Review

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Health Technology Assessment to assess value of biomarkers in the decision-making process

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Abstract: Clinical practice guidelines (CPGs) on screening, surveillance, and treatment of several diseases recommend the selective use of biomarkers with central role in clinical decision-making and move towards including patients in this process. To this aim we will clarify the multidisciplinary interactions required to properly measure the cost-effectiveness of biomarkers with regard to the risk-benefit of the patients and how Health Technology Assessment (HTA) approach may assess value of biomarkers integrated within the decision-making process. HTA through the interaction of different skills provides high-quality research information on the effectiveness, costs, and impact of health technologies, including biomarkers. The biostatistical methodology is relevant to HTA but only meta-analysis is covered in depth, whereas proper approaches are needed to estimate the benefit-risk balance ratio. Several biomarkers underwent HTA evaluation and the final reports have pragmatically addressed: 1) a redesign of the screening based on biomarker; 2) a de-implementation/replacement of the test in clinical practice; 3) a selection of biomarkers with potential predictive ability and prognostic value; and 4) a stronger monitoring of the appropriateness of test request. The COVID-19 pandemic has disclosed the need to create a robust and sustainable system to urgently deal with global health concerns and the HTA methodology enables rapid cost-effective implementation of diagnostic tests allowing healthcare providers to make critical patient-management decisions.

Keywords: biomarker; biostatistics; cost-effectiveness; healthcare; statistical model.

Introduction

The pipeline of the biomarkers in routine clinical practice comprises several specific steps, from the discovery to the translational phase, and is aimed at the most effective clinical implementation [1, 2]. Accordingly, the clinical utility of validated biomarkers has traditionally been measured in terms of diagnostic/prognostic contribution added to other clinical tools and only in few cases (i.e., prostate specific antigen [PSA]) has been demonstrated by estimating the impact on morbidity trends, survival outcomes, and quality-adjusted life-years [3]. For instance, clinical practice guidelines (CPGs) in the oncology context focused on screening, active surveillance, and treatment of some cancers have recently strongly recommended the selective use of prognostic and predictive biomarkers with central role in clinical decision-making and moved towards including patients in the decision-making process [4]. The appropriate request for biomarkers and the appropriate management of results should allow clinicians to identify patients most likely to benefit from an intervention defined by a shared decision between the patient and the clinician [5]. For instance, the most recent recommendation to identify patients at intermediate and high risk of cancers characterized by a slow growth proposes to use biomarkers more selectively according to the presence of risk factors at baseline. This mandatorily implies that CPGs release clear and evidence instructions about who, when and how often to offer marker-based screening instead of releasing rather rough information about pros and cons related to the sensitivity vs. specificity trade off in the biomarker use [5, 6]. Noteworthy, for some cancers, overdiagnosis, overtreatment,

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and not patient oriented screening programs based on biomarkers measurement have been associated with an unfavorable benefit-risk balance at the individual level [4, 7]. In the best case scenario of a test with excellent sensitivity and specificity (i.e., relevant diagnostic likelihood ratios) and analytical performances, the low prevalence of the cancer, the presence of interfering conditions in the population eligible to be tested, and the nature of the cancer growth (too fast or too slow) may indeed influence the predictive probability values (PV) and the range of application of the test (i.e., ruling in or ruling out the diagnosis) and consequently its real clinical and healthcare effectiveness [1, 7]. For instance, in the context of breast cancer promising positive PVs (i.e., minimal threshold of 80% for rule in) estimated across the early stages of the biomarkers pipeline development are crucial to give impulse to their introduction into the clinical setting, where the appropriate biomarker request has to be pursued to preserve the promising positive PVs of the validation phase [1].

To this aim, with the first clinical introduction of the biomarker, the clinical research should optimize the application of the test (i.e., ordering PSA in patients at risk of advanced prostate cancer) and outcomes (i.e., identification of advanced prostate cancer) although there are several examples in the current literature showing that the estimated PVs of biomarkers have been strongly compromised by methodological weakness (i.e., design limitations) and poor statistical modeling of the results [1, 8]. This is an important point to be made when one considers that in the clinical algorithms the negative or positive PVs currently lead to the use of the biomarker to exclude or identify patients in order to recommend or not a second level test or an invasive procedure (generally more expensive than the first level test). Consequently, the value of biomarkers included in clinical decision algorithms, as part of broader panels or scores, should be established by cost-effectiveness analysis and estimating the impact on the patient risk-benefit, in agreement with the patient-centered focus of current guidelines. The use of clinical trial simulations, that can explore the effects of specific design assumptions on expected clinical outcomes, the use of well calibrated risk models, that show good agreement between the estimated risk of the individual subject and the actual risks, should be properly developed [9, 10]. A good discriminating performance (estimated by the "popular and simple" calculation of the area under the receiver operating curve statistics [AUC]) does not guarantee the clinical utility of a biomarker [10, 11]. For instance, this is the case of those biomarkers useful to identify those patients who most likely will benefit from an intervention defined by a shared decision between the patient and the clinician [12]. Indeed in this case, it is more important for the individual patient to know that the risk given by the model is close to his/her true risk than to know how well the model distinguishes between patients. We would argue that calibration is a more important statistic than discrimination. Calibration informs on whether the model correctly estimates the probability of disease for an individual whereas AUC gives us the probability that, for a randomly selected pair of individuals, one with the disease and one without, a model will give a higher score to the patient with the disease [10].

The evidence that the vast majority of biomarkers have not been assessed for their ability to improve outcomes in randomized trials adds another note of caution to their usefulness [10, 11]. Below we clarify the multidisciplinary efforts and interactions required to properly assess the value of biomarkers integrated within decision-making process and how Health Technology Assessment (HTA) methodology may deal with regulatory, ethics, and scientific aspects to measure the cost-effectiveness of biomarkers after the regulatory authorizations issued by the FDA and other regulatory Agencies (i.e., www.lawinsider.com/dictionary/regulatory-authorizations regulatory authorizations).

Health Technology Assessment in the translational marker pipeline

When attempting to introduce a biomarker in clinical practice, clinicians and laboratory professionals are called upon to establish the "clinical needs and endpoints" and the analytical/clinical performances of the assay, respectively [13]. However, additional expertise (i.e., biostatistical, econometric, etc.) should be involved to capture the benefits and risks associated with the use of the biomarker and to evaluate them. The assessment of the clinical utility of biomarkers should be pragmatically replaced by the analysis of the clinical pathways in which the inclusion of those is promising to: a) lead to substantial improvements in patients outcomes at acceptable additional costs or b) reduce costs and/or simplify patient's clinical management without compromising outcomes [11].

In the overall framework, it has to be claimed the introduction of the HTA defined as "multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system" [14]. Through the interaction between different

skills and expertises, it provides high-quality information on the effectiveness, costs, and broader impact of health technologies for those who use, manage, and provide care in Health Systems. Biomarkers and related technologies fit squarely into the broad group of the 'Health Technologies' defined as "the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives" [9, 15, 16].

HTA is likely to allow the cooperation required to ensure that:

- All the relevant questions are answered to advance the use of technology (i.e., biomarker test).
- Appropriate data and methods are used.
- All aspects that heavily affected decision-making are identified.

To this aim HTA Core Model enables standardized reporting in order to provide a common framework for the production of HTA. This model allows to make and share finding and to reliably and easily transfer the information into local contexts. The HTA Core Model accounts for nine content elements or domains to be accounted for providing exhaustive information and to avoid redundant overlaps across the various assessment elements (i.e., 1) health problem and current use of technology, 2) description and technical characteristics of technology, 3) safety, 4) clinical effectiveness, 5) costs and economic evaluation, 6) ethical analysis, 7) organizational aspects, 8) patients and social aspects, and 9) legal aspects), Accordingly each domain accounts for some specific topics, and each topic is further divided into several questions allowing the exhaustive exploration of each domain [17].

To date, HTA has entered the clinical laboratory to evaluate the introduction of innovative technologies and automation solutions with the aim of achieving cost-effective process and improving the efficiency and efficacy of tests' results and ultimately the overall quality of patients' care [18]. However, it should be emphasized that laboratory data, supported by strong evidence, represent a crucial source for updating and increasing cost-effectiveness of current diagnostic and prognostic workflows for several diseases. To this aim HTA methodology is really relevant since the introduction of new biomarkers and or of new indication on the use of traditional ones as well as the replacement with high-sensitive methods (e.g., troponin) have organizational and economical implications [19].

There is little knowledge on how currently the interplay of different skills and stakeholders (clinicians, laboratory professionals, biostatisticians, epidemiologists, health-economists, decision makers) applied to biomarkers with a crucial role in decision-making have actually modulated the implementation of several biomarkers for clinical use and guided appropriate ordering and management of the results. This in order to further recommend appropriate treatment options to the patients whose risk-benefit is the linchpin of overall process.

The ability of the HTA approach to answer questions about the effectiveness and cost-effectiveness of new biomarkers technologies relies on the availability of appropriate methodologies including biostatistics.

Biostatistics: the quantitative engine of HTA applied to biomarkers

Advanced statistical approaches are requested for dealing with extreme problems in rare and chronic diseases (e.g., gene therapy for very few individuals with monogenic disease corresponding with very high costs and glucose monitoring through sensors for type 2 diabetes with low costs but big number of patients). For laboratory markers of wide application in routine practice, statistical approaches for experimental design and analysis maintain a key role in quality control and monitoring. Within this framework a clear assessment of the costs related to assays development, validation, and quality maintenance according to the requested standard analytical and clinical performances is essential to drive laboratory technologies/procedures update in a full HTA perspective. These aspects are particularly relevant both for the introduction of new markers (e.g., miRNA, gene mutations, …) and the dismission or the reshape of the use of older ones.

More generally, traditional papers published by laboratory medicine experts, based on analytical data and a comparison between disease/no disease groups, and on the evaluation of procedure costs, are not sufficient for the HTA methods, while process costs and impact on the process by the use of marker are needed according to principled quantitative approaches for the assessment of statistical evidence and the following econometric implications.

Biostatistics in HTA supports the systematic, evidence-based evaluation of diagnostic procedures and biomarkers technologies. These are general critical tasks both for reimbursement of biomarkers, drugs, and medical devices and for their safe introduction in the healthcare [9, 15]. To this purpose, clinical trial designs for comparative effectiveness and the selection of surrogate endpoints that can replace clinically relevant endpoints, are often needed in

HTA setting. The interaction with HTA bodies such as the Federal Joint Committee (Gemeinsamer Bundesausschuss; GBA), the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany as well as the National Institute for Health and Care Excellence (NICE) in England, traditionally being regarded as examples for the right/appropriate implementation of evidence-based medicine, require strong evidence support [20].

Starting an HTA evaluation, clinical trial data represent the primary source of information for the new technology. Regulatory and HTA submissions for new interventions are extensively using clinical trial data and results. Regulatory submissions demonstrate quality, safety, efficacy, and benefit-risk whereas HTA submissions should demonstrate relative effectiveness and cost-effectiveness. HTA objectives can indeed be related to the prediction of long-term clinical and economical outcomes in the evaluation of the outcome of the new intervention compared to the current clinical practice. Estimate the impact of the treatment on relevant outcomes to patient (mortality, quality of life, adverse experiences, resources) is mandatory in HTA and update requires additional sources of information (i.e., cancer registries, Food and Drug Administration Adverse Event Reporting System [FAERS] database for monitoring of pharmacovigilance) [21, 22].

Concerning statistical training, much of the biostatistical methodology is relevant to HTA but the links are not yet very explicit, and there are few recommended expert consensus methodological documents [23].

Statistical guidelines have been developed in areas relevant to HTA, in particular drug regulation, and in systematic reviews of randomized trials, through the Cochrane Collaboration [24]. The linchpin technology in both of these areas is the randomized controlled trial. However, these guidelines mostly emphasize principles and ways of working rather than detail, with only meta-analysis covered in depth.

Concerning study design, much of the statistical literature related to HTA on drugs and medical devices is coming from clinical trials whereas for biomarkers most of the evidence is obtained from the corresponding sub-studies [25, 26]. In particular in the framework of biomarkers as vitamin test, the ASTUTE group has shown that the conduction of systematic reviews of primary studies is not feasible and useful, but according to HTA model, the identification of snowball references from papers identify by experts may aid in writing local guidelines [27].

However, in these frameworks there are relatively few publications that cover the more complex experimental designs, meta-analysis or studies safety [28].

Concerning the analysis methodology, the statistical literature relevant to HTA largely relies on analysis of follow-up studies, both survival and longitudinal data feature regularly occur. Within the medical literature, survival analysis is extremely common, particularly proportional hazards Cox regression but advanced methods for regression modeling in the competing risks setting are increasingly needed [29]. Much of this work is in the context of cancer and heart disease.

Statistical approaches are needed to estimate the benefit-risk balance ratio assigning scores to favorable and unfavorable effects together with relevant probabilities representing their uncertainties [9]. Several statistical tools (e.g., probabilistic/Markov simulations, conjoint analysis for characterizing the tradeoff between favorable and unfavorable effects, settings and patients requirements) may be adopted to this purpose, starting from Bayesian methods which provides valid posterior inference that can be used to design decision models from evidence and prior probabilities [15].

Many promising biomarkers for stratifying individuals at risk of developing a chronic disease, for early disease detection (i.e., cancer, acute myocardial injury) and subsequent complications (i.e., heart failure) have been identified. Research into the potential cost-effectiveness of applying these biomarkers in actual clinical settings is still lacking. Among the stakeholders, manufacturers, and investors may improve their venture decision-making by having indicative estimates of the potential costs and effects associated with a new biomarker technology already at the early stages of its development [1]. To assist in obtaining such estimates, general method for the HTA of a novel biomarker technology have been proposed in the setting of primary and secondary prevention programs where initial screening to select higher-risk individuals eligible for a subsequent intervention occurs (i.e., prevention of type 2 diabetes, prediction of breast cancer) [1, 6, 30]. The method is based on quantifying the health outcomes and downstream healthcare consumption of all individuals who get reclassified as a result of moving from a screening variant based on traditional risk factors to a screening variant based on traditional risk factors plus a novel biomarker. As these individuals form well-defined subpopulations, a combination of disease progression modeling and sensitivity analysis can be used to perform an initial assessment of the maximum increase in screening cost for which the use of the new biomarker technology is still likely to be cost-effective.

There is an increasing need to face regulatory aspects as well as ethics and scientific ones in the health technology research after the market authorization. Traditionally,

Phase IV studies, have been considered mainly aimed to the assessment of the new drug safety profile but a large room of improvement can be related to the health technologies and in particular to biomarkers under the compelling need of the benefit/risk assessment. The approach of "Explanatory Trials" and "Pragmatic Trials" proposed for drugs under the HTA horizon calls for the extension to biomarkers use, both in the secondary and tertiary prevention settings according to personalized treatments following biomarkers targets [31].

Biomarkers of clinical use undergone HTA judgment

Several biomarkers underwent further HTA evaluation combining clinical efficacy with appropriateness and economic analysis and prioritizing a patient-centered risk-benefit assessment.

There are five key elements that should be considered in the test assessment process including the evaluation of: a) analytical performance, b) clinical performance or clinical validity, c) clinical effectiveness, d) cost-effectiveness, and e) impact of the test on social, psychological, legal, ethical, societal, and organizational aspects. By considering that there is an interplay between these five key elements, a cyclical test evaluation approach likely maximizes the interaction of different skills and expertises and thus the benefits of applying HTA methodology. Indeed, the intended use of the test, the role in the clinical pathway may change as more evidence on clinical effectiveness is published and/or as more improvement of the technology is added [32]. These enhancements may in turn increase cost-effectiveness data which therefore may modulate the clinical pathway and improve the appropriate use of the test according to a favorable benefit-risk ratio [3, 32]. This goal has been achieved in the case of some tumor markers as PSA, and in any case in cancer setting HTA has pragmatically addressed a redesign of diagnostic algorithms based on the biomarkers of clinical use [3, 33]. PSA ordering and use has been recently modulated by HTA methodology to improve decision-making for prostate biopsy referral and to reduce the harms of overdiagnosis and overtreatment. The resulting change has been to optimally address the use of PSA to shift the balance between harms and benefits by building individualized, risk-adapted approaches to cancer screening, biopsy referral, and treatment [3, 4]. In the diagnosis of neuroblastoma the HTA process has allowed to identify predictive and prognostic biomarkers as Neuron Specific Enolase (NSE) with the potential to change the morbidity and mortality trends [34]. However, the HTA panel of experts has endorsed the promotion of multicentric collaborative studies and the improvement of research methodology and statistical modeling because of the low level of evidence. It has been highlighted that the low prevalence of the disease, the wide heterogeneity of the case series, the poor study design and the heterogeneity of the reports represent the greatest limitation to the evidence [34].

In promoting cancer prevention the HTA approach has driven the appropriate request of fecal blood tests for referral to colonoscopy and of BRCA for risk reducing surgery of breast and ovarian cancer in view of the favorable cost-effectiveness ratio [33, 35]. In the case of Crohn disease the HTA approach has allowed to identify an array of biomarkers with potential predictive ability for inclusion in diagnostic algorithms [36].

Presepsin represents an example of biomarker whose clinical de-implementation has been gauged on HTA methodology since there is no robust evidence on the contribution of this marker to the prediction of sepsis, of patients' outcomes and to antibiotics stewardship. Although the quality of the research may seem the main drawback of the clinical validation of presepsin, the HTA report does not support public investment either to promote further investigations or to use the assay into the clinical practice, until further and better research should provide higher evidence [37]. The HTA approach has boosted the introduction of biomarkers of pre-eclampsia to assess the risk of maternal and perinatal morbidity and mortality and to manage the drug stewardship. The HTA process has shown that ordering these biomarkers is cost saving in the management of pre-eclampsia and may slightly improve the quality of life of pregnant women. However, further HTA reporting is required to address economic evaluation, to assess the diagnostic accuracy of the marketed immunoassays and to determine the suitability of biomarkers to replace other co-requested tests (i.e., proteinuria) [38].

The management of the appropriate ordering of folate test according to the principles of HTA represents one of the main examples of laboratory cost saving. Anyway, by considering the healthcare outcomes, the cost-effectiveness of folate testing compared to not testing and to providing targeted supplementation is still unclear. Indeed, formal economic evaluations and pharmacovigilance data are not available for appraisal. Furthermore, the poor harmonization of the available assays likely affects the characterization of folate deficiency in the tested subjects and this has to be dealt with by the laboratory professionals involved in the HTA process in order to optimize FA supplementation in the population at risk [39].

The previous evaluations are examples of a wider field of evaluated biomarkers, anyway also the methodology in several cases has undergone HTA evaluation leading to organizational changes in the provision of health care and/or to changes in the diagnostic pathway when cost-effectiveness has been reported. Two main examples are the replacement of cardiac troponin conventional assays by high-sensitive methods for early rule-out of acute myocardial infarction and the implementation of point-of-care methodology (i.e., blood gas analyzers) often shifting the estimation of biochemical parameters from central laboratory to local health care units [40, 41].

The clinical effectiveness of biomarkers and/or of the improvement of the methodology has been demonstrated by the interaction of laboratory professionals, researchers, statisticians, and manufacturers of *in vitro* diagnostics (IVD). This information has further been shared with clinicians, epidemiologists, and guidelines teams allowing the design of diagnostic pathways more responsive to clinical and patients needs. The extension of the collaboration to regulatory bodies and policy makers has further allowed to evaluate if the improvement of health outcomes is enough for the marker to meet regulatory approval and achieve reimbursement requirements [32].

Conclusions

The HTA model has highlighted that one of the key issues for the failure of the biomarkers implementation and use in clinical practice is the overinterpretation of the research findings in the meta-analysis of the original studies on diagnostic accuracy, on predictive and prognostic value. The spin (i.e., distortion) of the results of the original studies and systematic reviews has been most frequently associated with the poor research methodology and unsuitable statistical modeling adopted in both the selected original articles (i.e., "almost ubiquitous significant results") and the meta analytic approach [11, 42].

HTA allows the concerted action of scientists with different skills as well as various stakeholders and allows first to overcome the methodological drawbacks of the evidence-based literature and then to properly address the estimation of the biomarker value as a part of a decision-making process. However, clinical evidence regarding patient relevant outcomes and the benefit-risk balance is the basis for biomarker eligibility for reimbursement [9]. The appraisal of predictive biomarkers within complex algorithms with the potential to maximize the clinical benefit of certain therapies displays several closely interlinked potential pitfalls. The full characterization of the marketed assays, the assessment of the inter-method bias and the potential impact of method change on patients' risk classification have to be clarified before moving on to the subsequent statistical and economical analysis. There are several examples in literature showing that the use of biomarkers' results obtained from different assays can greatly contribute to the miscalibration of predictive models of adverse outcomes. This is a crucial point to account for in some frameworks (i.e., cancer immunotherapies) where side effects, high costs, limited number of responders, impose the computation of unbiased and well calibrated predictive models to maximize the clinical benefits of the treatment [43]. The introduction of HTA methodology into the development pipeline of biomarkers for clinical use should be seen in the perspective to increase the value of the laboratory stewardship, currently limited to monitoring the appropriate a) request, b) retrieving, and c) interpretation of the laboratory test results, shifting the endpoint from patient safety to patient benefit. More recently the COVID-19 pandemic has disclosed the urgent need to create a robust and sustainable system to urgently deal with global health concerns [44].

In this context rapid HTA methodology has been developed to early evaluate and disseminate the evidence on the diagnostic accuracy of the various SARS-CoV-2 serological tests, to assess the cost-effectiveness of SARS-CoV-2 point-of-care tests, and to suggest the use of individual protection device and of contact tracking systems [45–47].

In conclusion the HTA methodology fully addresses this unmet healthcare requirements by enabling rapid development, dissemination and cost-effective implementation of diagnostic tests, finally allowing healthcare providers to make critical patient-management decisions. Therefore, HTA approach allows to assess value to laboratory results evaluating whether these could effectively improve health care outcomes and quality at sustainable costs. To this aim laboratory professionals engaged to increase the value of the laboratory stewardship are now asked to embrace a value-based health care approach [43].

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