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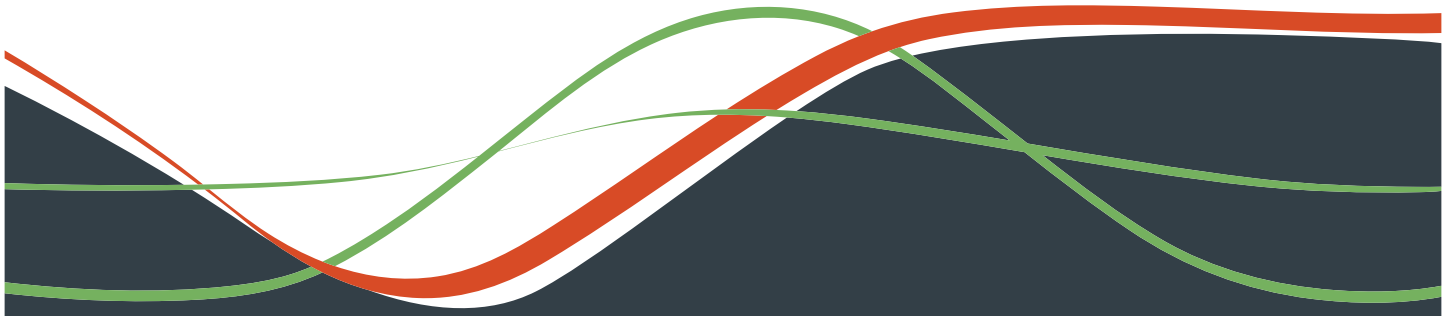

The Value of Knowing and Knowing the Value:

Improving the Health Technology Assessment of Complementary Diagnostics

WHITE PAPER

July 2016

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The study was supported by EPEMED including its members
Janssen Diagnostics Inc.
Genomic Health Inc.
Boston Healthcare Associates Inc.
Abbott Molecular

and received the patronage of the Luxembourg Ministry of Health

LE GOUVERNEMENT DU GRAND-DUCHÉ DE LUXEMBOURG
Ministère de la Santé

Disclosure Statement

Jorge Mestre-Ferrandiz and Bernarda Zamora are employees of The Office of Health Economics. The Office of Health Economics receives a programme research grant from the Association of the British Pharmaceutical Industry. No separate funding from ABPI was received for this paper. Lou Garrison, Professor, University of Washington was a paid OHE consultant for this project.

Acknowledgements

We thank Lydia Mutsch, Luxembourg Minister of Health, for granting the patronage of the Ministry to this work which specifically addresses some reflections made at the July 2015 High Level European conference on Personalised Medicine and European priorities addressed under the Luxembourg EU Presidency.

We thank the OHE team for their management, patience, flexibility and tremendous work.

We thank the editorial committee for its commitment and continuous drive, with special thanks to Ralph Riley and Daniel Lesteven for their exceptional support in leading this initiative over 2 years.

Finally, we thank Mike Drummond (Professor, Centre for Health Economics, University of York), Adrian Towse (OHE Director), Gil L'italien (Senior Director HEOR at Biogen and Adjunct Professor at Yale School of Medicine) and Eric Stanek (Global Market Access Director, Near Patient Testing (NPT) at Novartis) for their external contribution as peer like reviewers.

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Garrison, L., Mestre-Ferrandiz, J. and Zamora, B. 2016. The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics. White Paper. Office of Health Economics and EPEMED.

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EXECUTIVE SUMMARY

NEED FOR AN EXPANDED VALUE FRAMEWORK FOR COMPLEMENTARY DIAGNOSTICS

This White Paper develops a comprehensive framework for assessing the potential value contribution of medical diagnostics and makes related policy recommendations to support its implementation. Two developments motivate this work:

1. A growing recognition that medical diagnostics are used in a wide range of clinically different applications as complements to other medical inputs;
2. A growing appreciation that the traditional framework and metrics applied in the health technology assessment (HTA) of medicines and devices may overlook or undervalue important elements of value provided by diagnostics - in particular, value related to the diagnostic information itself.

We define "complementary diagnostics" (including companion diagnostics) as using biomarkers for the purposes of risk assessment, diagnosis, prognosis, monitoring, and guiding therapeutic decisions; and they are used in the sense of economic complements, that is, medical products or technologies that are used in combination to produce a synergistic effect.*

This collaborative project between the Office of Health Economics (OHE) and the European Personalised Medicine Association (EPEMED) had two major aims:

1. To identify the currently applied practices by HTA bodies for complementary diagnostics, identify the gaps and deficiencies, and propose recommendations to improve such practices;
2. To review, in particular, approaches for addressing the lack of attention in current applied HTA practices to measuring the value of knowing (or of greater certainty) delivered by diagnostics.

Two major reviews were undertaken (and are available as supplementary appendices) to support this policy analysis: a) A systematic literature review summarising different proposed value frameworks and specific valuations for complementary diagnostic, and b) Health economic evaluations of three complementary diagnostics conducted by two HTA agencies (National Institute for Health and Care Excellence-NICE, Haute Autorité de Santé-HAS).

KEY FINDINGS

Traditional cost-effectiveness analysis conducted as part of HTA focuses on three key elements:

1. Life years gained
2. Improvements in patient quality of life
3. Cost-savings within the healthcare system (also called "cost-offsets").

Elements 1 and 2 are often combined in the quality-adjusted life year (QALY) by HTA bodies. Elements 1, 2, and 3, plus the cost of the technology, are then used to assess the cost-effectiveness of the technology.

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* It should be noted that the FDA has recently begun to use the term complementary (versus companion) to refer to "diagnostics that are not required but provide significant information about use of a drug" (Mansfield, 2015). The FDA refers to a companion diagnostics device as "an in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product" (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm). Our economically-oriented definition of complementary diagnostics encompasses the FDA's regulatory-oriented definition, emphasizing the broad role that diagnostics can play guiding care choices in clinical pathways.

The next element most often included is “productivity” or “time value”, reflecting gains and losses related to the value of the patient’s time either when receiving medical care or related to the impact of absenteeism or presenteeism due to illness. Another element - less commonly measured - is nonmedical cost-savings outside the healthcare sector, such as transport costs and family caregiving.

Based on our systematic literature review, we identified and defined five additional elements related to the value of knowing and the value of information:

- Reduction in uncertainty - additional value from knowing a technology is more likely to work
- Value of hope - willingness to accept greater risk given a chance for a cure
- Real option value - the value of benefiting from future technologies due to life extension
- Insurance value - psychic value provided by invention of an innovative medical product and by the accompanying financial risk protection afforded by a new treatment
- Scientific spillovers - value due to other innovations that become possible once a new technology has been proven to work.

These five information-related elements are not unique to complementary diagnostics and, indeed, by definition apply to complementary technologies having an informational aspect. These elements have been recognised in the literature but have not generally been taken into account in HTA, including reimbursement policy.

These ten elements of value for complementary diagnostics are largely independent and additive, and aggregable at a societal level. However, distinct elements could be measured with the same instrument. Any specific assessment of value should not double-count effects. Questions about the weighting, measurability, and commensurability of the elements are separate issues, and are not addressed in this White Paper.

HTA FRAMEWORKS IN ENGLAND AND FRANCE AND APPLICATION TO SPECIFIC DIAGNOSTICS

NICE begun a diagnostic assessment programme (DAP) in 2011, separate from the technology assessment of new medicines. The French HAS has issued two different methodological guidance documents related to the assessment of medical devices, in 2009, and in 2014, of companion diagnostics. It has been argued that DAP does not consider the broader set of outcomes outlined before, as the measure of patient benefit is purely based on the QALY, and the method follows very closely to that used for medicines. French guidelines on companion diagnostics lack recommendations for the use of economic evaluation, limiting the assessment to clinical efficacy.

We also applied our expanded value framework to specific diagnostics (including BRCA1/2 for familial breast cancer, gene expression profiling, and procalcitonin tests), by ascertaining the relevance of each dimension of value and whether the literature has addressed the specific elements, and where possible tried to measure it. As expected, some elements are more relevant for different diagnostics, especially when thinking about predictive or prognostic biomarkers. Evidence on measuring our five additional elements of value, beyond the traditional ones, is scarce.

POLICY RECOMMENDATIONS

Change in evidentiary requirements. Any assessment of value relies on the evidence generated, but what evidence is generated depends on the incentives to do so. Value frameworks used to assess complementary diagnostics require a more comprehensive perspective to include the less tangible benefits. Diagnostics should not be evaluated using the same framework currently used for therapies. Collecting prospective data for many diagnostic companies is, however, often not feasible given the cost of gathering that evidence and the shorter product life cycle. We recommend assessing the use of “coverage

with evidence development" agreements, where the diagnostic is reimbursed for a specified period of time whilst further evidence is collected in clinical practice.

Change in reimbursement to value-based pricing. Incentives matter and thus reimbursement mechanisms are a critical driver of investment on healthcare technologies. We recommend that value-based reimbursement of complementary diagnostics should account for all the elements of value. Cost-effectiveness can be adapted and/or augmented to consider the additional elements of value using, for example, contingent valuation of other specific elements such as the value of reducing uncertainty or the value of hope. We also need to explore how to divide the value, e.g., between diagnostic and therapy when they are complements, to promote dynamic efficiency.

Incentives for the uptake of complementary diagnostics. The potential health impact of complementary diagnostics is very large given the high burden of diseases for which complementary diagnostics can improve stratification and use of treatments, as well as predicting disease progression. It is critical for payers to acknowledge the potential value realised by the implementation of testing, so they may want to include other incentives (carrot and stick) to facilitate more appropriate use of testing across the patient journey. It will be important to monitor the uptake of complementary diagnostics with routine collection and publication of data. Finally, ongoing, repeated validation of diagnostics is important, leveraging technological enhancements. For instance, a scorecard for publication at the governmental level that measures uptake of testing may be useful in raising awareness and demonstrating commitment of the health authorities.

Equity issues. While economics focuses on issues of efficiency, most HTA processes explicitly recognise the need to consider equity. Equity issues are also complex and multidimensional. We recommend that policymakers also measure how the different barriers and challenges to the evaluation and use of diagnostics today can create inequities within and across EU countries. It will also be important to understand the implications of the different perspectives (health care or societal) on HTA processes.

CONCLUSIONS

- The full value that well-validated complementary diagnostics can bring to patient care is underappreciated in healthcare systems around the world.
- A comprehensive consideration of these distinct elements of value is a prerequisite to the realisation of the promise of personalised medicine.
- As healthcare systems evolve toward more accountability for outcomes and move to value-based reimbursement, the framework described here should provide a sounder basis for the HTA of complementary diagnostics as well as for appropriate reimbursement and rewards for innovation.

The promise of personalised medicine can only be realised under a comprehensive value framework. The framework described here is a first step in that direction, but further research is needed on specific weighting, measurability, and commensurability of the different elements of value.

1 INTRODUCTION AND OBJECTIVES

This White Paper presents the key conclusions from a collaborative project between the Office of Health Economics (OHE) and the European Personalised Medicine Association (EPEMED) to address key issues in the health technology assessment (HTA) of complementary diagnostics. In particular, it develops a more comprehensive framework for assessing the potential value contribution of complementary diagnostics. Two developments related to medical diagnostics motivate this work: 1) a growing recognition that medical diagnostics are used in a range of clinically different applications, and 2) a growing appreciation that the traditional framework and metrics applied in the HTA of medicines and devices may overlook or undervalue important elements of value provided by diagnostics - in particular, value related to the diagnostic information itself[1].

Regarding the first trend, the focus is on what we term "complementary diagnostics". To our knowledge, there is no generally accepted or official definition of complementary diagnostics. We understand that the US Food and Drug Administration (FDA) is currently working on a definition, but is yet to be published. Our starting point in defining complementary diagnostics is Roth (2013): "A complementary diagnostic is a diagnostic that is utilised by a healthcare practitioner to assess disease state and assist in diagnosis, patient management and treatment decisions. Unlike CDx [companion diagnostics] which are tied to one specific drug and are proven to work with and are approved for use only with that drug, complementary diagnostics can be utilised across a disease state, independent of one specific therapy but useful to guide therapeutic treatment across the classes of therapies". We build on this definition in two ways: (1) recognising that predicting disease progression (i.e., prognostic use) is a diagnostic application, and (2) viewing companion diagnostics[2] as a subset of complementary diagnostics. We thus use the term "complementary" in the sense of economic complements, that is, goods or technologies that are used in combination to produce a synergistic effect.*

Based on these considerations, for the purposes of this White Paper, we define complementary diagnostics as using biomarkers for the purposes of risk assessment, diagnosis, prognosis, monitoring, and guiding therapeutic decisions. Figure 1 depicts the range of these purposes graphically.

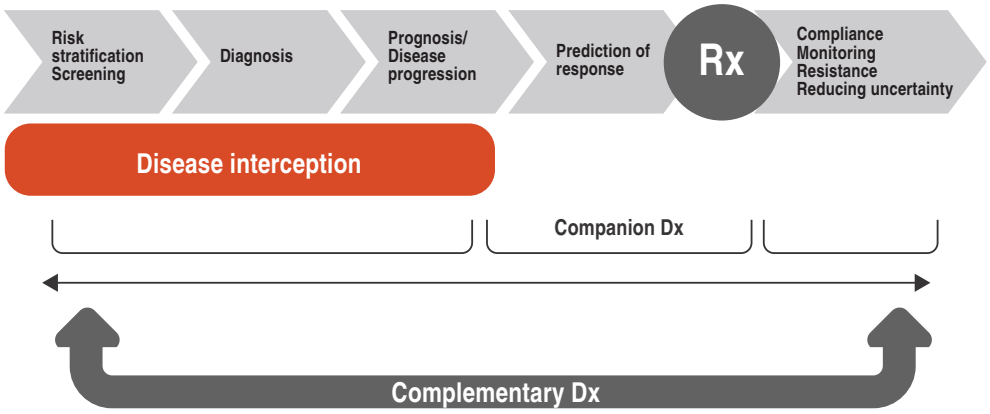
[1] It is outside the scope of this paper to discuss the appropriateness of current HTA methods for other technologies, and medicines in particular. We will argue that such methods may in general not be appropriate for the information provided by diagnostic testing.

[2] The FDA defines a companion diagnostic as a "medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks" [Source: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm].

* It should be noted that the FDA has recently begun to use the term complementary (versus companion) to refer to "diagnostics that are not required but provide significant information about use of a drug" (Mansfield, 2015). The FDA refers to a companion diagnostics device as "an in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product" (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm). Our economically-oriented definition of complementary diagnostics encompasses the FDA's regulatory-oriented definition, emphasizing the broad role that diagnostics can play guiding care choices in clinical pathways.

FIGURE 1

Defining complementary diagnostics



Source: authors' analysis (based on material shared by Janssen Diagnostics)

In other words, this range of applications in personalised medicine goes beyond the traditional focus of "companion" diagnostics, which identify patient subgroups for targeted treatment. Following our economic rationale for this term, in the extreme, a companion diagnostic and the associated medicine might be deemed as perfect complements, i.e., the medicine - for reasons of benefit-risk balance - can only be used following the complementary diagnostic. This is because companion diagnostics imply a test that is included in the product label (and thus any improved companion diagnostic would require product label changes). As illustrated nicely with the HER2 testing, the companion diagnostic came after the first therapeutic product was approved, so product labels were continually updated as the testing modalities improved. This could explain why drug developers are averse to linking a therapy (stable over time) to a diagnostic (evolving over time) which mandates product label changes.[3]

With regard to the second trend, diagnostics can provide valuable information that helps to guide medical decisions. Greater information generally means a reduction in uncertainty that can improve patient well-being and healthcare decision-making. For purposes of our work, we refer to this information aspect broadly as the "value of knowing". A key aim is to understand the various elements of this value in different applications. This is particularly important if HTA bodies apply the same, often narrow value framework to diagnostics that they apply to medicines. We have to acknowledge, however, that this reduction in uncertainty requires considerable correlational validation (i.e. level of test corresponds to the level of disease severity) and longitudinal validation (i.e. level of test predicts disease progression), which come at a cost.

This White Paper, which is the final output of this project, identifies key issues facing the HTA of complementary diagnostics in Europe, defines options for addressing challenges and barriers, and recommends approaches for dealing with them. The objectives are twofold:

1 To identify the currently applied practices by HTA bodies for complementary diagnostics, identify the gaps and deficiencies, and propose recommendations to improve such practices.

2 To review, in particular, approaches for addressing the lack of attention in current applied HTA practices to measuring the value of knowing (or of greater certainty) delivered by diagnostics.

For the purposes of this paper, we do not distinguish - though some distinctions could be drawn - among the various synonyms for personalised medicine (PM), such as precision medicine, stratified medicine, tailored treatment, and others. PM uses (mainly molecular) biomarkers for purposes of risk assessment, diagnosis, prognosis, monitoring, and guiding therapeutic decisions (EPEMED, 2014). All diagnostics covered in this definition of PM fall under our concept of complementary diagnostics. Companion diagnostics and next generation sequencing (NGS) are viewed, for example, subsets of complementary diagnostics. The term stratified medicine (SM) is used by Fugel et al. (2014) to include diagnostics used to

[3] We thank a reviewer for raising this important point.

identify responders/non-responders to a treatment such as in companion diagnostics and prognosis, while the Academy of Medical Sciences (2013) defines “stratified medicine” as the grouping of patients based on risk of disease or response to therapy by using diagnostic test or techniques.

Broadly speaking, we could then have two types of biomarkers: predictive and prognostic. The former relates to markers that predict treatment response; the latter are markers correlated with disease severity and predict diseases progression. Predictive biomarkers can be closely tied to the companion medicine and thus are likely to be specified in the product label for the indicated therapy. Prognostic markers, on the other hand, are more likely to evolve as general knowledge increases and their value is likely to improve based on the quality of the evolving evidence. And such outcomes are also not linked to any one therapy, but linked to the disease. This White Paper considers both types of biomarkers, but when relevant differences are identified between them, we comment on those. We do not provide policy recommendations as to which of the predictive or prognostic markers tend to be the more valuable type.

The project has been developed in two prior phases - each with their corresponding report - which can be found as separate Appendices in www.ohe.org and www.epemed.org.

The Phase I report - Complementary Diagnostics: A Literature Review on the Value of Knowing - presents the findings of a systematic literature review which summarises different proposed value frameworks and specific valuations for complementary diagnostics. The Phase II report - Landscape review of complementary diagnostics in Europe - analyses the health economic evaluation of three complementary diagnostics presented by the HTA agencies of England (National Institute of Health and Care Excellence, NICE) and France (Haute Autorité de Santé;HAS), where available.

This White Paper incorporates the findings of the Phase I and Phase II reports from the perspective of our proposed value framework, which draws upon and builds upon previous value frameworks - in particular, those of Lee et al. (2010) and Garau et al. (2013) - and the interpretation of personalised medicine put forward in a recent experts’ workshop (Rogowski et al., 2015).

This paper is organised as follows. Section 2 analyses and summarises our value framework under ten main elements of value, which are assumed to be largely - though not perfectly - independent and additive: however, they do reflect important conceptual distinctions that can be further disaggregated to acknowledge for differences in concept and/or quantification method. We test the utility and limitations of our framework with a selection of diagnostics (as identified by our literature review in the Phase I report). Section 3 compares the societal perspective of HAS with the health system perspective of NICE to summarise the main issues and guidelines used in the three case studies. Section 4 presents summary tables of the relevant elements of value in the three case studies analysed in greater detail (based on case studies in the Phase II report). Section 5 presents policy recommendations under four broad topics, and Section 6 offers our Conclusions.

2 ELEMENTS OF VALUE FOR COMPLEMENTARY DIAGNOSTICS

The literature review presented in the Phase I report identified several, somewhat different frameworks to consider the different elements or dimensions of value of complementary diagnostics. Importantly, these value frameworks generally take a broad societal perspective, considering how value might be perceived by all the stakeholders in the healthcare system as well as identifying benefits and costs beyond health gain and beyond the health system. For example, the broad value framework presented in Lee et al. (2010) delineates value in three non-exclusive dimensions - one in terms of health benefits ("medical value" dimension) and two in terms of non-health benefits from the patients' point of view, described as "planning" and "well being" dimensions. Alternative value frameworks present independent and additive conceptual dimensions of value. In particular, Garau et al. (2013) analyse, for diagnostic tests broadly defined[4], five independent elements of medical and economic value or health benefits from a societal perspective. Building on these frameworks, Figure 1 distinguishes among ten elements of value for complementary diagnostics that are seen - from a conceptual perspective - as largely independent and additive, and aggregable at a societal level. However, distinct conceptual measures could be measured with the same instrument: For instance, some of the quality-of-life instruments include a dimension for anxiety or distress dimension that might pick up elements of reassurance provided by the information from a diagnostic test. Of course, any specific assessment of value should not double-count effects. Questions about the weighting, measurability, and commensurability of the elements are separate issues, and are not addressed in this White Paper.

Traditional cost-effectiveness analysis conducted as part of HTA focuses on three key elements:

1. Life years gained
2. Improvements in patient quality of life
3. Cost-savings within the healthcare system (also called "cost-offsets").

And, of course, elements 1 and 2 are often combined in the quality-adjusted life year (QALY) by HTA bodies. Elements 1, 2, and 3, plus the cost of the technology, are then used to assess the cost-effectiveness of the technology.

The next element most often included is "productivity" or "time value", reflecting gains and losses related to the value of the patient's time either when receiving medical care or related to the impact of absenteeism or presenteeism due to illness. Nonmedical cost-savings outside the healthcare sector, such as transport costs, and family caregiving are also considered to be in the traditional societal perspective used in cost-effectiveness analysis, even though they are less commonly measured.

Our working assumption, which was supported by the literature review, was that complementary diagnostics provide additional information to healthcare decision-making that reduces the uncertainty about the consequences of care choices, not just from a patient perspective; we label this informational aspect broadly as the "value of knowing", as we include several other information-related elements.

This investigation into the value of knowing led us to identify several other, less recognised, elements related to the value of information. It should be noted that these additional elements can apply to medical technologies more generally and may not be as closely linked to diagnostics as is the reduction in uncertainty apparent with companion diagnostics. In general, and throughout our analysis, our working hypothesis is that the combination of a treatment and a complementary diagnostic can yield more value (benefit minus cost) (along one or all of the elements depicted in Figure 2) relative to the situation of having either a treatment or complementary diagnostic alone. When no actionable medical treatment is

[4] In Garau et al. (2013), diagnostic tests include a broad range of techniques varying their level of complexity and their purpose (they can determine the risk of developing a disease, the presence of a disease, and individual's prognosis or their treatment response).

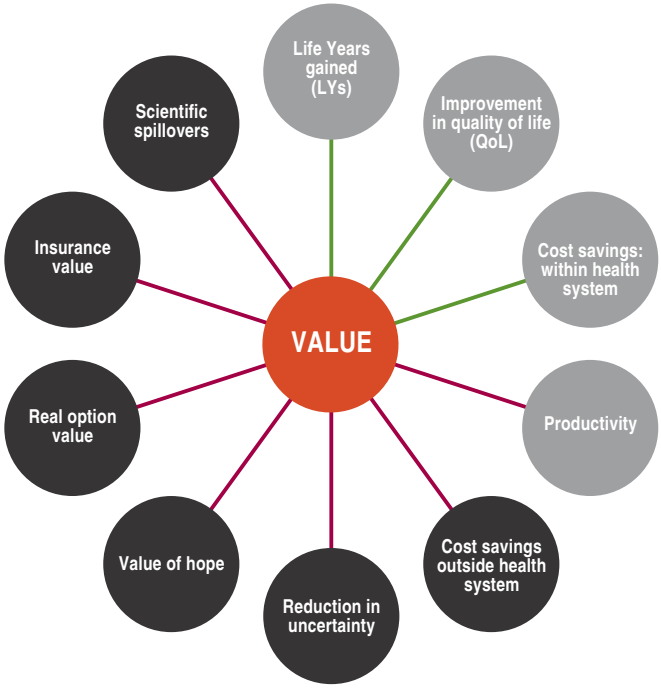
available, our working assumption is that having the complementary diagnostic at least yields some value in any or some of the elements we have considered - even in those elements that relate to medical technologies more generally. Moreover, part of the logic of ascribing these elements as a benefit of complementary diagnostics in particular is that these increase the general range of possibilities for innovative stand-alone therapies. Recognising the full range of value elements has important implications for rewarding medical technologies. This is discussed further in Section 5 (Policy Recommendations).

The first relates to risk and time preferences in an end-of-life context. This element is defined as the "value of hope" (Lakdawalla et al., 2012) which is the point that in an end-of-life situation, patients may be willing to take risks or pay for options with greater immediate mortality risk if there is a significant chance of increased long-term survival. The second is real option value: an investment in health care, such as a diagnostic test, can open other potential treatment pathways for patients in the future as other new technologies become available (which could, or could not, be used jointly with the original diagnostic). The third is "insurance value", which relates to both protection from the physical and mental health risk and from the financial risk. Finally, we have identified "scientific spillovers" as a source of value in both complementary diagnostics and other new healthcare technologies. This is essentially about an information externality from new ideas (including those generated by genetic testing) that result in new adaptations. For example, HCV subtype genotyping preceded development of new more potent antiviral therapies that are used within defined sub-genotype categories. Or, patients with a range of diseases may benefit from an idea arising from using the genetic information generated by next-generation sequencing.

Before we discuss each of these elements in more detail, it is important to highlight that it is outside the scope of this paper to offer any views on the relative importance (or 'weight') of each specific dimension in any evaluation. Indeed, dimensions will have different importance depending on the type of diagnostic or type of health care technology as well as for specific patients with different diseases. This is illustrated by our case studies (Tables 2 and 3 below).

FIGURE 2

Elements of value for complementary diagnostics



Notes:

Light grey circle: traditional elements of value as considered by HTA

Dark grey circle: expanded value framework: elements not traditionally considered/measured

Green line: value from health system perspective

Red line: value also included in societal perspective

HEALTH GAIN

As noted above, most healthcare interventions aim to ultimately produce health gain measured in terms of extended years of life years and/or improved quality of life. Complementary diagnostics can help to generate health gain in several ways, including directing patients to the treatments that maximise expected health gain or giving them greater confidence to utilise particular treatments or to be more adherent to them. Diagnostic information can help to assess if a patient will respond well or not to a particular medical intervention, including by predicting adverse events from this intervention, and saving the patient the time and consequences of other processes based on trial and error (Goldman et al., 2013): this will be the case primarily with predictive markers, where the outcomes tend to be binary, i.e., the patient is either a responder or not. When these have a direct link with treatment, the health gain derives from a better stratification of responders to the treatment and avoidance of adverse events in non-responders. Also, prognostic information about the course of the disease can be used for improving the disease management, both by optimising treatment and by inducing preventive behavioural changes in the patients[5]. This can also slow down the progression of the disease, and then the health effects will be reflected more as a continuum rather than as binary (as with yes/no respondents).

Appropriate testing cannot only inform initial decisions, but also can help guide decision to switch treatments or amend the regimen. At the patient level, the health gain achieved depends on the effects of medical intervention if provided, on adverse events avoided when such intervention is not appropriate, and on the patient behaviour in terms of adherence and compliance with the subsequent treatment. We treat better adherence to the treatment as a mechanism to achieve health gains, as a result of the information provided. That is why adherence is not explicitly included in Figure 2. Prognostic information can also be valuable to define tumour aggressiveness, as well as inform targeted therapy selection. For instance, should the patient progress on targeted therapy or be unable to tolerate it, such information also helps the patient understand their disease and make determinations of how aggressive to be with alternative therapy.

At aggregate level, patients' preferences can influence uptake of the diagnostic. In traditional cost-effectiveness assessments, costs and benefits (measured by health outcomes, whether measured as QALYs or not) of any one intervention are compared to an alternative (or comparator) and tend to focus on a representative patient. But the value of knowing also may have (positive) aggregate-level impacts on uptake in a population (Garau et al., 2013; Garrison and Towse, 2014). If patients are more certain that they are likely to benefit, then a greater share of the population may use a technology. If use in the new users is also cost-effective, then the aggregate value to the health system will increase. For example, our Phase II report shows the relatively low uptake of the test for familial cancer (BRCA1/2) among eligible patients at risk of breast cancer relative to what could be considered as an optimal level, especially for patients with no personal history (with uptake around 50%). Nonetheless, the predictive diagnostic information from BRCA1/2 genetic tests, which assesses the risk of future breast or ovarian cancer, is clinically actionable (defined in terms of clinical utility) since there are available risk-reduction treatments - mainly surgery and chemoprevention.

Therefore, the health gain resulting from adding a diagnostic to the care pathway depends on the interaction between the test results and the complex choices and care pathways that are downstream. For example, the care pathway for a companion diagnostic can be direct but complex depending on the impact on patient adherence or uptake at the population level.

It can also be the case that the drugs might not be developed in the first place were it not for the use of complementary diagnostics in the context of pivotal trials, since therapeutic performance might otherwise be lacking. Those health gains would have never accrued (as well as any other spillovers arising from the use of those medicines). For instance, Towse et al. (2013) reflect on the fact that the potential for a molecular marker to be used to identify patients with advanced non-small cell lung cancer to likely benefit from epidermal growth

[5] We deem "changing patients' behaviour" as an intervention that can be the result of the information generated by the diagnostic.

factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has allowed two such treatments to now become commonly used in a subset of patients in many markets, even though the prospects for one in particular looked dire.

Garrison and Austin (2007) point out that the diagnostic test and the associated treatment are "economic complements", both synergistically contributing to the total value created, and that it is essentially arbitrary - in a static situation - to apportion the value between them. Garrison and Towse (2014), however, offer a proposal for dividing that value from a dynamic perspective, rewarding the treatment for the mechanism of action and the test for separating the better responders from the worse responders. It should be noted that this proposal relates primarily to predictive markers and companion diagnostics (and is less relevant for prognostic ones) though more subtle and complex aspects of economic complementary may come into play, e.g., in the case of NGS.

COST-SAVINGS

The direct medical costs of a diagnostic relate to the costs associated with their use: the cost of the diagnostic itself may add cost to the treatment, but cost-savings - also called "cost-offsets" - may reduce the net medical cost. The use of a diagnostic can result in additional resources being required: these might include treatment costs (which fall under the health care system if reimbursed), and out-of-pocket payments made by patients outside of the health care system to support their medical treatment, for instance, transport to the hospital, or additional care from the private sector, paid and unpaid. Diagnostics which have multiple uses, like imaging diagnostics, also generate downstream indirect costs within the health care system, in particular from incidentally detected findings, which can affect more than half of the patients called for a primary diagnosis (Ding et al., 2011) and over long time horizons. Of course, illness also has indirect costs such as those supported by the family and the employer.

To measure the offsetting cost-savings generated by a complementary diagnostic, there must be a specification of the perspective and the type of costs to include. The NICE Diagnostic Assessment Programme (DAP) adopts the perspective of the health care system, so only includes costs of health system resources. Under this situation, the baseline costs should be measured assuming current standard practice and then compared to those projected under the use of the new diagnostic. To measure this incremental cost in practice, there is an identification of the specific resources implied in the use of the diagnostic and a measurement of their change. Also, the better stratification of patients can imply organisational and managerial gains in patient access and allocation to unmet needs (Garau et al., 2013). Nonetheless, most of the overhead costs and those from other tiers of the health care system, including management costs, are assumed unaffected, as in the case of NICE's evaluation of the diagnostics of familiar cancer and gene expression profiling analysed in the case studies of phase II report.

Regarding nonmedical cost-savings outside of the health system, these are rarely measured even in HTA systems adopting a societal perspective. In HTA guidelines, there is not a clear specification about how to collect these data, for example on cost for paid and unpaid care, including for the patient's family.

NICE's 2014 proposals for value-based assessment - to potentially take into account burden of illness and wider societal benefits - ended up with a recommendation to undertake further work before making changes to the way it appraises new medicines and other technologies for use by the NHS (https://www.nice.org.uk/news/press-and-media/nice-calls-for-a-new-approach-to-managing-the-entry-of-drugs-into-the-nhs). This example shows the complexities around taking a "societal perspective", but should not hinder further work exploring the feasibility and impact of implementing such an option more generally across other countries, including the UK.

Yamauchi et al. (2014) present an example of measurement of cost-savings in terms of patient time for patients treated with Oncotype DX in Japan, where the savings are derived from avoiding chemotherapy with patient time valued according to wage indices published by the Japanese Ministry of Health, Labour and Welfare.

PRODUCTIVITY

The burden of disease accounts for productivity or output lost (market or nonmarket) as measured by consequences on paid, unpaid work, and leisure time, not only from absenteeism but also from presenteeism and compensation mechanisms in the work place. Knies et al. (2010) reviews the recommendations about the valuation of lost productivity due to illness in national pharmacoeconomic guidelines. The US Public Health Service Panel notes that lost productivity may influence ratings of the health-related quality of life of people and that consequently these losses might be assessed in the QALY - at least for those HTA bodies that use QALYs. Others argue that this is rarely the case in practice and that the lost productivity should be incorporated in the costs, and propose to use either the human capital approach or friction cost method to measure the productivity costs of disease. Knies et al. (2010) find that even though most national guidelines recommend a societal perspective which should value productivity, only two countries, South Korea and France, clarify how to measure lost productivity. The most difficult part is to measure lost productivity in the work place and from unpaid work, where wages must be substituted by shadow prices elicited through questionnaires.

VALUE FROM REDUCED UNCERTAINTY

The reduction in uncertainty resulting from diagnostics information has been identified as generating value in several ways (Garau et al., 2013; Garrison and Austin, 2007). Firstly, there is a reduction in uncertainty which depends on the clinical validity of the diagnostic and which generates value in the medical dimension by improving the clinical and costs evidence of available treatments. Also, the more accurate knowledge of the disease in terms of epidemiology serves to optimise R&D investment, and allocation of health resources across health needs. This element has already been considered as generating health gains and cost savings as explained above. Secondly, and for inclusion in this element of value, there is evidence that patients value the information received and the consequent reduction in uncertainty, independently of the expected health outcomes. This value may mainly be a psychological benefit for risk-averse individuals, or also for the possibility of better planning future finances and care when predicting the future onset of a disease. Moreover, information can lead to behavioural adjustments (lifestyle, adherence) by patients - and the benefits from such adjustments can also be tangible (especially if the prognostic impact has been validated). These are the dimensions labelled as “well-being” and “planning” value by (Lee et al., 2010) although the consideration by Asch et al. (1990) of “well-being” or “psychic” value is a somewhat different distinction.

The quantitative methodology used in the 1990s to value the “psychic” value from diagnostic information or “value of knowing for the sake of knowing” was based on computer sciences and the statistical properties of the tests (Asch et al., 1990; Johnson, 1995; Somoza and Mossman, 1992). Later, there were some applications of behavioural economics to this area, as explained in Phase I literature review. However, since the uptake for predictive diagnostics (especially for those related to diseases with no available treatment like Alzheimer’s) depends on patients’ preferences, the most common method to measure psychic value is through surveys based on contingent valuation and willingness to pay (WTP) (Neumann et al., 2012).

VALUE OF HOPE

Lakdawalla et al. (2012) define the value of hope as a subjective psychological value for cancer patients facing end of life and then assigning greater value to the uncertainty of survival, showing that patients in the end-of-life context behave as risk-seekers preferring therapies with a wider spread of outcomes which offer some possibilities of longer survival (‘hopeful gambles’), to therapies offering similar average outcomes but less chance of a larger gain (‘safe bets’). The authors recommend the incorporation of this “value of hope” into the value of end-of-life therapies or setting a higher threshold for an acceptable cost-effectiveness ratio in the end-of-life context. NICE and the Scottish Medicine Consortium are HTA agencies which include cost-effectiveness criteria in the assessment of drugs and diagnostics and which have considered the end-of-life context as a modifier when considering the cost-effectiveness threshold. Their position is not to explicitly raise the threshold per se, but to give greater weight to QALYs achieved at the end of life (under certain circumstances),

which results in larger incremental cost-effectiveness ratios for some approved end-of-life medicines, albeit focusing on the expected gain, rather than any element of "hope" in a long tail of longer, low-probability life extensions.

As far as we know, Lakdawalla et al. (2012) is the only study providing a quantitative estimation of the value of hope for a particular clinical scenario. Nonetheless, the large participation of cancer patients in clinical trials, as exemplified in Phase II report for the French case of gene expression profiling, and also in BRCA1/2 clinical trials, may be incentivised in part by the value of hope. As reported in Sweeney and Goss (2015), clinical trials for cancer therapies are tested for patients during the last stages of cancer, that is, at the end of life. Besides the patient's consent, there is a medical consideration of "compassionate treatment" aligned with the value of hope, and also with the "option value". Krzyzanowska et al. (2011) also illustrate this point for its relevance to the valuation of cancer research trials, with evidence showing that patients who participate in clinical trials are different from those who do not participate, regarding case-mix in medical and social characteristics toward more complicated and sicker patients. These patients are also well-informed patients, educated, and arguably hopeful to participate in the clinical trial searching new options. Of course, patients' willingness to participate in a trial is not the same as a payer's willingness to pay for a long-shot health improvement: payers will require that the long shot be somewhat feasible.

REAL OPTION VALUE

The concept of real option value in the context of oncology innovation has been explained by Cook et al. (2011) in the case of stepwise incremental innovation. The basic insight is that innovation may be speeded up by taking smaller incremental, "path dependent" steps. The concept of "options" is most commonly used in finance, where investors can buy "call options" to purchase the right to buy a commodity or financial instrument for a fixed price in the future[6]. Patients perceive option value from treatment as getting one treatment increases the likelihood of benefiting from a better treatment in the future. This could be as basic as having a treatment that keeps the patient alive, making it possible for them to gain further benefit from subsequent new treatments as Philipson et al. (2010) illustrate with AZT treatment in HIV. It may happen on the supply side. Patients adopting new treatments make it more likely that competitors will continue to progress fast followers that may offer further improvements in health. Investing in diagnostics (now) could also improve trial enrolment, with the consequent benefits generated from such trials, including the evidence generated by such trials, which might also be considered a type of scientific spillover (see below). Ignoring this value, which is perceived by the patient or citizen, in rewarding pharmaceutical innovation would reduce the incentive to invest in R&D.

INSURANCE VALUE

From a welfare economics perspective, it is generally understood that the healthcare system aims to deliver not only health gains but improved well-being through insurance protection against both financial and illness catastrophes. People usually behave as they are risk averse, so both financial risk protection and health risk protection are important. Financial risk protection also provides utility to patients and they are willing to pay an extra insurance ("a risk premium") for it.

This perspective has only recently been applied in work related to HTA, in the global health field. There is a new methodological development that has been labelled "extended" cost-effectiveness analysis (ECEA) (Verguet et al., 2015; Verguet et al., 2013). The method aims to value this financial risk protection and also the distributional consequences. They measure the financial risk protection and also the distributional consequences of global health programmes in developing countries. By looking at the distributional consequences of using public finance to subsidise an intervention it is possible to estimate the likely impact in reducing household debt and therefore poverty in different income cohorts. Thus the value of providing public insurance to cover an intervention can be estimated to include the health gain and the consequences of it being publicly funded rather than paid for by patients.

[6] They can also buy "put options" giving them the right to sell at a particular price.

In the same vein of risk protection, Lakdawalla et al. (2015) explore this both theoretically and empirically. They emphasise the distinction between the physical risk-protection and financial risk protection, and suggest that the welfare effects of physical health insurance are likely to be larger than that of financial insurance covering the same intervention. The mean additional health gain offered by a new treatment is usually compared with the additional cost. Financial insurance will protect the citizen from the financial consequences of needing the new treatment. However, the health effect on the patient lowers their health outcomes risk. It does this because the impact (reduction) on the patient's health of getting sick is now less. The patient will be closer to full health. If patients are risk averse, this has value over and above the health effect.

SCIENTIFIC SPILLOVERS

R&D investment in clinical trials benefits from economies of scope within and across pharmaceutical companies and research institutions. This means that it is likely to be (i) less costly to undertake any two R&D projects within the same company than in two different companies and (ii) there is a strong correlation between a company's own innovative achievements and the success of rival firms' efforts because knowledge generated by one company helps its rivals. In the case of (i), the company can internalise the benefits. In the case of (ii) they cannot and there is a risk of underinvestment[7]. The seminal literature in this area is referenced in Phase I. Besides the spillovers within and across research, the characteristics of new molecular diagnostics and treatments require continuous evidence from real-world clinical practice after a diagnostic or treatment has achieved marketing authorisation. This evidence also needs to be supported with continuing education of practitioners (and patients) on how to properly apply the diagnostic (and what to do when the information is generated).

As illustrated by Sweeney and Goss (2015), the market authorisation of a new cancer therapy marks the "starting point" for additional study of the therapy, followed by the development of a larger body of evidence to help us understand the full value of the treatment and, more importantly, to help clinicians understand how best to use all available therapies when treating their patients. Moreover, combinations of approved therapies are used in successive clinical trials, increasing scientific spillovers over time. One point to note is that samples collected from patients for testing can provide research value to health care systems and the life sciences sector. With patient consent, researchers can carry out further investigations into the genetic biomarkers and factors that sit behind health conditions. This can help us to discover future treatments (BIVDA, 2015). Indeed, it has been argued that patients "should at a minimum be informed that others may profit from the research or products that derive from their tissue as part of the consent process."(L'Italien, 2016).

Krzyzanowska et al. (2011) also mention other scientific spillovers from cancer research such as the retention and attraction of scientific human capital, and the creation of organisational and physical infrastructures for multidisciplinary health and social care.

RELATED FRAMEWORKS

There is a relationship between the elements considered in Figure 2, Garau et al. (2013) and Lee et al.'s framework. Rogowski et al. (2015) conclude, based on an experts' workshop, that there are two alternative interpretations of personalised medicine. On the one hand, personalised medicine has a physiological interpretation, which covers the medical domain in Lee et al.'s framework. This includes some benefits and cost outside of the healthcare system, such as managerial and operational efficiencies, and whose value should be measured from all medical data, including the complex pathways and downstream costs and benefits generated by diagnostics, and the spillovers to the labour market and the science. This physiological interpretation should be taken into account to measure the value of five of the ten elements in Figure 2: health gain in life years (LY) and QALYs, cost-savings, productivity, and perhaps scientific spillovers.

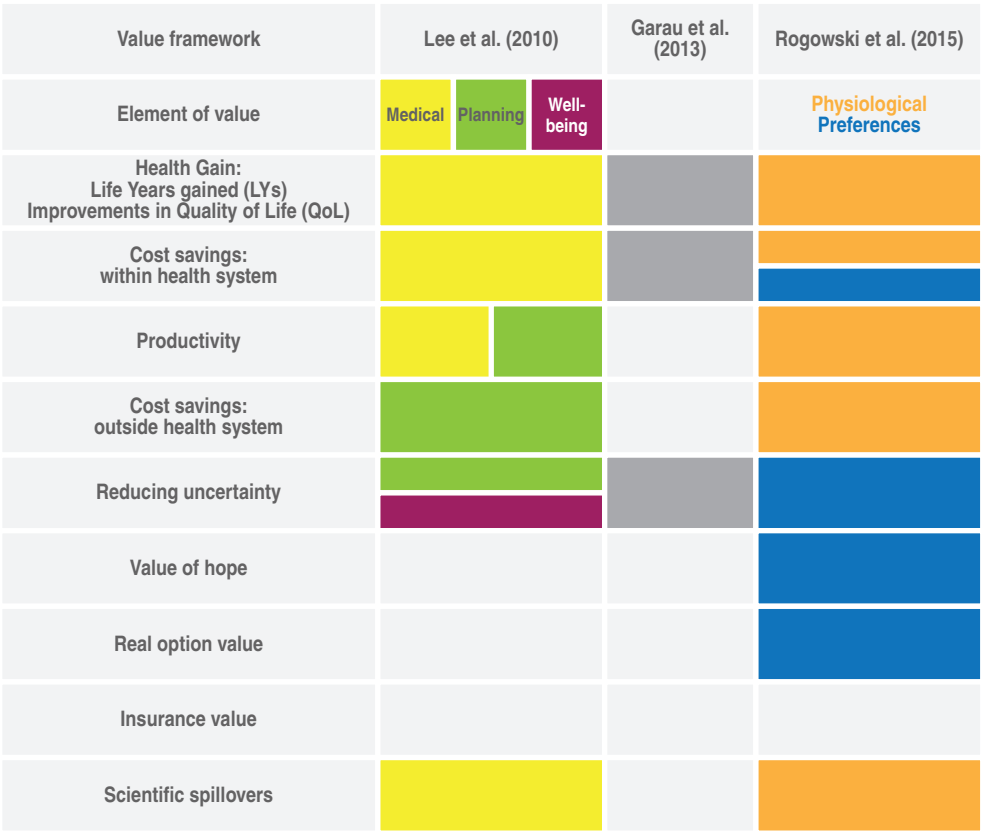
[7] This effect will in part be offset by an expectation that they may benefit from the knowledge generated by others.

On the other hand, personalised medicine has an interpretation in terms of patient preferences about health state valuation and risks, and that the treatments chosen consider those. This view suggests that stated preferences - elicited with willingness-to-pay (WTP) methods could be an approach to measuring the value of four of the elements presented in Figure 2: reduction in uncertainty, value of hope, real option value and the insurance values of reduced financial risk and reduced health risk. The value of reduction in uncertainty can be valued per se as the well-being value generated from knowing (reduction in ambiguity and reassurance) (Asch et al., 1990; Lee et al., 2010). A reduction in uncertainty can be also used for life planning purposes, including reproductive planning and managing finances and future care. However, the diagnostic information has a psychological value derived from changes in risk attitudes toward risk-seeking behaviour inducing innovative treatments, which is captured by the "value of hope" (Lakdawalla et al., 2012). These innovative treatments and medical advances are also valued by patients in terms of real option value.

Table 1 presents a pattern of relationships between four value frameworks: our value framework with ten elements, Lee et al. (2010), Garau et al. (2013) and Rogowski et al. (2015) (and its associated two perspectives).

TABLE 1

Related value frameworks



Source:
authors' interpretation

Notes:

For Lee at al. (2010): different coloured cells relate to the medical, planning and/or well-being dimension in Lee et al. (2010)

For Garau et al. (2013): grey shaded cells represent dimensions of our value framework included in the value framework in Garau et al. (2013)

For Rogowski et al. (2015): different coloured cells relate to the Physiological and/or Preferences dimension in Rogowski et al. (2015)

A blank, white cell indicates the relevant framework does not address that element of value

Specific to clinical trials for cancer patients, the American Society of Clinical Oncology (Schnipper et al., 2015) has developed a - somewhat controversial - value framework which includes “bonus points” depending on the statistical significance of the trial results regarding improvement in symptoms and treatment-free intervals related to non-progression of the disease. The consideration of these surrogate outcomes measured during clinical trials, or others such as “objective response rate”, “overall survival”, “progression-free survival”, and “time to progression” (Sweeney and Goss, 2015) has shown to be key in the approval of innovative therapies by regulatory authorities[8]. However, approval is not the end of the evidence collection period since evidence from real-world applications is important to reinforce outcomes results from clinical trials, in the developments of new indications for these therapies and the application of the therapy in early stages of the disease.

Table 2 highlights the most important elements of value for six different diagnostics, ranking this importance in three levels when the value is relevant, acknowledging also empty cells when the value is not relevant. It also shows which elements of value have been addressed by literature, possibly by trying to measure them. We have selected six different diagnostics with different purposes, from companion diagnostics, to prognosis and predictive use.

The companion diagnostics HER2/neu and NT-proBNP concentrate the value in the health gain and costs savings derived from an optimised treatment for responders and avoidance of adverse events for non-responders. Conversely, Alzheimer’s and Huntington’s diseases are neurological inherited diseases, therefore, the relevant value of a genetic test informing with (at least some) certainty about the future onset or absence of Huntington’s disease, or about the probability of the future onset of Alzheimer’s disease, is derived from the reduction in uncertainty. This reduction could be deemed as pure psychic/well-being value and/or as planning value to anticipate the consequences and needs during a possible future disease. However, it is also true that there are numerous ongoing trials for Alzheimer’s diseases with some confidence (value of hope) that their disease can be delayed. This aspect of the benefits of trial enrolment and potential to help the development of effective cutting edge treatment (via spillover effects) was discussed above.

We also included prenatal diagnostic and newborn screening (NBS). For the former, where the patient is the foetus, the decision is (primarily) made by the parents. For the latter (patient is the newborn), the decision is made by the health system with explicit or implicit consent from the parents. In the case of prenatal testing, most of the value has been studied under the focus of reproductive planning when the final decision involves termination of pregnancy in the most unfavourable results. However, the literature reports cases where the reduction in uncertainty has a unique psychological value which is not actionable or linked to a subsequent planning decision regarding the termination of pregnancy. Also, some literature considers the effects on costs savings in terms of future health care costs avoided. In the case of NBS, the focus is to test diseases with onset in early childhood, mainly metabolic diseases, when the prognosis can be predicted by the NBS test which helps with both prevention and disease management.

[8] An important issue relates to the use of surrogate end points and survival in oncology, and whether regulatory agencies may be basing too much on surrogate endpoints: see Prasad, V., C. Kim, M. Burotto, and A. Vandross, 2015. The strength of association between surrogate end points and survival in oncology: a systematic review of trial-level meta-analyses, JAMA Internal Medicine 175(8), pp. 1389-1398. This issue is beyond the scope of this White Paper.

TABLE 2

Relevance of elements of value in some complementary diagnostics

	HER2/neu	NT-proBNP test: safety of COX-2 Inhibitors	Prenatal testing	Newborn screening	Huntington Disease test	Alzheimer Test
Purpose / Element of value	Linked to cancer treatment (companion diagnostic)	Linked to treatment of cardiovascular disease (companion diagnostic)	Predictive for reproductive planning	Predictive for helping disease management in early childhood	Predictive of risk of disease	Predictive of risk of disease
Health gain: LY	***	***		***		
Health gain: QALY	***	***		***		
Costs: health system	***	***	*	***		
Productivity	*	**				
Costs: outside health system	*	**	**	***		
Reducing uncertainty (Well-being)	***	**	**	*	***	**
Reducing uncertainty (Planning)			***	***	***	**
Value of hope	***					
Option value	***	**		**	*	*
Insurance value	**	*	*	**	**	**
Scientific spillovers	***	**	**	**	**	**

Source:
Authors' interpretation and analysis of literature in phase I literature review

Notes:

Relevance of value graded from more (***) to less (*) important, and no relevance (blank)

Yellow cells: literature has addressed this element, and where possible tried to measure it

HER2/neu: A protein involved in normal cell growth. It is found on some types of cancer cells, including breast and ovarian. Cancer cells removed from the body may be tested for the presence of HER2/neu to help decide the best type of treatment (source: http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44945)

NT-proBNP test: diagnostic test to predict adverse cardiac events from COX-2 inhibitors

3 VALUATION BY HTA AGENCIES: ENGLAND AND FRANCE

The perspective taken in a health economic evaluation affects the consideration of particular elements. If the perspective is that of the health care system or "extra-welfarist" perspective, many of the elements of value included in Figure 1 are not usually measured since the focus is on health gain and cost-offsets; and in particular, the value of reducing uncertainty. Spillovers to the family and carers, and the scientific spillovers are also explicitly not recognised. In contrast, the societal or welfarist perspective considers all of these elements - in principle. Also, it is important to note that the QALY measure is not exclusive to an extra-welfarist perspective. As has been emphasised in the Phase I literature review, the patient can consider family effects in the perceived clinical utility (Basu and Meltzer, 2005) and also lost productivity (Knies et al., 2010). Similarly, the valuation through WTP comes from revealed preference, but this can include the views from health sector professionals and payers as well as patients or general population.

In our case studies of complementary diagnostics, we reviewed HTA guidelines from two HTA bodies with different traditions regarding the perspective adopted in their technology assessment guidelines. On the one side, the English National Institute of Health and Care Excellence (NICE) has a health system cost, and patient health as measured by QALYs, perspective. Other HTA agencies adopting a similar perspective are that from Canada, Belgium and New Zealand (Knies et al., 2010). On the other side, the French Haute Autorité de Santé (HAS) pharmacoeconomic guidelines recommend a societal perspective (Boulenger and Ulmann, 2004). Many other countries, including the US, also have guidelines recommending a societal perspective. Nonetheless, there is not an established methodology for capturing the different elements of societal value in any country. The French pharmacoeconomic guidelines recommend using surveys to measure lost productivity in economic evaluations (Knies et al., 2010) although it remains unclear how these are weighted by HAS.

The evaluation of diagnostics has been specifically regulated by NICE and HAS. NICE began a diagnostic assessment programme (DAP) in 2011, separate from the technology assessment of new medicines (NICE, 2011). HAS has issued two different methodological guidance documents related to the assessment of medical devices, in 2009, (Haute Autorité de Santé, 2009), and in 2014, of companion diagnostics (Haute Autorité de Santé, 2014).

NICE DAP framework is a cost-effectiveness valuation aiming at including in final QALYs all the health gains, included those measured through surrogate and intermediate outcomes, and includes the relevant costs for the NHS. In contrast, the HAS framework for evaluation of medical devices focuses mainly on clinical utility of the device in terms of "Actual Benefit", which depends on the risk-benefit ratio, the position of the device in the therapeutic strategy, and the public health benefit. Equally, the HAS companion diagnostics guideline only mentions the evidence on clinical utility of the diagnostics as a prerequisite for marketing authorisation and/or to be approved as a companion diagnostic for a given therapy. France has a system of reimbursement specifying a list of products and services qualifying for reimbursement where medical devices and complementary diagnostics could be potentially included. However, their reimbursement is not yet systematically based on cost-effectiveness (although cost-effectiveness might inform the final assessment), and thus there is no mention in the guidelines about a monetary threshold in terms of cost-effectiveness.

Garau et al. (2013) argue that the DAP recognises a different evaluation for diagnostics (relative to treatments), mainly because diagnostics do not have a 'direct' impact on health outcomes, i.e., they do not treat or prevent like a treatment or medicine. However, the current approach of DAP does not consider the broad set of outcomes, as illustrated in Figure 1, including the value of information on a patient's condition independent of health gains. This is because, as Garau et al. (2013) argue, the measure of patient benefit is purely based on the QALY, and the method follows very closely that used for medicines.

4 CASE STUDIES

This section presents a summary of the relevant dimensions of value for the three cases studies of complementary diagnostics presented in more detail in the Phase II report. The three case studies are: BRCA1/2 for familial breast cancer, gene expression profiling, and procalcitonin tests. We reviewed any assessments carried out by NICE, either in their de novo economic model or in the systematic review included in NICE's reports. For the case of gene expression profiling, the French Institut National du Cancer (INCa), as an independent expert reference body, undertook a systematic review of clinical evidence and health economic evaluations, which is analysed along the NICE diagnostics assessment report (see the Phase II report for more details). INCa's assessment is not strictly speaking an HTA, but rather a literature review of clinical and economic data which is somewhat dated. Since then, new data were published on genomic tests, including prospective outcomes data following the use of the Oncotype Dx test (Shak et al., 2015; Sparano et al., 2015; Stemmer et al., 2015) and the HAS recently announced that they would be assessing breast cancer genomic tests in 2016. This assessment is now officially part of the HAS working agenda for 2016 (Haute Autorité de Santé, 2015).

The three complementary diagnostics analysed in the case studies derive most of the value from prognostic information (which helps predict the course of disease). There are two diagnostics predicting the prognosis of breast or ovarian cancer for patients with personal history (BRCA1/2 and gene expression profiling), but also the tests of BRCA1/2 is used for predicting the risk of future disease for patients with no personal history of the disease. In particular, BRCA1/2 tests have been approved by the FDA in the US as a companion diagnostic for the treatment of ovarian cancer with a biological medicine, olaparib, which has been also approved by the European Medicines Agency for use within Europe. NICE has not published yet a Technical Appraisal Report about the recommendation for reimbursement of this therapy[9].

The prognostic information obtained with diagnostics based on gene expression profiling (Oncotype and MammaPrint) is more accurate than current methods (e.g. Adjuvant! Online) in estimating the risk of recurrence from breast cancer. This information helps in supporting chemotherapy treatment decisions for patients with early stage breast cancer and at intermediate risk of recurrence according to traditional clinical and pathological criteria.

The third diagnostic, based on the procalcitonin biomarker, is being used in some English hospitals as part of the protocol for treating sepsis in intensive care units and in emergency care. However, the use of the procalcitonin diagnostic has not been recommended by NICE in its recent DAP report for the general hospital clinical practice, even though the report recommends the continuation of its use to reinforce the evidence on added clinical value over and above the antibiotic stewardship practice.

Table 3 illustrates the relative importance of the different elements of value in our three complementary diagnostics. It also highlights which elements of value have been addressed by the literature.

[9] http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/can-you-tell-me-about-olaparib#available

TABLE 3

Relevance of elements of value in case studies

Purpose / Element of value	Familial Breast Cancer BRCA1/2	Gene Expression Profiling	Procalcitonin
	Linked to cancer treatment (approved companion diagnostic by FDA)	Linked to cancer treatment, specifically breast cancer	To detect and monitor sepsis in hospitals
Health gain: LY	***	***	***
Health gain: QALY	***	***	***
Costs: health system	***	***	***
Productivity	**	**	
Costs: outside health system	**	**	**
Reducing uncertainty (Well-being)	***	***	
Reducing uncertainty (Planning)	***	***	
Value of hope	***	***	
Option value	***	***	
Insurance value	***	***	*
Scientific spillovers	***	***	***

Source: Authors' interpretation and analysis of literature in Phase I literature review

Notes:

Relevance of value graded from more (***) to less (*) important, and no relevance (blank)

Yellow cells: literature has addressed this element, and where possible tried to measure it

5 POLICY RECOMMENDATIONS

The differences between diagnostics and other healthcare technologies, especially medicines (i.e. treatments), are important and thus should be considered when exploring the way forward for assessing the value of complementary diagnostics.

We are aware that given the policy environment described above, and the institutional nature of HTA reviews (and indeed for most payers), to alter the methods of assessment for complementary diagnostics will require coordinated policy changes. We recommend several amendments in the areas of evidence requirements, pricing, incentives, and equity.

5.1. CHANGE IN EVIDENTIARY REQUIREMENTS

Any assessment of value relies on the evidence generated, but what evidence is generated depends on the incentives to do so. For instance, Miller (2014) presents the strengths of the US FDA's pragmatic approach to the requirements for diagnostic evidence. This approach considers (a) allowing data from analytical validation together with prior community-generated clinical validation and (b) generating data from adaptive trial designs like those currently used for multiple cancer drugs and NGS panels.

Our policy recommendation on evidence requirements focuses on two key issues:

1. Evidence of clinical utility: we have argued in this White Paper that, currently, evidence of clinical utility is generally tied exclusively to 'traditional' outcomes measures and hence is not inclusive of the broader array of metrics shown in Figure 2. Thus, we recommend that value frameworks used to assess complementary diagnostics require a more comprehensive perspective to integrate less tangible benefits into it. A corollary is that diagnostics should not be evaluated using the same framework currently used for therapies. Lastly, HTA bodies should derive guidance specific to diagnostics that mandates rigorous evidence of value. We think QALYs can be applied as one element if informative and traditionally accepted by the HTA, but not in all cases: they are likely to be necessary but not sufficient.

2. Sources of evidence: evaluations generally tend to require prospective data, which for many diagnostic companies is not feasible given the cost of gathering that evidence, and their shorter life cycle relative to other technologies. Our recommendation would be to assess the use of "coverage with evidence development" agreements, where the diagnostic is reimbursed for a specified period of time whilst further evidence is collected in clinical practice. This issue is related to our recommendations on pricing and incentives.

Payers, who represent their covered population, can reward investment in diagnostic evidence (e.g., by variable and greater reimbursement for stronger evidentiary packages or by reimbursement conditional upon inclusion in a registry study, as under coverage with evidence development). These practices that reward evidence generation are in line with the recommendations proposed by Towse and Garrison (2013), which include encouraging the payers to accept higher diagnostic prices as a premium to reward value and support a regulated, but flexible market-oriented system to generate the appropriate evidence. Miller (2014) provides examples of the current tendency in the US toward pragmatic and flexible approaches for the assessment of medical devices (which share some, but not all, characteristics of diagnostics). Thereby, differential characteristics of diagnostics can affect evidence requirements, by allowing or encouraging the use of analytical evidence and prior community clinical evidence as well as data generated in adaptive trials, especially for multiple technologies (such as imaging diagnostics, which have several uses) and NGS panels. The situation in Europe is diverse as recognised by Fugel et al. (2014), who provide examples illustrating the variability in the assessment of the value of companion diagnostics and in reimbursement across different European countries.

The recent marketing authorisations for several cancer drugs provide examples of the process of an accelerated pathway applied to end-of-life treatments (Sweeney and Goss, 2015). The evidence required for the accelerated approval is based on "surrogate" outcomes

and intermediate clinical endpoints, before demonstrating gains in terms of survival or quality of life. This process not only improves the access to new diagnostics and medicines, but also leverages further research which starts by collecting evidence from clinical practice: this, in turn also improves the quality of the cost-effectiveness assessment, and extends the use to new indications, for example, to different types of cancer or from second-line to first-line use.

It is important to recall and consider a key difference between predictive and prognostic biomarkers, and whether there is a link to a specific therapy. As commented above, they face different challenges: predictive biomarkers can be embedded in the product label. This means that changes (including improvements) could imply revised labels, with its associated cost.

5.2. CHANGE IN THE REIMBURSEMENT TO VALUE-BASED PRICING

Incentives matter and thus reimbursement mechanisms are a critical driver of investment on healthcare technologies: this applies to complementary diagnostics as well as the broad range of other technologies. In many countries where healthcare is publicly funded, HTA agencies recommend reimbursement for new medical technologies, and particularly branded pharmaceuticals on the basis of a cost-effectiveness criterion (e.g. in the UK, Australia, and Canada). This assessment is made after a medicine or diagnostic has obtained marketing authorisation. In the UK, there is a cost-effectiveness threshold which can be a key determinant driving NICE's and the Scottish Medicines Consortium's (SMC) recommendations for medicines (Dakin et al., 2015). To our knowledge, these two agencies are the only ones with an explicit threshold though other countries do regulate or negotiate pricing and reimbursement in other ways.

To reward innovation to promote societal efficiency, reimbursement of complementary diagnostics should account for the all the elements of value affected by diagnostic information. HAS in France adopts this perspective but their guidelines on companion diagnostics lack recommendations for the use of economic evaluation, limiting the assessment to clinical efficacy.

To move toward this value-based reimbursement, whether including only health system value or considering broader total societal value, the first change needed is an administrative one: the reward for diagnostics should not be based on costs, but on value. And historically there has been a lack of a linkage to value. The second change needed is an institutional change related to the responsibility of the HTA agency. Miller (2014) praised NICE as best practice for having a specific programme on Diagnostic Assessment which aims to be aligned with its Technology Appraisal programme (although Garau et al. (2013) raise some important issues around DAP's methodology, in that it still resembles closely the methods used for other technologies).

Given the defined ten elements in our expanded value framework, the next key consideration is how to measure them. To arrive to this point, cost-effectiveness can be adapted and/or augmented to consider additional elements of value. The full estimation of overall value based on only willingness to pay (i.e., using hypothetical contingent valuation) is not really practicable given the complexity of diagnostic-driven medical care and given individuals do not directly face the full cost of health care due to insurance/third party funding. However, taking the tools to estimate QALY gains and cost-offsets as valid and given in many circumstances, it may be feasible to augment them with contingent valuation of other specific elements such as the value of reducing uncertainty or the value of hope. One approach towards this broader definition of value could be to simply recognise the need to reward innovation more than would be justified by a strict, narrow approach based on a threshold applied to QALY gains and cost-offsets. QALYs or other measures of health gain are used to assess value in therapeutics, but application to diagnostics has been very limited. We need better metrics that reflect the full range of elements associated with the value of knowing. Of course, resources remain constrained and the opportunity cost of funding interventions needs to be reflected somewhere in the decision making process.

Value-based reimbursement systems should also encourage competition. Higher-value diagnostics should be appropriately rewarded. Also, diagnostics that are deemed to be similar to existing ones could then be priced at similar levels. And these systems could be adapted for managed entry arrangements, including coverage with evidence development and pay for performance.

There is also the need to recognise that diagnostics and associated therapies can be considered complementary goods, raising the issue of how to divide the value to promote dynamic efficiency (Garrison and Towse, 2014). This issue, which was beyond the scope of our analysis, merits further research. Economic theory alone does not provide the optimal division of rewards between the complementary diagnostic and the treatment (if it exists). Garrison and Towse argue that the rewards should be split to encourage dynamic efficiency, i.e., the optimal amount of innovation. Even when no treatment is available, the additional elements of value we have identified should be recognised when assessing complementary diagnostics.

The final issue relates to the process used to assess complementary diagnostics, and in particular, whether they should have their own evaluation process (and distinct from other technologies). Garau et al. (2013) suggest a diagnostic-dedicated process when the diagnostic is linked to a treatment (i.e. it is a companion diagnostic) and either the diagnostic is launched separately or there are multiple diagnostics launched with the same clinical use. They also suggest that when the diagnostic is not linked to a treatment, the same dedicated process should apply. Only when the companion diagnostic is launched jointly with the treatment could the diagnostic be assessed via the drug process - which could also use our expanded value framework when assessing both the drug and diagnostic. Moreover, for diagnostics that are not direct companions to specific medicines, the value of the diagnostic should be demonstrated independent of the therapy, and thus the reimbursement path for complementary diagnostics should be independent of the reimbursement path for associated therapies. This is due mainly to the fact that diagnostic enhancements occur more rapidly than the life cycle of the associated therapies.

5.3. INCENTIVES FOR THE UPTAKE OF COMPLEMENTARY DIAGNOSTICS

The potential health impact of complementary diagnostics is very large given the high burden of diseases for which complementary diagnostics can improve stratification and use of treatments, as well as predicting disease progression. For example, by assuming an effect of personalised medicine on the reduction in the incidence of six major diseases (cancer, diabetes, heart disease, hypertension, lung disease, and stroke), Dzau et al. (2015) project dramatic improvements in US population health over the next 50 years. Further, by simply reducing the incidence of disease through the use of traditional prevention methods to those patients who were deemed by prognostic testing to be at higher risk, the estimated value impact is more than USD 2 trillion.

For England, for example, Cancer Research UK has shown that a large proportion of pa-tient population is missing out on important molecular diagnostic tests (for melanoma, lung and bowel cancer) (Cancer Research UK, 2015). Cancer Research UK recommends specific actions to promote uptake of such tests. Concerns from payers and health au-thorities from the potential increase in the number of treatable patients that enhanced diagnostics can provide, with its associated costs, is understandable.

We have already highlighted the importance of incentives to support the development of diagnostics. It is critical for payers to acknowledge the potential value realised by the implementation of testing, so they may want to include other incentives (carrot and stick) to facilitate more appropriate use of testing across the patient journey. This could include rebates for adoption of near-to-patient testing for infectious diseases for exam-ple, or penalties for inadequately profiling a patient's tumour. However, although it is socially desirable to encourage greater appropriate uptake of complementary diagnos-tics, manufacturers most often do not have the right incentives (reimbursement- or regulatory-related) to assume the high risk of failure and delay to success to invest in novel molecular diagnostics (Danzon

and Towse, 2002), and patients do not have the proper information on the predictive value of diagnostic results. The literature reviewed in our phase I report confirms the misalignment of incentives for health providers, pay-ers, and manufacturers (Aspinall and Hamermesh, 2007; Dzau et al., 2015).

Monitoring the uptake of complementary diagnostics, with routine collection and publication of data is thus desirable. This will also help with the needed ongoing, repeated validation of diagnostics, leveraging technological enhancements. For instance, a scorecard for publication at the governmental level that measures uptake of testing may be useful in raising awareness and demonstrating commitment of the health authorities.

5.4. EQUITY ISSUES

While economics focuses on issues of efficiency, most HTA processes explicitly recognise the need to consider equity. Equity issues are also complex and multidimensional. For example, variation in access to care is a persistent issue in most healthcare systems, and adjustments for severity of disease or rarity are also common in HTA processes. This issue has been widely examined for medicines in particular, but less so for diagnostics. We recommend policymakers to also measure how the different barriers and challenges to the evaluation and use of diagnostics today can create inequities within and across EU countries. As mentioned above, scorecards could be developed, which can help establish national and regional benchmarking of test penetration. Any good practices that ensure equal access to diagnostics (and indeed, any other health care technologies) in any one country could then be used in other jurisdictions. Examples to explore could include screening initiatives for breast and colorectal cancer.

Another aspect related to equity is to understand the implications of the different perspectives (health care or societal) on HTA processes that consider equity.

6

CONCLUSION

The full value that well-validated complementary diagnostics can bring to patient care is underappreciated in healthcare systems around the world. By identifying those elements of value related to information and other elements of the value of knowing, among others, this White Paper aims not only to increase appreciation but also to provide a basis for evaluating and valuing their impact. A comprehensive consideration of these distinct elements of value is a prerequisite to the realisation of the promise of personalised medicine. We acknowledge proper validation of diagnostics is complex and costly, but this should not be a reason to avoid addressing these challenges. As healthcare systems evolve more accountability for outcomes and move to value-based reimbursement, the framework described here should provide a sounder basis for the HTA of complementary diagnostics as well as for appropriate reimbursement and rewards for innovation.

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