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Reflections on Market Access for Personalized Medicine: Recommendations for Europe

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ABSTRACT

This article aims to provide an overview of the current literature focusing on the reimbursement of personalized medicine across the European Union. The article starts by describing types of perspectives that are possible (general public, patient, payer, provider, service commissioner, and policymaker). The description of perspectives also explains the importance of understanding the different possible decision criteria and processes from the various perspectives by taking into account budget constraints. The article then focuses on an example of personalized medicine, namely, the use of companion diagnostic-medicine combinations, to describe the role of reimbursement/payer agencies across the European Union to control the introduction and coverage of such companion diagnostic-medicine technologies. The article touches on the strategic challenges and the use of economic evidence to introduce personalized medicine from a health policy perspective. The article also draws on empirical studies that have explored patients' and clinicians' views of examples of personalized medicine to illustrate the challenges for developing patient-centered and timely health care services.

Keywords: economic evaluation, personalized medicine, reimbursement.

Introduction

Personalized medicine is moving away from being a hyped theoretical concept to applications used in clinical practice. Specifically, personalized medicine is becoming a practical reality with the targeting of medicines by using a biomarker or genetic-based diagnostic to identify the eligible patient population. To date, the most common applications are the targeting of cancer medicines by using knowledge of pharmacogenomics to develop companion diagnostic-medicine combinations [1]. There are also, however, some clinical examples of using a person's genotype to target the safe use of medicines, such as thiopurine methyltransferase (TPMT) testing in patients treated with azathioprine [2], in noncancer conditions such as autoimmune diseases. At the moment, the available diagnostic technologies aim to detect a single biomarker or variant in a single gene, but new next generation and whole genome sequencing technologies will soon make genomic profiling of tumors or individuals a practical reality in common practice. Although true advances in science that lead to clinically useful applications are to be welcomed, it is clearly necessary to take account of the context in which new technologies are introduced into practice. The global economic climate is putting greater emphasis on the need to effectively use finite, and often limited, health care budgets.

There is substantial diversity in how health care systems are provided and funded across European countries [3]. There is a commonality, however, in the need for decision makers working within these health care systems at local, regional, or national levels to think about how best to spend the available health care budget effectively. Ideally, the decision makers want a sufficiently robust evidence base to reassure them that they are spending the resources in the best way possible. This need for information presented as a structured evidence base has stimulated the development of funding streams, dedicated organizations, and processes to produce health technology assessments (HTAs). The general concept of an HTA—"a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner" [4]—is well described and generally accepted. Best practice guidance has also emerged [5]. There is substantial variation, however, across Europe in the process of funding and producing HTAs, the technical details used in the evaluative methods, and the intended use of the HTA reports [6]. HTAs can potentially be used to inform clinical guidelines or reimbursement decisions for local, regional, or national use. In some jurisdictions, HTAs have a more formal legal status and are used by national decision makers working for third-party health care payer organizations. In England, there are national HTA processes in place, led by the National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, selecting and targeting the funding of assessments of specific technologies. The HTAs are used by

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decision makers across the UK's National Health Service (NHS), but selected reports are subsequently used by the National Institute for Health and Care Excellence (NICE) in the appraisal of health care technologies and public health interventions and programs to inform recommendations published as national guidance. In Belgium, there is a dual track. In one track, diagnostic tests for which reimbursement is claimed by the manufacturer undergo a process and a judgment by a technical commission within the National Institute for Health and Disability Insurance on the basis of unclear criteria; and in a second track, the Belgian HTA body "KCE" can select specific diagnostic tests to perform a full HTA. In other countries, such as Greece, there are no dedicated HTA organizations and no economic evidence is used to inform reimbursement decisions or guideline development [7].

The concept of personalized medicine is being introduced into health care systems working with this varied backdrop of HTA funding, design, and use across Europe. Another layer of variation occurs if the type of technology is more carefully considered, and different processes may exist within countries for different types of technologies. Companion diagnostic-medicine combinations could potentially be the Holy Grail of payers and reimbursement agencies because they allow a clinician to predict who will respond and how they will respond before a medicine is prescribed and any money is spent. Furthermore, patients could favor targeted medicines because they will be more likely to be offered an effective and safe medicine with a good chance of relieving symptoms or curing disease. Using the theory of personalized medicine to develop a companion diagnostic test means that populations are stratified into subgroups such that only patients identified as having a high probability of responding well are offered treatment. By definition, however, the combination technology is now two technologies that are linked but distinct. They are distinct in terms of the scientific knowledge needed to develop them into a clinical application, the evidence base needed to license the technology, and the system for setting the price of the product, and in terms of the requirement for, and type of, reimbursement/payer systems in place. Garrison and Austin [8] succinctly point out the difference in resource- or cost-based approaches to setting the price of a diagnostic compared with a broad value-based system for medicines.

The variation in the evidence base available for a diagnostic compared with a medicine has potentially emerged because of the perception in different types of potential harms and the risk associated with a particular technology. The entry of a new pharmaceutical into the market is highly controlled, with a need for robust evidence on the efficacy, safety, and quality of the product. Diagnostic tests are viewed to have lower risks in terms of causing immediate and direct harm from the use of the product, which is reflected in the "risk category" they have been assigned by regulatory agencies. This does not acknowledge, however, the potential long-term, or indirect, harms, which could result from a diagnostic that provides clinicians with probabilistic rather than a definitive answer, and the impact on patient morbidity and mortality associated with false-negative or false-positive test results. Taking account of the regulatory backdrop is important when considering if, and how, reimbursement and payer decisions are then informed and made. The regulatory system will drive the evidence base for the available future HTA and consideration of whether the technology offers added benefits in terms of its clinical effectiveness and cost-effectiveness compared with current practice [9]. Faulkner et al. [10] acknowledge the roles of two key players involved in producing and using the evidence base: the manufacturers and the payers. In their article, Faulkner et al. echo the broad recommendations of Meckley and Neumann [11], who suggest a need for manufacturers to generate a stronger better clinical evidence base to prove the added value and clinical utility of their companion diagnostic-medicine product. Faulkner et al. [10] add to the literature by describing five key areas requiring development to produce the evidence base necessary to support the introduction of personalized medicine into clinical practice, including the need to harmonize the processes for diagnostics and medicines. This view was supported by Fugel et al. [12], who acknowledge the difference in pricing and reimbursement frameworks between diagnostics and medicines within and across European countries as a result of case-by-case assessment of diagnostic tests at the local or regional level.

This article aims to add to the current literature on how best to meet the challenge of ensuring appropriate market access for personalized medicines by suggesting the need for a strategic approach to reimbursement across Europe. The article starts by describing types of perspectives that are possible. The description of perspectives will also explain the importance of understanding the different possible objective functions from the various perspectives taking into account budget constraints. The article delineates the challenge of taking a strategic approach, and the use of economic evidence, to introduce personalized medicines from a health policy perspective. The article also draws on empirical studies that have explored patients' and clinicians' views of examples of personalized medicine to illustrate the challenges of developing patient-centered and timely health care services. The article concludes with recommendations for improving the evidence base for reimbursement/payer agencies charged with controlling the introduction of companion diagnostic-medicine technologies within Europe.

Reimbursement of Personalized Medicines: Whose Perspective?

Taking an economists' view of the world, it is important to be explicit whose perspective is being considered and which evaluative framework should be used to inform the reimbursement of technologies such as companion diagnostic-medicine combinations. Previous authors, such as Beitelshees and Veenstra [13], have already defined some key perspectives to consider in the context of personalized medicine from a US viewpoint, including the federal government, the science-based clinical academic community, the pharmaceutical industry, managed care organizations, and pharmacy benefits managers, clinicians, and patients. Similar perspectives can be defined relevant to a health care market for personalized medicines in the European context. The divide between supply and demand in a health care market is not always distinct. Given the need to identify who might be responsible for meeting the burden of proof in terms of showing the added value of companion diagnostic medicines, it is useful to define perspectives as being predominantly that of a supplier or user of health care. Implicit in this statement is the assumption that it is the suppliers of health care who are responsible for providing evidence of added value for a new technology. Table 1 lists some key potential perspectives and defines them as suppliers or users of personalized medicine.

Table 1 illustrates how a number of stakeholders in the health care system have a duality of roles, acting as suppliers and users of health care technologies such as personalized medicine. This means that the stakeholder may also have to be flexible in terms of whether they are suppliers or users of an evidence base that supports or refutes the added value of a companion diagnostic medicine. Understanding different perspectives is useful to identify how there are potentially different objectives and associated budget constraints, which will affect the incentives for a provider to produce the required evidence base and a potential user to take up a new technology. Society, made of current and future patients, represented by the