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Personalized Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ipme20

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To cite this article: Brett Doble & Paula Lorgelly (2015) Clinical Players and Healthcare Payers: Aligning Perspectives on the Cost–Effectiveness of Next-Generation Sequencing in Oncology, Personalized Medicine, 12:1, 9-12, DOI: 10.2217/pme.14.81

To link to this article: https://doi.org/10.2217/pme.14.81

Editorial

Personalized Medicine

Clinical players and healthcare payers: aligning perspectives on the cost–effectiveness of next-generation sequencing in oncology

"What is needed is a fine balance between testing for treatment identification (including identifying entry into a clinical trial) and testing to enhance innovation in targeted drug development, all within an environment of limited scarce resources."

Keywords: cancer • clinical tumor sequencing • cost–effectiveness analysis • economic evaluation • reimbursement • value assessment • whole-genome sequencing

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Background

Recent discussion surrounding the clinical implementation of genome sequencing has touted its cost–effectiveness [1]. However, the simplistic assumption that lowering the cost of next-generation sequencing (NGS) testing equates to cost–effectiveness is misguided and lacks evidence. Wide spread NGS testing in oncology will incur large upfront screening costs; potentially with no impact on treatment outcomes. In those instances where valuable information is revealed the use of an expensive targeted therapy is likely to be indicated. Therefore, it is essential to have reliable clinical and economic evidence supporting the clinical implementation of tumor-focused NGS testing. Inappropriate use could result in inefficiencies; reducing societies' ability to provide (quality) healthcare to others.

There are a number of challenges facing cancer centers looking to implement NGS and healthcare payers responsible for its reimbursement. Cancer centers need to determine the most suitable patient populations to receive NGS testing, where suitability is supported by the test's analytical validity, clinical utility and cost–effectiveness. Payers will require this supporting evidence to determine if testing results in beneficial and cost-effective outcomes. Additionally, the uncertainty surrounding test outcomes, means payers will need to be more flexible in their approach to reimbursement – that is, share the risk with the cancer centers providing testing.

This editorial reflects on these issues as they relate to the economic evaluation and eventual clinical implementation of tumor-focused whole-genome sequencing. From the onset we acknowledge that there are potential ethical issues and economic impacts of reporting incidental findings from the normal sample of a tumor-normal sequenced dyad (see Parsons *et al.* [2]).

What cancer centers need to know

As the main users of NGS testing, cancer centers will play an important role in selecting patient populations to receive testing during routine clinical care. Initially, testing is likely to be limited to patients with incurable metastatic and recurrent forms of cancer, as these patients have limited treatment options and/or poor prognosis and their oncologist will most likely be seeking trials of investigational agents. This, however, will create a conundrum, as the evidence base requires a large number of tumor genomes to be sequenced across all types of tumor streams and stages to further individualized cancer treatment. As such, selecting the patient population to initially receive NGS testing requires careful consideration. What is needed is a fine balance between testing for treatment identification (including identifying entry into a clinical trial) and testing to enhance innovation in targeted drug

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development, all within an environment of limited scarce resources.

There are a number of potential benefits in expanding NGS testing to include newly diagnosed, treatment naive patients. First, molecular profiling is already required to guide many first-line treatment decisions using companion diagnostics (e.g., lung adenocarcinoma and *EGFR*/*ALK* testing) [3]. Biopsied tissue may be more efficiently used if a single NGS-based assay can replace multiple companion diagnostics tests. Furthermore, NGS tests are more sensitive than companion diagnostics, both in terms of the number of genes/alterations being profiled and the analytical sensitivity for detecting low allele frequency mutations. As a result, potentially actionable mutations can be identified in a greater number of patients. Second, cancer centers have invested large amounts of capital to obtain genome sequencers, many of which require a large number of samples for batching, creating economies of scale. Constraining the testing population could lead to delays in receiving results or higher testing costs as a smaller number of patients are eligible. Finally, testing at diagnosis may avoid delays in selecting treatment for second and subsequent lines of therapy if a non-targeted first-line therapy fails.

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Such a comprehensive testing approach is however not without disadvantage, the biggest being the limited action-ability of NGS testing results [4]. To further increase the number of actionable markers and generate the required evidence of NGS testing's clinical utility more investigational, molecularly-guided therapies should be tested as first-line therapy. This comes at an increased risk of unknown clinical benefit and the potential for toxicity; however, evidence suggests that matching therapies to genomic profiles of tumors can lead to beneficial outcomes [5]. Lastly, tumors evolve and new driver mutations become apparent over time especially after exposure to targeted therapies. Repeat testing seems inevitable, potentially leading to increased resource use and testing costs. Tumor heterogeneity is also an issue in more advanced cancer patients and they too may also require multiple or repeat testing to fully understand the tumor's molecular profile.

Once cancer centers have determined the optimal patient population to receive NGS testing they need to collect data emphasizing the clinical benefit of these tests. Enrollment in patient registries should be a condition for receiving testing so long term outcomes can be measured (e.g., overall survival) and used to support expanding the testing population [6]. Ideally, evidence of clinical utility should also be linked to resource use captured in administrative data sets to support economic evaluation of the testing program. Furthermore, evidence related to diagnostic test characteristics (e.g., analytical validity) is rarely available [7]; evidence of the sensitivity and specificity of the diagnostic test is required when assessing the cost–effectiveness of a test-and-treat strategy [8]. False-positive patients can receive an expensive and possibly harmful targeted therapy, while false-negative patients will be denied the benefit of an effective therapy.

Many important data parameters are highly uncertain and likely to have a large impact on cost–effectiveness analyses. Such parameters (test turn-around-time, proportion of patients with actionable mutations or entering an investigational trial, overall survival) can be identified in exploratory analyses, and they may change dramatically as NGS testing improves and diffuses into clinical care.

What payers need to know

Healthcare payers need evidence that the results of testing will lead to 'meaningful treatments' (and in some jurisdictions that testing/treatment is cost-effective). Currently identified molecular aberrations and their associated targeted therapies lack evidence of clinical utility and their use is limited to certain tumor streams, and arguably are not 'meaningful'. While many patients will not have an actionable aberration identified rendering the testing a sunk cost with no 'meaningful' benefit. Many payers might see testing as a gamble, with wide ranging estimates of 28 [9] to 80% [10] of patients receiving a targeted/investigational therapy or having a clinically actionable alteration respectively identified through testing.

To minimize their risk, healthcare payers may only reimburse NGS testing in even narrower patient populations than those identified as acceptable for testing by cancer centers. Criteria may be applied that limits testing to specific tumors streams harboring aberrations with available clinical therapies. Further restrictions could be placed only on tumor streams that harbor genomic aberrations with relatively high frequencies (>5%). Somatic frequencies of 1% are essentially impossible to differentiate from noise and setting a threshold above 5% would reduce the number of false-positive calls substantially [11]. Higher mutational prevalence of a single marker (>5%) has also been shown to improve the cost–effectiveness of a test-and-treat strategy as the screening cost to identify

one positive patient is lower [12]. The identification of enriched testing populations is likely to increase the cost–effectiveness of the test-and-treat strategy [13]. Healthcare payers might also be unable to distinguish between the value in paying for testing and the off-label use of targeted therapy [14]. Increased communication between payers and cancer centers will be necessary to agree on appropriate testing populations and facilitate the collection of supporting data to ensure continued investment by cancer centers in offering NGS testing.

Payers are unlikely to be able to come to a blanket conclusion that tumor-focused NGS testing is cost-effective in oncology. This is due to the heterogeneity that exists across tumor streams and stages of diseases in terms of knowledge of existing genomic aberrations, availability of targeted therapies, current standards of care and survival projections. Even when limiting a model-based economic evaluation to a single tumor stream and disease severity, a gene-by-gene, variant-by-variant economic assessment of NGS testing will be difficult. Doble *et al.* [15] has highlighted the challenge of increased model complexity and uncertainty when assessing a test with multiple molecular markers. The use of alternative evaluation frameworks that quantify the risks and benefits of NGS testing [16] or combine testing results into a genomic algorithm that assigns a score or probability to an event of clinical interest [17] may address this challenge.

The appropriate balance between the required evidence of improved clinical outcomes and new ways of paying for testing and the resulting treatment is also an area that needs to be addressed by healthcare payers. Technology leasing agreements that are based on commonly applied decision making frameworks (e.g., cost–effectiveness analysis) may reduce the risk from the payer's perspective associated with the uncertain outcomes of testing [18]; whereby cancer centers receive payment only for delivered outputs ('meaningful treatment') rather than delivered technology (tumor-focused NGS testing). The payer is protected against unnecessary expenditure while the cancer center is motivated to provide reliable and meaningful tests that are beneficial to patients.

The key to shared success is improved flexibility from both stakeholders. In its absence we will see limited investment in NGS testing from cancer centers and reimbursement claims for testing being rejected, all at the detriment of cancer patients.

Conclusion

The clinical application of NGS testing in oncology to select appropriate targeted therapies for each individual patient is on the cusp of being realized. Cancer centers and healthcare payers are facing a number of challenges in assessing the economic value of a NGS test-and-treat strategy. Cancer centers are best placed to define the most appropriate patient population for integrating NGS testing into the clinical setting, but restricting or broadening this eligible population must be weighed against its consequences such as further innovation and the action-ability of testing information. Reliable data supporting the use of NGS testing in the identified patient population will also be necessary to convince healthcare payers to reimburse for NGS tests. Understanding the current challenges will allow clinicians, policy makers and payers to make more reliable decisions about the cost–effectiveness of using tumor-focused NGS testing. To necessitate this requires increased communication – only then will the true value of NGS testing be revealed. Until then, careful consideration should be used when expanding NGS testing due to its uncertain economic impact.

Financial & competing interests disclosure

B Doble is supported by research scholarships from Monash University. P Lorgelly is a recipient of a Victorian Government Translational Research Grant through the Victorian Cancer Agency. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review and approval of the manuscript; or decision to submit the manuscript for publication. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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