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COMMENTARY

What Evidence Is There for the Reimbursement of Personalised Medicine?

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A review by Frank and Mittendorf in this issue of the journal indicates that, from the population health perspective, the clinical utilisation of prognostic and predictive biomarkers in colorectal cancer is ahead of its evidence base [1]. In some ways this is understandable, as the standards for establishing evidence on effectiveness and cost-effectiveness of personalised medicine technologies are considerably less well defined than those for conventional health technologies, most notably, pharmaceuticals [2]. In an increasingly constrained resource environment, the lack of clear standards for demonstrating the value of personalised medicine technologies represents a significant threat to both the uptake of truly valuable interventions and the protection and promotion of population health through health care.

Drug development for cancer treatments follows an established pathway from preclinical research followed by early- then late-phase clinical trials. The pathway and the evidence that it delivers are designed to meet the needs of the regulators and clinicians who have historically governed access to markets and patients. Pharmaceutical regulators such as the US Food and Drug Administration (FDA) and the European Medicines Agency are long established with defined and broadly harmonious evidence requirements for new pharmaceuticals, which include the quality of manufacture, safety and efficacy.

The regulation of diagnostic tests, including in vitro diagnostics (IVDs), has been less rigorous due to a real or apparent lower risk of direct harm. Standards in Europe are established by a European Union Directive with a requirement for CE marking granted by one of a number of commercialised assessment organisations. Similar standards are in place in the USA implemented by the FDA. Recent safety scandals such as that involving breast implants manufactured by Poly Implant Prothese (PIP) have brought the apparently soft-touch regulation of medical devices under scrutiny [3]. This, combined with the key role of companion diagnostics in targeted therapy and the personalised medicine paradigm, has triggered high level review of regulation in this area. There is currently a strong push for more rigorous processes and standards of evidence [4].

Whilst these emerging requirements are to be welcomed, they give little or no consideration to the extensive development of reimbursement authorities, as an additional and vital determinant of market access for expensive new technologies. Such organisations are more heterogeneous than licensing organisations in both their stated objectives and their evidence requirements. They range from national bodies with statutory powers like the National Institute for Health and Clinical Excellence (NICE) in the UK to individual insurance companies and private health-care providers. Whilst harmonisation of decision-making criteria is challenging, arguably impossible, such organisations tend to be interested in how efficacy translates into effectiveness (or outcomes in real-world non-research situations) and value for money; as such, there is likely to be substantial scope for harmonisation of evidence requirements such as

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the acceptable measurement for quality of life, discounting standards or methods for representation of uncertainty [5].

The generation of evidence on the value of a diagnostic test presents a number of challenges over and above those encountered with drugs. Diagnostic tests giving information about one or more biomarkers in cancer have long been used to provide *prognostic* information; i.e. a biomarker gives some indication about the likely natural history of the disease (such as survival outcomes) in a defined group of patients. Personalised medicine, however, requires *predictive* markers, which seek to provide information about how the benefit from a treatment differs between biomarker-defined subgroups of patients. The *kirsten rat sarcoma viral oncogene homolog* (*KRAS*) gene mutation, highlighted in this edition of the journal, indicates whether a patient's cancer has a higher chance of responding to targeted therapy with epidermal growth factor receptor (EGFR) inhibitors [1]. As such, they can be used to identify a population of patients in whom there is a much higher chance of efficacy, and hence cost-effectiveness. It is becoming increasingly clear that evidence for a predictive biomarker moves beyond mere association [6]. Demonstrating predictive performance will require additional and different types of research to that provided by conventional clinical trial programmes [7]. Depending upon the order in which the evidence for the biomarker and a companion treatment emerges, effectiveness trials may be larger or smaller than for a conventional trial; and may require longer or shorter patient follow-up. Given the commercial imperative for tests and treatments to reach the market at the same time, efficient development of biomarkers and companion diagnostics may require re-engineering of the conventional clinical development pathway.

The challenges in evidence development for new drugs, with parallel development of companion diagnostics, have led to new efficient models for clinical trial design. These include Bayesian adaptive trials and more advanced design models such as the multi-arm, multi-staged (MAMS) adaptive phase II/III design of the UK MRC FOCUS4 trial in colorectal cancer [8]. However, if such trials are to inform reimbursement decisions in a timely manner, then they will need to meet the evidence needs of reimbursement authorities. As such, the control treatments will need to facilitate comparisons to current clinical practice; recruited patients will need to reflect more closely real-world populations; additional outcome data, such as health-related quality of life, will need to be captured, as well as resource utilisation data to enable country-specific economic evaluation.

Whilst re-engineering the clinical development process is likely a necessary component of developing predictive biomarkers efficiently to meet value-based market access criteria, routine utilisation of decision analytic modelling will also need to be central. Modelling is essential to estimate the full value of innovative personalised medicine technologies to health-care systems. Just as trials for diagnostic technologies present significant methodological challenges, so will modelling the cost-effectiveness of diagnostic technologies. Establishment of the relative value of further research as well as the real value of reimbursement will also require significant methodological advances. The challenges include, but are not limited to:

(a) Characterising the uncertainty in the test performance characteristics of a biomarker, when it is a function of inter alia variation in individual patient characteristics not captured in the test; variation in sample capture, transport and storage practices; variation in analytical performance across platforms and between laboratories; sampling variation in the test estimation and sampling variation in the test validation sample.
(b) Identifying the optimum case definition threshold (e.g. a defined cut-off for a continuous quantitative biomarker readout) based upon a value threshold (such as a cost-effectiveness threshold) rather than clinical utility (such as survival outcomes alone, without consideration of cost) when the threshold for value varies across health-care systems and reimbursement authorities [9].
(c) Capturing the population health impact of false negative and false positive decisions, in the assessment of the value of the new technology.
(d) Establishing the relative value of further research into the effectiveness of the treatment and the test performance characteristics of the biomarker, when the two are causally linked.

By highlighting the current absence of agreed modelling standards, Frank and Mittendorf point to the urgent requirement to harmonise methods and increase modelling transparency in the evaluation of biomarkers and diagnostic tests [1]. Their structured approach is welcome and represents a useful start to a vital research and policy discussion. Developments in modelling will not add significant value unless they are co-ordinated with developments in clinical trial design and the construction of tools for assessing the quality of evidence for personalised medicine technologies [10]. Only through the development and adoption of high-quality methods across the clinical translation pathway—from early clinical development through to regulation, reimbursement and adoption—can we expect to receive the desired return on society's substantial investment in the science of personalised medicine.

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