Healthcare Technology Assessment of Medical Imaging Technology

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Abstract

This chapter provides a view of how due to the health systems and technologies development in the last century a series of functions have been developed to achieve an optimal health for the entire population with available resources. Considering the particularities of the imaging technology area, the authors describe in what manner the value of these technologies should be defined, what are the approaches proposed for assessing this value, both by academia and by several institutions and finally by looking specifically at the SPARTACUS case an approach to compare two diagnostic modalities in terms of their impact on patient outcome is described. The author's description of the SPARTACUS project is particularly informative. The results of this project made the authors concluding that, although RCT are not commonly used in the context of evaluating diagnostic tests, its use allows for the assessment of a wider scope of outcomes that are arguably relevant from an HTA perspective.

1 Health Technology Assessment

The beginning of this century is being characterized by an exponential development of disruptive (e.g., Hepatitis C drugs) and innovative (e.g., hybrid technologies such as PET-MRI or MRI for prostate cancer) health technologies

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which are accessing the healthcare market. Additionally other technologies are emerging, and expecting, to quickly also access the market (e.g., molecular diagnostics). These new technologies usually are costly, either in their acquisition, installation, operation, or maintenance. This trend is paralleled with the growth and aging of populations which will imply an increased demand for medical imaging services, obviously associated to higher costs. These expected raising costs are a concern for finite healthcare budgets of health systems. Policy decision-makers, healthcare managers, and clinicians have to be wise on how to allocate these scarce economic resources. They need to base their decisions in comprehensive, objective, health system tailored information. Questions faced by decision-makers when deciding on one innovative and new health technology (HT) include: is this new HT necessary for my country/hospital? Is the new HT justified sufficiently by the overall benefits achieved in terms of safety, health outcomes, and costs in my country/hospital? Which patients can benefit the most from this new HT in my country/hospital? Among the big number of choices of HT, which are the most appropriate for a specific health problem in my country/hospital?

Healthcare Technology Assessment (HTA) aims to explore in what way and under what conditions the use of specific healthcare technologies can help to create value for patients and society at large (Banta and Luce 1993). Such value may derive from the fact that healthcare technologies can help to restore functioning, alleviate suffering or pain, or avert death in an affordable and sustainable way. Value may also derive from fostering moral values such as bolstering patients' autonomy and promoting equity. HTA provides with the information decision-makers need to base their decisions. HTA is a tool used more and more around the world by health system decision-makers in their process of deliberating and deciding which innovative and emerging technologies deserve allocation of resources. The International Network of Agencies for Health Technology Assessment (INAHTA) define HTA as "the systematic evaluation of the properties and effects of a health technology, addressing the direct and indirect effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies" (INAHTA 2017). HT is defined as "an intervention that may be used to improve health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation". Therefore, HTs include pharmaceuticals, devices, procedures, and organizational systems used in healthcare (INAHTA 2017). The goal of HTA is provide input into decision-making in policy and practice (Health Technology Assessment 2009), it is not research for research or for the sake of knowledge, it has to be aimed to advice and influence decision-making.

HTA takes a broad view of the HT; it takes into account a comprehensive set of aspects that can impact in the healthcare system when the HT accesses the market. The aim of HTA is to determine the "added value" that the HT brings into the system, especially considering its benefits and financial costs, what is it known as cost-effectiveness analysis (i.e., looking at the incremental cost-effectiveness ratio, ICER). Besides to consider costs and effectiveness (i.e., the effects of HT in real life), HTA include in their analysis, insofar as possible, information on organizational impact (i.e., how the technology is going to impact the current provision of care), patient impact (i.e., how the HT is going to impact the quality of life of the patient and in its relations with his/her environment), and ethical, legal, and social consequences of using the HT. Moreover, sometimes it gives guidance on where and how the HT should be implemented in clinical practice (Goodman 2014). To notice that the comprehensive amount of information that HTA embraces make it different from the evidence requirements asked by regulatory agencies when granting the market access for a HT, which are mainly based in looking at the safety (i.e., HT is not going to incur in an unacceptable risk for patients) and efficacy (i.e., benefits from the HT in "ideal"/"controlled" conditions of practice). Figure 1 depicts the differences in informational requirements from regulatory agencies and HTA agencies; it also

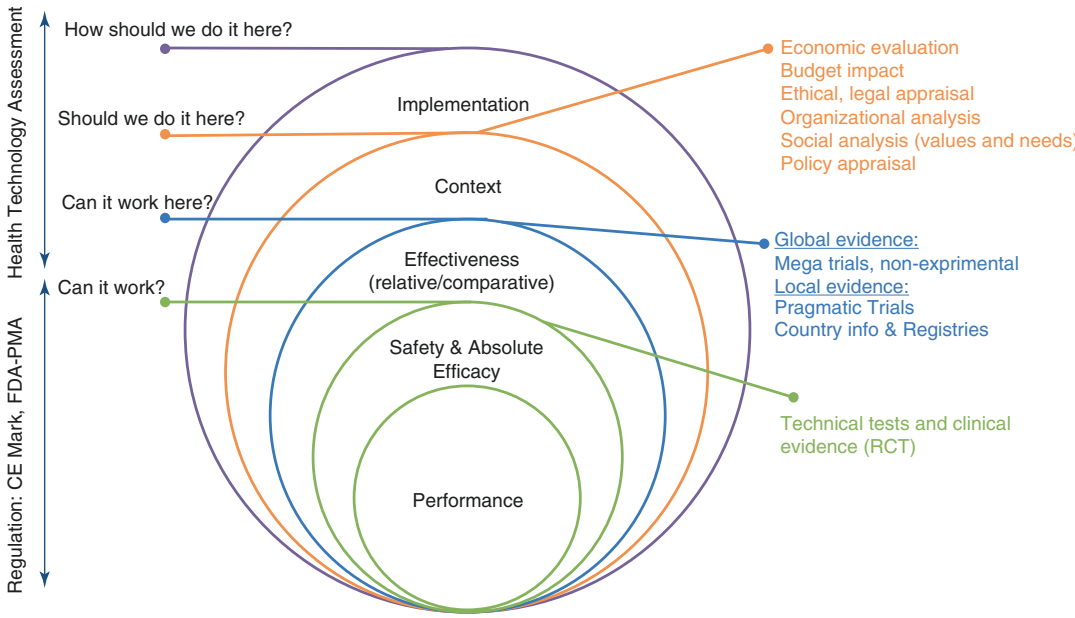

Fig. 1 The path for the assessment of health technologies

shows the sources where information is obtained. Although ideally an HTA report would have to include all the steps and information shown in Fig. 1, the real world make that this happens in few occasions. This is so because decision-makers not always asked for all these information, moreover since the main feature of HTA is that considers the context where the decision should be taken (Sampietro-Colom 2012; Kidholm et al. 2015), different healthcare context ask for different types of information or conducts the assessment process differently. For example, in France, the organization in charge for assessing HTs (i.e., HAS) look first at the effectiveness of the HT; if the available data is not good enough, they do not look at the cost aspects. For the contrary, in the United Kingdom, the organization in charge of doing the assessments (i.e., NICE) performs directly a cost-effectiveness analysis comparing the effects and the cost of the new HT with the current standard of care (Oortwijn 2017).

Given the wide scope of HTA, it needs to be a systematic interdisciplinary process based on scientific evidence and other type of information (Health Technology Assessment 2009). HTA aims to achieve this by producing, critically appraising, and synthesizing relevant evidence. Such evidence may derive from various sources, e.g., randomized controlled trials (RCTs) and clinical registries, and entail the use of both, qualitative and quantitative research methods (Bailar and Mosteller 1992).

In their process to elaborate the HTA report, a wide range of professionals such as clinicians, nurses, economists, social scientists, ethicists, public health and health services researchers and, more and more, patients and their relatives are included. The most frequent activity and product of HTA has traditionally been the systematic review of published evidence regarding the HT, and cost-effectiveness analysis also based on published data (Goodman 2014). Nevertheless, more and more HTA is being introduced in prospective clinical studies, which collect information in all the aspects required to inform a decision in a specific context (Zboromyrska et al. 2016).

As mentioned before, HTA is aimed to advice and influence decision-making. HTA since its origins, in the 80s decade, was devoted to inform coverage and reimbursement decisions. Nevertheless,

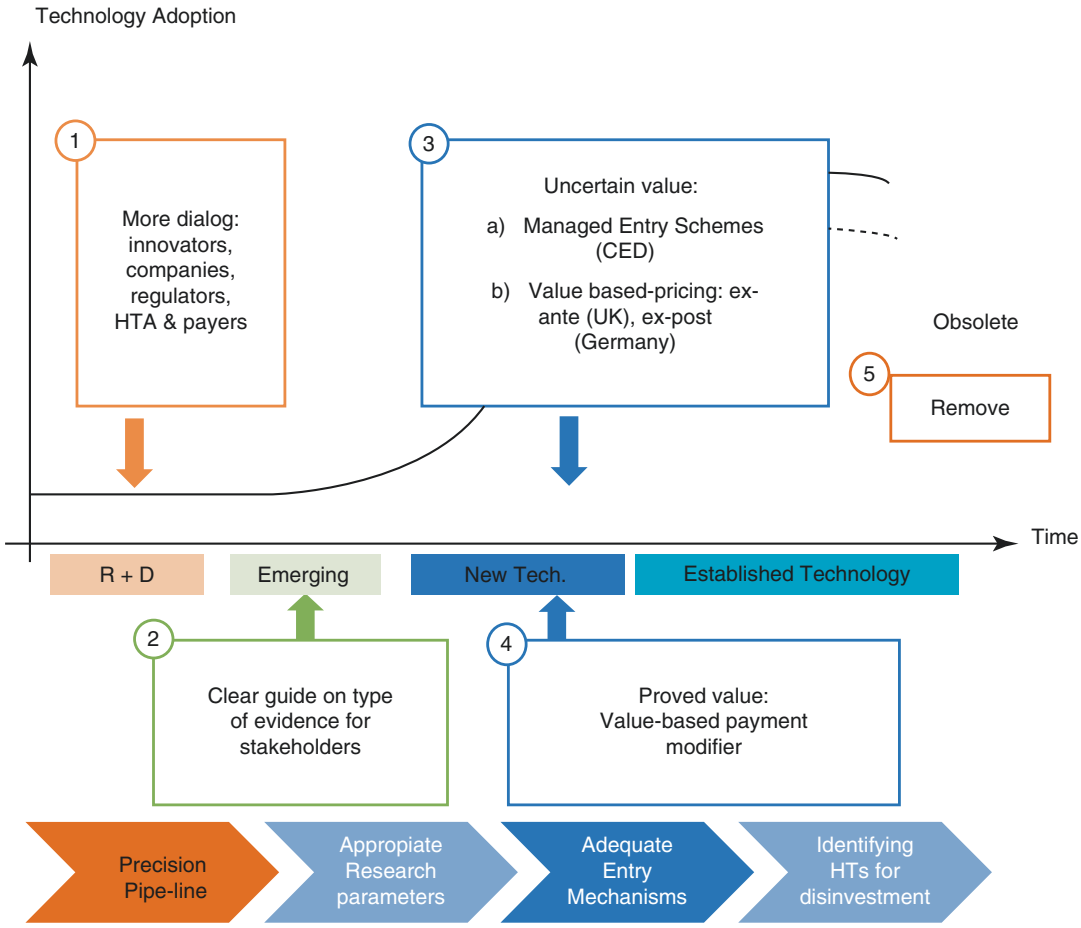

Fig. 2 Use of HTA in the life cycle of health technologies and in the decisions across development

currently HTA is used along the life cycle of the HT to either inform early decisions about whether to pursue development of a HT in the stage of R&D, to later decisions on disinvestment of HT (Facey et al. 2015; Henshall et al. 2012). Figure 2 shows the uses of HTA along the lifecycle of a HT and across the several decisions that should be made in their development.

The use of HTA around the world is continuously expanding. Nowadays, the International Network of Agencies for Health Technology Assessment (INHTA) includes 47 public HTA organizations from all the continents. These are mainly governmental agencies. Besides there are a growing trend to establish hospital-based HTA units (HB-HTA) around the world (Sampietro-Colom and Martin 2016). Moreover, the use of HTA when deciding the added value of HT is being strongly promoted by the European Union and the World Health Organization (WHO). The former has formally established an HTA Network that is aimed to fulfil the Directive 2011/24/EU which enforces to use HTA before introducing innovative technologies in Europe (Health Technology Assessment Network 2017). Additionally, the 67th world health assembly approved a resolution in May 2014 urging member States "to consider establishing national systems of health intervention and technology assessment, encouraging the systematic utilization of independent health intervention and technology assessment in support of universal health coverage to inform policy decisions, including

priority-setting, selection, procurement supply system management and use of health interventions and/or technologies, as well as the formulation of sustainable financing benefit packages, medicines, benefits management including pharmaceutical formularies, clinical practice guidelines and protocols for public health programmes" (WHA67.23 2014). Finally, HTA is also being grounded in the USA through the enforcement of comparative-effectiveness research (Riaz et al. 2011).

The current paradigm of evidence-based policy and clinical decision-making requires that the potential value of any specific healthcare technology be defined and operationalized through an HTA. In addition, it requires an understanding of the factors that jointly determine a healthcare technology's actual value in a specific context. Both of these—how should value be defined and what factors seem to determine a healthcare technology's actual value in a specific context—are highly relevant to the HTA of imaging technologies.

2 HTA and Diagnostic Imaging

2.1 Recognizing the Challenges

New diagnostic imaging technologies, as any HT in the era of evidence-based decision-making, need to prove what added value brings to what it is already in place. Nevertheless, worth to mention that to assess diagnostic imaging technologies is more complex than assessing treatments. Metrics for assessing the effectiveness of treatments usually include surrogate outcomes (e.g., bone mass levels) and end-point outcomes (e.g., clinical morbidity, functional status, quality of life, and mortality) and usually a direct relationship between the treatment and the result can be established. For diagnostic imaging technologies there is not such a direct relationship between their use and final patient outcomes; its final impact in patient outcomes depends on the effect of the clinical intervention selected from the information provided by the diagnostic image (Fryback and Thornbury 1991). Therefore, one challenge for assessing diagnostic imaging technologies is the need to evaluate the technology in the context of its effect on the pathway of care, which makes the assessment more complex. Moreover, it is not always obvious where in the care pathway the diagnostic technology is best placed, which require evaluating different strategies. Additionally, since diagnostic tests are frequently done in conjunction with other tests or measurements, it is the composite of the results from the series of tests that is used in decision-making and, therefore, what should be assessed. Another challenge deals with the fact that diagnostic technologies, especially those based on electronics, often change rapidly as new methods, upgrades, and capabilities are added. This situation poses difficulties when looking for the right comparator for the assessment (i.e., risk of outdated comparisons). Comparisons are also challenged by machine and inter-reader variability, and operator learning curves which impact on diagnostic performance and, finally, in outcomes (Gazelle et al. 2011).

2.2 Assessing the Value of Medical Imaging Technology

Although challenges for assessing diagnostic imaging technologies exist as mentioned above, frameworks for assessing their value have been in place for long time. The most used framework dates from 1991 (Fryback and Thornbury 1991) and includes six progressive levels of efficacy assessment: level (1) technical efficacy (e.g., imaging resolution); level (2) diagnostic accuracy efficacy (e.g., test sensitivity/specificity); level (3) diagnostic thinking efficacy (e.g., pre- and post-test changes in subjective determined outcome); level (4) therapeutic efficacy (e.g., effects of diagnostic on choice of therapy); level (5) patient outcome efficacy (e.g., value of test information including measures of morbidity, quality of life, and mortality); level (6) societal efficacy (e.g., cost-effectiveness analysis from societal point of view). This framework was mainly addressed to be guidance for making

decisions on the type or characteristics of the research needed for assessing the value of a specific technology.

Building on this framework, the Working Group on Comparative Effectiveness Research for Imaging has recently developed taxonomy for classifying diagnostic imaging technologies according to the extent of outcomes data needed for determining their added value (Gazelle et al. 2011). The taxonomy is based in three pillars, which are: (1) size of the at-risk population (i.e., number of people affected by the technology); (2) anticipated clinical impact (i.e., expected net health benefits compared with the standard of care); and (3) potential economic impact (i.e., unit cost downstream healthcare cost, and relative cost of the technology compared with standard of care). Each of these three pillars has three levels of impact: small, medium, large. The combination of the pillars and their levels determines the characteristics and robustness of data and outcomes requirements to prove the added value of the technology. For example, the higher the population at risk and the smaller the anticipated clinical impact the higher level and robustness of outcome data required. The data and outcomes considered in this taxonomy relates to the six levels of efficacy assessment mentioned above. To mention, that the type of outcomes considered relevant can differ substantially depending on the type of decision-maker looking at the value of the technology. Regulators, politicians, healthcare managers, clinicians, and patients can all have different requirements for the type of data and outcomes they consider relevant. This is very important to take into account when designing original research studies as well as when synthesizing the available evidence for testing the added value of a technology. Involvement of all relevant stakeholders is highly advisable to look at the most appropriate outcomes to include in the assessment.

Traditionally, the value of imaging technology has been defined in terms of its capacity to accurately distinguish between persons who do, and persons who do not have a particular condition of interest. Key parameters to express such diagnostic performance are sensitivity, specificity, positive and negative predictive value, and likelihood ratio. Such measures determine to what extent prior probability of disease is affected as the result of diagnostic test information.

Increasingly, however, such diagnostic test parameters are considered surrogate endpoints, and patient outcome is considered the key parameter of interest (Schünemann et al. 2008). In other words, the value of a diagnostic test cannot be inferred from its capacity to establish or exclude disease, but from patient outcome: how does using the diagnostic test improve the prognosis of patients? Clearly, this requires a different study design to produce the requisite data. Classical diagnostic test research requires a systematic comparison of results of an index test with results of a reference test (gold standard). Data are analyzed through cross-tabulation, yielding parameters such as sensitivity and specificity and positive and negative predictive values. When patient outcome is used as a criterion for a diagnostic test's value, an RCT is required, randomly allocating eligible patients to two or more different diagnostic trajectories, followed by clinical management on the basis of these trajectories. Patients are then followed up for sufficiently long periods of time to allow to decide whether the different diagnostic trajectories translate into clinically meaningful and statistically significant differences between the groups of patients. Recent examples of such RCTs include the studies of computed tomographic angiography in patients with clinically suspected coronary disease (Douglas et al. 2015; Newby et al. 2015; see Table 1 for a summary of these trials).

An advantage of this approach is that it also allows for assessment of other endpoints, such as cost-effectiveness of a novel diagnostic test as compared to current diagnostic practice. Another advantage is that there is no need for a gold standard. A possible drawback of this approach is that it represents the combined assessment of a diagnostic test and subsequent clinical management. Theoretically, it is possible that a novel diagnostic test outperforms currently available diagnostic tests, but that this fails to translate into improved clinical outcome because there are insufficient therapeutic opportunities to take advantage of such difference.

Table 1 Examples of recently published findings of RCTs of diagnostic technologies

Reference	Patient population	Comparison	Primary endpoint	Follow-up	Results	Conclusion
Douglas et al. (2015)	Patients with clinical symptoms suggestive of coronary artery disease (mostly chest pain and dyspnea on exertion); $n = 10{,}003$	Coronary computed tomographic angiography (CTA) vs. functional testing (FT); (exercise electrocardiography, nuclear stress testing, or stress echocardiography)	Composite endpoint consisting of death, myocardial infarction, hospitalization for unstable angina, or major procedural complication	Median of 2 years	Occurrence of primary end-point event of 3.3% (CTA) vs. 3.0% (FT); HR = 1.04 (95% CI 0.83–1.29; $p = 0.75$)	In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CTA, as compared with FT, did not improve clinical outcomes over a median follow-up of 2 years
Newby et al. (2015)	Patients with suspected angina from coronary heart disease; $n = 4146$	Standard care plus CTCA vs. standard care alone	Certainty of the diagnosis, change of planned investigations and treatments, 6-week symptom severity, admittance to hospital for chest pain, fatal and non-fatal myocardial infarction	1.7 years	Certainty of CAD increased (RR 2.56; 95% CI 2.33–2.79, $p < 0.0001$); change in planned investigations (15% vs. 1%, $p < 0.0001$) and treatments (23% vs. 5%, $p < 0.0001$); no difference in 6-week symptom severity or in admittance to hospital for chest pain; 38% reduction in fatal and non-fatal myocardial infarction (HR 0·62, 95% CI 0·38–1·01; $p = 0·0527$)	In patients with suspected angina due to coronary heart disease, CTCA clarifies the diagnosis, enables targeting of interventions, and might reduce the future risk of myocardial infarction

CTCA computed tomographic coronary angiography, *CTA* computed tomographic angiography, *FT* functional test, *CI* confidence interval, *HR* hazard ratio, *CAD* coronary artery disease, *RR* relative risk

Thus, such trials aim to optimize the entire patient-pathway instead of determining the best possible diagnostic strategy. In that sense, RCTs testing combinations of different diagnostic strategies and successive treatment may be considered truly pragmatic trials: they aim to establish whether different diagnostic strategies result in better outcomes that matter to patients, not in evidence of different diagnostic test performance (Ford and Norrie 2016).

Besides the frameworks proposed by academia, the European Network of Agencies for Health Technology Assessment (EUnetHTA) has also developed the HTA Core Model for Diagnostic Technologies (2008). This Core Model is proposed to standardize the assessment of diagnostic technologies and it is addressed mainly to scientists performing HTA. Nevertheless, this framework could also be a guidance to take into account when designing clinical trials for imaging technologies in order to include all relevant data that will be asked when the HT will want to access the market. This Core Models uses ten main domains of assessment including: (1) current use of technology (implementation level); (2) description and technical characteristics of technology; (3) safety; (4) accuracy; (5) effectiveness; (6) cost (economic evaluation); (7) ethical aspects; (8) organizational aspects; (9) social aspects; (10) legal aspects. For each domain, there are a variable set of topics to consider (e.g., for clinical effectiveness the topic could be life expectancy, or for societal aspects could be ability to work). Moreover, for each topic, there are different issues to take into account or explore (e.g., for the domain on clinical effectiveness and the topic mortality, two issues could be the effect of the intervention on the mortality caused by the target disease and the effect of the intervention on the mortality due to other causes than the target disease).

Public organizations performing HTA (e.g., Governmental agencies, hospitals, universities) have been assessing diagnostic imaging technologies for long time. A research performed under the Euro-Bioimaging Project which include 33 organizations performing HTA from 17 European countries showed their experience in assessing diagnostic images technologies as well as the type of contribution these organizations could provide in a network assessing this type of technologies (Fig. 3). Therefore, considering the existence of available frameworks for assessing diagnostic imaging technologies and the experience and willingness of collaboration from orga-

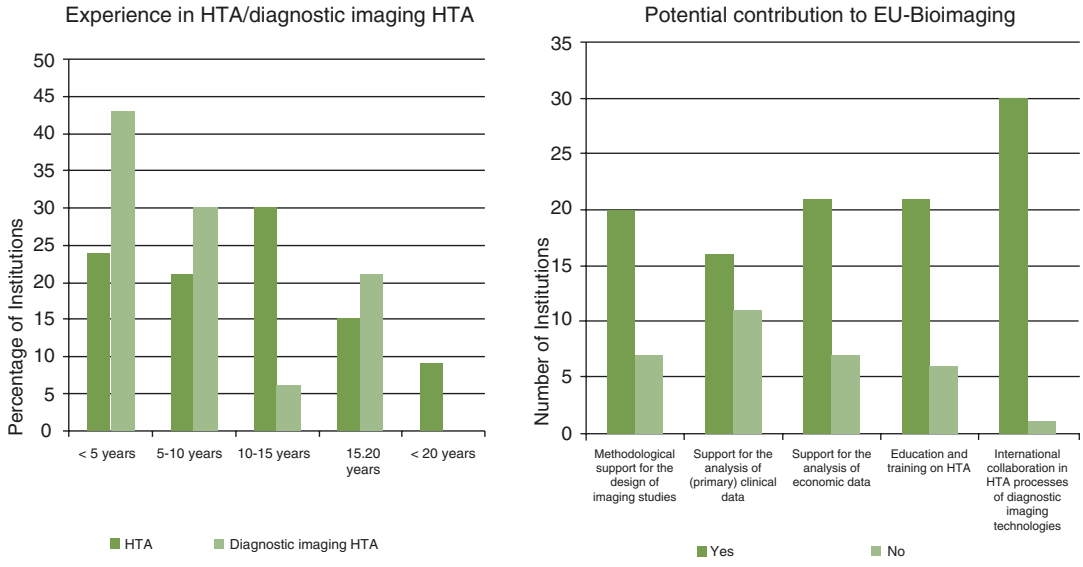

Fig. 3 EU experience in HTA on diagnostic imaging technologies

nizations performing HTA, the assessment of the added value of innovations in the field of diagnostic imaging should become a systematic procedure before their access to the healthcare arena.

2.3 Considering Determinants of Value of Medical Imaging Technology in Daily Practice

It is widely recognized that results from RCTs need not translate into similar results in daily practice. Patients may be selected more carefully, users may be more experienced, or more appropriate action may be taken in case of adverse events in the context of an RCT as compared to daily practice. This definitely also seems to hold with respect to imaging technology. Although the value of specific imaging technologies itself need not be challenged, the overall "community value" is seriously challenged because of suspected wide and systematic over-utilization (Hendee et al. 2010). Average annual growth rates of use of CT of 10.2% (1998–2005) and of 4.2% (2005–2008) among HMO enrolees in the USA have been reported; for MRI, these figures were 14.5% and 6.5%, respectively. Concurrently, associated radiation exposure has increased during this period (Smith-Bindman et al. 2012). An estimated 20–50% of imaging is deemed unnecessary, and imaging is by far the most common service on the list of unnecessary tests and procedures of the Choosing Wisely campaign. In response, professional organizations have started to put more focus on the development of criteria for the appropriate use of imaging technologies (e.g., Carr et al. 2013), which, of course, requires a relevant and reliable evidence base, in conjunction with some form of monitoring (Durand et al. 2015). In the remainder of this chapter, we will present a more detailed example of an RCT of an imaging technology (the SPARTACUS trial, comparing CT scan versus Adrenal Vein Sampling in patients with hypertension due to primary aldosteronism). This will serve as a basis for a discussion of the strengths and weaknesses of such approach, resulting in concrete recommendations for deciding when an RCT might be appropriate to assess the value of medical imaging technology.

3 Case Study: Imaging Versus Functional Testing in Patients with Primary Aldosteronism: The SPARTACUS Trial

The SPARTACUS trial was conducted to assess whether imaging (computed tomography, CT) or functional testing (Adrenal Vein sampling, AVS) is the preferred mode of distinguishing between bilateral adrenal hyperplasia and unilateral aldosterone-producing adenoma in patients with primary aldosteronism (PA) (Dekkers et al. 2016). Increasingly, PA is being recognized as an important cause of hypertension and its squeals (Abad-Cardiel et al. 2013). PA may originate from bilateral adrenal hyperplasia (BAH) or from unilateral adenoma-producing adenoma (APA). Clinically, it is important to distinguish between the two subtypes of PA, since patients with BAH are treated with mineralocorticoid receptor antagonists and patients with APA are offered adrenalectomy. Conventionally, imaging (CT) is used to differentiate between the two subtypes. The limitations of this particular use of CT have been widely recognized (e.g., Patel et al. 2007). On the one hand, the resolution of CT may be insufficient to detect small nodules. On the other hand, it may lead to the detection of non-productive nodules. AVS involves a percutaneous femoral vein approach, taking blood samples from the inferior vena cava and both adrenal veins, allowing for the measurement of aldosterone and cortisol levels at each of these sites (Daunt 2005). Although AVS is less readily available, technically more demanding, more invasive, and more costly than CT, it might still be the preferred option if it would more accurately discriminate between BAH and APA. The SPARTACUS trial was designed to address this issue. In the absence of a gold standard, we chose to conduct an RCT. This allowed

us to compare the two diagnostic modalities in terms of their impact on patient outcome (achieving target blood pressure: <135/85 mmHg according to daytime ambulatory blood pressure monitoring). The hypothesis was that if the two diagnostic modalities (imaging (CT) and functional test (AVS)) would differ in their capacity to accurately distinguish between APA and BAH, this would translate into a difference in optimal treatment (adrenalectomy for patients with APA and mineralocorticoid receptor antagonists for patients with BAH), which, in turn, would translate into differences in proportion of patients reaching target blood pressure. However, since the effect of suboptimal treatment of PA may be masked by more intensive antihypertensive medication, the primary endpoint of the study was intensity of antihypertensive medication needed, expressed in daily defined doses (ddd). The trial was designed to achieve a 80% statistical power to detect a difference of 0.8 in ddd between the two groups. All patients were followed up for a period of 1 year. The RCT design also allowed us to assess whether the two diagnostic modalities resulted in differences in quality of life and costs. The trial was an investigator-driven study, conducted at five university-based hospitals in Europe.

At 1 year follow-up, no differences were found between the two groups in terms of median intensity of antihypertensive medication (ddd of 3 in both groups, $p = 0.52$), median number of antihypertensive drugs (2 in both groups, $p = 0.87$), proportion of patients achieving target blood pressure (43% and 45% in the CT group and AVS group, respectively, $p = 0.82$), or median 24 h ambulatory blood pressure (systolic: 127 (IQR: 120–138) vs. 128 (IQR: 121–135) mmHg; diastolic: 80 (IQR: 75–86) vs. 81 (IQR: 76–85) mmHg, in the CT and AVS group, respectively). No difference was found in terms of median quality adjusted life years either (1.29 (IQR: 1.23–1.35) and 1.24 (IQR: 1.18 1.30) in the AVS and CT group, respectively; $p = 0.26$). Median total costs were higher in the AVS group (€6746; IQR 5965–7527) as compared to the CT group (€4228; IQR 3604–4852), $p < 0.001$. Costs included costs of drugs, surgery, AVS, CT, ambulatory visits, and costs associated with complications. These figures translate into a low probability that AVS should be considered a cost-effective alternative to CT in the diagnostic workup of patients with PA, with a probability of 0.02, 0.24, and 0.35 at cost-effectiveness thresholds of €20,000, €50,000, and €80,000 per QALY, respectively.

Although on theoretical grounds AVS might be expected to be superior to CT in distinguishing between patients with BAH and patients with APA, the results of our trial suggest that this may not actually be the case. Although the design of our trial does not allow to draw conclusions regarding the diagnostic performance of the two modalities (accuracy of identifying the two subtypes of PA), the results do suggest that even if there were such a difference, this does not translate into clinically meaningful and statistically significant differences in patient outcomes (blood pressure control, quality of life). Also, from a societal perspective, using AVS instead of CT in the diagnostic workup of patients with PA is unlikely to constitute an efficient use of resources. An RCT, then, although not commonly used in the context of evaluating diagnostic tests, allows for the assessment of a wider scope of outcomes that are arguably relevant from an HTA perspective. A drawback might be, however, the higher costs that are associated with conducting an RCT as compared to conventional diagnostic test research. It would be important, then, to assess upfront whether conducting a specific RCT might be worthwhile. In the following, we will briefly outline a modelling procedure that could be used for such purpose.

4 Value of Information Analysis

Resource scarcity does not only hold for healthcare interventions, it also holds for research into the safety and clinical and cost-effectiveness of those interventions. Spending wisely is not only a mandate for healthcare, it is also a mandate for healthcare research. It would be helpful to assess

upfront, then, whether a specific RCT might constitute a worthwhile use of resources. A potentially fruitful approach to this question might be value of information analysis (Keisler et al. 2014). Basically, in this approach, conducting research is a matter of reducing uncertainty. In addition, it is acknowledged that uncertainty can incur certain costs. The approach offers a framework for integrating costs and anticipated benefits (resulting from reducing uncertainty) of conducting a specific study. In the case of AVS and CT in the diagnostic workup of patients with PA, this could work out as follows. At the time, prior to the conduct of the SPARTACUS trial, there was genuine uncertainty regarding the benefits of AVS as compared to CT in the diagnostic workup of patients with PA. Theoretically, AVS could be superior to CT, but there was hardly any evidence to substantiate such claim. In such a situation ("equipoise"), it is defensible to subject half of the patients to AVS, and half of the patients to CT. In the absence of evidence of the comparative value of AVS versus CT, this could mean that there is a 50% probability that patients are subjected to AVS, while it has no added benefit to patients. Likewise, there is a 50% probability that patients are *not* subjected to AVS, while it would confer a benefit to patients. In the former case, a more invasive and (arguably) more expensive diagnostic test is being used, in the absence of an added benefit. In the latter case, costs are incurred because patients are treated suboptimally, resulting in unnecessary persistence of poorly controlled blood pressure and associated cardiovascular events. Conducting a study should result in either reducing or increasing the likelihood that AVS is beneficial to patients. Assuming that clinical practice will be adjusted accordingly (i.e., AVS is offered less, or more, frequently to patients with PA), this would result in a reduction of those costs. This represents the "value of information" in this context. This value can be compared with the costs associated with conducting the trial. Those costs need not be prohibitive, if we may assume that, as long as the evidence has not been produced, it is reasonable that half of the patients would get the experimental procedure, and half of them would not. The incremental costs of conducting a trial would, then, consist of developing a research protocol, obtaining approval from the relevant review boards, developing patient information, setting up an infrastructure for screening, informing and randomly allocating patients, collecting, analyzing, interpreting, and reporting the data. A realistic estimate of such costs would, in case of the SPARTACUS trial (five centers, two European countries, 200 patients, 3 year follow-up) be approximately €650 K. Such costs should be compared with the costs associated with reducing the then existing uncertainty. These can be estimated through modelling, which would, of course, require several assumptions from experts. Scenario analysis could be used to calculate best and worst case scenarios. Important assumptions underlying the value of information approach are the following: (1) the study will, in fact, reduce uncertainty. This assumption critically hinges on the methodological quality of the trial and features such as inclusion of an appropriate trial population, accurate measurement of relevant endpoints, maintenance of randomization throughout a sufficiently long follow-up period (i.e., limited loss to follow-up, limited missing values, limited cross over or contamination, etc.). (2) How the data from a novel trial compare to currently available evidence. (3) Adjustment of clinical practice in accordance with trial results. If the trial results would suggest that AVS has, in fact, added value as compared to CT, capacity for conducting AVS would have to be augmented. If, as was the case, the results of the trial suggested that AVS does not have such added value, the community needs to accept this and revise guidelines and practice accordingly. As already mentioned in the introduction of this chapter, this may prove a considerable challenge (Durand et al. 2015). A further challenge is posed by the rapid pace of technological development: by the time the results of a trial have become available, the technology may have changed in such a way as to make these data of limited relevance (the "moving target problem") (Sorenson et al. 2008). Arguably, these aspects need to be taken into account, alongside the formal value of information analysis.

Conclusion

The HTA of diagnostic imaging poses several challenges. A key problem in recent years has been the indiscriminate use of diagnostic services, rather than the value of those services per se. This has renewed interest in the development of guidelines and in the monitoring of the compliance with those guidelines. Clearly, this requires the availability of evidence that is both, robust and relevant to daily clinical practice. Following recent methodological guidelines (e.g., Schünemann et al. 2008), we have argued that conventional diagnostic test research, resulting in information of diagnostic test characteristics (sensitivity, specificity, etc.) is insufficient to produce such evidence. Instead, RCTs comparing different diagnostic strategies in terms of their impact on clinical outcomes, quality of life, and costs appear to be more useful and capable of producing information that is needed for a comprehensive HTA of medical imaging technologies. A drawback of such studies may be that they are time-consuming and costly. We suggest that a value of information approach may be helpful in deciding whether a particular RCT seems a worthwhile use of R&D resources.

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