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Nullius in verba: Version 2.0 of the University of Minnesota, School of Social and Administrative Pharmacy Program, Proposed Guidelines for Formulary Evaluation

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Abstract

The principal objective in introducing Version 2 of the proposed Minnesota Guidelines for Formulary Evaluation is to recognize the challenges faced by formulary committees and other health care decision makers with the introduction of next generation sequencing (NGS) in therapy choice across a range of disease areas. The adoption of NGS promises to disrupt accepted standards in product development and formulary assessment. Although the standards expected in presenting, evaluating and replications clinical and cost-effective claims will still be central to the assessment process, the application of NGS platforms to link therapy choices to identified mutation clusters will require a robust evidence base. These Guidelines are intended to provide the framework for that evidence base by setting protocol driven standards for (i) choosing the appropriate NGS platform and (ii) evaluating NGS platforms in the identification of therapy pathways for target populations in disease states.

Key Words: Minnesota Guidelines, next generation sequencing, evaluation credibility, submission protocols

INTRODUCTION

The theme that links Version 1.0 and Version 2.0 of the Minnesota proposed *Guidelines for Formulary Evaluation* is the importance of establishing a robust, coherent and growing evidence base to support therapy decisions [1] [2]. This evidence base applies not only to claims for clinical efficacy and effectiveness but also for claims for cost-effectiveness and budget impact. If health technology assessments are to inform resource allocation in health care, then these assessments must be defensible. They must meet the standards of normal science. Claims must be credible, evaluable and replicable [3] [4]. Unfortunately, over the last 20 years the focus of health technology assessments (otherwise referred to by the unfortunate term pharmacoeconomics) have put credibility, evaluation and replication on one side in favor of the construction of what have been described as imaginary worlds [5]. These imaginary modeled claims are best exemplified in the reference case methodology set center stage by the National Institute for Health and Care Excellence in the UK [6]. By construction, reference case claims, notably in the case of chronic disease, ask manufacturers and their ready helpers in consulting to construct lifetime or long term cost-utility models where the acceptance or otherwise of a new therapy is judged by its ability, over 20 or 30 or even more years of the model treatment cohort to meet discounted cost-per-quality adjusted life year (QALY) willingness to pay thresholds. They were never intended to support claims evaluation or replication [7] [8].

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The willingness to suspend belief in the empirical assessment of comparative therapy claims, to opt for pseudoscience rather than science, intelligent design rather than natural selection, is not confined to the UK. Reference case model standards have been adopted in Ireland and New Zealand, proposed as the basis for health technology assessment in the European Union and underpin standards established by the Academy of Managed Care Pharmacy (AMCP) in the US and, on a more global stage, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [9] [10] [11] [12] [13] [14]. Although there is little if any interest in the US in modeled reference case claims utilizing QALY estimates, the Institute for Clinical and Economic Review (ICER) has developed an audience for such claims [15]. The fact that these fail to meet the standards of normal science appears to have been overlooked.

To add a further element to the support for non-evaluable claims, the editors of leading technology assessment journals, *Value in Health*, *Pharmacoeconomics* and the *Journal of Medical* economics have published, and continue to publish reference case models with claims expressed in non-evaluable cost-utility terms [16] [17] [18]. It is unclear whether these analyses resonate with health care decision makers to have even a minimal impact of formulary decisions.

Against this, admittedly depressing, background the Minnesota Guidelines have attempted to make the case for hypothesis testing in formulary assessments, arguing that long-term reference case models should be abandoned in favor of short term evaluations that are credible, evaluable and replicable. Claims that can be assessed and the results reported to formulary committees, treating physicians and patients. While this does not deny the contribution of retrospective assessment of drug impacts in target populations, the fact remains that unless claims for new

therapies and models of therapy choice are not put in evaluable and replicable terms, then we lack a robust basis for formulary and treatment decisions.

THE CHALLENGE OF NEXT GENERATION SEQUENCING

Version 1.0 of the Minnesota *Guidelines* was focused on the evidentiary standards required to support informed choice in the selection of single therapies. Following, the classical comparative randomized clinical trial (RCT) model, the standards proposed for claims credibility, evaluation and replication in formulary submissions were to provide feedback to formulary committees in a short-term timeframe following product launch. To accomplish this, the *Guidelines* proposed that formulary submissions be accompanied by a study protocol detailing how the claims for clinical outcomes, cost-effectiveness and budget impact, were to be evaluated. The *Guidelines* did not suggest that formulary listing be contingent upon feedback from the implementation of the study protocol, but that the claims should be considered provisional. Until an assessment of the claims was made, formulary positioning, pricing and the role of the products in treatment guidelines would be treated with caution. In part, this emphasis on evaluation and replication reflected long-term and growing concerns over the limited evidence base supporting all too many clinical claims with the difficulties independent assessors had in replicating claims.

The uptake of next generation sequencing (NGS) platforms, in linking mutation expression to therapy choices, promises to make the need for claims feedback even more pressing [19] [20]. Rather than single product claims, with a low response rate, NGS assessments propose to link sub-populations within the target population to single or combination therapies. The presumption being that targeting specific mutation or mutation clusters will improve overall response and possible reduce treatment costs. Hence the perceived need for *Guidelines* to set the evidence standards to support the application of specific NGS therapy choice claims to target populations within disease areas.

As described in the Background (Section 1) of Version 2.0 of the guidelines, the challenge of NGS lies: (i) in the standards required for an NGS platform and the choice between platforms; and (ii) the evaluation of platform-driven therapy choices. These are decisions a formulary committee will have to make, let alone acceptance by treating physicians and patients, and panels charged with treatment guideline recommendations. The decisions must be evidence-based and we do not have the luxury, if we ever did, of developing reference case models that generate non-evaluable claims.

STRUCTURE OF THE GUIDELINES

The Guidelines are in six sections. These are:

1. Background
2. Evaluating Formulary Submissions: Key Elements
3. Value and Cost Outcomes Claims
4. Product and Comparator Assessment Protocol
5. Next Generation Sequencing Platform Assessment Protocol
6. Requests for Submissions

Section 1: Background

The focus of this section is on the importance of presenting claims for competing therapy interventions that are credible, evaluable and replicable. This applies with equal force to single product claims, whether or not they have genetic targets or simply target populations defined by clinical characteristics, as well as to claims from NGS. In the latter case, the assessment of competing therapy claims involves a number of reference points: (i) the standard of care as defined by a treatment guideline or options within this general reference point; (ii) therapy claims for the individual therapy pathways defined by an NGS platform that links mutation clusters to drug combinations (or single therapies) where the reference point may be the therapy pathways generated by a competing NGS platform; and (iii) the overall therapy outcomes and costs for all therapies identified for the target population by the NGS platform.

Four types of formulary submission are identified: (i) standard submission for single drug products where the target population is defined in clinical or behavioral terms; (ii) single, molecule submissions where the drug target is the expression of a single molecule or gene mutation; (iii) NGS platform submissions where the formulary committee is judging the relative merits of competing platforms; and (iv) therapy target submissions where an NGS platform is supporting therapy choices matched to individual mutation clusters.

The background section also considers a number of other issues. Possibly the most important is the question of NGS uptake. There are substantial barriers to the willingness of formulary committees, physicians, patients and guideline panels to accept the 'promise' of NGS in therapy choice and the assumed benefits conferred on patients. If NGS is to be accepted, and that means going beyond getting a platform approved by the Centers for Medicare and Medicaid Services (CMS) or the Food and Drug Administration (FDA), then platform developers will have to invest in a research program to demonstrate that their platform yields clinically meaningful outcomes across a range of disease states and target populations. At the present, this is far from being achieved. After all, the evidence base for all too many pharmaceutical products is thin with substantive issues, as the *Guidelines* point out, concerning the failure to replicate phase 3 claims.

A further issue is the identification of the target population for drug product and NGS platform assessment. This is not simply an issue of a clinical or genomic profile by stage of disease, but a framework that identifies the major outcomes in the disease state (e.g., median survival in late stage cancer) and the direct medical costs of treatment. This should be identified in terms of treatment guidelines that map disease progression and indicate at which disease stage an NGS assessment would be appropriate.

In addition, an aspect of therapy intervention that is often overlooked is the presence of comorbidities. In older populations, where it is expected (or hoped) that NGS treatment choices may have a significant impact, patients will typically present with one or more comorbidities. A treatment intervention, therefore, needs to accommodate comorbidities and assess the extent to which the presence and treatment of comorbidities may qualify NGS claims.

NGS claims should also take account of the impact of therapy choices on side effects. In particular, toxicity of the proposed therapy and the experience (and management) of pain in late stage cancer.

Adherence to and persistence with therapies are also a key issue. These are seldom factored into modeled claims and are obscured by trial protocols. However, with the potential for toxicity and adverse side effects from NGS driven therapy, in particular combination therapy for complex mutation targets, the issue of early discontinuation should be addressed.

Section 1 also points to the need for a robust evidence base; an evidence base that meets recognized standards for: (i) diagnostic accuracy and quality; (ii) systematic reviews; (iii) reporting randomized trials (e.g., multiple platform basket trials); (iv) application of evidence hierarchy criteria; and (v) standards for evidence to support treatment guideline recommendations (e.g., National Cancer Comprehensive Network).

Section 2: Evaluating Formulary Submissions: Key Elements
The next section of the *Guidelines* considers key elements in evaluating formulary submissions for both single products and NGS platforms. These are:

- Product and comparator descriptions and pricing for individual drugs and NGS platforms
- Descriptions of target populations and sub-populations
- Evidence for significant adverse events and contraindications
- Primary and secondary outcomes
- Evidence from direct and indirect comparisons
- Replication of product claims and NGS platform curating
- Adherence and persistence
- Evidence summaries for drug product comparisons and for competing NGS platforms

Section 3: Value and Cost-Outcomes Claims
Claims for drug product or NGS platforms should meet the evidence standards for credibility, evaluation and replication. At the same time, all claims evaluations should provide feedback to decision makers in a meaningful time horizon. In practice, this means less than two years. The claims for individual therapy pathways should be presented and evaluated to the same standards for individual drug product claims against comparator therapies. The only difference is that those marketing an NGS platform should report on both the clinical and cost-effectiveness claims for each pathway as well as for the therapy pathways overall. As detailed in sections 4 and 5, a claims evaluation protocol is a required component of these assessments.

There is no fixed format for the framework submitted for claims assessment. Claims can be based on the results of RCTs with a model driven by the RCT protocol or as short term models. Markov processes are not excluded or even discrete event simulation. The objective after all is not to justify a model structure but to present a coherent basis for establishing claims which can be evaluated, reported on and replicated.

It is at the discretion of those making the submission as to the choice of outcomes. Clearly, there are outcomes common to many disease states which may be considered 'standard'. Even so, other outcomes may be considered relevant such as patient satisfaction and quality of life. Where patient reported outcomes are proposed as part of the assessment protocol detail should also be provided on how they are to be assessed. There are, for example, a range of QALY measures none of which are typically collected as part of electronic records. If a prospective observational tracking is proposed for an NGE platform, then it needs to be demonstrated how these various measures are to be reported.

The standards also ask for adherence and persistence to be modeled explicitly. This reflects the evidence across many disease states than within as short a period as two years, the majority of patients are either non-adherent to therapy or have discontinued therapy [21]. Where an NGS platform is driving therapy choice, adherence and persistence should be tracked for each arm over the study period.

Section 4: Product Claims Assessment Protocol
A submission should be considered incomplete if it is not accompanied by a claims assessment protocol. The protocol standards for claims assessment for both individual drug products and NGS platforms for target populations in disease area follow from the PROST protocol presented in Version 1.0 of the *Guidelines* [22]. A format for protocol assessment is provided which has been amended from the previous recommended protocol to include NGS platform application and NGS platform choice. This is followed by a series of questions a formulary committee should ask to ensure the submission meets the required standards. These questions are:

- Has the submission detailed the study objectives?
- Has the submission provided a context for the protocol claims assessment?
- Has the submission identified a target population rationale and description?
- Have the proposed claims been detailed?
- Has the submission defended the choice of study design?
- Has the submission detailed how the study is to be implemented and feedback provided?

Section 5: Next Generation Sequencing Platform Assessment Protocol
This section focus on the standards to be applied by formulary committees in the choice of NGS platform. Given the number of platforms likely to appear in the next few years, it would be foolhardy to assume that all platforms are similar in their identification of mutations and proposed matching to therapy choices. Formulary committees need to be assured that the platform is effectively curated and the library maintained. There is also, of course, the possibility that NGS platforms may be disease specific. The standards for claims evaluation and replication apply equally to comparative assessments of NGS platforms as they do to evaluating the impact of drug and therapy options for target populations.

A submission structure for comparative NGS platform assessment is provided together with questions a formulary committee might consider to assess the content and quality of the submission protocol. The questions are similar to those detailed in Section 4.0:

- Has the comparative assessment detailed the study objectives (e.g., performance standards for NGS platforms)?
- Has the submission indicated why an assessment is necessary?
- Has the submission justified and identified a target population for the comparative assessment?
- Have the claims for comparative assessments been detailed?
- Has a study design and rationale been provided?
- How is the study to be implemented and the results reported?

Section 6: Request for Submissions
The final section merely emphasizes that unsolicited submissions are not allowed. Submissions should be by request whether for a drug therapy or NGS driven therapy, or for a comparative NGS platform assessment.

IMPLEMENTING NEW GENERATION SEQUENCING
It is made explicit in the *Guidelines* that advocates of NGS are going to face two hurdles before health systems will be willing to introduce NGS even on a limited scale for specific target populations. The first of these is the need for a robust evidence base. So far this does not exist. Essentially, all we have are phase 2/3 RCT claims and some observational data on single gene targeted therapy. This is a far cry from NGS and represents more an unwillingness to reject the classic phase 3 RCT design than a recognition that if therapy interventions are to be accepted they must address the range of mutation heterogeneities in, for example, late stage hard tumor interventions. Second, NGS developers need to invest in a research program that evaluates their platform against competing platforms in therapy choice in a range of target populations. Given the complexity of mutation loads and the presence of multiple mutations for individual patients with a similar hard tumor diagnosis, formulary committees would be unwise to assume that robust evidence for a platform and the matched mutations to therapy choices in one disease area would necessarily translate to a similar robust outcome in other disease states.

The protocols proposed in the *Guidelines* will go some way to meeting these evidence requirements. This does not mean that a demonstration can wait until a platform has been approved for a target population. The presumption is that the manufacturers of the various platforms will have already invested in phase 3 or equivalent basket trials to support their claims.

The need to develop a robust evidence base also puts pressure on drug manufacturers to develop the appropriate trial frameworks to support the place of a new compound in therapy. With the distribution of mutations driving therapy choice it may well be that a new compound, given choice of NGS platform, will be not only targeted to specific mutations but may also have to be part of a combination therapy

package for that sub-population of patients in the target group.

Even so, the onus is still on the commitment by NGS manufacturers and, to a lesser extent, pharmaceutical manufacturers and biotechnology companies to commit to an investment in robust basket trials and observational studies. Unless a high quality evidence base is available, health guideline panels are unlikely to agree on the place of NGS in therapy. Whether NGS manufacturers will commit to this is a moot point. The business model may not have captured this aspect of an evidence base. The manufacturers may have thought solely in terms of putting a platform on the market. If so, it is unlikely to become a commercial success.

CONCLUSIONS

At this juncture it is unclear as to how widely and how quickly NGS will be taken up. In the absence of a robust evidence base, as detailed in these *Guidelines*, for the clinical and cost-effective contribution of NGS the take-up is likely to be slow. The most promising avenue is probably through a focus of NGS in late stage cancers where there are few options and the patient has poor survival and quality of life prognoses.

The formulary submission standards proposed here are designed to set the parameters for the development of an evidence base. This is the critical next step. The evidence base for specific platforms needs (i) to differentiate that platform from competitors as being 'first to market' is no guarantee that the drug or NGS platform will be commercially successful, and (ii) to demonstrate that there is value in integrating an NGS assessment and linked therapy options within specific target populations.

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