11-23-2016

Creative Destruction: Next Generation Sequencing in Drug Development, Formulary Evaluations and Pricing

Paul C. Langley

University of Minnesota, langley@maimonresearch.com

Creative Destruction: Next Generation Sequencing in Drug Development, Formulary Evaluations and Pricing

Paul C Langley, PhD
College of Pharmacy, University of Minnesota, Minneapolis, MN

ABSTRACT

Next generation sequencing (NGS) has the potential to disrupt not only the accepted process of drug development but also the hurdles a drug manufacturer would be expected to face in securing formulary approval and a possible premium price for the new compound. The purpose of this commentary is to consider the role of NGS in this process, one which is characterized as a process of creative destruction, where adoption of NGS in personalized medicine sets in train a mechanism of incessant product and process review. A mechanism driven by continuing modifications and extensions to NGS platforms as our understanding of the role of mutations and mutation load in therapy choice expands. At the same time this mechanism has significant implications for the continued revision of treatment guidelines and their adoption of NGS as integral parts of the treatment pathway. There are, however, a number of unresolved issues which have to be addressed. These include the choice of NGS platform, barriers to integrating evidence to support NGS-based therapy choices in treatment guidelines, the implications of NGS for drug development and the modification or rejection of current trial structures, the integration of comorbid disease states and the standards that formulary committees should adopt to evaluate NGS claims. The overarching theme, however, is the need to invest in a robust and credible evidence base. While we are a long way from achieving this, the focus must be on putting claims for therapy choice forward that are credible, evaluable and replicable.

Keywords: NGS, creative destruction, therapy pathways, credibility, evaluation, replication

INTRODUCTION

Next generation sequencing (NGS) has the potential to disrupt not only the accepted process of drug development but also the hurdles a drug manufacturer would be expected to face in securing formulary approval and a possible premium price for a new compound. NGS is not simply 'one new test'. The implications of the adoption of NGS testing go much further. NGS testing may be usefully considered as one supporting Schumpterian 'creative destruction' in the development and adoption of new therapies [1]. Adoption of NGS in personalized medicine sets in train a mechanism of incessant product and process review. A mechanism driven by continuing modifications and extensions to NGS platforms as our understanding of the role of mutations and mutation load in therapy choice expands.

The purpose of this commentary is to consider: (i) the role and choice of NGS platform; (ii) possible barriers to integrating evidence to support NGS-based therapy choices in treatment guidelines; (iii) the implications of NGS for drug development; (iv) the modification or rejection of current trial structures; (iv) the integration of comorbid disease states; and (v) the standards that formulary committees should adopt to evaluate NGS claims. The overarching theme, is the importance of developing a believable evidence base to support NGS-sourced claims for therapy interventions.

Unfortunately, all NGS platforms are not created equal. The various platforms have the potential not only to yield different profiles of mutation clusters and mutation load within disease states but also to overlook mutations due to restrictions on the genes that are captured as inputs.

A recent draft guidance issued by the Food and Drug Administration (FDA) argues for public access to a database of human genetic variants 'that aggregates and curates reports of human phenotype-genotype relationships to a disease or condition' both with documentation to support linkages and assertions regarding specific genotype-phenotype correlations [2]. Access to a genetic variant data base could support claims for the clinical validity of an NGS test (and support comparative test assessments) and alleviate concerns for the test's safety and validity.

The principal concern of the FDA is with valid scientific evidence. However, it is not clear from the draft guidance whether the FDA sees its remit as limited to the evaluation of clinical validity or whether the concern for the clinical outcomes from the application of the NGS links to therapies in target populations is the ultimate target. This would raise the evidence bar significantly higher and, given the elapsed time to undertake trial-based clinical assessments (or even protocol driven observational studies) would put a brake on

Corresponding author: Paul C Langley, PhD
Adjunct Professor, College of Pharmacy
University of Minnesota
Email: langley@maimonresearch.com
Web: www.maimonresearch.net

the adoption of NGS-based precision medicine interventions. A further question, inevitably, is whether access to such a database (or databases) would eliminate the incentive for the commercial development of NGS platforms?

CHOICE OF NGS PLATFORM
NGS platform tests vary in their scope in the number of genes that are reviewed. As the number of mutations, their clusters and overall mutation load will be a function of the test platform, apart from the tests analytical and clinical validity, care has to be taken by manufacturers, formulary committees and treatment guideline panels in selecting the test that is adopted as their 'gold standard'. In a recent commentary the issue of test standards and the criteria that should be applied in both choosing a test and assessing the merits of competing tests was examined [3]. The commentary pointed to the absence of NGS test standards other than those in place for analytical and clinical validity by the Centers for Medicare and Medicaid Services (CMS) and the Food and Drug Administration (FDA). As noted above, there is uncertainty as to how the FDA might evaluate and approve NGS tests if, as expected, they are considered class 3 medical devices.

In any event, the issue facing manufacturers, formulary committees and guideline developers such as the National Cancer Center Network (NCCN) in the absence of recommendations for platform NGS tests is the choice of a test to link mutation profiles to therapy options. Competing tests may, if there is no public access variant database, yield different frequencies of mutations and estimates of mutation load in the same target tumors. This places an additional burden on health system decision makers and those reviewing and updating treatment guidelines if, as expected, there is a push towards integration of NGS within treatment guidelines. If the FDA brings in standards, then guidelines may refer simply to any FDA approved platform. One implication is that if a manufacturer presents a case for a therapy linked to specific mutations in a target population based on a basket trial design covering multiple therapy options, then the NGS test supporting the basket trial should be a test that is endorsed by the formulary committee. If the preferred formulary test generates a distribution of mutation clusters at variance from those generated by the basket trial, then there is no basis for accepting trial based claims. This becomes more worrisome if, in presenting a modeled case for an intervention, the model brings together data elements to populate a trial pathway structure that rest upon disparate trials that rely on a range of competing NGS platforms.

In the last resort, of course, if guidelines are in place that require claims to be evaluated and replicated in a target population, then the issue is resolved if the formulary committee insist on a specific NGS platform to support all randomized clinical trial (RCT) and observational study protocols. To date, however, only one US proposed guideline, developed at the University of Minnesota, has recommended that any submission for formulary approval and pricing for a therapy should be supported by a claims assessment protocol [4]. Such a protocol, where NGS-based therapy claims are the focus of an assessment would be funded by the manufacturer hoping to bring a new compound into therapy, as a substitute for or a complement to existing compounds. Given the sheer complexity of attempting to model NGS driven interventions in late stage cancer, to give the most obvious area for NGS interventions, a premium must be placed on the need to establish a coherent and believable evidence base. One avenue would be to endorse standards for the modeling of NGS interventions, with the focus not only on developing credible, evaluable and replicable claims but ensuring documented feedback to decision makers. Submission protocols for claims assessment would be an integral part of this process.

TREATMENT GUIDELINES
At the present time, treatment guidelines are silent on references to NGS assessments by disease stage. The melanoma guidelines, for example, recommend 'mutational analysis' as a workup at stage III of disease progression for patients being considered for either routine treatment or for clinical trials while at the metastatic stage IV it is recommended if a patient is being considered for targeted therapy or if required for eligibility in a clinical trial [5]. There is no explicit recommendation for NGS or how to interpret the results of an assessment for therapy choice.

If treatment guidelines are to inform clinical decisions, far more needs to be done to make explicit the contribution and application of NGS platforms to guide therapy choice for individual patients. Far more also needs to be done to provide a robust evidence base. A feature of many treatment guidelines, and melanoma is no exception, is the relative paucity of evidence to support pharmacological treatment decisions, in particular in late stage disease. In the melanoma guidelines, for example, evidence to support pharmacological interventions in late stage III and IV disease is typically classified as low level 2B: without uniform consensus of the assessment panel (below the NCCN default consensus category, still low level, of 2A). In advanced Stage IV metastatic therapy options are limited (i) to systemic non-molecular targeted therapy with nivolumab, pembrolixumab or ipilumab, (ii) single mutation targeted monotherapy with vemurafenib or imtinib for patients with BRAF mutant tumors and BRAF wild type tumors; (iii) combination targeted BRAF/MEK inhibitors with trametinib or cobimetinib (respectively targeting MEK1 and MEK2 signaling molecules or (iv) imatinib for c-KIT mutations. In all cases the response was considered acceptable, ranging as high as 60% for nivolumab, with others in the range 20% to 40%. The

drawbacks are that only half of patients with cutaneous metastatic melanoma harbor a BRAF mutation and of these some 50% relapse within six months. While the combination BRAF/MEK therapy improved response, time to relapse was little different from BRAF monotherapy. To illustrate the limitations of non-targeted monotherapy, the NCCN guidelines note that trials for unselected patients with imatinib failed to yield a therapeutic response.

The implications of experience with targeted monotherapy in metastatic melanoma should come as no surprise. While evidence for overall survival is lacking, the favorable response rates have to be set alongside a median time to relapse of six months. At the same time, little attention is given to the role of toxicity and adverse events in discontinuation. The promise of NGS platforms is that linked to therapy options they may not only provide recommendations for therapy links to mutation clusters, but there may be a choice between therapy options that are projected to yield a more benign side effect profile.

DRUG DEVELOPMENT

From the perspective of drug development, the adoption of NGS by formulary committees and health care systems raises three concerns:

  (i)   that the target population is essentially a 'niche' population which, unless a premium price can be guaranteed argues against drug development;

  (ii) that by the time the product, with an expectation of a premium price, reaches the formulary submission and price negotiation stage, the application of NGS by the health system may have identified low cost compounds to support interventions in particular therapy pathways which further limit the market (and may even replace the new entrant), weakening the bargaining position for a premium price; and

  (iii) that modeled cost-outcomes claims will have to be not only credible, evaluable and replicable but presented in a framework that recognizes the frequency of mutation clusters, mutation load and the multiplicity of treatment pathways linked to specific mutation clusters.

The standard model of drug development from preclinical to a possible post-market entry phase is well established. With a growing appreciation of the power of NGS testing and the hypotheses formulated by the matching of single or multiple drug combination to a particular class or group of mutations, this process is expected to be modified substantially. NGS can be applied at any stage of drug development as well as supporting phase 4 effectiveness studies that may be required by formulary committees to establish the credibility, evaluation and replication of NGS-modulated drug assessments in target populations.

The role of NGS testing in drug development is essential if we are potentially to avoid the 'wastage' associated with the standard model (historically non-genomic for the large part) of drug development. This applies equally to the more recent attention given to evaluating drugs in terms of a single molecular marker. As noted above, combining targeted therapy with immunotherapy in BRAF-mutant melanoma may enhance the relatively high initial response rates as well as enhancing survival by substantially increasing median time to relapse [6]. NGS offers the possibility of a full genomic screen with the identification and the matching of multiple mutation combinations, mutation load, to corresponding monotherapy, or more likely, combination therapy treatment pathways. Again, in the case of melanoma, an NGS screen of hotspot regions in 46 genes not only identified mutations in 43 of those genes but one-third of the melanomas had > 1 mutation detected, with the number and type of mutations per tumor linked to melanoma subtype [7] A new compound, therefore, has to face comparison against, not just a notional standard of care (or even placebo) but has to be assessed in the context of multiple treatment pathways by stage of disease in tumor types. It also has to take account of changing tumor expression and the possibility that a pathway may become redundant as the tumor evolves. It must also recognize that there may be no evidence to match mutations to therapy options and patients may have to be assigned to palliative care. Indeed, the contribution of a new compound maybe more of a transitory phenomenon as further NGS profiling maps changing mutation expression and suggests modification or abandonment of prior recommended pathways, bring in a range of existing and new compounds. Manufacturers may have to face the reality that investment in a new compound, or the acquisition of a new compound at late development, may simply be bringing to market a compound that is put alongside hundreds of others in the library of compounds for matching to mutation profiles.

Even at phase 1 of clinical development, the dose ranging evaluation will have to be in terms of the genetically defined target population within a stage of disease specific tumor type. If done properly, the NGS assessment in a notional target population (defined by stage of disease and response to previous therapies) will yield a distribution of mutation clusters and estimates of mutation load which can be linked to clinical outcomes [8][9]. This can be extensive and may involve dozens of clusters. Each cluster will define a target population with the recommended matched therapy involving either a single compound (the one being developed) or a combination of therapies that include the new compound. This is the context for future drug development or, more likely perhaps, a decision to abandon development. Put simply, the target mutation cluster 'niche' may simple be

too 'small' to justify drug development and the possible obstacles to achieving a premium or rent-seeking price.

At the same time, care has to be taken in establishing the assessment framework. With multiple mutation clusters and complementary treatment pathways, there is the possibility that the performance of drugs in a given pathway will be impacted by the choice of competing pathways with the possibility of drug-drug interactions modifying the pathways defined within the assessment platform. Single molecule claims may, therefore, be misleading as a basis for choosing therapy options. At least, looking ahead to the standards a formulary committee is likely to set for claims assessment, failure to consider possible interactions, in clinical designs at phases 1, 2 and 3 of drug development, may qualify outcomes claims. Once again, the question is one of establishing a robust and coherent evidence base. Integrating NGS sequencing in drug development is only the first step. Manufacturers have to convince reimbursers that their product adds value in its contribution to therapy specific pathways.

COMORBIDITIES
Older patients who are seen as a major target group for NGS sequencing in late stage cancers will also present with a number of comorbidities. The question then becomes one of whether or not the patient will potentially benefit from an NGS evaluation that also captures the mutations present in the comorbid disease states? In diabetes, for example, which is one of the more common comorbidities in older populations, a patient may also be receiving tailored therapy based on NGS profiles [10]. This could also be directed towards issues such as the presence of pain as a side effect of choices in specific therapy pathways. NGS profiling could be an important adjunct in the management of pain both as a side effect and as a disease in its own right.[11] A patient may have tailored NGS-based therapies for a number of comorbid disease states, with little guidance from the NGS profile for possible drug-to-drug interactions or more complex interactions at the molecular level.

While it might be argued that neglect of complementary treatment pathways is no different from comorbidity exclusion criteria in classical trial design, the case of tumor suppression is more complex. The presence of comorbidities not only makes the personalized medicine package more complex at the patient level (with implications for possibly closer monitoring of patients) but also raises questions as to the appropriate design of basket trials. The options open and the potential costs of targeting multiple pathways within trial design may also lead to greater emphasis on post-marketing approval observational studies to re-assess trial-based and modeled claims.

FORMULARY COMMITTEE REQUIREMENTS
Standards in place for formulary submissions by groups in the US such as the Academy of Managed Care Pharmacy (AMCP) and the Institute for Clinical Effectiveness Research (ICER) are not designed to accommodate NGS-driven clinical and cost-outcomes claims [12] [13]. Neither the AMCP guideline focus nor the ICER attempt to replicate the NICE reference case meet the standards that modeled claims should be credible, evaluable and replicable (e.g., lifetime cost-per-quality adjusted life year [QALY] claims). To date, no attention has been given to the standards for basket trial designs and the modeling of specific claims based on an NGS platform. From the perspective of a formulary committee, there is no appreciation of the challenge posed by the need to evaluate claims for a new compound in the context of an NGS-driven mutation profile linked to multiple intervention pathways.

As an example of this single-molecule modeling that puts to one side the contribution of NGS to therapy choice and the positioning of new compounds in a basket-trial approach to drug development and claims, consider the ICER report on treatment options for non-small cell lung cancer (NSCLC) [14]. The primary aim of the analysis was to estimate the cost-effectiveness of treating NSCLC patients with first-line tyrosine kinase inhibitors (TKIs) versus a chemotherapy doublet (cisplatin+pemetrexed) for epidermal growth factor receptor (EGFR) patients, and second-line treatment with programmed death 1 receptor (PD-1) immunotherapy versus docetaxel among patients who have progressed on a first-line chemotherapy doublet. Comparative clinical effectiveness was based on evidence from not the EGFR mutation but on EGFR patients without any driver mutation. Evidence for PD-1 immunotherapy as first or second line treatment was also limited. The systematic reviews of available evidence were unable to distinguish between the TKIs in overall survival and quality of life, although all three TKI compounds (afatinib, erlitinib and gefitinib) were superior to chemotherapy. Similarly, with PD-1, different assays and cut off points to measure programmed death ligand 1, the evidence was inadequate to compare PD-1 therapies for any outcome.

Nevertheless, building on this limited evidence base, ICER proceeded to undertake a comparative value analysis focusing on costs, outcomes and cost-effectiveness. Evidence for comparative cost-effectiveness was constructed in the framework of a partition survival model for two FDA-labeled indications: (i) first line TKI treatment strategies; and (ii) second-line PD-1 treatment strategies. Three health states were assumed for the model: (i) progression free; (ii) progression; and (ii) death. Mean time spent in each state, quality adjusted time, and direct medical costs were estimated and summed to provide estimates of life expectancy, quality adjusted life expectancy, and total costs. A cycle length of one week was applied to reflect the dosing

schedules for drug regimens. The model took a lifetime horizon, modeling patients from treatment initiation until death.

Outcomes from the model were: (i) quality adjusted life years (discounted); (ii) life years (discounted); (ii) mean time in the progression-free and post-progression health states (discounted); (iii) pre-progression, post-progression, and total costs (discounted); and (iv) Incremental cost-effectiveness ratios for each intervention versus the standard comparator (cisplatin+pemetrexed or docetaxel), in pair wise comparisons. None of these outcomes were presented in an evaluable form. Nor was any protocol suggested to assess the various claims although the survival times were relatively short (under 30 months). As noted in previous commentaries, non-evaluable modeled claims do not meet the standards of normal science and should be rejected. Indeed, in the absence of a prospective study which stipulates the collection of quality of life data (from, presumably, a 'gold-standard' generic measure) claims for cost-per-QALY (even if non-discounted) are impossible to verify. This is unfortunate as projected (non-evaluable) cost-per-QALY claims are central to ICER pronouncements on whether WAC pricing is 'cost-effective'.

The absence of NGS-driven basket trials for the various compounds in an attempt to link the various compounds to therapy pathways is a major, if not a fatal flaw, in attempting to make a case to a formulary committee. Much of the blame must attach to the manufacturers choice of trial design and the limited evidence base available for any comprehensive comparative analysis. For a formulary committee that adopts an NGS-driven assessment program the claims presented by ICER are of little interest. Although the ICER recommendations for value-based price benchmarks, with their recommendations for wholesale acquisition cost (WAC) discounts to achieve the notional $100,000 per QALY gained threshold have, no doubt, attracted the ire of the respective manufacturers, the more substantive criticism is that in the context of treatment guidelines driven by NGS, such a partial exercise is really a waste of time.

The ICER approach faces two major objections: (i) the model framework does not meet the standards of normal science in generating credible, evaluable and replicable hypotheses and (ii) the modeling framework is focused on a single molecule. In the context of a commitment by a health system to NGS as the basis for the choice comparative assessments of therapy options targeted to the distribution of mutations and mutation load, the single molecule approach is not only redundant but potentially misleading for formulary acceptance, therapy pathway choice and pricing.

Formulary committees are unlikely to find single pathway models linking a specific mutation to the manufacturer's target therapy convincing. If a modeled case is made for the therapy, then the manufacturer will, by analogy to the inclusion and exclusion criteria of the classical phase 3 trials, have to justify which of the potentially large number of treatment pathways have been selected for inclusion or exclusion. This may be a hazardous exercise given the potential for interactions between the therapy choices defining individual pathways. One possible criterion would be the most frequently expressed mutation complexes so the model may focus on integrating the new compound in a model structure that traces out five or six therapy paths. These paths would have common endpoints of, say, median survival or median time to relapse in a late stage metastatic intervention, together with possible metrics of satisfaction, pain and quality of life. A clinical and cost-effectiveness model might then be constructed to generate credible claims. The model would be designed to generate claims for each pathway as well as across all pathways for the sub-targeted population that the mutation choice represents.

CONCLUSIONS
The adoption of NGS to drive treatment guidelines and formulary decisions implies a need for a major rethink of the process of drug discovery and the evidence base for therapy clams. Moving away from a 'one size fits all' paradigm in drug development where the target populations are defined by clinical characteristics rather than genomic profiling is likely to disrupt the traditional process of drug discovery. Rather than being satisfied with a relatively low response rate, high rates of relapse and limited survival prospects, NGS assessments promise through personalized medicine a more clinically rigorous and targeted approach to therapy choice. At the same time, single molecule targeting of therapies is also likely to be rejected.

This process of restructuring in drug discovery and treatment choice, Schumpterian 'creative destruction' or 'industrial mutation', holds the promise of greater productivity in drug discovery and treatment. As our understanding of the molecular basis of disease improves, NGS platforms will evolve. This mechanism of incessant product and process innovation will not only face manufacturers with the challenge of justifying investments in new compounds but will also, hopefully, encourage practitioners in health technology assessment to abandon their commitment to modeling non-evaluable artificial cost and outcomes scenarios; an appreciation of the standards of normal science through fashioning claims that are credible, evaluable and replicable. It is only in this context that the benefits of NGS can be realized.

REFERENCES

[1] Schumpeter JA. Capitalism, Socialism and Democracy (3rd Ed.). New York: Harper & Row, 1950

[2] Food and Drug Administration. Use of public human genetic variant databases to support clinical validity for next generation sequencing (NGS) - based in vitro diagnostics. Draft guidance for stakeholders and Food and Drug Administration Staff. Draft Guidance. July 8, 2016.
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509837.pdf

[3] Langley PC. Next generation sequencing claims in precision medicine.: Questions a formulary committee should ask. *Innov Pharm*. 2016; 7(4): No. 11

[4] Langley PC. Nullius in verba.: the University of Minnesota Social and Administrative Pharmacy Program Proposed Guidelines for Formulary Evaluations. *Innov Pharm*. 2016;7(2): No. 10

[5] National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Melanoma (version 3.2016).
www.NCCN.org

[6] Hu-Lieskovan S, Robert L, Moreno BH et al. Combining targeted therapy with immunotherapy in BRAF-mutant nelanoma: Promise with challenges. *J Clin Oncol*. 2014;32(21):2248-2254

[7] Siroy AE, Boland GM, Milton DR et al. Beyond BRAF^{V600}: Clinical mutation panel testing by next-generation sequencing in advanced melanoma*. J Invest Dermatol*. 2015;135(2):508-15

[8] Roszik J, Haydu LL, Hess KR et al. Novel algorithmic approach predicts tumor mutation load and correlates with immunotherapy clinical outcomes using a defined data set, *BMS Me*dicine. 2016;14:168

[9] Johnson DB, Frampton GM, Rioth MJ et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. *Cancer Immunol Res*. 2016;a(11):959-967

[10] Pollastro C, Ziviello C, Costa V et al. Pharmacogenomics of drug response in Type-2 diabetes: Toward the definition of tailored therapies? *PPAR Res*. 2015;2015:415149

[11] James S. Human pain and genetics: some basics. *Br J Pain*. 2013;7(4):171-8

[12] Langley PC. Modeling imaginary worlds: Version 4 of the AMCP Format for Formulary Submissions. *Innov Pharm*. 2016;7(2): No. 11.

[13] Langley PC. Great expectations: Cost-utility models as decision criteria. *Innov Pharm*. 2016;7(2): No.14.

[14] Institute for Clinical and Economic Review (ICER). Treatment options for advanced non-small cell lung cancer: effectiveness, value and value-based price benchmarks. *Evidence Report*. ICER, October 2016
https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Evidence_Report_Plus_Supplement_101716.pdf