Unless a coherent and believable evidence base is established it is doubtful that the promise of precision medicine utilizing next generation sequencing (NGS) will be achieved. In common with all too many pharmaceutical products and devices, the initiators and early developers of genomic assay platforms, in particular NGS platforms, have focused on the clinical and scientific performance of assays with investors led to believe that the scientific merits of an assay will lead automatically to reimbursement, formulary acceptance and uptake by treating physicians. The truth will more likely be that NGS platforms will need to compete and the majority of these will fail to attract the support of health system decision makers. A situation that is no different from that obtaining in drug and device development. The purpose of this commentary is to point to the need for a robust and believable evidence base to support the clinical outcome and cost-effectiveness claims made for the various assays presently competing (and expected to compete) in the market place. Claims made for assays must be credible, evaluable and replicable in their target patient populations. Three issues are addressed: (i) the standards required of an evidence base; (ii) the standards that formulary committee should apply in evaluating competing NGS platforms; and (iii) the standards that a formulary committee should apply in determining whether or not a new drug or drug combination targeted at identified mutations is both clinically beneficial and cost effective within the treatment pathway for the target patient population. These issues are addressed in the context of the recently released Minnesota Guidelines for formulary evaluation which highlight the barriers to NGS platform acceptance and the standards a health system should consider in their assessment.
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. 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. These standards apply equally to the introduction and application of NGS platforms that are proposed to link clinical mutations, or clusters of mutations identified as inputs to, for example, predictive simulation models. This will match products to therapy pathways in treating populations and set a standard for integrating new drug products with such therapy choices.

Unfortunately, over the last 20 years the focus of health technology assessments has put credibility, evaluation and replication on one side in favor of the construction of what have been described as imaginary worlds. 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. By construction, reference case claims, notably in the case of chronic disease, ask manufacturers to construct lifetime or long term cost-utility models where the acceptance or otherwise of a new therapy is judged by its ability to meet discounted cost-per-quality adjusted life year (QALY) willingness to pay thresholds. They were never intended to support claims evaluation or replication.

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 must be rejected also in the evaluation of NGS platforms. While this does not put models to one side, the key point is that the models must generate evaluable claims that can be reported back to formulary committees, treating physicians, patients and treatment guideline development panels. Relying on modeled unevaluable claims to guide therapy choices in precision medicine is simply a contradiction in terms.

Required evidence standards

While it is clearly at the discretion of health care decision makers whether to accept claims for an NGS platform based on its analytical and clinical validity without further evidence to support its clinical utility in matching mutation clusters to viable therapy options in target patient populations, the argument here is that a broader and more credible evidence base is required. Indeed, even if the application of a NGS platform can be shown to be beneficial in one target population in a disease state (e.g., late stage metastasized melanoma) it does not follow that the similar performance standards will be found in other target populations. For an evidence base to be accepted, NGS platforms would be expected to demonstrate their benefits across a range of target populations across disease areas. Evidence presented should be specific to the various target populations, with the NGS platform ‘indicated’ for the respective disease states and stage of disease.

If, as anticipated, the therapy options matched by the NGS platform involve compounds that are ‘off-label’ for the target group, even if used in combination with the indicated standard of care approved by the Food and Drug Administration (FDA), then the need for feedback is all the more important. It might not be unreasonable to think of formulary committees imposing risk management strategies to ensure that claims made are tracked for individual patients and reported in real time to an NGS platform oversight group. This points, as will be detailed later, on the need for a protocol to be submitted as part of an NGS platform submission.

The evidence base to support NGS platform claims need not require the reporting of randomized clinical trials (RCTs) for the intended application for a random selection of patients in the target patient group (e.g., patients diagnosed with stage 4 malignant melanoma). Undertaking the number of basket trial models needed to support an evidence base would be not only expensive but would delay significantly the adoption of NGS platforms. Rather, a range of evidence could be considered to establish modeled claims for a platform and set the parameters for a subsequent observational tracking study in the individual health system. These inputs could be from observational and protocol driven submission support studies, phase 3 basket trials as well as smaller scale phase 2 studies and individual in vivo validation results. Of course, once a number of observational studies were reported, the NGS platform submission could piggy-back on these. Hence the need for early feedback on NGS platform claims evaluation.

If we consider the potential focus of NGS platforms initially on therapy options in late stage cancer, particularly metastatic stages, then the claims for outcomes, whether modeled or based on prior observational studies, would include clinical markers such as response, relapse, median survival and discontinuation, as well as toxicity, pain and side effects. It would be expected that the claims would match those considered ‘standard’ in that ‘end-stage’ cancer, but would certainly have to encompass resource utilization (e.g., physician visits, emergency room visits), repeated assays and patient reported outcomes.
At this stage it is doubtful if the ‘big data’ trough will provide an acceptable source for monitoring the impact of NGS platforms in claims assessment. It is not just a question of genomic markers but on identifying mutations and matching those mutations to therapy choices. Certainly, an integrated health system could establish the required data elements, but we are probably a long way from being able to assess comprehensively the impact of therapy choice. The challenge for those advocating the application of NGS platforms is the range of mutation clusters that are required to be matched to therapy options. Tumor heterogeneity (and the evolution of tumors over time) would point to a potentially large number of therapy choices and combinations, and the exclusion of patients from expected non-viable choices. Claims would have to be specific to each therapy option treatment arm with, overall, an aggregate assessment of the benefits from the choice of NGS platform in the target population.

Choosing an NGS platform

All NGS platforms will not be created equal. Some will perform ‘better’ than others (although minimum performance standards for matching mutations to therapies have not been proposed); some will be better curated and updated. Choice of a platform is not only critical for health care delivery but is also critical if treatment guidelines are to endorse specific platforms to drive therapy choices in late stage disease. NGS platforms will also act as risk assessment vehicles for early stage disease or for family members ‘at risk’ with subsequent impacts on therapy pathways and monitoring of family members.

The Minnesota Guidelines propose that when considering whether or not to adopt an NGS platform for target patient groups that any submission must justify acceptance of an assay in comparative terms. An NGS platform assessment protocol is presented that sets the parameters for an evidence base. The focus of the comparative assessment is on (i) the type and distribution of mutations identified for a specific tumor type and (ii) the drugs or combination therapies that are matched to these mutations. The submission should include:

- A description of the proposed NGS platform and comparator platforms.
- The approval status of the NGS platforms.
- Credible, evaluable and replicable comparative performance metrics.
- Criteria proposed for a comparative assessment.
- Comparative mutation distributions.
- Comparative recommended therapy pathways.
- Comparative evidence for the clinical and cost-effectiveness of the comparative therapy pathways.
- Conclusions regarding comparative value.

Product claims assessment protocol

As well as providing a protocol for evaluating competing NGS platforms, the Guidelines also provide a protocol for evaluating competing product claims. These are considered from two perspectives: (i) as a stand-alone product directed at a target population as a potential substitute for the current standard of care and (ii) a product which is targeted to a population where the standard is for product choice to be driven by NGS. The former case may be characterized as the ‘classical’ cost-effectiveness assessment that has dominated the health technology assessment literature over the past 25 years and, as far as genomics is concerned, is also seen in the one gene + one product approach to target interventions. The latter case is likely to become more common with the adoption of NGS platforms where, rather than targeting a single gene, the assay yields a distribution of mutations and targets therapies to patients with a particular mutation profile.

The primary role of an NGS...
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Conclusions

The adoption of NGS into drug evaluations and therapy choice for targeted populations and mutation driven sub-populations promise a disruption in traditional models of drug development and commercialization. An impact that may reasonably be seen as one described by economists as a process of Schumpeterian creative destruction. A disruption of the process of drug development and the evidentiary hurdles a drug manufacturer would be expected to face in integrating the product into a ‘matrix’ of NGS driven targeted therapies, securing formulary approval and a possible premium price for new products. Similar hurdles are likely to be faced by NGS platform developers if health care systems insist on a robust and credible evidence base to support comparative product claims for

NGS platform approval in target populations. In both cases, the landscape is likely to change quickly as the NGS platforms evolve to capture more evidence for mutation-targeted therapy and, from the patient perspective, the targets changing as tumors evolve.

References


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