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The Value of Routine Pharmacogenomic Screening – Are We There Yet?:

A perspective on the costs and benefits of routine ADMET and HLA profiling – Shouldn't everyone have this done?

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Introduction

While there are several examples where pharmacogenomic testing appears to provide clinical and economic value, use of pharmacogenomics as a tool to improve drug therapy through routine screening of unselected patients is currently tentative. An informal evaluation of the clinical benefits and economic costs of pharmacogenomic screening suggests that improving the evidence base, addressing uncertainty, and improving implementation can lead to practical and cost effective pharmacogenomic screening programs.

The value of improving drug safety and effectiveness through pharmacogenomic (PGx) testing has been an alluring promise for well over a decade. While there are a few examples where pharmacogenomic testing appears to provide clinical and economic value, consideration for widespread use as a tool to improve pharmacotherapy remains tentative outside of primarily academic research institutions. Specifically, implementation of routine PGx screening, or 'pre-emptive' pharmacogenomic testing has been pursued by several healthcare systems.^{1,2} But should all healthcare systems implement PGx screening? Because screening strategies entail 'touching' a broad swath of patients, health technology assessment and evidence thresholds for screening have traditionally been rigorous.³

However, with regard to evidence levels and clinical implementation, PGx screening could be compared to another screening strategy routinely deployed for drug therapy: evaluation of drug-drug interactions. While drug interaction screening itself could be improved, it is standard of care in hospitals, doctors' offices, and your neighborhood pharmacy. What differentiates PGx screening from DDI screening? Perhaps most importantly: cost, convenience (time costs), and evidence of clinical risk-benefit trade-off. These factors can be considered using a formal cost-effectiveness analysis framework.

Let us assume the cost of providing PGx screening, C_{pgx}, includes the cost of providing sample collection, analysis, patient/provider education, as well as other pragmatic costs.

Other key parameters are:

- P_{var}, the probability a patient will have a clinically relevant variant
- P_{drug}, the probability a patient will be exposed to a drug affected by the variant

- Bpgx, the incremental clinical benefit derived by improving drug effectiveness or avoiding harm, per patient tested and receiving a PGx drug, measured in Quality-Adjusted Life-Years (QALYs)
- Csav, incremental healthcare costs saved (or spent) as a result of modifying drug therapy and avoiding adverse outcomes, per patient tested and receiving a PGx drug

While Pvar and Pdrug are relatively straightforward to estimate, Bpgx and Csav are more complex because they incorporate both the probability that an adverse outcome is avoided (baseline risk $\times$ risk reduction) and the clinical and economic impact of the avoided event.

Fortunately work over the past decade quantifying the outcomes (Bpgx and Csav) of specific PGx tests, as well as more recent PGx screening pilot efforts, enable us to make some generalized estimates. Let's consider the following drugs for which PGx is relevant: 1) warfarin to avoid bleeding events, 2) clopidogrel to improve antiplatelet effectiveness, 3) phenytoin and carbamazepine to avoid severe adverse drug reactions, and 4) abacavir to avoid hypersensitivity reactions. In each of these cases the outcomes are rather severe and expensive: major bleeding, major cardiovascular events, severe and potentially lethal adverse drug reactions, and lack of use of a major antiretroviral agent.

However, when the clinical benefit per patient tested (and receiving drug), on average, is considered, it is relatively small: warfarin 0.003 QALY,^{4,5} clopidogrel 0.05 QALY,⁶ phenytoin/carbamazepine 0.02–0.03 QALY,^{7,8} and abacavir 0.003 QALY.⁹ To put these findings in context, 0.05 QALY is about 2.5 weeks of increased life expectancy (with perfect health), and 0.003 QALY is just 1 day. Why are these per patient tested benefits so low? The common culprits must be considered: how many patients have the relevant variant, what is the probability the patient with the variant will have an adverse outcome, how much can we modify that risk by taking clinical action, and what are the risk-benefit tradeoffs of that action? These factors also lead to the common finding that PGx testing is not cost saving. In other words, while there are some cost offsets for patients who avoid an adverse outcome, they generally do not offset the cost of testing all patients.

Screening patients not currently receiving the target drugs adds some complexity to the assessment. The classification of the 'severity' of a variant is highly correlated with the probability a patient is a carrier. Recent work at Vanderbilt with the PREDICT program provides some valuable insights.¹ For example, when all 'actionable' variants were considered, 91% of patients were found to be carriers. Yet when 'high risk' variants were considered, the proportion dropped to just 5%. Furthermore, the probability a patient will receive a relevant drug is highly dependent on how those patients are selected. Imagine that everyone in the US was tested for warfarin-related *CYP2C9* and *VKOR* variants. What is the lifetime probability of being exposed to warfarin for patients with a variant? In the PREDICT pilot work nearly a quarter of patients with a variant received warfarin – because the patients were from an intentionally selected population.

Given the background above, we can make some estimates that enable us to consider the value landscape for routine PGx screening – at least conceptually.

- Cpgx: a range of \$50 to \$250 to explore impact of dropping testing costs
- Pvar: the probability of having a variant is already incorporated in the Bpgx estimates from the published studies cited above, as well as the Csav estimate, and generally ranges from 5–30%
- Pdrug: let's consider a relatively unselected patient population, 20%
- Bpgx: based on the examples discussed above, a range of 0.005 to 0.025 on average seems reasonable, measured in Quality-Adjusted Life-Years (QALYs)
- Csav: assume a relatively modest cost offset of \$10 on average per patient who ends up receiving a PGx drug (and who may or may not have a variant)

These estimates can provide us with a snapshot of the value landscape for PGx screening (Figure). The incremental cost is $(C_{pgx} + (C_{sav} \times P_{drug}))$ and the incremental benefit is $(B_{pgx} \times P_{drug})$. How do we interpret the value (vertical) axis? There are several thresholds to consider: below \$50K/QALY is considered highly cost effective, \$50–\$100K/QALY is cost effective, and above \$100K/QALY is not cost effective, in general. Thus combinations of Cpgx and Bpgx in the two shades of blue produce a screening intervention that would be considered a reasonable value compared to other currently reimbursed healthcare technologies in the US.

Given that Bpgx for commonly cited example tends to be at the lower range of the scale, the total cost (i.e., including sample collection, analysis, interpretation, and return of results) of PGx screening per patient likely would need to be in the \$50–150 range given our current assumptions. In other words, given the relatively small benefit of PGx per patient, the economic value is highly sensitive to the cost of screening. The results are only modestly sensitive to cost offsets, Csav, but highly sensitive Pdrug. For example, doubling the probability of a patient population being exposed to a PGx drug (a 'higher risk' population) would double the value of PGx screening. Importantly, these estimates do not account for uncertainty – and doing so only increases the evidentiary and affordability demands. An explicit policy model more detailed than the schematic presented here would be helpful.¹⁰

While quantification of the evidence levels and economic value of drug interaction screening are generally lacking, it is not a stretch to postulate that PGx screening is beginning to look like drug interaction screening with regard to evidence levels. The current evidence and conceptual considerations discussed herein suggest that three areas of focus are needed to bring PGx screening into the realm of routine clinical care:

1. **Develop evidence.** Identify additional PGx applications and determine reasonable estimates of their clinical and economic value, even if potentially low. Identifying variants in different populations and establishing or confirming plausible mechanistic hypotheses are a first step. Evidence of an association between the variant and adverse outcomes (clinical validity) should be established at least for the gene and drug, if not the specific variant. Lastly, there should be either a highly plausible benefit-risk tradeoff, indirect evidence of clinical benefit, or direct (e.g., from randomized controlled trials, RCTs)

evidence of clinical benefit. RCTs should be pursued on a selected basis given the tremendous sample sizes needed to detect most PGx intervention effects.

2. **Address uncertainty.** While we will never have ‘gold-standard’ RCT evidence across the board for PGx applications, there are two strategies that can help decision makers address the ‘insufficient evidence’ trap. First, routine screening panels should include only variants that have clinical validity and highly plausible clinical utility. While adding more genes and variants to screening panels would seem to offer greater return, and may to some degree, doing so increases the uncertainty about the value of screening. Guidelines and reimbursement policy makers respond to uncertainty as expected – by asking for more evidence. Second, we need to create decision-making frameworks that are more transparent about evidence uncertainty and evidence thresholds, particularly in relation to non-PGx based individualized drug therapy such as management of drug-drug interactions.
3. **Refine implementation.** Approaches that offer low-cost PGx screening and practical delivery and utilization of the results are essential, including refinement of algorithms to select patients for screening. Continued development of implementation guidelines and formal economic evaluations of the type outlined here are needed. Lastly, clinical researchers and implementation scientists should engage retail, hospital, and specialty pharmacy and pharmacist organizations to identify practice needs and pragmatic processes for incorporating PGx screening into routine care.

So, are we there yet? There are good reasons to think we are getting close: an increasing evidence base, dropping cost of testing, and promising early implementation work. Perhaps most importantly, there is an increasing recognition that ADMET/HLA testing needs to be viewed as a tool to improve drug therapy that is incremental and affordable, rather than revolutionary and cost saving. To use the ‘Moneyball’ analogy from baseball, affordable singles hitters – not expensive home run sluggers – will win the game.

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Figure.

Value landscape of PGx screening. Clinical benefit of PGx testing (per patient receiving a PGx drug) is shown on the horizontal-axis, total cost of screening (per patient screened) on the depth-axis, and the value of PGx screening on the vertical-axis. Below \$100K/QALY is generally considered cost effective in the US, although results presented do not account for uncertainty.