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Interpreting the clinical utility of a pharmacogenomic marker based on observational association studies

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Abstract

It is increasingly recognized that the clinical utility of a pharmacogenomic marker is a fundamental characteristic influencing the likelihood of successful clinical translation. Although appropriately designed and executed randomized controlled trials generally provide the most valid evidence for the clinical utility of a pharmacogenomic marker, such evidence may not always be available. Observational pharmacogenomic association studies are a common form of evidence available, but the assessment of clinical utility based on such evidence is often not straightforward. This paper aims to provide insight into this issue using a range of illustrative examples.

Keywords: pharmacogenomics, pharmacogenetics, personalized medicine, clinical utility, observational study, association study

One of the main goals of pharmacogenomics is to improve medical decision making through better prediction of treatment response (safety and effectiveness).[1, 2] It is increasingly recognized that clinical translation of a pharmacogenomic marker is strongly dependent on its clinical utility – that is, whether routine testing improves patients' outcomes.[3, 4] Towards this end, it is important to understand whether treatment response differs between pharmacogenomic subgroups. Cost-effectiveness, another important characteristic influencing clinical translation, is also dependent on the treatment response estimated for pharmacogenomic subgroups.[5-7] Observational association studies are a common form of evidence for pharmacogenomic markers. However, it is often not well appreciated that interpreting the clinical utility (and consequently the cost-effectiveness) of a pharmacogenomic marker is not straightforward based on such evidence.[1] This paper therefore aims to provide insight into this issue using a range of illustrative examples.

Types of pharmacogenomic markers and study designs

There are two major ways in which a pharmacogenomic marker may affect the risk of a clinical or surrogate outcome. As there is currently no standard terminology we use the terms 'prognostic' and 'predictive' which are commonly used in the oncology literature.[8]

Using this standard framework, a marker is 'prognostic' if it influences the natural course/history of a disease and thus 'prognostic' markers generally affect the risk of outcomes irrespective of the intervention. Thus, a purely 'prognostic' marker will not influence treatment response - defined in this context as the relative risk (RR) or relative risk reduction (RRR) associated with treatment. For example, blood lipid levels predict the risk of cardiovascular outcomes, but are not generally though to influence the RRR associated with statin therapy.[9]Thus, lipid levels would be considered 'prognostic' for cardiovascular outcomes but not 'predictive' of statin effect on cardiovascular outcomes. It is important to note that although a 'prognostic' marker does not influence RRR, it can influence the absolute risk reduction (ARR) and the number need to treat (NNT). For example, individuals with higher lipid levels receive the same RRR with statin treatment as individuals with lower lipid levels, but the will have a greater ARR as a consequence of their greater underlying cardiovascular risk.[9]

'Predictive' markers are specific to a drug or drug class and identify subgroups for which the treatment response (RR or RRR) differs. The most useful examples of 'predictive' markers are able to separate a subgroup with substantial treatment response from a subgroup with no treatment response (RRR=0). The ability of a 'predictive' marker to potentially identify a group with no treatment response (as compared to the ability of a 'prognostic' marker to identify a group with reduced response) is a key reason why 'predictive' markers are particularly sought after It is important to note that some pharmacogenomic markers have a mix of both 'prognostic' and 'predictive' effects – that is, affect both the natural course of the disease and treatment response. The complexities associated with combined 'prognostic' and 'predictive' effects will be explored in more detail later.

In general, an appropriately designed and executed randomized controlled trial (RCT) will provide the highest quality evidence of the clinical utility and cost-effectiveness of a pharmacogenomic marker.[10-12] Such a study may provide estimates of the treatment response for each pharmacogenomic subgroup and assess whether there is differential treatment response between pharmacogenomic subgroups. To do so the RCT would need to include the appropriate groups of

participants. For a simple example in which the pharmacogenomic marker has only two possible values (e.g. positive and negative) and there are only two relevant treatment options (e.g. treatment vs. no treatment) then four groups would ideally be studied (i.e. treatment + positive marker, no treatment + positive marker, treatment + negative marker, no treatment + negative marker).[1]

Nonetheless, a common approach for initial assessment of the value of a pharmacogenomic marker is an observational association study. These are predominantly cohort or case-control studies which assess the correlation between the pharmacogenomic marker and an outcome of interest. Importantly, these studies generally include only individuals on a specific treatment – that is, only two of the four patient groups are studied. Because two of the four groups are missing, it is not simple to interpret the clinical utility and cost-effectiveness of the marker without further information/assumptions concerning the 'prognostic' and 'predictive' character of the marker.

Illustrative example

Assume that a particular treatment is the standard of care for reducing the risk of an adverse clinical outcome and that a mutation in a particular gene is proposed as a pharmacogenomic marker of the treatment's effectiveness. Individuals are classified into two subgroups depending on whether they have or do not have the mutation. A cohort study is undertaken which enrolls individuals that are using the treatment. The results indicate that individuals with the gene mutation have double the risk of the clinical outcome (10% risk vs 5% risk for individuals without the gene mutation). Does this pharmacogenomic marker have clinical utility? If so, how should a test for the pharmacogenomic marker be used to guide selection of therapy?

As indicated previously this pharmacogenomic association study only provides information on two of the four groups. Figure 1 displays the clinical outcome results for patients who are on the treatment (right hand side of each figure) with a range of plausible scenarios for the clinical outcomes of patients who are not on the treatment (the left hand side of each figure). Lines that join the clinical outcomes of patients with and without treatment highlight the treatment response (ability to reduce risk) for each pharmacogenomic subgroup.

Assuming a purely 'predictive' marker

If it is assumed that the gene mutation is a 'predictive' marker with no 'prognostic' effects, the difference in the risk of the clinical outcome identified in the association study must be due to differential treatment response. As the gene mutation is not 'prognostic', the mutation only influences clinical outcomes for individuals who are on the treatment. Figure 1a displays an example in which individuals with the mutation are assumed to receive no benefit (RRR = 0%). Under these assumptions, there would be clinical utility (i.e., health gain) in screening for the gene mutation as the adverse effects and the cost of unnecessary therapy would be avoided with no loss of therapeutic benefit. Unless the mutation is very rare or the pharmacogenomic test is very expensive this scenario is also likely to be cost-effective.

However, alternative scenarios for a purely 'predicative' marker are also plausible. Figure 1b displays an example in which individuals with the mutation do receive benefit from treatment (RRR = 20%) but it is substantially less than individuals without the mutation (RRR = 60%). In this case, the clinical utility of screening for the gene mutation is not straightforward and may depend on whether the

treatment has substantial adverse effects that may outweight the therapeutic effect for individuals with the mutation or whether there is an alternative treatment available that has a superior therapeutic effect for the individuals with the mutation. The clinical use of the pharmacogenomic marker may also be potentially justified on the basis of cost-effectiveness ifthe modest benefit for individuals with a mutation is not considered to be an effective use of finite healthcare resources. This is most likely to be relevant for high-cost treatments. .

Assuming a purely 'prognostic' marker

It may also be plausible that the gene mutation is a purely 'prognostic' marker. In such a case, the mutation only influences the disease; and has no effect on the treatment RRR. As the marker is 'prognostic' individuals with and without the mutation will have different risk of the clinical outcome even if they are not on the treatment. Figure 1c demonstrates a 'prognostic' marker for which the treatment response is the same (RRR of 30%) irrespective of whether the individual has the mutation. In this case, individuals with the mutation will be at higher risk without treatment and consequently will receive the greatest ARR from treatment. Importantly, although there are similarities with the prior example (i.e. both group receive some benefit from treatment) the subgroup that receives the greater ARR is reversed (see Figure 1b and 1c).

Examples with RCT based evidence

One of the best examples of a 'predictive' pharmacogenomic marker routinely used in clinical practice is *KRAS* genotype to guide use of anti-EGFR monoclonal antibodies in advanced colorectal cancer. Figure 2a summarises the results of a pivotal RCT in which individuals with a *KRAS* mutation demonstrated no survival benefit from treatment.[13] *BRAF* mutations have also been studied for guiding the same therapy, but current evidence suggests that *BRAF* mutations are 'prognostic' rather than 'predictive' (Figure 2b).[14] As both BRAF subgroups appear to benefit from treatment this marker is not commonly used to guide treatment of anti-EGFR antibodies. However, if evidence were only available from on-treatment association studies (see right hand side of Figures 2a and 2b) it would be difficult to distinguish the clinical utility of *KRAS* and *BRAF* mutations in this setting. It is also worth noting that although BRAF mutations are not 'predictive' for this treatment and cancer, they are thought to be 'predictive' for vemurafenib therapy in advanced melanoma.[15] That is, the prognostic/predictive characteristics of the same pharmacogenomic marker may differ between settings (e.g. different disease types and treatments).

The Oncotype DX breast cancer test, which is based on the expression of 21 genes in a tumor sample, is another test used in clinical practice. An RCT has suggested that the Oncotype DX breast cancer test has both 'prognostic' and 'predictive' characteristics (Figure 3a).[16] That is, the test score provides insight into both the underlying risk of cancer recurrence and the ability of chemotherapy to prevent cancer recurrence.[16] Of note, if the marker has both 'prognostic' and 'predictive' characteristics the results of a pharmacogenomic association study can be particularly difficult to interpret. For example, if an association study had been undertaken including only individuals using chemotherapy little difference in the risk of cancer recurrence would be expected between individuals with high and low recurrence scores (see right hand side of Figure 2c). Thus, an association study that does not find a difference in event risk between pharmacogenomic groups does not necessarily mean that the marker is without clinical utility.

Although there are few examples outside of oncology of 'predictive' markers that currently have a strong evidence base and clear clinical utility, examples from other therapeutic areas can still provide insight into the difficulty of interpreting clinical utility from association studies. For instance, many studies have assessed whether cytochrome P450 (CYP) 2C19 genotype influences adverse cardiovascular outcomes for individuals on the anti-platelet agent clopidogrel.[17-19] Figure 3a displays the results from an RCT substudy comparing clopidogrel to an alternative anti-platelet agent, ticagrelor.[20] Although it does provide modest support for a 'predictive' effect it also suggests that ticagrelor is likely to have benefit over clopidogrel irrespective of *CYP2C19* genotype. This insight into the expected clinical utility of assessing *CYP2C19* genotype is difficult to gain from the large number of published association studies.[21]

KIF6 genotype has been suggested to be associated with both the cardiovascular risk and the response to statin drugs. Although the evidence supporting the clinical utility[22] and cost-effectiveness[23] of *KIF6* genotyping is controversial the example is still useful for illustrative purposes. Figure 3b displays the results of a study in which the subgroup with a *KIF6* mutation demonstrated a greater relative reduction in coronary events due to statin therapy ('predictive' effect), but also a higher general risk of coronary events ('prognostic' effect).[24] A meta-analysis of observational studies subsequently was not able to identify a significant association between *KIF6* genotype and coronary artery disease which suggested there was no 'prognostic' effect.[25] However, it has been argued that if *KIF6* genotype is truly predictive of statin treatment response then little difference in risk would be expected between *KIF6* genotype subgroups if the majority of individuals in the association study were using statin therapy (see right hand side of Figure 3b).[26]

Evidence-based pharmacogenomics: balancing quality and feasibility

There is a growing awareness of the evidence dilemma with respect to the clinical translation of pharmacogenomics.[27] In the era of evidence-based medicine there is a clear interest in developing the highest quality evidence to guide whether a pharmacogenomic test should be integrated into standard medical practice. Decisions on whether a drug should be used in clinical practice are typically based on evidence from one or more RCTs and thus it is reasonable to question whether similar levels of evidence should be required for pharmacogenomic markers which guide drug and dose selection. The major caveat is the feasibility of undertaking prospective RCTs to support each pharmacogenomic marker. The expense of undertaking adequately powered RCTs of clinical outcomes for new drugs may be justifiable for the pharmaceutical industry due to the substantial potential return on investment for drugs. However, a similar return on investment is not anticipated for pharmacogenomic tests and public funding is unlikely to be sufficient to support such research. This is likely to be particularly problematic for pharmacogenomic markers that are rare (e.g rare genetic variants) and/or predict rare clinical outcomes (e.g. severe adverse drug reactions[28]). To date there have been very few examples of RCTs specifically designed to assess the clinical utility of a pharmacogenomic marker that are adequately powered to detect relevant clinical outcomes. Prominent examples are the RCTs of genotype-guided warfarin dosing (COAG[29] and EUPACT[30]) and expression profiles to guide use of chemotherapy in early breast cancer (TAILORx[31] and MINDACT[32]).

A practical option for developing high quality evidence of clinical utility may be the retrospective analysis of conventional RCTs that have archived biological samples (sometimes also called a genetic or genomic substudy of an RCT). This approach allows evidence based on randomized treatment allocation to be developed relatively quickly and inexpensively.[10-12] The examples described above for KRAS, Oncotype DX, CYP2C19, and KIF6 were all based on evidence developed from secondary analysis of a conventional RCT. The validity of such secondary analyses depends on the manner in

which the study is undertaken. In particular, it is important that a hypothesis driven statistical analysis plan is prespecified, and that a large proportion of the RCT participants have biological samples available for analysis.[11, 12] It is likely that secondary analysis of existing RCTs will often be underpowered to detect 'predictive' markers and this will particularly be the case for rare clinical outcomes and rare pharmacogenomic markers. Secondary analysis of RCT data will not always be possible. For example, for older drugs the pivotal RCTs may have taken place at a time when biological samples were not archived for future use. Additionally, RCTs may not be available with the appropriate treatment comparison for the pharmacogenomic marker. As major RCTs more commonly compare different drugs rather than different doses of a drug, secondary analysis of RCTs is likely to be most useful to provide evidence for pharmacogenomic markers that guide choice of drug rather than choice of dose. Consequently a prospective RCT will often be the only option if RCT evidence is required to confirm that genotype-guided dose adjustment improves treatment outcomes.[29, 30]

If RCT based data is unavailable additional observation studies may be of some value to better understand the likely clinical utility. Specifically, observational studies of the same pharmacogenomic marker in a similar patient cohort that are not on the treatment of interest may help provide support for whether the marker is likely to have 'prognostic' and/or 'predictive' effects. For example, if the pharmacogenomic marker is associated with a similar effect on the clinical outcome irrespective of whether the study participants are using or not using the treatment of interest then this provides some support to the hypothesis that the marker is predominantly 'prognostic' (see Figure 1c). Conversely, if there is differential risk between pharmacogenomic marker subgroups only for studies in which individuals are using the treatment then this provides some support to the hypothesis that the marker is 'predictive' with respect to the treatment (see Figures 1a and 1b). It is also possible to quantitatively synthesize the observational evidence for the pharmacogenomic marker in order to indirectly estimate the treatment response within pharmacogenomic subgroups.[33] This approach has been utilized to gain insight of both clinical utility and cost-effectiveness.[18, 34, 35] However, it is important to be aware of the strong assumptions that are generally required for such modeling and hence there is a significant risk of bias associated with the indirect estimates.[33] Finally, if the biology of the pharmacogenomic marker and the disease, and the pharmacokinetics and pharmacodynamics of the drug treatment are all well understood they may provide corroborative support of whether the marker is more likely to affect the disease process (prognostic) or the drug's effect (predictive).

Conclusion

We provide here insight into the difficulties of interpreting clinical utility from pharmacogenomic observational studies of individuals using a specific treatment. Data from an RCT generally provides more valid and interpretable evidence for clinical utility and observational data is most useful in the context of prioritizing and building a case for acquiring RCT-based data. Secondary analysis of existing conventional RCTs with archived biological samples is a practical approach for deriving RCT based evidence that may be possible for some but not all pharmacogenomic markers. For cases in which secondary analysis of existing RCTs is not possible prospective RCTs are an option but will often be impractical due to cost. There is clear need for innovative policy and methods for effectively progressing the clinical development/translation of pharmacogenomic markers for which observational evidence suggests potential clinical utility but there is little prospect of obtaining RCT-based confirmatory evidence.

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Figure 1: Interpretation of the clinical utility for a hypothetical pharmacogenomic marker based on an association study result assuming; (A) a purely 'predictive' marker which is able to identify a subgroup with no benefit from treatment, (B) a purely 'predictive' marker which is able to identify a subgroup with reduced benefit from treatment, and (C) a purely 'prognostic' marker.

NNT: number needed to treat

Figure 2. Examples of oncology pharmacogenomic markers; (A) *KRAS* mutations and third-line cetuximab therapy for colorectal cancer, (B) *BRAF* mutations and first-line cetuximab therapy for colorectal cancer, (C) Oncotype Dx breast cancer test and adjuvant chemotherapy.

RS = recurrence score

Figure 3. Examples of putative cardiovascular pharmacogenomic markers; (A) cytochrome P450 2C19 genotype (loss-of-function allele) and clopidogrel therapy for individuals with acute coronary syndrome, and (B) *KIF6* genotype for statin therapy.