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Potentially Actionable Targets: Evidence Standards for Credible Next Generation Sequencing Technology Assessment Claims

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Abstract

Despite considerable resources devoted to developing databases to support competitive credible claims for next generation sequencing (NGS) claims, we have yet to meet the standards required in health technology assessment to support such claims. The purpose of this commentary is to consider options open in establishing claims for NGS recommendations. Although NGS platforms offer potential promise in improving clinical outcomes, supporting cost-effectiveness and reducing the overall cost of care in target populations, this has yet to be demonstrated on a scale that is likely to satisfy reimbursers and health care decision makers. Issues addressed include (i) the importance of credible, evaluable and replicable claims from individual NGS platforms; (ii) the difficulties in moving beyond broad-brush claims for improved survival; (iii) the standards required for an NGS evidence base; (iv) protocol designs in establishing the independent contribution of NGS actionable therapy recommendations to outcomes claims; (v) the role of NGS registries; and (vi) protocols to support ongoing credible, evaluable and replicable claims in target patient populations. The critical issue is not analytical and clinical validity but clinical utility. This has yet to be demonstrated.

Keywords: NGS, credibility of claims, evaluation and replication, evidence base, clinical utility

Introduction

The last decade has witnessed a flurry of activity in identifying potentially actionable targets for therapy choices under the umbrella of genomic profiling for next generation sequencing (NGS) recommendations. Utilizing genomic profiling, research groups and commercial vendors of assay platforms have attempted to identify actionable targets for therapy interventions, notably in late stage cancer. Irrespective of the intrinsic technical merits of competing platforms, their analytical and clinical validity, a reimburser will require evidence for clinical utility: the ability of the platform to improve outcomes, reduce direct medical expenditures and provide information regarding the benefits and harms of testing [1] . These requirements are no different from those expected from any other medical intervention. Reimbursers may inquire as to whether or not the various vendors have undertaken: randomized clinical trials (RCTs) in target patient groups, whether these trials have demonstrated clinically meaningful differences in outcomes and adverse event profiles, whether claims modeled from such trials have generated unbiased credible, evaluable and replicable claims and whether these claims have been assessed through prospective pragmatic or effectiveness trials, through retrospective data or in observational tracking studies. These standards for establishing a credible evidence base are not new and have been explored at length in previous commentaries in *INNOVATIONS in Pharmacy* as well as providing a focus for version 2 of the proposed *Minnesota Guidelines for Formulary Evaluations* [2 3 4] .

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The previous commentaries addressed two issues: first, the impact of NGS on drug development, characterized as one of creative destruction where the adoption of NGS sets in train an incessant program of product and process review as NGS platforms evolve; and second, the questions a formulary committee should ask in establishing the clinical utility of an NGS platform. The overall conclusion from these two commentaries is that the NGS evidence base is inadequate. There is limited evidence for clinical utility and, unfortunately, limited appreciation of the steps required to establish such an evidence base. Unless NGS developers are prepared to undertake the investments necessary to create such an evidence base and to support the ongoing curation of their NGS platform, physicians, patients and health care decision makers will, understandably, be reluctant to reimburse and encourage their introduction into routine clinical practice. Simply claiming analytical and clinical validity for an NGS platform is not sufficient. the marketplace will require substantive evidence for clinical utility in treatment practice.

The purpose of this commentary is explore a number of issues that need to be addressed in establishing the evidence base to support claims for the clinical utility of individual NGS platforms. These issues apply irrespective of whether the NGS platform is designed to generate a menu of potential therapy targets linked to a genomic mutation assessment or whether the platform takes a more targeted approach in identifying therapy options or even 'ideal' mono- or combination therapies.

The critical issue is one of scientific credibility: do the claims made for NGS platforms meet the standards of normal science? Are the claims credible, evaluable and replicable in the target patient population? This standard is hardly revolutionary; it has been in place since the 17th century and is clearly articulated in the motto of the Royal Society (founder 1660; Royal Charter 1662): N*ullius in verba* (take no one's word for it) [5].

Reimbursers will ask two questions: (i) are the claims for the NGS platform credible, evaluable and replicable; and (ii) are claims for the superiority of one assay platform over another, not only credible, evaluable and replicable, but does the claimed' superior' platform offer advantages that are meaningful in the target population? If there is, for example, a recommendation for a switch between platforms, can the vendor claim that the clinical benefits and harms from switching in a target population are worth the possible increase in assay costs associated with its adoption in routine practice?

In exploring these issues, the underlying theme will be that, outside of establishing analytical and clinical validity, the evidence base required to address potential reimburser concerns for clinical utility is potentially biased and limited in its ability to support NGS claims. Both issues have to be addressed. The first in terms of the designs of randomized clinical trials (RCTs), observational studies and registries, the latter in terms of a commitment by NGS vendors to a structured program of RCTs and observational studies. Whether registries can contribute is an open question.

Failure and Survival

Physicians investing in an NGS platform to identify potential target therapies based on the patient's genomic profile are, to date, typically presented with a menu of 'benefit' options for the individual patient. In addition, reports sent to the physician may also provide information on clinically significant alterations, available clinical trials and response markers. As well as detailing therapies where the patient may be expected to be of potential benefit, a list may also be provided where the predicted response is 'intermediate' or where no potential benefit is expected.

If the claims made for an NGS platform are focused on overall measures for a target population such as survival care has to be taken to account for failures in therapy recommendations. Consider, for example, a recently published claim for matched versus unmatched therapies by Herzog et al [6]. In this study claims for targeted therapies in recurrent epithelial ovarian cancer (EOC) taken from the CARIS molecular registry were classified as matched as opposed to unmatched. A matched claim was defined to include subjects receiving at least one treatment associated with predicted benefit and no treatment associated with lack of benefit at any time following diagnosis. Subjects with an unmatched claim were those not included in the benefit cohort (i.e., they received at least one treatment associated with a potential lack of benefit). To demonstrate the contribution of biomarker profiling the survival profiles of the two groups were compared. The study claimed that the matched patients experienced a significantly greater improvement in overall survival time from molecular profiling of 36 months compared to 27 months for the unmatched group.

The concern with this approach to establishing claims for actionable targets is that subjects who were initially introduced to a therapy that had a predicted benefit but who subsequently were introduced, either sequentially or in combination, to a 'non-benefit' therapy were included in the unmatched group. A more rigorous assessment approach, which would reduce claims for survival benefit from matching to benefit therapies, would be to include this group in the matched category, recognizing that those who were introduced to non-benefit therapies could be considered targeted 'failures'. This would, of course, reduce the claimed differences in median survival times while presenting a more realistic profile for platform performance in treatment practice.

A further issue which should be addressed is whether or not individual actionable therapies provided a significant survival advantage over each other. In the Herzog et al paper this issue could not apparently be addressed because of the relatively small sample size. As a result, the claims made were for a 'bundle' of actionable benefit therapies. The potential importance of separately identifying actionable therapies had been brought out by Kim et al in an earlier paper on predicted short-term therapeutic response and long-term survival for, again, EOC [7]. A retrospective assessment of predictors for targeted response with three standard chemotherapy drugs (paclitazel, cyclophosphamide and topotecan) were compared in terms of (i) median survival time difference between responders and non-responders and (ii) survival outcomes for treatment for recurrent disease. The authors reported major differences between the three therapies, supporting the importance of drilling down to individual therapies.

The potential different 'survival' responses to menu items judged 'potentially actionable or beneficial' raises concerns in the design and replication of clinical trial results (and the potential for bias in poorly designed trials). First, the need to control for the distribution of mutations and the matching of 'actionable therapies' and, second, the need to control for physician choice or, more specifically, to address the issue of why physicians select particular menu items and, equally importantly, why do physicians reject menu items in their choice of therapy?

External Validity

The question of whether or not the results of phase 3 trials have external validity has long been of concern. Can claims based upon phase 3 trial results, including modeled cost-outcomes claims, be evaluated and replicated in target patient populations? A concern that is further amplified by the apparent inability of researchers to replicate phase 3 results under identical protocols. The net result is that all too many marketing approvals are taken at face value on what latter transpires to be a limited and even misleading evidence base. This situation is further aggravated by non-evaluable technology assessment claims extrapolating from these clinical trials. If we apply the standards of normal science, at least in respect of modeled cost-outcomes claims, if these cannot be evaluated (e.g., lifetime cost-per-QALY claims from groups such as the Institute for Clinical and Economic Review) then they should be rejected [8]. We don't know whether the claims are right or if they are wrong and, in the majority of cases, we will never know.

Given these concerns with the classical program of drug development and the reliance on two phase 3 placebo controlled trials (often producing conflicting results), the task facing NGS platform developers is daunting. Are they to underwrite a program of phase 3 equivalent RCTs, which is both time consuming and expensive, to generate claims within target populations, or are they to fall back upon less rigorous (probably non-randomized) observational or similar designs to expedite time to market? While RCTs may address the issue of the distribution of mutations across target populations, where the standard of care is referenced against an active 'potentially actionable choices' arm, the issue of external validity still arises as there is no control for physician choice. One answer may be to reduce menu choices, but this does not get around the question of bias due to non-randomization and the attempt to claim for overall survival or other outcome benefits in target populations where the mutation distribution may vary.

To add a further level of complexity, there is the question of whether claims based upon well conducted RCTs in one target population can be taken as evidence for clinical utility for the application of the particular NGS platform in other target populations? If the principal target is oncology, NGS platform vendors will have to come to terms with both the number of potential oncology targets and the positioning of the NGS platform by disease stage in the continuum of care. Guideline developers and professional groups may recommend a genomic assessment at particular stages of therapy, but on the evidence available they are hardly likely to go further in recommending a particular platform, let alone how to evaluate platform recommendations.

Physician Choice

Irrespective of whether or not the physician is presented with a menu of options or a single option, many will decide to put the NGS recommendations to one side for individual patients. This may occur for specific patients or the physician may decide not to follow the NGS recommendations for many if not most patients. To date, there is a dearth of evidence as to why a physician may decide to accept or reject NGS recommendations. Are there factors, such as comorbidities, the presence of polypharmacy, general symptoms of fatigue or frailty that may determine other choices? After all, if comorbidities such as cardiovascular disease and diabetes are present, let alone depression, anxiety, adverse sleep experience and the presence of pain, these may override any NGS recommendation? At present, NGS recommendations fail to take these into account. It is left to the physician to factor these elements into treatment choice.

The presence of comorbidities and other potential decision variables in treatment choice will not necessarily be addressed in randomized clinical trials (RCTs) let alone non-randomized observational studies and registries. Assigning patients in an RCT to non-NGS informed treatment choice versus an NGS treatment arm does not solve the issue of physician choice. Where a menu of options is presented in the NGS-arm, RCTs would typically overlook the questions of why a specific menu selection was made or why a physician failed to select (if treatment choice is not 'forced' in the NGS arm) the NGS recommendation? Forcing an NGS selection may simply reduce any claims for external validity.

The potential for bias in protocol design is more worrying in the case of non-randomized observational studies and registries. If registries, for example, only track patients where the physician has accepted an NGS recommendation, claims made will lack both the confidence that might attach to randomization as well as to the failure to capture outcomes for those where the NGS recommendation is put to one side by the physician. At the same time, the issues of (i) why a particular menu choice was accepted and (ii) why a physician may decide not to assess the genomic profile as an input to therapy choice are not addressed. It is one thing to compare physicians who have accepted/rejected an NGS recommendation and another to compare these groups to physicians who opted out of an NGS assessment altogether. Even if a registry or an observational study captures both patients where the physician has accepted/rejected an NGS recommendation, the failure to capture non NGS-influenced (or driven) treatment choices is a significant limitation on the willingness of formulary committees and other health decision makers to support NGS evaluations. Indeed, it could be argued NGS vendors need to address this question before supporting an NGS platform; after all, the belief that a genomic profile 'necessarily' supports choices that yield improved outcomes is still an open question.

If claims for first generation sequencing are to be credible, care has to be taken to capture and track physician choice. The

physician may accept or reject any of the recommended therapies that are considered of likely benefit. Wherever possible, however, it is important to record the actual therapy choices (whether these are mono- or combination therapy), to include appropriate dosing. Unfortunately, this 'unbundling' of therapy recommendations is often not possible or simply ignored in making platform claims in target patient populations. This, as noted below, raises concerns over the ability to replicate claims for the platform recommendations in target treating populations. With physicians free to choose from the indicated 'benefit' therapies then overall claims for survival in the target population will reflect the 'unknown' distribution of therapy choices by physicians between patients in the target population. Attempts to replicate survival claims for the platform in comparison target populations will reflect an implicit assumption that the 'matched' distribution of therapies is the same.

Target Population Claims

Ideally, claims for NGS platforms should be based on target patient populations within defined disease types by stage of disease. One option is to consider the bundled therapy or 'black box' model where, irrespective of the choices made between those therapies linked to gene mutations, subjects are classified as having either been initiated to a 'benefit' therapy or have been initiated to a 'non' or 'indeterminate' benefit therapy. The claims for competing platforms would then contrast those who were initially 'matched' to those who were 'unmatched'. As described above, this is the approach taken in assessing the Caris platform.

A concern with NGS platforms where menus are presented is, possibly paradoxically, the flexibility given to the treating physician in the choice of therapies from a smorgasbord of matched 'benefit' options. Given that it would be impractical to try to drill down to determine why the physician chose specific items from the matched 'benefit' therapies, the fact is that different benefit combinations (or monotherapy choices) are likely to yield difference outcomes.

If overall survival is the primary outcome, then (putting to one side other potential confounding factors) the distribution of subject survivals will, presumably, reflect the initial therapy choice and, if judged appropriate by the treating physician, switches to other matched 'benefit' options or the introduction of 'indeterminate' or 'non-benefit therapies'. Claims for overall survival benefit for 'matched' versus 'unmatched' therapies will depend, therefore, on the joint contribution of (i) isolating the 'benefit' therapies and (ii) physician initial and subsequent choice involving those benefit therapies. We have no idea, unless each therapy combination is tracked, whether or not more guidance given to the treating physician where matched therapy combinations were ranked as more likely to confer benefits, might yield an improved survival profile. A situation, it might be noted, that is no different from a classical phase 3 RCT where we can claim that, overall, introduction of a new product yields an improved survival profile but we have little idea why some subjects respond better than others. In this case, it would be possible to determine responses to selected menu combinations, but we would still not know why patients presented with the same menu of options responded differently to the same menu option choice.

One answer would be to record the outcomes associated with each possible therapy combination. this would dilute a specific 'bundled' claim if, as might be anticipated, individual therapy combinations from the designated menu yield clinically and significantly different outcomes in the target population. Given this, reimbursers might be wary of claims that rely on an assumption of a given weighted distribution of initial therapy choices in the target population with the potential for bias in the weights selected. A situation which, as noted, is made more opaque by the fact that we may have no idea what prompted a physician to choose a particular therapy combination. This situation becomes even more troublesome if attempts are made to assess competing NGS platforms.

Independent Contribution

One possibility (albeit remote) would be to consider, within a multivariate, as opposed to a descriptive overall survival framework, the contribution of physician selection of therapy benefit' recommendations. Rather than the bundled 'black box' approach, a Cox survival model could be specified where specific combinations of therapies from the menu of matched therapies are captured as dummy variables and the marginal or independent impact evaluated.

Broad-brush claims for outcomes such as median survival across cancer types are unlikely to be convincing; a 'black box approach where platforms are compared in terms of gross outcome measures rather than on asking the more fundamental question: what is the independent contribution of NGS-driven 'actionable therapy choices' on the clinical, cost-effective and budget impact outcomes of therapy? The critical issue is to identify, by analogy to classical RCT designs, the independent effect of therapy recommendations from competing NGS platforms. The fact that an NGS platform generates recommendations for actionable therapies is only a first step. The critical question is whether or not, in the target disease population, a claim for the independent effect of that recommendation can be justified; is it credible, evaluable and replicable? Irrespective of whether the claim (hypothesis) is expressed in purely clinical terms, in terms of overall survival, progression free survival, quality adjusted life tears or cost-per-QALY, the independent contribution of the contribution of the actionable target has to be evaluated. This requirement is unexceptional. Unfortunately, it is often overlooked.

Isolating, for a particular target population the independent contribution of a platform linking drugs to likely actionable targets requires, in the first instance, a systematic review of the literature in that cancer state or stage of disease, an assessment of potential confounding factors and, second, the likely quantitative impact of these on treatment outcomes. Typically, there is a substantial literature to be evaluated. If the outcome of interest is survival than questions that need to be addressed would cover the contribution of demographic and socio-economic characteristics to survival (e.g., age, gender, race, access to care, employment status), the presence of comorbidities (e.g., cardiovascular status, diabetes), the presence of pain, adverse sleep experience, depression, anxiety, somatic status and adverse events (both from the target disease state and comorbidity treatment). To these should be added compliance with therapy, (including both adherence and persistence – and their potential determinants). If the outcome of interest is quality adjusted life years (QALYs) then, clearly, many of these comorbidities will impact quality of life. If resource utilization and costs enter the analysis then these need to be identified, costs rather than charges captured and, if possible, resources used and costs contributed by the target disease separated from those resources and costs that are associated with comorbidities. Probably of equal importance, if a range of treatment sites are contributing, the question of whether the individual treatment site might be considered 'typical' in its resource utilization and cost structure.

A number of potential confounding factors together will require decisions as to the choice of patient reporting outcome (PRO) instrument or summary measures. If fatigue, for example, is considered a potential confounder in qualifying outcomes claims then which measure of fatigue is to be used? Similar arguments apply to evaluating the impact of depression (likelihood of major depressive disorder?), anxiety, pain (pain experience in terms of severity and frequency, likelihood of chronic pain) and sleep experience. How are comorbidities to be captured? Should key comorbidities be flagged as dummy variables or should a measure such as the Charlson comorbidity index be used?

Survival and Quality of Life

While broad brush claims for increased overall survival or progression free survival following application of NGS guided-interventions are increasingly made, it is a moot point as to whether such claims are meaningful to reimbursers, let alone patients and treating physicians [9] . Given the experience in late stage cancer therapies including the impact of competing regimens on adverse effect profiles, the likelihood of adverse events and factors such as depression and anxiety on adherence and persistence, a case can be made that the quality of life and quality adjusted life years (QALYs) are more meaningful. Rather than taking an easy way out and simply comparing survivorship profiles, reimbursers may be more interested in competing cost-per-QALY claims.

If this argument is accepted and without necessarily going into the issue of cost-per-QALY willingness to pay thresholds for NGS pricing negotiations, there is the question of the choice of QALY measure. Should a vendor express claims in terms of a generic QALY measure (EQ-5D-3L, EQ-5D-5L) or an instrument that generates items for a 'generic' measure such as the SF-6D (SF-36, SF-12), a cancer or a disease specific measure? In the last case there are a number of platforms that have proposed cancer-specific measures of quality of life. At the same time there are questions to be addressed regarding the measurement properties of the instrument (e.g., does the instrument have interval scoring properties?).

Establishing and Replicating Claims

If the independent contribution of an NGS platform is to be evaluated then it must be within the framework of a multivariate model. The choice of model should capture characteristics of the targeted population, the stage of disease, the standards for intermediate and final endpoints, the required data elements, the timing of data collection and the timeframe over which the claim is to be assessed. This is elementary. As noted in earlier commentaries, reimbursers should require a protocol to be submitted detailing how the claims are to be evaluated. This protocol should be agreed with the reimbursers and IRB approval sought.

As it stands, there is a virtual absence of evidence to support claims for the clinical benefits and the cost-effectiveness of competing NGS platforms in target populations. There have been no attempts, as far as can be ascertained, to either develop models with evaluable claims and evaluate those claims or to report directly from observational studies on the cost-effectiveness of competing NGS approaches utilizing multivariate modeling. At best, there is one proposal for a RCT design to support comparative-effectiveness claims in patients with colorectal cancer/polyposis syndromes [10].

The Role of Registries

Although establishing registries in NGS has become popular, it is not clear what the registries are intended to achieve or even whether establishing a registry is appropriate given the diversity of potential disease states and stage of disease and the choice of actionable targets. Unfortunately, evidence on the structure of the proposed registries, the specification of data inputs and the timing of data collection is unclear. From the descriptions presented, it is also not clear what the contribution from patients is expected to be. As detailed, in the discussion above of the need to capture potentially confounding factors in evaluating the independent contribution of actionable therapy choice to outcomes, patient inputs may play a critical role in claims assessment; let alone an assessment of why physicians make particular choices.

A patient registry is only relevant if it is appropriately managed, capturing the minimum data points and number of subjects necessary to support a multivariate assessment of the impact of targeted therapies. As noted, the structure and content of the registry should be justified in terms of the registry target patient populations and the ability of the registry to avoid claims of bias. A blanket commitment to a registry without justifying the design and content of the registry in terms of the target populations and claims to be assessed within those target populations should be avoided. The registry should report on the protocols for the target patient populations identifying the primary and secondary endpoints, number of subjects to be recruited and associated power calculations. In cancer, for example, one size of study design does not fit all. A 'lean' registry which focuses on claimed common outcomes (e.g., overall survival) is unlikely to capture the data points necessary to validate health technology assessment claims.

Questions should also be raised as to the projected 'size' of the registry, the anticipated recruitment of subjects and the timeframe within which claims assessments are to be reported. Is the registry designed to capture physicians who have requested a genetic profile but who fail to follow through on the recommendations? Are these physicians tracked as a control group? A further issue concerns the 'bundling' as opposed to the tracking of specific therapy interventions. If physicians have the option of choosing between therapies identified as actionable, are these individual therapies to be tracked? If so, is the registry designed to capture the required subject size for hypothesis testing with these specific drugs?

As noted above, claims for NGS actionable predictions should not only be compared across therapy platforms but, following the standard RCT designs, against a control group for these actionable therapies. It seems somewhat pointless to develop a registry that only reports on the outcomes for physicians who had requested a genetic profile and who may or who may not have acted upon the recommendations for therapy choice. Should account be taken of physicians who have not requested an NGS assessment? Does their absence imply any bias in the results claimed? What do we know, as discussed above, regarding the factors that influence whether or not a physician requests an NGS assessment in the first place?

At the same time, although this possibility can only be touched on here, there are a large number of cancer registries including state and regional registries as well as private registries in the US. Rather than reimbursers asking NGS vendors, as part of their market entry strategy, to propose establishing a registry for their product, there is the option of either working with specific cancer registries to record NGS requests and adoptions or to utilize these registries to establish benchmarks [11].

Conclusions

If claims for NGS platforms are to be considered in formulary decisions and, equally importantly, accepted by patients and treating physicians, then the claims made must be, for the target populations, credible, evaluable and replicable claims. Unfortunately, previous commentaries in this series have pointed out that health technology assessments over the past 30 years have shown a dogged commitment to building models to support cost-effectiveness and cost-utility claims that are unevaluable [12]. Particularly egregious are lifetime cost-per-QALY claims that clearly fail the standards of normal science. Unfortunately, there is growing evidence of the difficulty of weaning manufacturers and consultants off pseudoscientific modeled claims, as seen for example in the recent Li et al study that models the cost-effectiveness of an NGS panel of 34 cancer-associated genes in metastatic melanoma and similar modeled studies in BRCA1 and BRCA2 testing for ovarian cancer and breast cancer [13] [14] [15].

Unless vendors are prepared to invest resources in establishing a viable evidence base that meets the standards of normal science, there must be concerns as to whether the vaunted claims and expectations for precision medicine and NGS will be realized. Establishing analytical and clinical validity is the easy part; establishing clinical utility is by orders of magnitude more difficult. Understandably, investors may be reluctant to underwrite a vendor's program of randomized and observational studies given the uncertainties not only in respect of comparative platform performance but the reluctance of health systems and professional groups to adopt a specific platform.

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