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Health technology assessments in personalized medicine: illustrations for cost–effectiveness analysis

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"Health technology assessments have proven to be very useful in analyzing new innovative pharmacotherapies at the national population level ... the health technology assessment process defines the procedures and requirements that provide the suppliers of the technologies with clear-cut pathways to market access and reimbursement for population-wide use."

In the last decade, there has been an upsurge of health technology assessments (HTAs) and corresponding bodies producing, judging and disseminating such assessments. Notably in the area of clinical pharmacology, HTAs have become a prerequisite before widespread clinical use of pharmacotherapies in Western countries can be considered. In particular, HTAs use evidence-based medicine techniques and provides a toolkit (often in the framework of reimbursement decisions) comprising of criteria, standards, procedures and guidance for use in practice [101]. Application of HTAs leads to reimbursement decisions in countries such as The Netherlands, Belgium and Sweden and guidance on use in the UK as provided by the NICE for England and Wales and the Scottish Medicines Consortium.

Health technology assessments have proven to be very useful in analyzing new innovative pharmacotherapies at the national population level. In particular, the HTA process defines the procedures and requirements that provide the suppliers of the technologies with clear-cut pathways to market access and reimbursement for population-wide use. Indeed, in many Western economies the pathways for manufacturers to get new drugs to market are fairly straightforward, with clear steps and decision criteria centered around strong clinical pharmacological information. Specific procedures exist for outpatient and inpatient drugs and guidelines for cost–effectiveness analysis provide methodological standards for reporting, for example, the economic evidence in accordance to generally accepted decision criteria. Examples of some recent innovative therapies that have gone through HTA in Western countries include various new antithrombotic therapies, antimicrobial agents, psychotropic drugs and orphan drugs [1,2].

"...health technology assessment uses evidence-based medicine techniques and provides a toolkit ... comprising of criteria, standards, procedures and guidance for use in practice."

A trend towards personalizing medicine provides a new challenge for HTAs [3]. With personalized medicine, a diagnostic or testing element must be considered in addition to the pharmaceutical technology itself. For example, genetic testing prior to choosing the exact pharmacotherapy is

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increasingly being used in oncology, depression, infectious diseases and others [4]. However, there is an absence of implemented procedures, criteria and standards in generically assessing tests in personalized medicine. Thus, compared with manufacturers of innovative drugs, manufacturers of innovative testing technologies are faced with much higher uncertainties and vagueness with regards to strategies for achieving reimbursement and positive recommendations for use.

In general, the criteria for consideration within a HTA for a new technology include [102]:

- Current use of the technology (dissemination so far);
- Epidemiology of relevant disease(s) and treatment patterns;
- Burden of the disease and medical need;
- The exact technology and its characteristics;
- Toxicity/safety;
- Efficacy/effectiveness;
- Costs and economic evaluation.

As mentioned, this set of criteria has been well accepted for evaluations in clinical pharmacology of population-based treatments. For new innovative drugs, these criteria are generally considered without exception. Assessment of current use and epidemiology may include burden indicators. The technology itself is critically reviewed, including potential characteristics that may increase the use of the technology such as route of administration. Decisive factors for actual recommendations are those relating to effectiveness and safety on the population level, which are often inferred from efficacy and toxicity evidence from randomized controlled trials. In addition, costs and economic evaluation are crucial elements in any HTA, inclusive medical need, exact cost–effectiveness estimates, extensive sensitivity analyses, budget impact predictions and sometimes explicit thresholds for willingness-to-pay [5].

> "Effectiveness/safety estimates the outcomes of an intervention on a population/real world level, whereas efficacy/toxicity estimates the results of an intervention under ideal controlled conditions of a clinical trial setting."

Methodological standards and guidelines exist for assessing the HTA-criteria described above and the quality of the available data. We may illustrate this in the area of cost–effectiveness in clinical pharmacology. Guidelines for cost–effectiveness are quite comparable between countries and institutions. For example, the Dutch guidelines resemble the Belgium guidelines and those of NICE resemble those of the Scottish Medicines Consortium [6]. Some areas of concern were common among the different guidelines. In particular, transparency in reporting is an important issue because cost–effectiveness analyses are often performed by the manufacturer or at least under the strict supervision of the manufacturer. Another issue is one relating to effectiveness versus efficacy (safety vs toxicity). Effectiveness/safety estimates the outcomes of an intervention on a population/real world level, whereas efficacy/toxicity estimates the results of an intervention under ideal controlled conditions of a clinical trial setting. As the goal of economic evaluations is to analyze on a population level, we prefer cost–effectiveness over cost–efficacy analysis. A related issue is the desire to measure effects in 'hard' end points for morbidity and mortality rather than intermediate end points, such as biomarkers and subclinical or asymptomatic disease. Intermediate end points have been used in Phase III registration trials and are allowed according to guidelines if adequately motivated, but they do require the use of models to extrapolate to relevant clinical measures. In practice, most cost–effectiveness within HTAs involve some level of modeling to infer from efficacy (toxicity) to effectiveness (safety) and from intermediate to 'hard' end points, reflecting a well-accepted approach here.

> "We noted that aspects of the guidelines address issues that were common between clinical pharmacology and personalized medicine. For example, all guidelines refer to discounting issues, choice of comparator and measurement of quality-adjusted life years."

Given the general lack of the HTA-approach in personalized medicine, the question arises whether the set of criteria, outlined above, for clinical pharmacology would also be applicable to personalized medicine. Although some specific aspects should be considered and slight revisions may be appropriate, we argue that this set of tools indeed seems adequate to apply beyond clinical pharmacology only. The final set can be considered as an integrated approach that assesses the clinical, economic, ethical, legal and social issues and consequences specifically related to personalized medicine. For defining this set, we recently analyzed the published literature on economic evaluations of pharmacogenetic technologies using the set of tools represented by the guidelines for cost–effectiveness analysis [7,8,101].

We noted that aspects of the guidelines address issues that were common between clinical pharmacology and personalized medicine. For example, all guidelines refer to discounting issues, choice of comparator and measurement of quality-adjusted life years [9,10]. However, we found that compared with population-based innovative drugs' assessments, various aspects of the guidelines require specific attention for personalized medicine. For example, potential negative effects resulting from false-positive outcomes of testing warrant consideration, including quality-adjusted life years impacts. Moreover, ethical aspects may not be in line with economic arguments seeking optimal sensitivity, specificity and cost combinations. Notably, the level of economic (but also technical) evidence may differ from what is generally experienced in clinical pharmacology; thus stressing the need to include all evidence including potentially conflicting results from case-control and observational settings into the economic analysis. Given genetic variability, the question as to

whether the patients in the studies on the testing and diagnostic technologies are representative of the target groups for personalized medicine is one of utmost importance. Furthermore, and fully in line with efficacy/effectiveness issues rather than clinical validity, the test should show a high clinical utility in practice, translating into an acceptable cost–effectiveness that is robust in extensive sensitivity analysis regarding uncertainty in test characteristics such as accuracy and predictive value. Finally, it is noted that the economic analyses often appear to be conducted to increase awareness of cost-effective possibilities and perspectives of (genetic) testing rather than to influence policy decisions on reimbursement.

In general, we conclude that following the economic guidelines developed for clinical pharmacology as a set of standards would also be an adequate approach for evaluating personalized medicine technologies, although slight changes and specific foci should be made to optimize applicability in testing strategies. These should comprise various aspects for consideration, inclusive evidence synthesis of associations between disease and tested characteristics, analysis of the related pharmacotherapy, accuracy and predictive values of testing technologies, clinical utility, representativeness of the available studies on the technology, study perspective and scope of the sensitivity analysis.

In addition, recent attempts for HTAs in personalized medicine are increasing, for example, regarding genetic profiling and self testing [11,12]. If specific points listed are taken up in the coming years and further applications are undertaken along these lines, HTAs in personalized medicine may highly benefit from the abundance of experience that has been gathered with clinical pharmacological HTAs.

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