: To evaluate evidence thresholds for clinically guided PM versus genomically guided PM.

Methods: We develop an "evidence threshold criterion" (ETC), which is the time-weighted difference between expected value of perfect information and incremental net health benefit minus the cost of research, and use it as a measure of evidence threshold that is proportional to the upper bound of disutility to a risk-averse decision maker for adopting a new intervention under decision uncertainty. A larger (more negative) ETC value indicates that only decision makers with low risk aversion would adopt new intervention. We evaluated the ETC plus cost of research (ETCc), assuming the same cost of research for both interventions, over time for a pharmacogenomic (PGx) testing intervention and avoidance of a drug-drug interaction (aDDI) intervention for acute coronary syndrome patients indicated for antiplatelet therapy. We then examined how the ETC may explain incongruous decision making across different national decision-making bodies.

Results: The ETCc for PGx increased over time, whereas the ETCc for aDDI decreased to a negative value over time, indicating that decision makers with even low risk aversion will have doubts in adopting PGx, whereas decision makers who are highly risk-averse will continue to have doubts about adopting aDDI. National recommendation bodies appear to be consistent over time within their own decision making, but had different levels of risk aversion.

Conclusion: The ETC may be a useful metric for assessing policy makers' risk preferences and, in particular, understanding differences in policy recommendations for genomic versus clinical PM.

Keywords: evidence threshold criterion, precision medicine, value of information.

VALUE HEALTH. 2019; 22(9):988–994

Introduction

Precision medicine (PM) has been defined generally as the customization of healthcare, with medical decisions being tailored to the individual patient using patient-specific information that can be genomic or clinical (ie, nongenomic) in nature. Many evidence-based evaluations of genomic PM have concluded that there is insufficient evidence to make recommendations, often citing the lack of randomized-controlled trial data.[1] Yet there are examples of clinical PM commonly used in practice for which such data are also lacking, such as contraindication of potential drug interactions to guide pharmacotherapy.[2] Are there different evidence thresholds for genomic versus clinical PM?

If the decision maker is risk-neutral, then given current information she or he will adopt the treatment that has the highest expected returns in outcomes of choice; uncertainty in these returns should not deter her or him to wait for future information. In specific situations, if the probability of future research is affected by the adoption decision today and costs of treatment are front loaded, it has been shown that even a risk-neutral decision maker may find the maximum expected returns criterion to be insufficient for adopting a treatment decision today.[3,4] Nevertheless, in practical settings decision makers seldom adopt treatment based on maximum expected outcomes. Uncertainty in outcomes plays a role in decision making not only at the individual level, but also at the population level, and implies that decision makers are inherently risk-averse. Real-world decision makers may also account for many other contextual factors in decision making. Our focus is on a rational decision- maker who maximizes some outcome, such as health or net monetary benefits, but who may

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https://doi.org/10.1016/j.jval.2019.03.023

also be risk averse. Indeed, there is a large literature base demonstrating the risk aversion of social and population decision makers.[5,6]

Our goal was to gain a clearer understanding of evidence thresholds for genomic versus clinical PM. To facilitate this goal, we derive an "evidence threshold criterion" (ETC), reflecting the decision maker's risk aversion, where she or he will be indifferent between accepting current levels of uncertainty in the incremental returns from treatment and the potential value gained from perfect future research. Because different decision makers may make recommendations at different points in time, we explore the temporal trends of these evidence thresholds. Finally, we deduce bounds on the evidence thresholds using the revealed preference for 2 real decision makers through their recommendations and discuss their implications.

Methods

Motivating Case Study in Precision Medicine

We consider a pharmacogenomic (PGx) intervention as the genomic PM example and avoidance of a drug-drug interaction (aDDI) intervention as the clinical PM example in equivalent populations of acute coronary syndrome patients who are indicated for antiplatelet therapy with the drug clopidogrel (Plavix®). Both interventions are intended to avoid adverse cardiovascular events associated with decreased activity of the cytochrome P450 2C19 (CYP2C19) enzyme, which facilitates the necessary metabolism of clopidogrel to its active form in the body.[7,8] The evidence bases for both types of interventions generally consist of post-hoc observational data from randomized studies. In general, aDDI is the standard of care, whereas use of PGx information is not.

The PGx intervention consists of a genetic test for variants associated with decreased CYP2C19 activity; if variants are identified, the patient is indicated for a different antiplatelet drug that does not require CYP2C19 activation. The aDDI intervention consists of avoiding the concomitant use of clopidogrel with proton pump inhibitors (PPIs), used to prevent antiplatelet-associated gastrointestinal hemorrhage but also inhibit the function of CYP2C19, and thus act similarly to a disabling genetic variant with regard to mechanism and potential clinical effect.[7]

Decision makers have made preliminary, somewhat incongruous recommendations in regard to these 2 interventions.[9–11] American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines acknowledged the accumulating evidence and potential usefulness of clopidogrel PGx in multiple recent guidelines,[12–14] but refrained from recommending routine use, citing a lack of randomized controlled trial evidence as the primary rationale.[9,10,15] In contrast, in 2010, the US Food and Drug Administration (FDA) issued a boxed warning on the clopidogrel prescribing information, stating, "Consider alternative treatment or treatment strategies in patients identified as *CYP2C19* poor metabolizers."[11]

The aDDI intervention was recommended by the FDA in 2009, which included a warning on clopidogrel's label to "avoid concomitant use with drugs that are strong or moderate CYP2C19 inhibitors (eg, omeprazole)."[11] Nevertheless, more recent (2012) clinical guidance from the ACCF/AHA "does not prohibit the use of PPI agents in appropriate clinical settings."[9]

The landscape for evidence threshold considerations has notably changed since 2009. First, the evidence base for the PGx and aDDI interventions has evolved. Second, the new anticoagulants prasugrel (Effient®, FDA approved in February 2009) and ticagrelor (Brilinta®, July 2011) entered the market.[16,17] Third, in 2012 generic clopidogrel became notably cheaper than the newer antiplatelet drugs. Lastly, the cost of PGx tests has decreased over time.

To summarize, the modeled comparators for the PGx intervention are:

- *New intervention*
  - (a) Test for *CYP2C19* mutation; administer clopidogrel if patient is a noncarrier, and administer prasugrel or ticagrelor if patient is a carrier.
- *The most optimal standard care intervention*
  - (b) No test, all patients receive clopidogrel.
  - (c) No test, all patients receive prasugrel.
  - (d) No test, all patients receive ticagrelor.

The modeled comparators for the aDDI intervention are:

- *Standard care intervention*
  - (a) All patients receive clopidogrel with concomitant PPI.
- *The most optimal new intervention*
  - (b) All patients receive clopidogrel without PPI.
  - (c) All patients receive prasugrel.
  - (d) All patients receive ticagrelor.

Throughout, recommendations for precision medicine approaches for these patients have remained largely unchanged; this raises the question whether the ACCF/AHA and the FDA have different evidence thresholds, and if so, whether these thresholds are consistent over time.

A Theoretical Basis for Developing a Criterion for the Evidence Threshold

Let there be 2 treatments. Treatment A is the status-quo clinical practice. Treatment B is the new treatment. Consider the decision making of a rational clinical society chair whose job is to issue guidelines for which treatment should be adopted based on currently available information. This recommended guideline is implemented over 2 consecutive time periods, one of length t_1 and the other of length t_2. Note that $t = t_1 + t_2$ denotes the horizon of the analysis or the duration over which the comparative question of B versus A remains relevant. The duration t_1 represents the time it would take for any new research on this topic to produce results. Without loss of generality, let the expected net benefits (NB) of treatment B be greater than that of treatment A; that is,

$$E(NB_B(\Theta)) > E(NB_A(\Theta))$$

where Θ is the set of parameters determining the value of NB(.). Assume that considerable uncertainty exists for the incremental net benefits (INHB) between B and A because of uncertainty about the parameters, Θ. Lastly, we note that the expected value of perfect information (EVPI) is the difference between the INHB with perfect information, which is calculated by averaging the maximum INHBs among treatment strategies for each probabilistic sensitivity analysis iteration, and the INHB for the treatment strategy with maximum expected returns today, that is, B.[18]

In this setting, let us consider the choices for a risk-averse clinical society chair who aims to maximize her or his utility, which is a function of the net benefits of treatment. Note that if the chair was risk-neutral, she or he would have chosen treatment B without hesitation. The risk-averse chair must decide how much uncertainty is acceptable to her or him. One option is that she or he recommends treatment B under both time periods without further research because she or he considers that current evidence is sufficient for the adoption of the new treatment, despite the uncertainty surrounding it. Under this scenario, the expected utility or value to the decision maker for any unit time period would be the expected net benefit returns from using treatment B

Table 1. Expected returns under alternate decisions about adoption of treatment.

Scenario	Time period 1 (duration: t_1)	Time period 2 (duration: t_2)	Total returns
(1) Adopting treatment with uncertainty	$t_1 \cdot (E(NHB_B(\Theta)) + L)$	$t_2 \cdot (E(NHB_B(\Theta)) + L)$	$(t_1 + t_2) \cdot (E(NHB_B(\Theta)) + L)$
(2) Rejecting treatment because of uncertainty	$t_1 \cdot (E(NHB_A(\Theta)))$	$t_2 \cdot (E(\max_j NHB_j(\Theta))) - C$	$t_2 \cdot E(\max_j NHB_j(\Theta)) + t_1 \cdot E(NHB_A(\Theta)) - C$

$NHB_j()$ indicates net health benefits of treatment of treatment j; L, disutility effect from current levels of uncertainty; C, costs of doing perfect comparative research.

minus a "disutility" term (L) reflecting the risk-averseness of the decision maker, arising out of the uncertainty in the INHB.[19,20] This disutility term is often referred to as the Pratt-Arrow correction for absolute risk aversion in expected utility theory.[19,20] Another option is that she or he chooses status-quo treatment A for period one, and asks for "perfect research" to be conducted at a cost of C so that she or he can have perfect information in period 2 to recommend treatment.

These 2 scenarios are illustrated in Table 1. The point of indifference in the overall utilitarian returns between these 2 scenarios indicates the option value or the evidence threshold condition under which the clinical society chair should recommend adoption of a new treatment over status-quo, under current information. This threshold also identifies the degree of risk-averseness for the decision maker.

At the point of indifference,

$$\begin{aligned}(t_1 + t_2)(E(NHB_B(\Theta)) + L) = t_1 E(NHB_A(\Theta)) + t_2 E(\max_j NHB_j(\Theta)) \\ - C \Rightarrow (t_1 + t_2)L = [t_2 E(\max_j NHB_j(\Theta)) \\ + t_1 E(NHB_A(\Theta)) - C] \\ - (t_1 + t_2) E(NHB_B(\Theta)) \\ = t_2 \{[E(\max_j NHB_j(\Theta)) - E(NHB_B(\Theta))]\} \\ - C - t_1 \{[E(NHB_B(\Theta)) - E(NHB_A(\Theta))]\}\end{aligned}$$

In other words,

$$L = (1 - w_1)EVPI - w_1 INHB - C/(t_1 + t_2)$$

where $w_1 = t_1/(t_1 + t_2)$ is the proportion of the horizon time for this decision problem for new research to produce results. The INHB, EVPI, and C expressions could already incorporate a discount factor over time. Nevertheless, because in our framework the realization of INHB or the cost of C occurs in period 1 while EVPI is realized in period 2, the EVPI should be further discounted by $\beta\text{-}(t_1 - 1)$.

Hence $L = (1 - w_1)\beta\text{-}(t_1 - 1)EVPI - w_1 INHB - C/(t_1 + t_2) = ETC$

The ETC has a natural interpretation; it compares the expected incremental value of choosing a treatment that maximizes returns versus the maximum expected incremental loss if that choice is wrong. Hence, the ETC provides an upper bound for the disutility from the current uncertainty that is still acceptable to a decision maker in choosing a treatment that maximizes returns. That is, decision makers with L > ETC will adopt treatment B right away despite the uncertainty. Because ETC is the upper bound on disutility, it should take a negative value, so that $[(1 - w_1)^*EVPI - w_1^*INHB - C] < 0$. If $[\{EVPI - C\} - INHB] > 0$, and the decision maker still does not adopt the new treatment, one may infer that the decision maker may be risk seeking. As the INHB becomes increasingly large relative to the value of research net of costs, ETC becomes more negative, and the decision maker is believed to be acting in an increasingly risk-averse manner by not adopting the new treatment B straight away.

Because our theoretical result is generic in terms of net monetary benefits and EVPI, the ETC should apply across clinical areas. Therefore, if one considers 2 interventions with identical INHB and C, then EVPI alone could determine the evidence criterions and compare the clinical society chair's choices for these 2 scenarios, assuming that the chair has consistent objective function. Throughout our empirical examples we will assume that the cost of research for both ETCs is the same, simplifying our comparison of incongruous decision making across the 2 national decision-making bodies. Nevertheless, we will keep the estimates for cost of research implicit and hence will report ETC plus cost of research $(ETCc) = (1 - w_1)^*EVPI - w_1^*INHB$ for the empirical examples.

Cumulative Evidence Synthesis

We conducted 2 cumulative, random-effects meta-analyses of the relative effect estimate for major adverse cardiovascular events in (1) *CYP2C19* variant carriers versus noncarriers and (2) concomitant clopidogrel+PPI-treated patients versus those on clopidogrel without PPIs. We sequentially added included studies by publication date to assess the change in evidence levels over time. Our meta-analysis methodology is reported in detail in a separate publication,[21] and a brief summary is available in the Appendix (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.023).

Value of Information Model

We estimated the EVPI, INHB, and the ETCc over using the cardiovascular relative risk means and confidence intervals from each time point in our cumulative meta-analyses. We also varied drug costs by historical wholesale acquisition costs and PGx test cost by an assumed rate mirroring the general decline in genomic test costs. We then compared the models' ETCc results over time to consider their relative evidence levels and facilitate commentary on current clinical practice guidelines for these drug interactions.

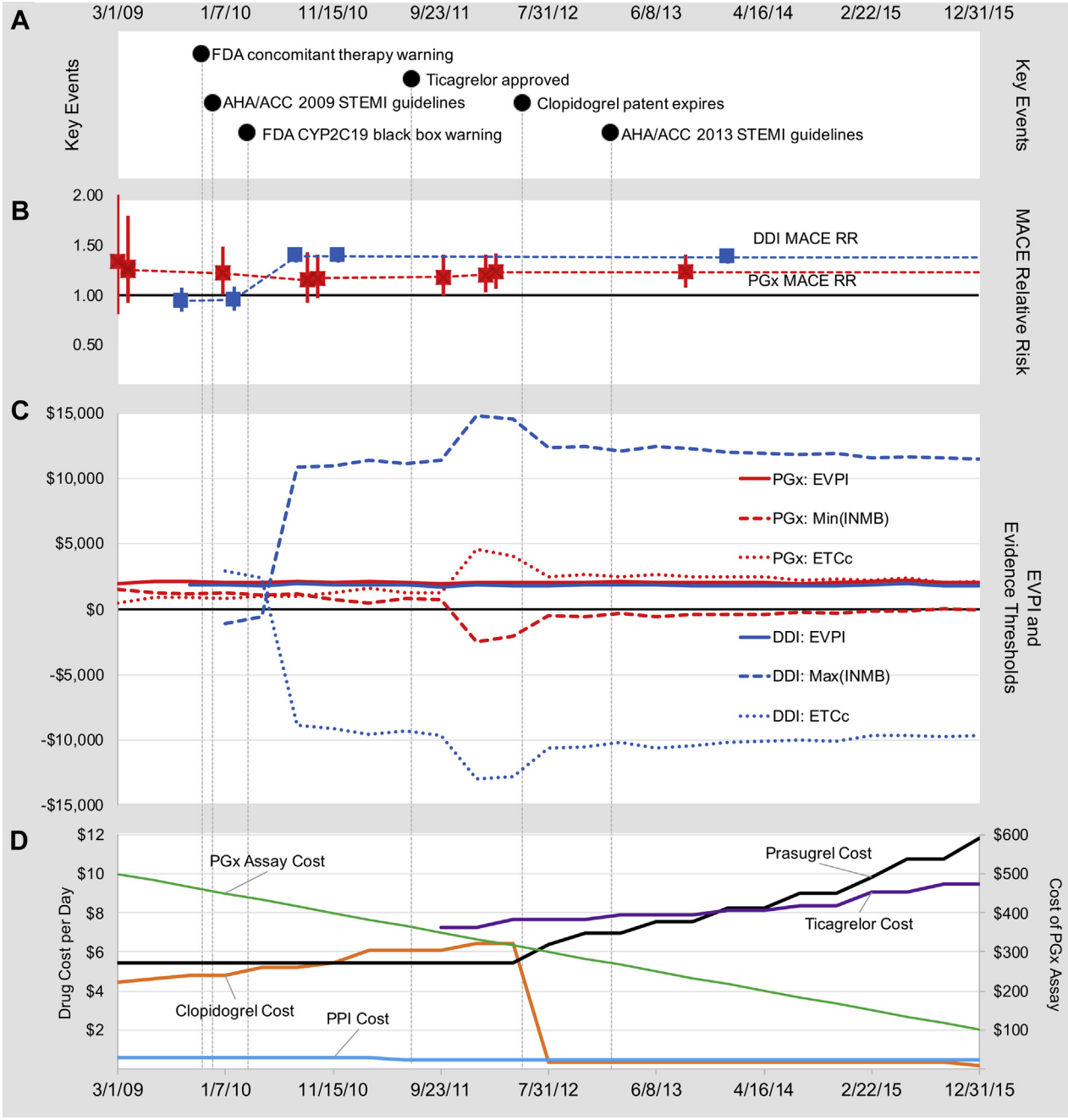
Because the comparison in the PGx intervention analysis is between using PGx versus the optimal (without testing) antiplatelet therapy, the ETCc is computed as $(1 - w)^*EVPI - w^*min(INMB)$, where INMBs reflect the incremental net benefits of PGx (comparator a) being the new intervention versus the most optimal antiplatelet without testing (comparators b, c, or d) being the standard of care. Alternatively, the aDDI ETCc is computed as $(1 - w)^*EVPI - w^*max(INMBs)$, where the reverse is used: INHBs reflect the incremental net benefits of the most optimal antiplatelet (comparators b, c, or d) being the new intervention versus clopidogrel+PPI (comparator a) being the standard of care.

Results

Cumulative Evidence Synthesis

Our cumulative meta-analysis of the PGx interaction (see Fig. 1B, and see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.023) included 19 016 PCI patients from 13 retrospective cohort studies (conducted using data

Figure 1. Evidence accumulation and evidence threshold criterion plus cost of research (ETCc) over time. All results are presented along the same *x* axis of time from March 2009 to December 2015. (A) Key events in the history of antiplatelets from 2009 to 2015. (B) Results of the cumulative meta-analysis over time for CYP2C19 variant vs no variant (pharmacogenomics, PGx) and clopidogrel+proton pump inhibitor vs clopidogrel alone (for more details, see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.023). (C) Primary results, including the ETCc over time. (D) Changes in drug costs (primary *y* axis) and PGx assay cost (secondary *y* axis) over time.



from RCTs) published from 2008 to 2013.[8,22–32] Sample sizes ranged from 690 to 3217 patients. The cumulative estimation of cardiovascular relative risk began with a single study (Trenk et al. 2008,[30] N = 797) with a wide, nonsignificant confidence interval. The addition of 2 studies published in January 2009 (Mega et al.,[8] N = 1459; Simon et al.,[28] N = 2208) had the greatest effects on the cumulative result. As we sequentially added studies, the point estimate trended toward statistical significance. By February 2012, the accumulated pharmacogenomic evidence suggested a significant association between reduced function *CYP2C19* and cardiovascular events, and this finding remained stable through 2013. The final cumulative estimate of cardiovascular relative risk for carriers was 1.23 (95% CI 1.07-1.41).

The aDDI cumulative meta-analysis (see Fig. 1B, and see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.03.023) included 32 936 PCI patients from 5

observational cohort studies published from 2009 to 2014.[33–37] Sample sizes ranged from 588 to 16 690. Drug-drug interaction evidence was initially not statistically significant; however, the confidence intervals were notably narrower than that in the PGx example. Interestingly, early cumulative estimates indicated that concomitantly treated patients were at *reduced* risk for cardiovascular events, but the addition of the large (N = 16 690) retrospective cohort study by Kreutz et al.[33] in 2010 led to an increase in risk (Fig. 1B). The total cumulative estimate of cardiovascular relative risk for concomitantly treated patients was 1.38 (95% CI, 1.31-1.45).

INHB Outcomes

The PGx min(INHB) tended to fall over time (Fig. 1C). The INHB for PGx was greatest (min[INHB] ≈ $1500) in 2009, when the mean estimate (and uncertainty) of the cardiovascular RR was greatest and branded clopidogrel cost was lowest. The PGx INHB then gradually decreased as the cardiovascular relative risk decreased (which lowered PGx antiplatelet selection favorability), and then became negative (min[INHB] ≈ −$2500) once ticagrelor was introduced because of its slightly greater efficacy and the still-high cost of branded clopidogrel. PGx then regained some favorability (min[INHB] = −$68 in 2015) once clopidogrel became generic, which decreased the overall cost of PGx in the INHB equation.

Conversely, the aDDI max(INHB) tended to increase over time (Fig. 1C). The INHB was negative (max[INHB] ≈ $1000) for the 2 periods where the mean cardiovascular relative risk for concomitant therapy was lower than 1.0, indicating a preference for concomitant therapy, and then increased once the point estimate became greater than 1.0 and the model favored one of the antiplatelet monotherapies (max[INHB] ≈ $11 000 to $15 000).

EVPI Outcomes

The EVPIs for both PGx and aDDI models were similar over time (Fig. 1C,D). The EVPI tended to rise and fall modestly for both models as evidence accumulated and drug costs evolved, with the EVPI for PGx being approximately $2000/patient over time and aDDI being approximately $1800/patient over time.

Evidence Threshold Criterion

Figure 1C shows the temporal trend of the ETCc for both the PGx and aDDI scenarios, respectively, along with the timing of the real-world recommendation decisions by ACC/AHA and FDA. As noted above, the PGx min(INHB) tended to decrease to negative value over time, whereas the aDDI max(INHB) tended to increase to positive value over time. Subtracting w*PGx min(INHB) from (1 − w)*PGx EVPI showed an overall increase to positive value in the ETCc value over time, whereas subtracting w*aDDI max(INHB) from (1 − w)*aDDI EVPI resulted in a negative ETCc value over time.

Assuming that cost of research is the same across 2 settings, the relative magnitudes of ETCc reveal likelihood of adoption for the DDI and PGx interventions. Imagine that we have decision makers with a distribution of L. Because ETCc is lower for DDI (in comparison to the PGx scenario), only decision makers who are very highly risk-averse (large negative values) will continue to have doubts about adopting aDDI. In contrast, among the same distribution of decision makers, even those with low risk aversion (smaller negative values) will have doubts in adopting PGx. In other words, as information changes over time, uncertainty in the context of aDDI becomes more tolerable than in the context of PGx.

Discussion

We assessed evidence accumulation and compared the novel ETCc over time for 2 precision medicine interventions for the same cardiovascular patient population. Our results were primarily affected by the cumulative evidence of cardiovascular relative risk until the period between 2011 and 2012, when the cumulative meta-analysis results stabilized and antiplatelet costs abruptly changed.

The first clopidogrel-related decision by the FDA in 2009 recommended adoption of the aDDI intervention (ie, issued warning against PPI+clopidogrel). In the same year, the ACC/AHA guidelines recommended against using the aDDI intervention. This implies that the disutility from adopting the aDDI intervention in the presence of uncertainty was less for FDA than for the ACC/AHA body. In other words, the ACC/AHA body appears to be relatively more risk-averse than the FDA.

Over time, the ETCc for adopting aDDI decreased as the RR of drug-drug interaction–related harm became clearer. This indicates that only more risk-averse decision makers would have doubts adopting aDDI over time. It is then expected that FDA would not need to alter their decision as the net utility of their recommendation for adopting aDDI has increased over time, and in practice the FDA did not issue any follow-up recommendation for aDDI. Nevertheless, the ACC/AHA-renewed recommendation in 2012/2013 continued to suggest limited use of aDDI. Their risk aversion appears to be primarily driven by their perception of risk from relying on observational studies. Despite considerable reduction of uncertainty in the cumulative cardiovascular RR over time arising out of observational studies, the ACC/AHA guidelines appeal for more randomized controlled trials until sufficient clinical evidence is available.[9]

In the PGx scenario, the ACC/AHA recommended against the use of routine PGx testing in 2009 while the FDA all but recommended the use of PGx testing in 2010, during which the ETCc was lower than in future years. Given the revealed risk preference of these 2 bodies from the aDDI case, it is not surprising to see this discrepancy in recommendations. Unlike the aDDI scenario, the ETCc in the PGx case actually *increased* over time primarily because min(INHB) declined over time as a result of the availability of newer antiplatelet monotherapies and the generic status of clopidogrel. Given that the ACC/AHA is deemed to be more risk-averse than FDA, there is no reason to expect that they would alter their recommendation as the ETCc was rising. Their 2012/2013 recommendation was consistent with this expectation. The fact that the FDA also did not alter their recommendation for adopting PGx testing indicates that FDA must be even less risk-averse than suggested by their 2010 decision.

These findings clearly indicate that different decision-making bodies have notable differences in their risk preferences that lead them to interpret the same evidence differently and make different recommendations. Understanding these risk preferences could be important in sorting out the confusion that different recommendations can create.

There are some caveats and considerations needed for the use of the ETC. We only consider 2 decision-making options: accept or reject with further research options. This is because the indifference point between these options is the key to highlight the evidence thresholds arising out of risk aversion. A third option, “accept with research,” may also be available to the decision maker.[38] Nevertheless, choosing this option against “accept without research” does not highlight the risk aversion threshold and hence is not considered here. Similarly, other

decision-making options such as "reject completely without research recommendation" is also not considered because its comparison to the next decision option in the hierarchy will not highlight the specified threshold.

It is important to note that the weighted ETC defines an evidence threshold that identifies the upper bound for the disutility to a risk-averse decision maker that is still acceptable for adopting a new technology. It does not identify the specific levels of risk aversion for a decision maker, and so the usefulness of this metric is only realized on comparing multiple scenarios of decision making for the same decision maker or across multiple rational decision makers. It should also be pointed out that comparisons across decision makers assume that they are rational decision makers trying the maximize the same objective function but with different levels of risk-averseness. The economic theory of revealed preferences across decision makers fundamentally makes the same assumption.[5,6]

We have used EVPI to form an upper bound of L. This upper bound is important to compare decision making at the margin. In contract, Expected Value of Sample Information (EVSI) for a specific realistic study can give a more accurate estimate of L for the clinical question at hand. Nevertheless, because different study designs (eg, Bayesian vs frequentist, ie, versus traditional) can produce different estimates of EVSI, any single estimate of EVSI may be a less clear measure of the maximum disutility acceptable to the decision maker to adopt a new treatment. A better option would have been $\text{Max}_{\text{Designs}}\{\text{EVSI-C}\}$, but we believe that EVPI serves that purpose with ease.

It is, however, important to consider the cost of associated research. In our empirical example, the comparison naturally set us up to ignore C as the research costs for each application are likely to be similar. But in other contexts, a reasonable estimate for the cost of the best research design possible should be considered.

It is important to consider that different decision makers may have different utility functions (ie, they may consider other factors, such as practice income, convenience, or budget impact), which could explain decision differences beyond the effects of risk aversion. In our example we believe that the decision makers (clinical guidelines group and FDA) likely have similar goals—maximizing net health benefits—for our PGx and aDDI examples. Nevertheless, concerns about drug interactions affecting drug uptake, challenges of implementing PGx in clinical practice, and interest in moving precision medicine forward all could have influenced decisions.

Last, the evidence bases for PGx and aDDI interventions are composed of retrospective analyses. Evaluation of study quality, which is difficult to capture in meta-analyses, likely contributes to the discrepancies in policy decisions. Nevertheless, we do not believe that this is a significant factor in our study given the general similarity of study designs used to generate evidence for each case study.

Conclusions

We demonstrated how evidence levels for 2 well-known precision medicine interventions intended to improve clopidogrel therapy can be quantitatively compared using an explicit value of information framework. We found that policymakers differed in their risk aversion but were internally consistent in their recommendations. Quantifying evidence thresholds using our novel proposed criterion may be useful for developing more consistent and transparent PM recommendations.

Acknowledgments

Financial support for this study was in part provided by a grant from the NIH Common Fund (1U01AG047109-01, Veenstra, PI) via the Personalized Medicine Economics Research (PriMER) project, and in part by a grant from the National Human Genome Research Institute (P50HG003374, Burke, PI) via the University of Washington Center for Genomics and Healthcare Equality (CGHE). Basu acknowledges support from National Heart, Lung, and Blood Institute R01 grant (R01 HL126804). The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.03.023.

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