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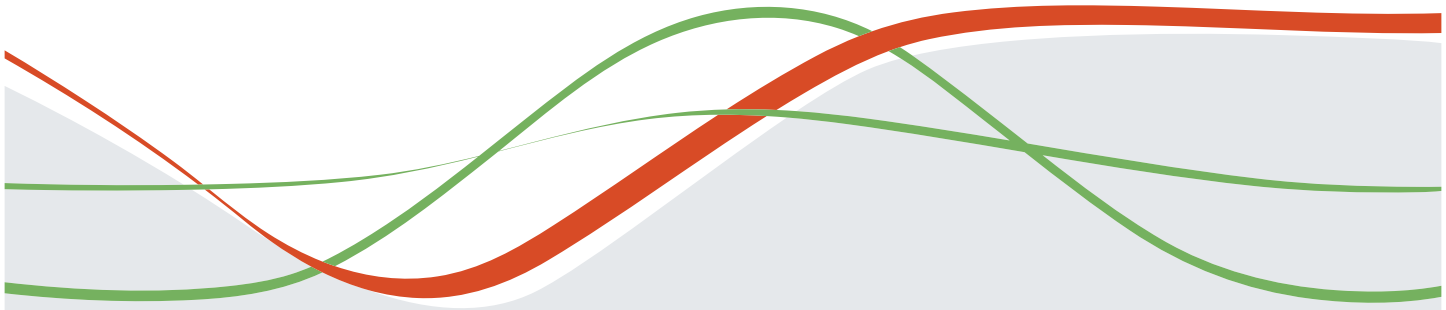

Phase I: Complementary Diagnostics: A Literature Review on the Value of Knowing

RESEARCH PAPER

July 2016

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TABLE OF CONTENTS

1 INTRODUCTION

1.1. MOTIVATION AND AIMS

This literature review and synthesis is motivated by two developments related to medical diagnostics: 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 health technology assessment (HTA) of medicines may overlook or undervalue important elements of value provided by diagnostics. A major aim of this report was to provide background and a conceptual foundation for a White Paper (OHE/EPEMED, 2016) that develops a more comprehensive framework for considering the value contribution of complementary diagnostics.

Roth (2013) has offered the following useful definition: "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 begin with this definition, but would argue that companion diagnostics should be considered 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.

Diagnostics, when used in combination in care pathways with other technologies, can provide valuable information that can help to guide medical decisions, and ultimately result in heath gains, cost-savings, and improved well-being. Greater information (irrespectively of whether a technology is available) generally means a reduction in uncertainty that can provide greater confidence and reassurance (i.e., greater peace of mind) for patients and can improve healthcare decision-making. For purposes of this review, we refer to this broadly as the "value of knowing": however, a key aim is to understand the various dimensions of this value in different applications.

This review and synthesis aims to address four key research questions:

1. How is the value of knowing provided by diagnostics currently described in the literature?
2. Does the value of knowing vary by type of complementary diagnostic? And if so, how?
3. What tools exist to describe or measure the value of knowing quantitatively?
4. What methods are used to account for and quantify the value of knowing in the current economic analyses applied by HTA agencies?

1.2. VALUE FRAMEWORK INCLUDING THE VALUE OF KNOWING

We embarked on this review with some preconceptions based on our previous work and thinking (Garau et al., 2013; Garrison and Austin, 2007; Towse and Garrison, 2013) of the potential importance of other factors besides health gain and cost savings usually considered in traditional HTA. Figure 1, based on Garau (2012) and Garau et al. (2013), provided a starting point for this to graphically represent the various elements of value of complementary diagnostics. In addition to the value of knowing/reduction in uncertainty, we also cite the "value of hope", "real option value", insurance value, and "scientific spillovers". We discuss these in more detail below.

There are a number of possible ways to parse or categorise these contributors to value. For purposes of this review, we thought the three dimensions identified by Lee et al. (2010) and reflected in Figure 2 would serve as useful, broad categorisation. They differentiate among medical value, planning value, and psychic value (i.e., psychological well-being). The medical

value is derived from the medical treatment which follows the diagnostic result, including reducing adverse events thanks to a better stratification of risk. The planning and well-being values are types of nonmedical value: the difference between them lies in their use. The planning value has instrumental or strategic use, for example, for contracting for insurance or for reproductive planning. In contrast, the individual does not plan to use the well-being value of information. The well-being value comes from the reassurance or the sense of self provided by knowing. Therefore, this is broader than Asch et al. (1990) "knowing for the sake of knowing" which only refers to one type of value – that of psychological well-being.

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]

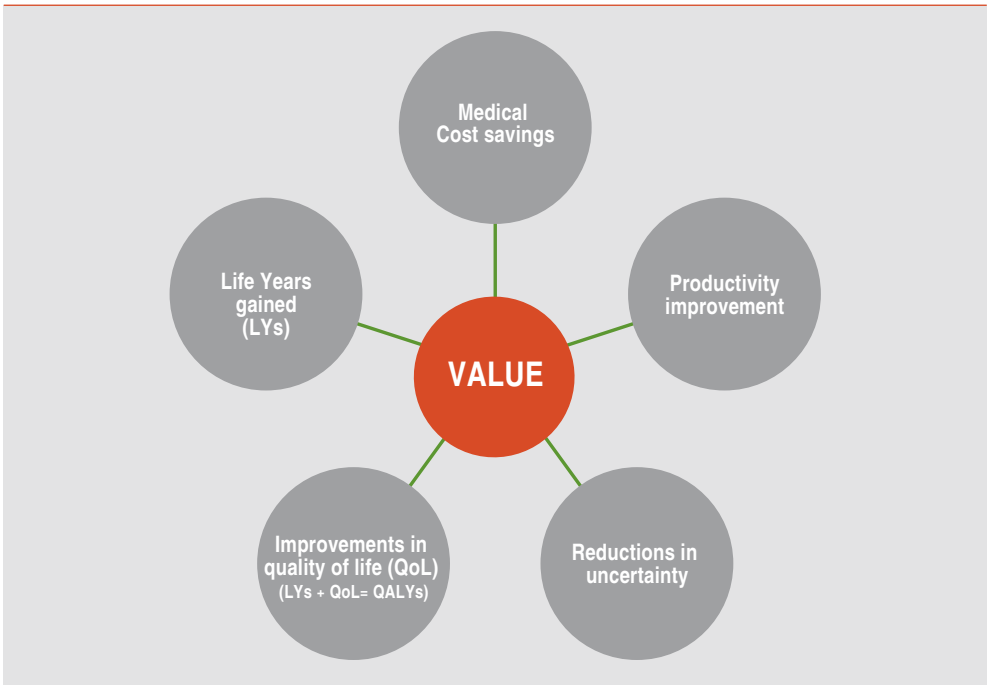
With regard to the second trend, diagnostics can provide valuable information that helps to guide medical decisions. Greater information generally means a reduction in uncertainty that can improve patient well-being and healthcare decision-making. For purposes of our work, we refer to this information 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.

FIGURE 1

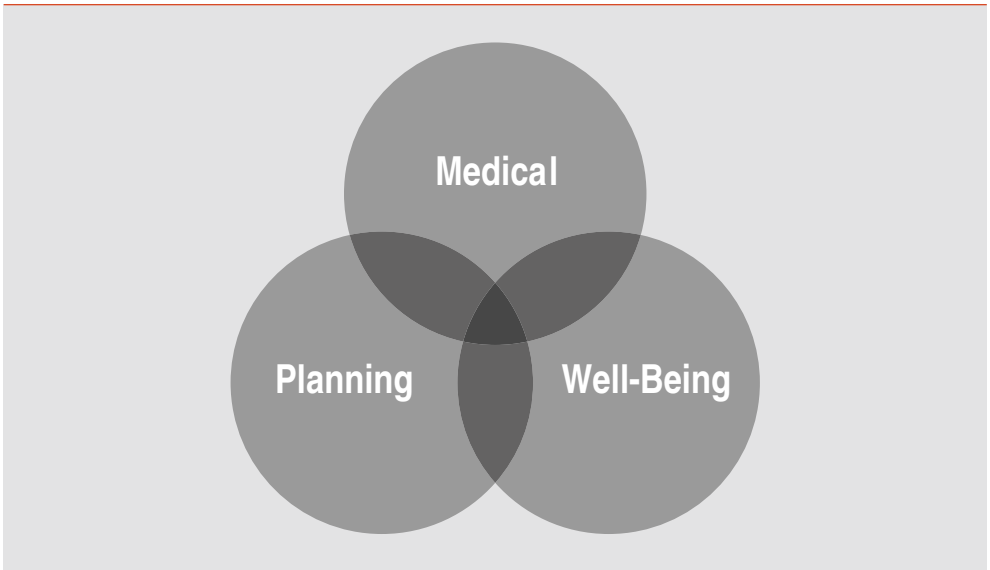
Preliminary value framework of complementary diagnostics



Source:
Adapted from Garau (2012) and Garau et al. (2013)

FIGURE 2

Dimensions of value (from Lee et al., 2010)



1.3. APPROACH AND ROADMAP

With these aims and frameworks in mind, we undertook a systematic and comprehensive literature search to identify peer-reviewed and other publications that discussed or analysed the value of knowing, particularly in the context of complementary diagnostics. Section 2 describes our search strategy and the body of literature that we identified. In Section 3, we summarise the literature that we reviewed, synthesising it into the three categories defined by the Lee et al.'s framework. Section 4 on qualitative methodologies describes and compares specific theoretical models and general evaluation paradigms proposed to evaluate the diagnostics from an economic point of view. Quantitative methodologies for measuring the value of knowing are described in Section 5. Finally, Section 6 summarises the key findings.

2 METHODS OF LITERATURE SELECTION

We reviewed peer-reviewed publications, in English language, discussing the different aspects of value that diagnostics can show for the different stakeholders involved in healthcare, as well as papers discussing the methodologies available in health economics to describe such value qualitatively and methodologies to quantify it.

To identify such literature, we pursued two different strategies: (1) based on our knowledge and experience in this area, mainly based on our previous work authored by Garau et al. (2013), we performed a bidirectional citation search (Hinde and Spackman, 2015) using a set of key papers identified to inform the value of information section of the aforementioned paper; (2) to be as comprehensive as possible, we designed a new search strategy, through electronic searches, to identify potentially relevant papers that the previous strategy might not pick up.

2.1. BIDIRECTIONAL SEARCH

Hinde and Spackman (2015) describe the bidirectional citation search as a searching method that through citation searching (both forwards and backwards) repeatedly sampling from existing identified relevant papers' citations to populate a pool of relevant literature. Our initial pool of literature comes from our knowledge of this area of research, mainly built through the work that was culminated in the publication by Garau et al. (2013), and also through our continued interest in this field of knowledge. The papers that compose our initial pool of literature are: the aforementioned Garau et al. (2013), Asch et al. (1990), Baker et al. (2008), Lee et al. (2010), Neumann et al. (2012), Miller (2014), and Goldman et al. (2013).

We list each one of the papers in our initial pool of literature and the titles of the papers from their reference list that initially selected for this project, as well as papers that have cited them after their publication (i.e., backwards and forwards citation search).

At this stage, we omitted papers that cite or are cited by each other within our initial pool of literature. We will also omit papers that cite or are cited by one of the papers in our pool of literature but that have already appeared under a previously searched paper from the pool.

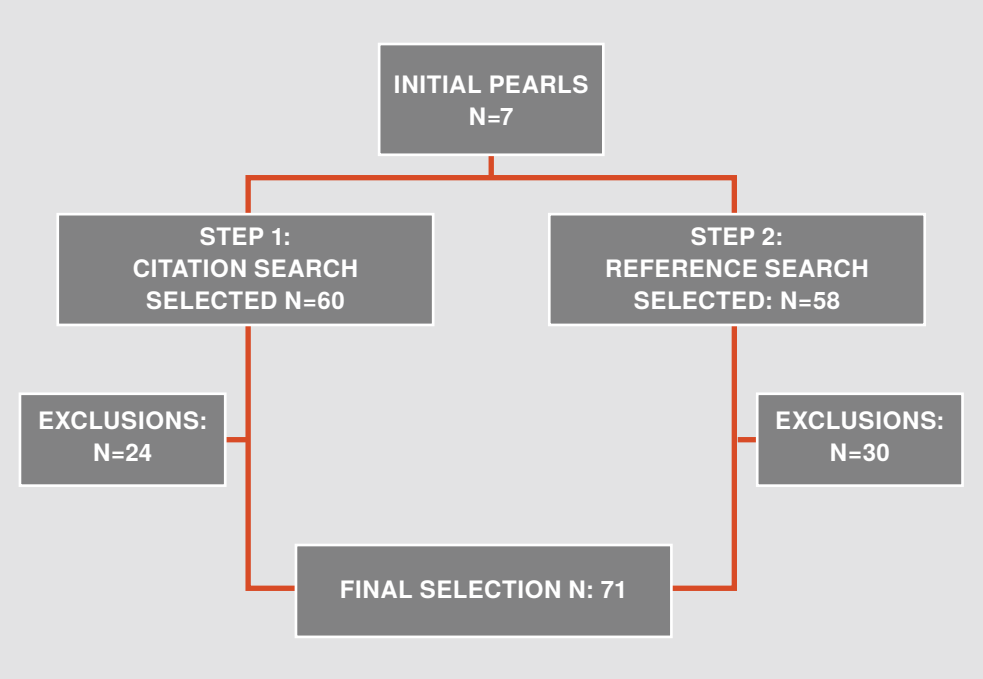
We excluded titles of economic evaluations of particular technologies to focus on papers that deal with a broader concept of value of diagnostics. We also excluded systematic reviews of economic evaluations where the title did not imply a review of the methodologies available for the HTA of diagnostics.

To find papers that cited those in our initial pool of literature, we used Google Scholar.

Figure 3 presents a flowchart summarising the selection.

FIGURE 3

Flowchart of bidirectional search



2.2. ELECTRONIC SEARCHES

For the sake of being as comprehensive as possible, we also run a search to pick up papers that we might have missed using the previous search strategy. To do so, we used the database Scopus, given that it contains economic literature. We used the following key words: "health technology assessment" AND "value of information" AND "diagnostics." As we reviewed our hits we confirmed the strategy picked up some of the key papers used for the previous search:

1. The search gave 193 hits.
2. The search found Garau et al. (2013), Lee et al. (2010), Miller (2014) and Baker et al. (2008).
3. First, we read the titles to do a first shortlist of potentially includable papers. Then, we reviewed the abstracts of the shortlisted titles to select or not the full article to be include in the literature review.
4. Our final selection includes 10 of these papers.

2.3. QUALITY ASSURANCE

Some of the selected papers have been excluded in the literature review because we did not find relevant information to be included in our review. In particular, we did not include papers on direct-to-consumer testing, and some general reviews of broad issues.

We selected additional papers after discussion with stakeholders, which completed our list of 103 references.

3 DIMENSIONS OF KNOWING

We have already defined dimensions of the value of knowing under different frameworks (Figure 1 and Figure 2). In this section we follow Lee et al.'s framework to illustrate the different dimensions of value of knowing. Before doing so, however, we first review the special characteristics of diagnostics affecting their economic evaluation, and explain how the public perceives the value of diagnostics in the dimensions considered (Section 3.1). Next, in Section 3.2 we review diagnostics within the medical realm, such as companion diagnostics, imaging diagnostics, and other complementary diagnostics that generate rights and obligations as a patient in the healthcare system, such as in the case of cancer screening. In Section 3.3, we review diagnostics within the nonmedical realm, for currently incurable diseases like Alzheimer's and Huntington's disease. Prenatal testing is considered in Section 3.4, as it illustrates nicely some of the issues that can arise when testing can provide additional information, even when there is no treatment.

3.1. DIAGNOSTICS AS INFORMATION

The first consideration to describe value of diagnostics is to characterise diagnostics in contrast with drugs in terms characteristics relevant to economic evaluation. Many HTA agencies, including the National Institute for Health and Care Excellence (NICE), provide economic evaluation of devices, which includes diagnostic instruments. There are some characteristics and uses of diagnostic instruments that have been recognised as pertinent to economic evaluation. For instance, Drummond et al. (2009) and Sassi et al. (1997) discuss these differences and the resulting challenges to the economic evaluation of devices since the evaluation processes and measures have been designed primarily for pharmaceuticals. Of the points raised by the authors, there are two main differences to be considered when evaluating diagnostic instruments. First, diagnostics generate information that comes as a result of a laboratory test or the use of diagnostic devices, such as imaging. Therefore, many of the differential characteristics recognised for the economic evaluation of devices also apply to diagnostics. Thus, the health outcome of the diagnostic is indirect, depending on whether the diagnostic information is "clinically actionable" or not. This concept is complex and its application is heterogeneous. Any action following a diagnostic or screening result depends on the "clinical validity" and "clinical utility" of the diagnostic. The clinical properties of the diagnostic define its clinical validity as the ability to accurately and reliably predict the clinically-defined disorder or phenotype of interest in the case of genetic tests. The clinical utility mainly depends on the availability of a clinical intervention with evidence of improved measurable clinical outcomes after the diagnostic result. Therefore, the current consideration of a test being actionable depends on its clinical utility and pertains to the medical realm since it is linked with the possibility of disease management.

A second consideration is that the diagnostic information can have multiple uses, not only for clinical purposes but also for life planning and well-being. In the case of imaging diagnostics, the diagnostic device has many uses, and the diagnostic information resulting from each use can also contain other unsolicited or "incidental" findings. The total diagnostic value could be defined as the (weighted) average of all values from their uses by patients and clinicians.

For the measurement of diagnostic costs, Califf (2006) and Steuten and Ramsey (2014) also highlight an important difference in the manufacturing development life cycle of diagnostic devices (relative to medicines) which are developed in an iterative process that evolves over a short period. This short life cycle complicates the collection of evidence on clinical and costs data from diagnostic devices for the evaluation agencies. These difficulties have also been discussed by Taylor and Iglesias (2009) under the focus of the collection of clinical and economic data for the assessment component of the HTA process, emphasising the special operator-device learning curve, causing a gradual increase in cost-effectiveness of the diagnostic device during the learning process by clinicians, and incremental device innovation, where new evidence opens new potential uses of the diagnostic device.

The preceding arguments on the special characteristics of diagnostics pertain to the medical domain. Therefore, our analysis of value of knowing relative to the "medical" domain is only related to the improvements in clinical validity and clinical utility of diagnostics, and not related to the consequences for costs and clinical outcomes. As a general principle of HTA value assessment, this value must be recognised and measured, and reimbursed when it does not exceed the agreed cost-effectiveness threshold (if such a threshold exists). As discussed below, the current application of this principle is fragmented depending on each specific diagnostic, country or region, but clinical utility should be augmented with information on health outcomes and costs and savings in the healthcare processes. We organise the rest of this section by grouping the literature in types of diagnostics according to the predominant value in these. Subsection 3.2 will provide examples of complementary diagnostics generating most of the value of knowing in the medical realm from their link to targeted therapies. The available evidence to measure this value has been generated by manufacturers.

For the nonmedical value, the main point of view is that of patients. Planning value is affected by changes in patients' behaviour following the reduction in uncertainty from a diagnostic result, and also by spillovers to the society, not only to family and carers, but also to employers. Subsection 3.3 reviews the literature on the diagnostics that have the dominant component of planning value, such as for reproductive planning. Lastly, the realm of "well-being value" only pertains to the patient and her sense of self after receiving a diagnostic result. The psychologist Gilbert claims that "people feel worse when something bad might occur than when something bad will occur" (Gilbert, 2009). This feeling is not universal, and it has been best measured by the reaction of patients to undergo and pay genetic testing to assess the risk of diseases without current treatment, such as Alzheimer's and Huntington's disease. Given non-actionability, the medical value of diagnostics may be limited, but it is difficult to separate the planning value from the well-being value, or even from a hidden "value of hope" (Lakdawalla et al., 2012) generated by expectations of treatment. The case studies are reviewed in Subsection 3.4.

The consideration of the value of knowing beyond the medical applications has opened a public debate on the pros and cons of diagnostics, mainly associated with genetic testing. The debate and ethical concerns are related to the predictive uses of diagnostics applied to asymptomatic individuals. With regard to public attitudes, Etchegary (2014) reviews literature on public attitudes toward genetics and highlights the general positive attitudes toward genetic research and willingness to participate in genetic research trials. Still, there are salient areas of public concern, for example, to use genetics to select newborn traits, as portrayed on the cover of The Economist (2015). The genetics community is ready to support genetic education and counselling to improve the public knowledge and translate decisions on genetic testing to positive behaviours. After surveying opinions from the Dutch Health Care Consumer panel in 2002 and 2008, Henneman et al. (2013) confirm that the positive expectations about genetic testing increased but worries on possible negative effects on equity remain.

With the growth of next-generation sequencing and the vast amount of data obtained, including incidentally diagnosed findings, the medical community has tried to agree on what type of information should be shared with the trial participants or the patients in the clinical practice. The recommendation is to return the "actionable" genetic results (Jarvik and al., 2014). As already noted, actionability is a concept related to clinical utility. The 2006 working group of the US National Heart, Lung, and Blood Institute (NHLBI) defined three (somewhat) ambiguous conditions for being "actionable" information: (1) when the associated risk for the disease is significant; (2) when the disease has important health implications such as premature death or substantial morbidity or has significant reproductive implications; and (3) when proven therapeutic or preventive interventions are available. Even if ambiguous, these conditions rely on a result of clinical utility, but if considered separately, any diagnostic for a condition with important health implications is an actionable test, even in the absence of an available intervention; for instance, the consideration of prevention as an intervention extends the concept of actionability to include the patient's point of view and preventive behaviours either for planning or for well-being purposes as behaviours that affect the quality of life. Nonetheless, Paulsen et al. (2013) rank different genetic diagnostics in terms of

(clinical) utility from high utility for those with highly effective and acceptable pre-symptomatic intervention (e.g. multiple endocrine neoplasia Type 2) to "harmful" for those with no effective intervention (e.g. Alzheimer's). The implications for patients' preferences and willingness to pay for diagnostic testing when an intervention is available, or not, is discussed in Section 4.

3.2. VALUE OF KNOWING FOR MEDICAL DECISIONS

Healthcare professionals have always used diagnostics to prescribe a treatment. When the diagnostics are based on symptoms or routine diagnostics such as blood counts, the medical treatment is known as empirical medicine or trial-and-error medicine. This assessment of risk considers both population prevalence and the symptoms of known diseases. This population prevalence and incidence of disease defines the prior probability of disease and the initial level of uncertainty. According to this consideration of risk assessment, everybody is at some stage of the "at-risk health status" which, according to Kenen (1996), is an ambiguous status with a continuum for non-legitimised to legitimised status. The legitimised at-risk health status defines obligations and rights within the healthcare system and then it is identical to the disease status. This is the range covered by stratified medicine linked to a therapeutic treatment. Within the value framework of Goldman et al. (2013), for example, the value of knowing accounts for the reduction in the costs of learning through trial-and-error, that is, the reduction in the costs of side effects and low adherence through a better targeting of a treatment to respondents. For example, for patients already diagnosed with breast cancer, the companion diagnostic HER2 predicts the efficacy of trastuzumab, and the stand-alone prognostic test Oncotype DX projects the likelihood of recurrence following adjuvant chemotherapy .

The other factors to consider the aggregate social value of knowing are the prices of the diagnostics and the medical intervention. In Goldman et al. framework which considers value as a consumer surplus, the value of the diagnostic increases with the cost of learning through trial and error and the cost of treatment, that is, with the severity of the disease. This could explain (at least partly) the uptake of personalised medicine in oncology.

All the five elements of value of personalised medicine identified by Garau et al. (2013) also pertain to the medical realm and can be interpreted as parallel with the arguments in Goldman et al. (2013) as a consequence of reduction in uncertainty relative to the trial-and-error medicine. These five elements of value are (i) reducing or avoiding side effects, (ii) reducing time delay in selecting the most appropriate intervention, (iii) increasing patient adherence and preventive behaviour, (iv) enabling a treatment effective only in a small fraction of the population to be made available, and (v) reducing uncertainty about the value of potential new treatments and likely effectiveness of available treatments. The last two elements relate to consequences for the uptake and the market size for personalised medicine that occur through the displacement of alternative drugs. In particular, as a result of diagnostics, drugs could be used in a smaller number of patients. This can be both a beneficial reduction and expansion of the market as exemplified by Goldman et al. (2013) for the NT-proBNP diagnostic test to predict adverse cardiac events from COX-2 inhibitors such as the anti-inflammatory drug rofecoxib. For instance, Sood et al. (2013) apply the value framework by Goldman et al. (2013) and Garau et al. (2013) to measure the cost-effectiveness ratio of COX-2 Inhibitors. Sood et al. (2013) consider how the use of companion diagnostics leads to a market expansion in responders and to market contraction in non-responders. These effects can be measured from population and clinical data.

Within the range of complementary diagnostics linked to a medical intervention, we reviewed the literature analysing the elements of value for (1) imaging diagnostics, and (2) pharmacogenetics. There are important differences in delivery and current deployment of both types of diagnostics, which will require different assessment of value, even though both fall into the realm of medical value.

The use of advanced diagnostic imaging such as PET, CT scan and MRI, has increased rapidly in most developed countries (Baker et al., 2008; Bradley and Bradley, 2014; Ding et al., 2011). There is no consolidated empirical evidence on the economic value of diagnostic imaging with a wide range of clinical consequences, from stratified treatments to incidentally

detected findings and routine treatments. This variety of imaging diagnostics applications has significant cost implications downstream for the use of healthcare services. The economic evaluation of imaging diagnostics has not resulted in conclusive evidence given (1) the difficulty of estimating long term cost and clinical effects (Adams et al., 2006; Baker et al., 2008; Ware and Hicks, 2011), and (2) the large number of patients diagnosed with relatively small expected clinical benefit (Gazelle et al., 2011). Ding et al. (2011) provide examples on the costs generated by incidentally detected findings, such as extra-colonic findings, during CT colonoscopy performed for detecting colorectal cancer, and also during abdominal CT. The results illustrate the cost burden of imaging diagnostics as a result of unintended diagnosis and consequent treatment that can affect more than one-half of the patients scanned for a primary diagnosis. The use of imaging diagnostics is ever increasing with the current tendency to combine biomarkers and diagnostic imaging for better stratification of the disease (Academy of Medical Sciences, 2013).

Pharmacogenetic treatments are based upon genomic, proteomic, or metabolomics analysis to understand the molecular basis of disease and the route of treatments. The Academy of Medical Sciences summarised the case of diagnostics based on oncogenes that have improved the treatment for cancer (e.g. for patients with locally advanced or metastatic non-small-cell lung cancer, for breast and ovarian cancer, myeloid leukaemia), for HIV treatment, and proteomic and metabolomics diagnostics developed in allergic asthma, ocular disease, and colorectal cancer. According to Miller (2014), over 120 U.S. Food and Drug Administration (FDA)-approved drugs have pharmacogenomics in their labelling. However, this labelling is only informational in most of the cases. Several distinct companion diagnostics have been cleared by FDA. The seven associated biomarkers of these approved companion diagnostics are: HER2 for breast cancer, CKIT associated with different types of cancer from stem cells growth factor, EGFR and KRAS for colorectal cancer, BRAF for melanoma, ALK for non-small-cell lung cancer, and BRCA1/2 for breast and ovarian cancer.

The use of genetic testing in next-generation sequencing (NGS) compares germline DNA with cancer DNA. The germline DNA contains personal unique information that can be used for screening purposes, such as to identify carrier status in asymptomatic patients. The actionability of these unique personal findings from genomic sequencing faces ethical, legal and counselling issues not only on the adequacy of the test but also on the reporting and storage of the information obtained, including form incidental or unsolicited findings (Lolkema et al., 2013; Shkedi-Rafid et al., 2014). By using the recommendations of reporting incidental findings from the American College of Medical Genetics and Genomics (Green et al., 2013), Bennette et al. (2015) find that the cost-effectiveness of returning incidental findings from NGS has been proven for certain patients and even for healthy individuals if the cost of NGS is sufficiently low (less than $500).

The available evidence is in the hands of clinical practice at patient level, where rules regarding patient privacy and confidentiality may clash with the actionability of the information for the family regarding the right to know about carrier status, for instance. Yet, reimbursement data can also contain clinical information. For HER2/trastuzumab and gene-expression profile Oncotype DX, Van Bebber et al. (2010), use payer data (public and private insurance and third parties) to measure clinical outcomes.

Even though there is a direct health benefit from treatment of patients diagnosed at early stages of cancer and other treatable diseases, thanks to complementary diagnostics, the public attitudes are not unanimously favourable. After the discovery of a genetic test to detect prostate cancer in 2008, some doctors declared “we are just feeding off this cancer phobia” (Kolata, 2008), claiming that there was already too much screening for prostate cancer resulting in too much treatment even for patients who would not develop aggressive cancer. On the other hand, since relatives of prostate cancer patients perceive an excessive risk of the disease, the prognosis information benefits these patients at psychological level (Bratta et al., 2000). Finally, cancer prognostication by genetic testing also presents ethical issues about autonomy and confidentiality as shown by surveyed attitudes of women tested for breast and ovarian cancer risk (Benkendorf et al., 1997).

Figure 1 also includes the dimension of “scientific spillovers” which can be ascertained as another value in the medical realm. In particular, for the pharmaceutical industry, the

scientific spillovers are driven by two factors. First, the economics of scope generated from the investment in developing different products (Cockburn and Henderson, 2001; Henderson and Cockburn, 1996); i.e. it is less costly to undertake any two R&D projects within the same company than in two different companies. This implies that spillover effects exist between R&D programmes within the company. Thus, additional R&D by any firm can result in positive externalities for R&D in other disease areas.

Second, Cockburn and Henderson (1994) have also shown the importance of externalities between mainstream pharmaceutical companies, i.e. spillover effects that occur outside companies. The evidence presented by these authors shows a strong correlation between a company's own innovative achievements and the success of rival firms' efforts. These spillovers come via routes such as the scientific literature and scientific meetings, because successful companies have to publish as well as patent, which brings benefits to the research efforts of others working in the field (Kettler and Towse, 2002). R&D has, through this second externality, positive spillovers to other competing R&D based companies. In other words, organisations that invest in R&D benefit from the R&D of other organisations in the industry.

The increase in productivity and success in medical discovery is based on a diverse knowledge base, and the medical institutions and pharmaceutical industry have incentives to invest in this knowledge base per se.

3.3. VALUE OF KNOWING FOR NONMEDICAL REASONS

Diagnostic information can be valued beyond its medical use in at least two other dimensions or uses: (1) for life planning, and (2) for the psychological well-being generated from reassurance. However, the use of the information from the availability of genetic testing for predicting the future onset of untreatable diseases has opened medical and ethical debates on the pros and cons of this information and the perils of misuse and misinterpretation (Etchegary, 2014; Henneman et al., 2013; Leventhal and al., 2013).

The value of knowing as a result of using complementary diagnostics for nonmedical reasons could be best tested for predictive diseases with onset in adulthood when a test is offered to adults, but when - in contrast to the case of many diseases - there is no known treatment or possibility of prevention even in the case of a positive result. Some neurological diseases have an inherited component and the gene mutation has been identified. This is the case of Huntington's disease (HD) for which genetic testing began with the localisation of the gene by linkage analysis in the early 1980s and became the standard of care with the discovery of the HD gene in the 1990s. Collaborative worldwide guidelines for predictive and diagnostic testing exist, and the test is recommended for predictive purposes under counselling by experts in HD. Also, an HD test is offered as a prenatal diagnosis for parents already aware of their genetic risk (Paulsen et al. (2013). The second case of neurological disease with available genetic diagnosis with predictive purposes is Alzheimer's disease (AD). AD is caused by genetic variations only in 58%-80% of the cases and the predictive diagnostic is based on a susceptibility gene, APOE, which was discovered in 1993. However, it has limited predictive power since the mutations inform about an increased risk between 3% with one APOE E4 allele to 15-fold with two APOE E4 alleles (Paulsen et al., 2013). The current practice does not recommend the predictive diagnostic for AD for asymptomatic persons; a major concern is the emotional effect of risk disclosure, added to the lack of treatment options and limited predictive value (Wikler et al., 2013).

For the case of HD, Paulsen et al. (2013) review health-related outcomes after the predictive testing, mainly psychological factors of depression, functioning and distress. In general, the test had beneficial effects on mental health and well-being, and reported benefits included a sense of personal control and planning for the future, including the decision of having children. Some studies include reports on discrimination or stigma, included by social relations, insurance, and employers (Paulsen et al., 2013). Twenty years after genetic testing for HD was made available, uptake remained at 10-20% in Canada, even though the surveyed disposition to take the test is more than 60% (Babul et al., 1993; Wiggins et al., 1992). Among those who had access to the test, the reasons for not taking the tests were related to concerns about coping with the burden of the disease risk while knowing that there

is no treatment, and difficulties to obtain blood for testing from family members. With regard to the dimensions of value of knowing, Wiggins et al. (1992) find beneficial psychological effects in the follow-up of 135 participants, of whom 60% took the HD predictive test. The disclosure effect is beneficial due to the reassurance from the reduction in uncertainty of disease risk, independently of the result of the test. Also, among the studies reviewed by Paulsen et al. (2013), the dimension of "knowledge and understanding" is the most cited reason for taking the test (38%), followed by life planning (17%).

The predictive testing for AD is more complex than for HD for technical reasons (lower accuracy since it is based on susceptibility and not on a Mendelian gene) and the cognitive nature of the disease (Drickamer and Lach, 1992), especially because of the high uncertainty of risk status even after the test and high complexity of the information based on susceptibility testing. The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, launched in 1999, is one of an ongoing series of multi-site randomised controlled clinical trials that provide empirical data to address these ethical, social, and translational issues in genetic susceptibility testing for common diseases. The disclosure of Apolipoprotein E (APOE) genotype as part of a risk assessment for Alzheimer's disease (AD) is the paradigm for the study, collecting information on the psychological and behavioural impact of AD risk disclosure. Paulsen et al. (2013) summarise results from several studies using the REVEAL data that suggest that the disclosure of the information on AD risk is not emotionally harmful. However, most participants did not perceive or recall well the information received. Many benefits of knowing were related with life planning such as buying medical and life insurance. Wikler et al. (2013) analyse a survey (designed according to the Health Belief Model) on attitudes on early diagnostic testing for AD in five countries to explain the expected benefits and harms of the test. Again, the life planning reasons were the most important considerations to favour the test, including the perception of a bigger threat of the disease for caretakers, and to take into account the cost of paying for future care if needed. However, a study on unaffected first-degree relatives of people with AD in the US (REVEAL study) finds that the desire to know from the point of view of the individual autonomy of the patients clashes with the concerns of the family members and doctors (Green and al., 2009; Maguire and al., 1996; Roberts, 2012). The current threat is the rise of unregulated offers of APOE testing direct-to-consumer (e.g. by 23andMe Inc. www.23andme.com) since this information can lead to adverse selection and discrimination by insurers and employers, among other uses of the information and misinterpretations which have not been tested. A key area of confusion and inconsistency is the interpretation of the clinical consequences of different types of mutations within a gene, as in the case of BRCA1/2 for breast cancer susceptibility. For direct-to-consumer testing (i.e. paid for directly by an individual), the individual might have even less consistent guidance on what to do when receiving negative results.

A recent study has shown that in the UK and Germany, a large percentage of respondents to a discrete choice experiment were not willing to take a diagnostic test for AD, perhaps for fear of receiving the bad news with no prospect of effective treatment (Mühlbacher et al., 2016). Moreover, these authors also find that the likelihood of rejecting AD diagnostic information was correlated with various attitude and health-history variables. However, Mühlbacher et al. (2016) conclude, citing also other research, "that people dislike ambiguous, uncertain situations and prefer certainty, even in the case of situations with negative consequences" (pp. 72).

Whatever the use of the information from genomic sequencing - including risk of AD and other neurodegenerative untreatable diseases - the advent of highly efficient DNA sequencing techniques is transforming the knowledge base for most human diseases. The technique is advancing quickly in clinical research trials, but there are no established standards or guidelines for the use, reporting, and storage of this information in the clinical practice. However, the clinical practice, supported by education from the genetics community and patients' associations (e.g. the European Society of Human Genetics and the American College of Medical Genetics and Genomics, Alzheimer's associations), is targeting early diagnosis and the education of patients, families and caregivers to face AD or other untreatable diseases. This implies a learning process for the medical profession and the patient/families/caregivers on how to benefit from the value of information for planning and well-being.

There is another psychological dimension that affects the demand for medical services. Therefore, we can arguably include it in the intersection between medical and well-being value in Figure 2. This dimension is the "option value/value of hope" which has been scarcely described in the literature. The value of hope has been defined in the context of end-of-life cancer patients by Lakdawalla et al. (2012). The value of hope is defined as a subjective psychological value for cancer patients facing end of life and then assigning greater value to the uncertainty of survival. These patients become risk-seekers and demand more innovative treatments with larger uncertainty in outcomes as long as there is some outcome allowing the patient to have a survival hope. The concept of real option value has been illustrated by Cook et al. (2011) in the case of stepwise incremental innovation. Patients perceive this as having option value 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. It may happen on the supply side. Patients adopting new treatments make it more likely that competitors will continue progress fast followers which may offer further improvements in health.

As in some other examples cited below, the value of hope is related with the personal perception of risk. People are risk averse in normal circumstances, and the demand for medical services responds to this degree of risk aversion so that the demand increases with the degree of risk aversion. In contrast, the case illustrated in value of hope is an example of the special case of end-of-life treatments and the change in subjective valuation of risky behaviours when people have nothing to lose. Some HTA agencies, such as NICE in the UK, have included consideration of end-of -life situations into the assessment of medicines, albeit focusing on the expected gain, rather than any element of "hope" in a long tail of longer, low probability, life extensions.

Also, illness could cause financial default for non-insured households. The public or private insurance coverage of health treatments, including diagnostics, is an important source of financial insurance. Using a welfarist HTA perspective, Verguet et al. (2013) and Verguet et al. (2015) 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.

Lakdawalla et al. (2015) 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.

3.4. GENETIC SCREENING FOR REPRODUCTIVE PLANNING, AND NEWBORN SCREENING

The possibility of identifying host genes responsible for adult-onset diseases, such as cystic fibrosis and neurodegenerative diseases, opens ethical discussion in the area of prenatal testing. In particular, the genetic testing and disclosure of results from amniocentesis are regulated under ethical guidelines (Human Fertilisation and Embryology Authority and the Nuffield Council of Bioethics in the UK). Asch et al. (1996) describe several reasons supporting genetic prenatal testing for the detections of carriers of cystic fibrosis and the strategies of health care professional to meet patient's goals. The possible strategies result in six final outcomes, which are the combination of a binary outcome (whether the foetus carries the disease or not) and the three outcomes from the pregnancy: delivery,

termination, and miscarriage. The economic evaluation of these six outcomes depends on the preferences of the parents and the value they attach to terminate a pregnancy versus having a baby who will develop the illness. This decision fits within the planning horizon of reproductive life and the possibility of having more children. While the health model values positively any health gain in years and quality of life of an individual, the different beliefs of parents about reproductive planning cannot be guided by a single economic evaluation model. In fact, even under the most unfavourable results predicting that the foetus carries the disease, many parents decide not to terminate the pregnancy.

Nonetheless, the role of economic evaluations and monetary measures have been proposed for prenatal diagnosis (Shackley, 1996) by using amniocentesis and chorionic villus sampling (CVS). The difficulty when defining health benefit in broad terms is how to capture not only the cost averted through terminating pregnancy of an affected foetus, but also the value of information in terms of psychological impact on the parents. However, most of the studies focus on measuring benefits in terms of the averted cost of having ill children. In the existing studies of elicitation of preferences in terms of contingent valuation and willingness-to-pay (WTP) (Berwick and Weinstein, 1985; Caughey et al., 2004; Ryan et al., 2005) it has been shown that WTP for prenatal tests is at the highest level, even above that for cancer testing (see Table 2 in section 5.)

On the other hand, newborn screening (NBS) is a public health program aimed at the early identification in asymptomatic newborns of conditions for which early intervention is possible. Table 1a presents the current guidelines of NBS in Europe and the US, adding the consensus achieved for the extension of NGS to NBS. Roberts et al. (2014) discuss the expansion of NBS programmes in the US, currently mandatory for all newborns and covering dozens of inherited diseases, and the prospects of using NGS for newborn screening (see Table 1b). Two key issues raised are the poor follow-up of the diseases diagnosed or predicted during the NBS programmes, and the privacy and consent on the part of parents to disclose information on incidentally detected findings, such as carrier status of a disease not targeted in the panel test, in the case of advanced screening through NGS. McGhee et al. (2005) estimate the cost-effectiveness ratio of newborn screening for severe combined immunodeficiency (SCDI) which is a rare treatable disorder. The test would be cost-effective under different assumptions on the costs, sensitivity, and specificity of the test, where the benefits are derived from years of life gained which have been adjusted for quality-of-life.

TABLE 1A

Guidelines for Newborn Screening Tests

Guidelines in Europe (Burgard et al., 2012; Cornel et al., 2014; Loeber et al., 2012)	• The number of conditions included in national screening panels ranges from 1 (Finland, Montenegro) to 29 (Austria) • Confirmation of screening results and information and communication to parents are regulated by guidelines and directives • In most countries, written information is available and consent is asked to prospective parents. But many countries do not ask for consent for storage of the blood samples
Guidelines in the U.S. (American College of Medical Genetics, 2006) Newborn Screening Expert Group Recommended Uniform Screening Panel from the Advisory Committee on Heritable Disorders in Newborns and Children	• Screening should be mandated for 32 conditions (because they have a screening test, an efficacious treatment, and adequate knowledge of natural history) • Secondary targets are defined on 26 conditions as part of differential diagnosis of the 32 mandated conditions, for which results should be made available to health care professionals and/or families but lack an efficacious treatment • Screening technologies such as mass spectrometry (MS/MS) or high-pressure liquid chromatography • Informed consent is not explicit. NBS is mandatory.

TABLE 1B

Discussions on advances for Newborn screening

Approach for genome sequencing technologies in NBS (Howard et al., 2015)	• The primary objective of NBS should be the targeted analysis and identification of gene variants conferring a high risk of preventable or treatable conditions, for which treatment has to start in the newborn period or early in childhood (e.g. carrier of cystic fibrosis). • A robust evidence base is a prerequisite for responsible and effective NBS, including on the variant causing the disease, the specificity and sensitivity of the test, the identification of the early intervention, the costs and clinical effects, and, finally, the determination of public acceptability. • New models of informed consent from parents have to be developed for NGS, including for report on unsolicited findings and storage and research use of samples and data. • Unsolicited findings should be reported to parents when clinically actionable or informing on carrier status relevant for reproductive choices.

4 QUALITATIVE METHODOLOGIES FOR DESCRIBING THE VALUE OF KNOWING

In this section, we review both specific theoretical models and general evaluation paradigms that have been used to evaluate diagnostics from an economic point of view with a focus on whether and how they incorporate considerations of the value of knowing. Firstly, we review the most general and innovative frameworks with several criteria. These could be deemed to be similar to broad HTA evaluation frameworks but have not been implemented to evaluate PM. In section 4.2, we review examples of the cost-effectiveness paradigms that are broadly accepted by some HTA agencies . In section 4.3, we review specific models that attempt to isolate the dimension of psychological well-being from the diagnostic information, and also other dimensions like spillovers within the family. These models can be theoretical models or contingent valuation questionnaires constructed to elicit value directly or stated preferences.

4.1. A GENERAL THEORETICAL VALUE FRAMEWORK

Sassi et al. (1997) suggest areas of research to expand the economic evaluation models based on cost-utility theory to the assessment of diagnostics. Three of their key proposals are: (1) a flexible definition of outcome and possible futures; (2) to consider the testing properties of the technology (i.e., sensitivity and specificity); (3) cost measurements going beyond the simple apportionment of the costs of shared resources. The consideration of the new dimensions of information and the ethical issues related to sensitivity/specificity of the test would go hand-in-hand with multi-attribute utility and multi-criteria decision models. The objective of these comprehensive approaches, including the risk-benefit frameworks suggested by Phillips et al. (2013), which compares the certainty of evidence of value with a risk-benefit ratio, is to generate evidence by organising and synthesising information and incorporating stakeholder perspectives.

We have already outlined the main dimensions of value of knowing under the three dimensions considered by Lee et al. (2010) where the multi-attribute utility model would imply expanding the objective of the decision maker beyond the healthcare sector, by adding the patient and the public attitudes (including risk aversion) for personalised medicine, even for “knowing for the sake of knowing”. This could involve using an extra-welfarist or a welfarist perspective. A common unit of currency for measuring all of the costs and effects would be needed. More recent proposals of this type recognise the short life-cycle innovative character of diagnostic development and propose an “early cycle economic evaluation” (Steuten and Ramsey, 2014). The early cycle economic evaluation model is an iterative evidence generation model which makes it possible to identify the key drivers of value as early as possible in a consultation process, taking into account the patients’ views. The greatest challenge is to elicit beliefs from stakeholders to populate early models and the usability of the information.

This challenge, as well as an account of the views from different stakeholders, is well illustrated by Housman (2011) and Fugel et al. (2014). In Housman’s words, “[…] a variety of stakeholders with different but related evidence needs for the evaluation of new diagnostic tests. First, scientists require a cogent explanation of the relationship between the biomarker and the disease. Next, the industry needs to know if the biomarker can be used to detect new clinical benefits and get new products to market earlier. Third, regulators have an interest in the effi¬cacy of the biomarker in determining a drug’s effectiveness. Finally, payors want to know if the biomarker will be adopted into medical practice and if the test is worth the cost. A manufacturer must be astute in understanding and addressing the needs of these various stakeholders.” Patients’ perspectives should not be excluded as we have discussed that patients can avoid taking invasive diagnostics or predictive diagnostics, and that many patients cannot understand the risk assessment information of some diagnostic results. The qualitative concept that contains and align these views is that of a “value proposition” defined as “a review and analysis of the benefits, costs and value that an organisation can deliver to its customers, to prospective customers, and to other groups”. Price and St John (2014) use the concept of value proposition aiming at valuing the outcome achieved in terms of the

impact across all stakeholders for laboratory medicine.

Another element of value that needs to be taken into account relates to healthcare providers involved in running clinical trials. This seems to be particular important for major cancer centres in the US. Such centres have financial interests in participating in trials as these can represent an important share of their revenues. Examples include trials that generate large genetic profiles in cancer. Many of the current complementary diagnostics have been developed and/or used in clinical trials, which account for an important part of cancer clinical interventions. Thus, the reimbursement of the diagnostic for a cancer patient may not be the main financial incentive for the provider: i.e., there are incentives for testing that go beyond the episode of treatment. Moreover, as patients participate in the clinical trials, the laboratories, hospitals, and pharmaceutical industry benefit from the knowledge base, the scientific spillovers, and the financial incentives from the research trial.

As far as we know, there are no empirical applications of this holistic value framework either as described by the early cycle economic evaluation model or by the value proposition. Nevertheless, there are applications of different models used in health economics in each part or stage of these frameworks. The models used are derived from economic models and information, among them the traditional cost-effectiveness analysis and cost-utility analysis, value of information analysis, and specific applications of economic theory and decision analysis. We present below a review of these valuation models from the theoretical perspective. The emphasis is on how the models have been adapted to consider the characteristics and dimensions of value of complementary diagnostics discussed above.

4.2. ECONOMIC EVALUATION PARADIGM OF HTA AGENCIES FOR PERSONALISED MEDICINE

Some HTA agencies have applied their economic evaluation frameworks based on cost-effectiveness and cost-utility analysis to diagnostics (and primarily companion diagnostics). In particular, the Canadian HTA agency issued the economic evaluation guidelines for personalised medicine (CADTH, 2006) that propose a type of evaluation based on cost-utility analysis where a final outcome is adjusted for health-related quality of life. A panel of experts reviewed these guidelines in 2012 and achieved consensus with this recommendation as the general principle (Husereau et al., 2014). Also, Rogowski et al. (2015) found consensus from a panel of 47 experts about the appropriateness of the use of existing "extra-welfarist" evaluation frameworks to PM. Even though the cost-utility paradigm is accepted, several aspects present challenges that need to be adapted to the particular concept of "personalisation" in each case.

There are many examples on the use of cost-effectiveness and cost-utility in the evaluation of complementary diagnostics. Durtschi and Julicher (2014) present a systematic review of economic evaluation for cardiac biomarkers; and Phillips et al. (2013) cite several structured reviews on economic evaluations of clinical genomics, the majority identifying cost-effectiveness and cost-utility evaluations. In particular, Phillips et al. (2013) detail the key drivers of cost-effectiveness and cost-utility analysis of Lynch syndrome screening, the most common genetic cause of colorectal cancer, including the effects of the attitudes of family members toward screening, and patient and provider preferences.

For NICE, the English and Welsh HTA agency, Payne and Thomson (2013) describe the use of the QALY for evaluating pharmacogenomic technologies. These authors use examples of medicine appraisals for companion diagnostic medicine uses in cancer treatments, and two device appraisals for stand-alone diagnostics appraised by the Diagnostic Assessment Programme (DAP), including for lung and breast cancer prognosis. By analysing the available published Technical Assessment Reports (TAs) of the companion diagnostic medicines, Payne and Thomson (2013) conclude that the assessment is mainly based on the medicine costs and clinical effect, while the diagnostic evidence is very limited and based on several assumptions of its unit costs and clinical efficacy from trials (rather than for clinical practice). Indeed, Garau et al. (2013) argue the DAP's measure of patient benefit is purely based on the QALY, and the method follows very closely that used for medicines.

The concept of cost-effectiveness is also used in an economic model by Danzon and Towse (2002) to evaluate the optimal price and the allocation for trastuzumab (a medicine for breast cancer with companion diagnostic for HER2) and nebucumab (a medicine for sepsis without companion diagnostics). The model and examples show that the cost-effectiveness principle can illustrate the different incentives of the stakeholders, the payer and the manufacturer, on investment in pharmacogenomics for which testing can be socially optimal.

Other agencies and organisations argue in favour of a new paradigm of economic evaluation for personalised medicine different from cost utility. The main arguments in favour of a different paradigm are originated by the impossibility of measuring the nonmedical value of information and the spillovers within the family in health related quality of life outcomes. For example, Buchanan et al. (2013) and Grosse et al. (2008) emphasise the limitations of QALY as the outcome for PM, based on a literature review of economic evaluations. The next subsection presents theoretical literature describing valuation models for these aspects although some of them are rooted in classical utility theory where the patient as consumer can present different degrees of risk aversion (Woodward et al., 1998)

4.3. INFORMATION, CURIOSITY, SPILLOVERS: MODELLING VALUE VERSUS ELICITATION

There is no doubt that complementary diagnostics contain information valued and used outside of the healthcare system and beyond the possible medical treatments. For example, Asch et al. (1990) show how the prognostic information from diagnostics generate optimal clinical decisions where the diagnostic information is valued independently from the treatment, which would be the same than prior to the diagnostic result. Different branches of science have been used to model the value from this information. These range from mathematics and economics to psychology applied to solve decision models. They also include exploring the cost of obtaining information modelled by value of information theory, including under the consideration of costs in cognitive terms for obtaining this information (Golman and Loewenstein, 2014; Pierson and Goodman, 2014).

From the theories of computer sciences, Asch et al. (1990), Somoza and Mossman (1992), and Johnson (1995) propose modelling the value of this information by using information theory as a tool to measure the reduction in uncertainty. The data needed are the statistical properties of the test such as its specificity and sensitivity, the prior probability of disease given by the prevalence, and a particular statistical distribution, normal or log-normal. Asch et al. (1990) also use the utility theory and some psychological concepts to measure the expected value by recognising the different subjective value given to bad versus good news, and also the statistical discontinuity created by total certainty. Other aspects of information that could be measured are delay and privacy, which are not explicitly considered in these models.

From the modern behavioural economics field which borrows from psychology, Rizzo and Lee (2012) combine the concepts of loss-aversion and cost-benefit (where WTP is considered a benefit, and “willingness-to-accept” (WTA) accounts for the costs), to create a mathematical model which describes how the medical diagnostics affect the patient’s sense of well-being, separately from medical consequences and even from life planning decisions. Thus, this model can be calibrated to predict the decision to undergo testing and how this depends on the accuracy of the test, the perceived risk of disease prior to the test, the time to the onset of the disease, and the severity of the disease. As we show in section 5 below, the model predictions are in line with some of the attitudes and WTP found in different surveys in “at-risk people” and in the general population.

In sum, people might avoid testing when they expect to receive “too bad news” but this is far from a simple statement because expectations are formed upon subjective factors such as perceived risk or time discount so that generates inequities and uniformed decisions. As confirmed by decision theory, there are conditions under which the information avoidance is a rational decision, termed as “denial” by Pierson and Goodman (2014) or the “ostrich” effect by Golman and Loewenstein (2014). The low propensity for the genetic testing for HD (where the instrumental or strategic information value is only the planning value because there is

no treatment) is interpreted under the Rizzo and Lee's and the Golman and Loewenstein's models. The first model would predict that nobody with a parent suffering HD would undergo testing "to know for the sake of knowing". In contrast, the second model can explain the empirical trends in testing by hypothesising that the driver to undergo the test is not only a change in the prior belief for an increased risk of the disease but also a change in the attention or ex ante worry, and that they would tend to delay testing while asymptomatic.

There is a dimension of value that has been partly considered in the nonmedical realm whereby the disposition to undergo complementary diagnostics is affected by the need for collaboration in the family just for doing blood test, or by potential stigma with relationships or employment and insurance discrimination. These are examples of negative spillovers, but the concept of spillover effects within the family is broader. It has been modelled and tested by Basu and Meltzer (2005) over the treatment choices of prostate cancer patients. The authors demonstrate that the cost-effectiveness analysis can include the social perspective and they use the QALY as the argument of a household utility function that considers these spillovers in the form of family altruism. They find clear differences in the treatment patterns between married and single people (unmarried, divorced, widow) and interpret the larger likelihood of treatment for married people at younger ages in terms of expected spillovers or survival benefits which become negative at older ages. This also explains why married people undergo less treatment than single people at the end of life. Nonetheless, the authors raise equity concerns due to the implications of differential payments according to marital status or any other demographic factors that might affect the value of medical treatments.

The theoretical models reviewed can predict the value of knowing by calibration on simulation under specific parametric assumptions on the relevant parameters, such as on the test accuracy or prior beliefs. For example, Rizzo and Lee (2012) assume ratios between 2 and 10 for WTA/WTP according to results from the literature relating the curvature of the functions. The alternative models are the elicitation models that design questionnaires based on contingent valuation models to measure WTP and WTA. In the subsection above, we introduce the limitations of using cost-effectiveness analysis to measure the value of complementary diagnostics given the restrictive consideration of quality-adjusted health outcomes, QALYs. Grosse et al. (2008) propose cost-benefit analysis as a better paradigm for measuring the value of complementary diagnostics, with WTP being the measure of benefit for all the dimensions of value - medical and nonmedical. Both the QALY and WTP need to use elicitation methods for measurement - health state preferences for the case of the QALY, and some monetary value ascertained in the contingent valuation questionnaire for the case of WTP. Nonetheless, health state preferences have been standardised in questionnaires like the EQ5D and SF-36, but there is not any standard measure to monetise the subjective disposition to pay for a medical treatment; for each medical treatment, there are as many WTP approaches, depending on the trial and questionnaires design. There are many systematic reviews on studies on WTP for medical treatments (e.g. Lin et al. (2013) for diagnostic technologies) and the next section presents some results relevant to complementary diagnostics.

5 QUANTITATIVE METHODOLOGIES FOR MEASURING VALUE OF KNOWING

Some of the models reviewed in section 4 have empirical applications and present cost-effectiveness ratios for complementary diagnostics (Danzon and Towse, 2002; Sood et al., 2013), for treatments (Basu and Meltzer, 2005), or other valuation measures (Rizzo and Lee, 2012; Somoza and Mossman, 1992) but they are reviewed as qualitative models because their main contribution is theoretical. In this section, we review (1) some empirical applications which attempt to improve the measurement of processes or outcomes which need special consideration in diagnostics (Clark et al., 2002) and (2) the results of several studies surveying patients, doctors, managers, or the public in general on their dispositions toward PM, either to take part in a test or to pay for it.

As noted in Garau et al. (2013), the operational/processes dimension of value as considered by Anonychuk et al. (2013) in terms of "operational efficiencies" or as "reducing time delay in intervention" is well recognised, but has not been measured. We did not find studies measuring the downstream costs and effects of diagnostics across the health care pathway apart from some attempts to measure value of imaging diagnostics (reviewed in Ollendorf et al. (2012)). As a notable example, Clark et al. (2002) present an excellent methodology and estimation to account for the duplicity of information and sharing of informational resources in the context of diagnostics in obstetrics. By using a statistical methodology based on stepwise analysis, they measure the clinical value added through new diagnostics moving from ultrasonography and hysteroscopy, which allows one to separate the value of diagnostic information from that of the background information available in the patient history.

Regarding the proposal of incorporating monetary estimates of WTP for genetic testing over the different dimensions of value of diagnostic information, as suggested by Grosse et al. (2008), Table 2 below presents results from contingent valuation and discrete choice experiments run over different sectors of the population. A relevant study surveying the attitude of the general population in the US is presented by Neumann et al. (2012). The questionnaire was designed to measure nonmedical value (planning and psychological well-being) since the instructions indicate that there is no available treatment. However, the authors recognise that the respondents can implicitly impute a value for expected treatment, especially for two types of cancer and arthritis, even though they may assume that there is no treatment for the other disease in the survey, i.e., Alzheimer's.

The results on WTP presented by Neumann et al. (2012) across the four diseases, jointly with the rest of results and the systematic review on WTP for imaging diagnostics by Lin et al. (2013), conform with some general trends discussed above. With regard to diseases for which there is a medical treatment, the WTP increases with the severity of the disease and the WTP for cancer diagnoses is larger than for less severe diseases such as gastroesophageal disease (e.g. Goldman et al.'s model prediction). In the realm of nonmedical value, it seems that the value of reproductive planning is large, with the largest WTP for ultrasound in prenatal diagnosis (Lin et al., 2013). The range of WTP for Alzheimer's disease testing is in the middle but it is remarkable that the disposition to undergo testing is the lowest among the four diseases in Neumann et al. (2012) survey. As argued by Mühlbacher et al. (2016), the low disposition for testing in AD might be due to the fear of having no effective treatment available if bad news are received. Lastly, the wide range of WTP for genetic test of retinal disease is explained because the top level corresponds to a scenario in which the additional value is a clear medical value of a companion diagnostic since the participants are told that "the diagnostic also identifies a new treatment that could stabilise your eye condition".

The perceptions of doctors and managers has been compared to that of patients regarding the WTP for diagnostic certainty (Hirth et al., 2000). They find that patients value more the information for the sake of knowing and that their desires are more aligned with doctors than with managers. The ranges found for WTP in Hirth et al. (2000) are included in Table 2.

TABLE 2

Results on WTP for Complementary Diagnostics

	Study and population surveyed	Disposition to test	WTP
Cancer	Neumann et al. (2012), Survey to US general population	79-88%	$508-$622
	Yasunaga et al. (2006), Survey Japanese men		$18.90
	Miron-Shatz et al. (2014), Canadian registers in breast cancer relatives	78%	$144
	Kilambi et al. (2014). Survey US general population		$1472-$1896
Arthritis	Neumann et al. (2012) Survey to US general population	77-80%	320-$385
Alzheimer	Neumann et al. (2012), Survey to US general population	71-74%	$409-$500
	Kopits et al. (2011). Survey on first-degree relatives of AD patients	60-71%	41% >$100 & 59% <$100
	Muhlbacher et al. (2016) Discrete choice experiment in UK and Germany	60-67%	€342 - $704
Ultrasound normal pregnancy	Berwick and Weinstein (1985)		$706
Ulcer and gastroesophageal disease	Hirth et al. (2000), survey US MCO insurance	84-87% patients, 52-61% physicians, 29-43% executives	$1-$50
Inherited retinal disease, genetic test	Tubeuf et al. (2015), UK patients with inherited retinal disease	72%-96%	$591-$7182

Severens et al. (2000) also present results on the disposition to pay for non-decisional diagnostic information in the case of an infection typical of speleologists who responded the questionnaire.

With regard to the disposition to undergo testing, there are also some empirical studies based on surveys. These include the specification of pros and cons to the test which can be chosen from a closed list (Wikler et al., 2013) or freely specified according to individual opinions (Wroe et al., 1998). Phillips et al. (2006) review studies surveying stated preferences for cancer screening and find that there is a significant percentage of people who prefer not to undergo the test. For those who prefer to test, they consider the test accuracy and the expected reduction in mortality as decision criteria. Moreover, Muhlbacher et al. (2016) find that those interested in taking an AD test preferred the less invasive diagnostic procedures, and that people are willing to pay for diagnostic clarity: i.e. significantly higher monetary values were obtained for more accurate (and less invasive) tests. Another review by Makeeva et al. (2009) states that 69% of British population expressed their interest in being tested for genetic susceptibility to heart disease, and 64% to cancer. Makeeva et al. (2009) also survey Russian inhabitants and find an ever larger disposition to undergo testing (85%) but taking into account that the test would allow to avoid the disease. Sassi et al. (2005) examine the decisions of patients and doctors for cardiac risk assessment in Italy and UK. Their results are in line with those found by Hirth et al. (2000) with patients showing stronger preferences than doctors for the test.

The general trends in disposition to undergo testing for several diseases show that people are more likely to have genetic test if they feel more at risk of developing the diseases (this is against the prediction from the model by Rizzo and Lee 2014), that there are not psychological harmed or regret effect after knowing the diagnostic result, even if it is bad news, and that the planning value is reflected because it seems that people with caretaker roles show larger disposition to undergo testing. Also, there is variability in the disposition to undergo testing by demographic group.

Any approach that aims to generate WTP estimates should be treated with caution. This applies even more to valuing complementary diagnostics. WTP approaches assume consumers are rational, which may not always be the case. This is part of the reason that the QALY approach is preferred in many jurisdictions. In the case of complementary diagnostics, and given the different dimensions of value outlined before, a WTP approach to attempt to measure overall unitary value might not adequately reflect all of the elements. Still, we believe WTP can give us interesting insights and some useful results.

Also, the WTP will mostly differ across jurisdictions, so comparisons across countries might be problematic. This is especially the case if the WTP depends on the organisation and funding of the healthcare system; for instance, European systems might be deemed as more “social” than the US system, given the significant proportion of healthcare covered by the national payer(s).

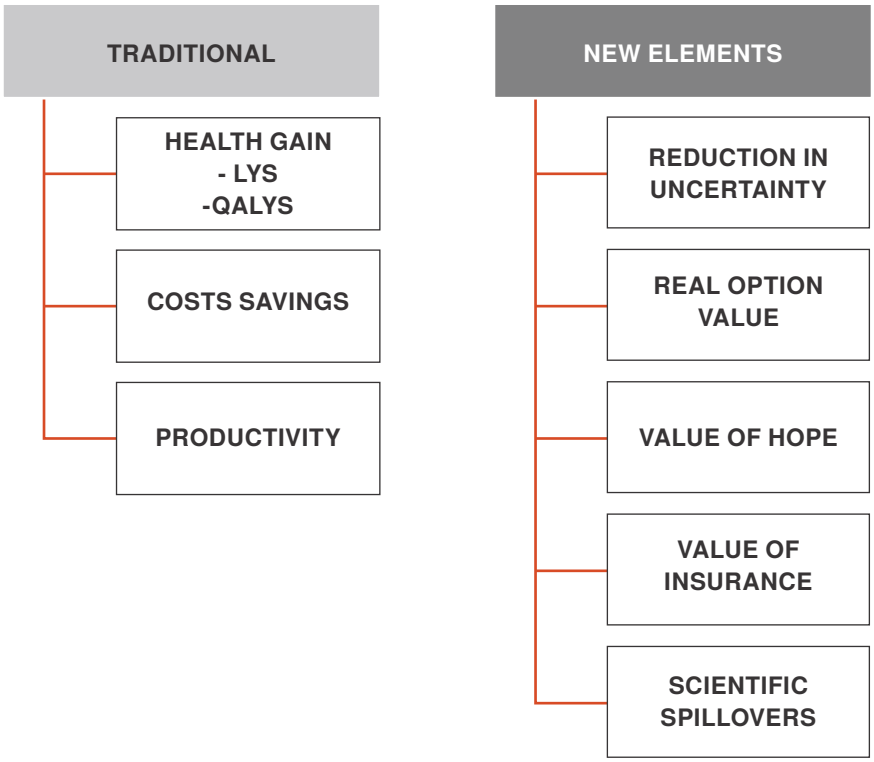
6 CONCLUSION: SUMMARY AND NEXT STEPS

This Phase I report summarises our literature review on the value of knowing. Overall, the literature strongly supports the view that information in itself has value for the healthcare system as well as for patients. This is particularly relevant for complementary diagnostics, irrespectively of whether the information is actionable or not. Diagnostics can provide valuable information that can help to guide medical decisions. Greater information generally means a reduction in uncertainty that can provide greater confidence and greater peace of mind for patients and can improve healthcare decision-making.

Figure 3 below summarises an expanded set - compared to our starting framework depicted in Figure 1 - of elements of value that we have identified in this review. We began with the traditional elements plus a recognition of role of the value of knowing. It should be noted that while the productivity impact is recognised as a core value element, it is actually measured in only a minority of cases. This investigation has identified five other concepts related to the value of information and knowing: value of planning, real option value, value of hope, value of insurance and scientific spillovers. Most of these could be applied to a wide range of medical technologies, but when used in combination with a complementary diagnostic, it is important to recognise and reward their contribution as a complement.

FIGURE 3

Toward a broader value framework for complementary diagnostics



Following this literature review, in Phase II we prepared a case studies report that: (i) reviewed the approaches to HTA in place for complementary diagnostics adopted in NICE, and in France by the Haute Autorité de Santé (HAS); and (ii) assessed three cases of complementary diagnostics, by reviewing, among other things, the available evaluations done for these by NICE and HAS.

Phase I and Phase II combined provide the foundation for our White Paper: “The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics” (OHE/EPEMED, 2016). The White Paper integrates and summaries the key findings from these two reports, and offers policy recommendations.

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