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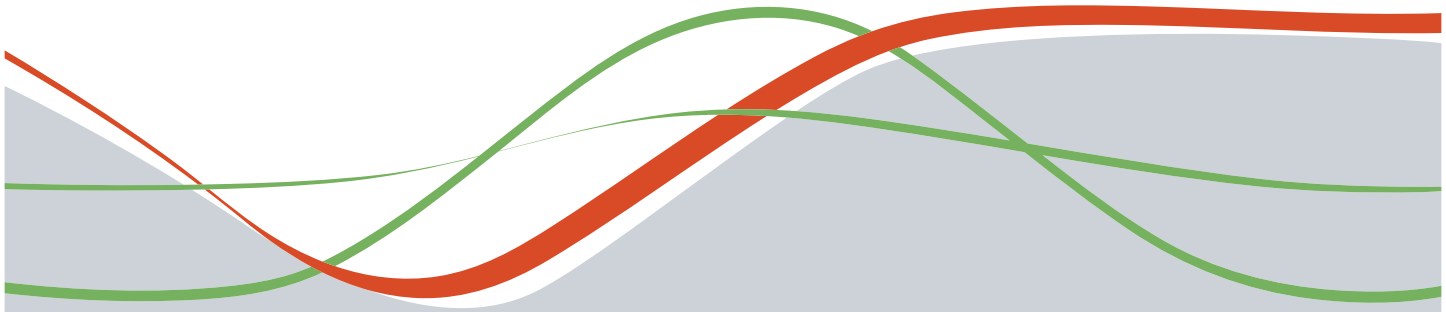

Phase II: Landscape Review of Complementary Diagnostics in Europe

RESEARCH PAPER

July 2016

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If you have any queries about this report, please contact: Dr Jorge Mestre-Ferrandiz, OHE, London. E: jmestre-ferrandiz@ohe.org or EPEMED, Luxembourg. E: contact@epemed.org.

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1 INTRODUCTION AND OBJECTIVES

This report completes Phase II of the collaborative project between the Office of Health Economics (OHE) and the European Personalised Medicine Association (EPEMED) to address health technology assessment (HTA) of complementary diagnostics. For this phase of the work, we have undertaken two main tasks: (1) reviewed the approaches to HTA in place for complementary diagnostics in England and Wales by the National Institute for Health and Care Excellence (NICE), and in France by the Haute Autorité de Santé (HAS); (2) assessed three cases of complementary diagnostics, by reviewing, among other things, the evaluations done for these by NICE and HAS (when available).

This report has been used for our White Paper "The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics". (For a literature review on the value of knowing, see our Phase I report "Complementary Diagnostics: A Literature Review on the Value of Knowing").

2 REVIEW OF EVALUATION APPROACHES FOR DIAGNOSTICS

2.1. ENGLAND AND WALES

The national HTA body in England and Wales is the National Institute for Health and Care Excellence (NICE).

NICE issued a diagnostics assessment programme manual in 2011 that can be useful to understand how they approach the assessment of complementary diagnostics (NICE, 2011).

To fully grasp the methods underpinning NICE's guidance in the area of complementary diagnostics, we summarise the above mentioned diagnostics assessment guidance document.

Diagnostics Assessment Programme (DAP) manual

A. Parts I & II: Introduction to the Programme and to diagnostic technologies, and Programme processes

"The DAP is suitable for evaluating diagnostic tests and technologies where such evaluation is complex, for example, where recommendations can only be made on the basis of clinical utility and cost-effectiveness analysis or where meaningful assessment requires the consideration of multiple technologies or indications."

NICE commissions the technical appraisals to the External Assessment Group (EAG), an independent academic group that prepares a review of the clinical effectiveness and cost effectiveness of the technology or technologies under consideration. The EAG assesses and presents the evidence in a diagnostics assessment report (DAR). The DAR does not contain recommendations on the use of a technology but it is included in the evidence base for the evaluation.

2.2. FRANCE

The national HTA body in France is the *Haute Autorité de Santé* (translated as National Authority for Health in their website – HAS).

HAS has issued two different methodological guidance documents that can be useful to understand how they approach the assessment of complementary diagnostics: the "Medical device assessment in France" guidebook (HAS, 2009); and the "Companion diagnostic test associated with a targeted therapy: definitions and assessment method" methodological guide (HAS, 2014). Each one of these document might cover different uses of complementary diagnostics.

2.3. HOW DO NICE AND HAS INCORPORATE OUR VALUE FRAMEWORK?

The value framework presented in the White Paper "The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics" presents our suggested framework, which considers several dimensions of value (and based on Lee et al. (2010), Garau et al., 2013; Garrison and Austin, 2007; Garrison and Towse, 2014). This value framework is used later for our three case studies, highlighting the information and evaluation made by NICE and HAS regarding the following elements of value.

Health gain. This element considers the gains in life years and in quality of life for the patients treated. This gain is aggregated in quality-adjusted life years (QALYs) which discount life years according to the disutility estimated from the disease status, from patient reported outcomes in EQ-5D surveys. The utilities are disease-specific and they should be considered from surveys run for similar patients. To measure health gain from diagnostics, a first step in the evidence gathering process is to search for studies that follow patients from testing, through treatment, to final outcomes (these are sometimes termed 'end-to-end studies'). If, as is likely, there are no end-to-end studies available for a diagnostic technology (given

the long lead times), then different types of evidence are collected and a linked evidence approach taken. If no data can be found for a parameter, expert input can be used to make educated assumptions, or the model can be redesigned to use other parameters. The value of health gain from a complementary diagnostic depends on the evidence on the clinical utility derived from the predictive value of diagnostic information. This evidence is linked to the specificity and sensitivity of the test and then to the accuracy in predicting responders and non-responders to an intervention. Also, the prognostic value of the diagnostic, as predicting the course and/or future onset of the disease, can derive clinical utility when used to optimise treatments or disease management; this is the case of diagnostics for cancer included in our second case study. From an aggregated epidemiological point of view, health gains extend to social health gains, for example by avoiding contagion in the case of infectious diseases. Also, the increase in adherence to prescription and increase in uptake of diagnostics can change the epidemiology of a disease by reducing incidence rates.

Cost-savings. NICE DAP guideline specifies that for the reference case, costs should relate to resources that are under the control of the NHS and personal social services (PSS) if it is possible to compare differential effects on costs between the technologies: the intervention versus the relevant comparator in standard clinical practice. These resources should be valued using the prices relevant to the NHS and PSS. Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included. However, in general indirect costs and external costs are not included in the assessment, neither societal costs for the patient and families. In contrast, the French societal perspective recommends to include also costs outside the health system in the economic evaluation of medicines (Boulenger and Ulmann, 2004), and we assume that by extension for diagnostics. For example, the early treatment and management of a disease as predicted by a diagnostic may induce additional direct non-medical costs incurred by patients and their families from the acquisition of goods and of formal or informal caregiving.

Productivity. The gains in life time and quality of life derive in productivity gains, for example reducing work absenteeism. The NICE perspective of HTA evaluation from the health-system, or extra-welfarist does not considers productivity as an element of value. The French position of HAS adopts a societal perspective which should account for productivity effects derived from the change in health care pathway after a diagnostic result, but the application in practice is scarce or limited to some general illustration more related to the disease than to the diagnostic, as we explain in the case study of familial breast cancer screening programme.

Value from reduced uncertainty. This value for the patient is derived from the prognostic information which does not drive treatment decisions and does not improve health outcomes directly other than through psychological effects from reduced uncertainty. This well-being value, also known as “knowing for the sake of knowing”, tries to capture a psychological effect void of any value which might be derived from behavioural and life planning changes (planning value). It can be difficult to quantify these benefits and they are not normally included in the base-case analysis. It is difficult to measure and as illustrated in Phase I Report, many studies try to measure it in terms of willingness-to-pay. NICE DAP guidelines, explicitly acknowledges: “Relevant outcomes include any health outcomes resulting directly or indirectly from the use of the test. They may also include informational outcomes of value to the patient for the relief (or imposition) of anxiety or for personal planning”. However, this outcome can be only monetised as included in the form of counselling sessions. For instance, in the first case study presented on familial breast cancer, the costs included genetic counselling. Prognostic information is information a test provides about future health events the patient can expect. The prognostic information from complementary diagnostics also allows patient to make life planning decisions under reduced uncertainty. These decisions can be financial decisions such as managing life insurance and last will, or life fulfilment wishes supporting the psychological well-being from reduced uncertainty.

Value of hope. This value accounts for the change in risk attitudes of people at the end of life, toward higher risk-taking behaviour, which induce terminal patients to undertake innovative treatments which may not have high expected gains in additional months of life expectancy,

but have a distribution of outcomes, such that some patients do make significant gains in life expectancy. For example, this could explain larger participation in clinical trials. As far as we know, Lakdawalla et al. (2012) is the only study providing a quantitative illustration of the value of hope for cancer patients. This element is considered neither in NICE nor in HAS diagnostic guidelines although NICE considers end-of-life criteria in the evaluation of drugs. NICE does not explicitly raise the threshold but allows higher QALY multipliers or more uncertainty in the clinical or costs evidence. However, this is around the estimate of the mean value.

Option value. The concept of option value has been illustrated by Cook et al. (2011) as a case of stepwise incremental innovation. Patients perceive this option value as long as it increases the likelihood of benefiting from a better treatment in the future.

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 physical and mental 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 people and they are willing to buy insurance ("a risk premium") to obtain it, via public or private health insurance.

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 in part by looking at the distributional consequences of illness and treatment. This value is picked up by neither NICE nor HAS guidelines.

Scientific spillovers, R&D in clinical trials benefits from economies of scope within and across pharmaceutical companies and research institutions. This fact has been referenced by seminal literature in Phase I Report. Moreover, 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 discover future treatments (BIVDA, 2015). This stepwise incremental innovation from authorisation to discovery of new indications is especially illustrated in diagnostics for cancer analysed below.

We now turn into our three case studies. They are presented below, and have been chosen jointly with EPEMED's Steering Group. These case studies are analysed as considered by NICE and HAS. They are diagnostics on:

1. Familial breast cancer: BRCA1/2 tests
2. Gene expression profiling tests
3. Procalcitonin tests to monitor sepsis in hospital patients

3 FAMILIAL BREAST CANCER: BRCA1 AND BRCA2 TESTS

Breast cancer is by far the most common cancer diagnosed in women worldwide, with higher incidence in Western Europe and North America. With worldwide estimated 1.7 million cases and 521,900 deaths in 2012, breast cancer accounts for 25% of all cancer cases and 15% of all cancer deaths among females (Torre et al., 2015). The majority of cases appear in women with no apparent close family history, and only about 5% of all breast cancers are largely attributable to inherited mutations in specific genes, including BRCA1, BRCA2, and TP53 (Solomons, 2013). However, the lifetime risk of breast cancer in women with a mutation in these genes is substantially increased compared to the general population. Therefore, the target of **"familial breast cancer"** programmes is to identify this inherited predisposition to breast cancer. Nonetheless, the high-penetrance breast cancer susceptibility gene mutations (BRCA, BRCA2, and TP53) have been also found in women with no apparent family history of breast cancer, referred as **"sporadic breast cancer"**. According to the results of the largest clinical research trial in the UK (Breast and Ovarian Cancer Susceptibility Genes), a 60% of genetic risk of breast cancer remain unexplained but "a meta-analysis of over 50 studies has shown that, overall, breast cancer is twice as common in women with a first-degree relative. Twin studies demonstrate that the predominant component of this familial aggregation is genetic. Moreover, these data demonstrate a markedly skewed distribution of genetic liability suggesting that the majority of genetic risk lies within a genetically predisposed minority".

BRCA1/2 are denominated high-penetrance susceptibility genes since these are the most common cause of a high lifetime risk of breast cancer (between 40% and 85%). These mutations are also related to higher risk of ovarian cancer (10%-60%) and prostate cancer for male carriers (25% risk for BRCA2 carriers) (NICE, 2013a). In case of carrying the BRCA1/2 mutation, breast cancer is mostly classified as oestrogen receptor negative (ER-), known as triple-negative or basal-like, according to more biomarkers, and with poor prognosis.

This case study analyses the position of the French and British national health policies to diagnose and treat familial breast cancer, in particular the HTA guidelines by the English NICE and the French HAS with the Institut National du Cancer (INCa). INCa is an independent expert reference body, and has different responsibilities to NICE. In particular, INCa does not have an HTA mandate to recommend or not the use of the diagnostic in clinical practice.

In the case of NICE, the first clinical guidelines for the diagnosis and treatment of familial breast cancer were issued in 2004 and they have been successively revised in 2006, and 2013 (with some modifications included in August 2015) (NICE, 2013d). The French public health system does not have a separate policy or guideline for familial breast cancer as compared to sporadic breast cancer. Both types are targeted by a public health programme of screening within the Plan National du Cancer which is running the third quinquennial edition 2014-2019, after completing the 2003-2007, and 2009-2013 Plan. Nonetheless, the screening programme includes a special procedure for the identification of women at high risk of breast cancer, including familiar breast cancer (Haute Autorité de Santé, 2014). The English NHS also runs a public health programme of screening for breast cancer, although it has lower frequency and coverage than the French programme. This is picked up later.

An important consideration is the fact that the breast cancer susceptibility mutations under consideration are mutations in germline DNA: that is, they are part of a person's DNA during his or her lifetime, independently of developing cancer or not. Therefore, these mutations can be diagnosed at any age, even in newborns, and they are generally used as prognostic tools. In the second case study, we analyse diagnostics realised for prognosis and prediction, based on genome from breast cancer cells, that is, when the tumour has developed and it has a specific genomic profile with proliferation of distinct mutations.

3.1. NICE GUIDELINES

Breast cancer is the most commonly diagnosed cancer in the UK and around 49,000 women and around 350 men were diagnosed with breast cancer in 2011[1]. Even though only about 5% of breast cancers and 10-15% of ovarian cancers are attributable to inherited mutations, up to one in five patients has a family history of these diseases. Therefore, many asymptomatic and healthy women with affected relatives are demanding information for their risk status to proceed with enhanced surveillance if needed, and optimal treatment under early detection.

These demands for enhanced surveillance for women with relatives affected by breast or ovarian cancer has tried to been addressed by the English health system. NICE launched the first guidelines of familial breast cancer in 2004, later updated in 2006 and 2013 (NICE, 2013d). First, we discuss the coverage and services recommended by this clinical guideline, focusing on the information content and the actionability of this information.

3.1.1. INFORMATION CONTENT

Firstly, the surveillance of familial breast cancer is not a public health programme in the UK, in the sense that is only offered under patient demand. The clinical guideline specifies "Healthcare professionals should respond to a person who presents with concerns but should not, in most instances, actively seek to identify people with a family history of breast cancer"(NICE, 2013d). Nonetheless, there is a public health programme: NHS Breast Screening Programme, where all women aged 50 to 70 registered with the NHS are invited for breast screening through a mammogram every three years, which is being extended for a larger age interval. For example, women over 70 are allowed to ask for an appointment to the screening programme, and younger women can be referred by the GP.

The first point of contact for an asymptomatic person who wants to know her risk of breast cancer is the primary care doctor who decides on the need of further surveillance according to the NICE clinical guideline protocol. There are tools to calculate the combined BRCA1 and BRCA2 carrier probability, which include data from a questionnaire on family history and personal characteristics. The methods used in the UK are mainly BOADICEA (Lee et al., 2014) and the Manchester scoring system but they are used in secondary care for patients referred from primary care due to assessment of moderate or high risk of lifetime breast cancer.

The mutation carrier probability is compared with the average prevalence in the population, which is 1.5% for patients without personal or family history of breast or ovarian cancer (Myriad Genetic Laboratories, 2010). A threshold of 10% carrier probability was established in 2013, lowering it from the previous 20% threshold[2], so that the patient is referred to a genetic clinic if the scoring tool results in a carrier probability higher than 10%. This threshold is quite conservative according to the mutation prevalence tables (Frank et al., 2002; Myriad Genetic Laboratories, 2010) which only show prevalence over 10% for individuals with personal history of breast or ovarian cancer, if individuals of Ashkenazi Jewish ancestry are excluded. This ethnic group presents higher prevalence and this factor is also considered in the risk-assessment. Moreover, the genetic test is only offered to a patient with no personal history of breast or ovarian cancer if an affected relative is unavailable for testing because there are no living affected relatives (The Institute of Cancer Research, 2015). The protocol is very restrictive in this sense since the FAQ establishes: "Can unaffected testing be undertaken in a family where affected relatives are unavailable but not deceased? No. At present NHS unaffected testing is limited to those families in whom affected relatives are deceased. Affected relatives who live abroad should seek testing in their own country.

[1] http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer.

[2] Because high throughput and more rapid testing are available. In particular the relevant recommendations were: "Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined BRCA1 and BRCA2 mutation carrier probability of 10% or more. [new 2013]; Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined BRCA1 and BRCA2 mutation carrier probability is 10% or more and an affected relative is unavailable for testing [new 2013]" (NICE, 2013c).

Individuals can have testing if they wish to pay for it". Therefore, the genetic test is not a screening programme since it is mostly performed on individuals with personal history of breast or ovarian cancer, even if the test is required by an unaffected relative since the relevance of the results extend to unaffected relatives who can be tested after the affected relative has resulted in carrying the mutation.

Therefore, an alternative to undertake genetic testing for BRCA1/2 mutations for unaffected women are direct-to-consumer genetic testing. Also, some women can be eligible to undertake genetic tests under clinical research trials. Currently, an unaffected patient can be offered to participate in the Breast and Ovarian Susceptibility (BOCS) Study[3] but eligibility is very restricted.

Another issue is the verification of family history which is not required via medical or death registries. According to the guidelines, "if substantial management decisions, such as risk-reducing surgery, are being considered and no mutation has been identified, clinicians should seek confirmation of breast cancer-only histories (via medical records/cancer registry/death certificates). Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with risk-reducing surgery". Therefore, the family history can be imprecise, especially in the case of second and third degree relatives. In particular, the age of the onset of cancer is not remembered for dead relatives, and the risk assessment tool consider 60 years to substitute these missing data. This adds to the uncertainty of the risk assessment exercise.

In the NICE clinical guideline, the classification of breast cancer risk categories and the derivation to treatment in secondary care and specialist genetic clinic is as in Table 1 below.

TABLE 1

Summary of breast cancer risk categories and related care settings (NICE clinical guideline 164)

Breast cancer risk category	Age 40 to 50	Lifetime risk from aged 20	Carrier probability (BRCA1/2 or TP53 mutations)	Treatment/ Care setting
Near risk population	Less than 3%	Less than 17%	Very low	Primary care
Moderate risk	Risk of 3-8%	Risk of 17-30%	Less than 10%	Secondary care
High risk	Risk of 8% or greater	Risk of 30% or greater	A 10% or greater	Specialist genetic clinic

According to Table 1 and the carrier probabilities found in population studies (Myriad Genetic Laboratories, 2010), people with moderate risk of suffering breast cancer have at least one first or second degree relative affected with breast or ovarian cancer (2.6% to 7.2% carrier probability). The majority of people under high risk have a personal history of breast or ovarian cancer for whom the risk assessment is then about recurrence of the disease.

[1] http://www.icr.ac.uk/our-research/research-divisions/division-of-genetics-and-epidemiology/genetic-susceptibility/research-projects/the-breast-and-ovarian-cancer-susceptibility-(bocs)-study

The national surveillance programme for the general unaffected population does not assess the risk of carrier probability of mutations BRCA1 and BRCA2. This surveillance programme is performed in primary care and consist of (1) offering information and support for people who have concerns about their cancer risk, including by taking a family history to inform a personal risk assessment, and (2) decide on primary care management, including referral to the NHS Breast Screening Programme, or referral to secondary care if the family history indicates a moderate or high risk of breast cancer. The GP can refer a patient to a specialist genetics service only in the case when a high-risk predisposing risk mutation has been identified (BRCA1, BRCA2, or TP53), for example if the person has paid for direct-to-consumer genetic testing.

The assessment of carrier probability risk is performed in secondary care by using the BOADICEA or Manchester scoring systems. Although a particular hospital can use other tools, BOADICEA and the Manchester score are the most recommended on the basis of accuracy. The implementation of these tools requires specific information on the family history according to the patient's knowledge. The NICE guideline has established that if any of these tools results in a carrier probability of 10% or more, the patient should be referred to a specialist genetic service to undergo genetic testing. If the patient has no personal history of breast or ovarian cancer, an affected living relative must undertake the genetic test first.

3.1.2. HEALTH ECONOMIC EVALUATION MODEL

The establishment of a risk threshold for eligibility was lowered from 20% to 10% in the 2013 NICE clinical guidelines. This risk threshold is based on cost-utility models which assess the costs from use of resources, and QALY gains for patients referred for genetic testing of BRCA1/2 mutations. For our purposes, it is important to remark that the calculation of costs only includes direct costs to the NHS that will arise from the implementation of the guideline. The direct or indirect costs incurred by the individual, private sector or the-not-for profit sector are not considered, nor the scientific spillovers arising from new developments in genetic testing and changes in practice.

Nonetheless, the assumptions and research data behind the cost-effectiveness evidence also illustrates some indirect and private costs and benefits. For example, the consideration of the uptake rates for genetic testing illustrates the psychological costs of the information and the actionability based on these results as the main reason of observing lower uptake among unaffected women. The full guideline (NICE, 2013d) describes the content of genetic counselling as discussions about the medical implications of a positive or a negative result, the psychological risks and benefits of genetic results and the risks of passing a mutation to children.

This NICE full clinical guideline 164 includes a summary table with research studies and the full cost effectiveness analysis with the evidence supporting the high risk threshold of carrier probability at 20% in the 2004, 2006 guidelines, and at 10% in the 2013 guideline (NICE, 2013b). In addition, NICE presents the Costing report (NICE, 2013c) and the Clinical evidence report (NICE, 2013a) on the different interventions linked to familial breast cancer, including genetic testing, the resource and clinical impact of the recommendations on enhanced surveillance, and on the available treatments with chemoprevention, which were recommended in the 2013 revision for women with no personal history of breast cancer.

Regarding the impact on resources, the recommendations to implement risk assessment tools to calculate the carrier probability and information support are not included in costs. This is because these recommendations are included in clinical practice and should not result in a significant impact on resources, apart from a redistribution of patients between primary care, secondary care and specialist genetics services. The recommendation for enhanced surveillance implies more frequent diagnostics (annual) and for extended age intervals by using mammography and MRI for women at moderate and high risk. The estimations affect 2,500 women at an additional cost of £0.9 million per year (considering the unit cost of MRI at £216 and mammogram at £93).

To compute the costs of genetic testing, there is an estimation of eligibility and acceptance to undertake the test. The eligibility for genetic testing to affected women is estimated at 5 women per 100,000 population, according to the established 10% carrier probability threshold and the percentage of cancers caused by the high-penetrance predisposing genes. Moreover, some unaffected relatives would be eligible for testing, an estimate of a further 14 people per 100,000 population. Based on research studies, the NICE cost report assumes that 86% of affected individuals take up the offered genetic testing. This produces an estimate of 39.56% for those who are offered and who take up the test. In addition, around 48% of unaffected individuals take up genetic testing. This gives an estimate of 31% of unaffected individuals who are offered and who take up a genetic test. The cost of genetic testing are £700 for an affected women and £240 for an unaffected family member (NICE, 2013c). On the costs related with communication of the results and genetic counselling, NICE assumes 2 or 3 counselling sessions per patient tested, at £125 per session.

Based on these costs and the clinical benefits, NICE proposes to lower the carrier probability threshold from 10% to a lower level allowing genetic testing of an average of 13 women per 100,000 population. The main impact on cost is derived from changes in the uptake of testing and eligibility for genetic testing. The introduction of treatments like chemoprevention have very limited impact on costs given the clinical restrictions for applicability and low costs of tamoxifen and raloxifene.

On the side of savings, the accounted medical savings of a cancer case avoided averages £12,715. Yet, there is no estimation on the number of cases avoided among the unaffected women undergoing genetic testing without further assumptions on treatments like preventive risk-reducing surgery. On the side of the clinical benefits, early detection is also important in terms of life years gained and QALYs.

The complete cost-effectiveness model used by NICE is based on a systematic review of prior studies of genetic testing of women for BRCA1/2 mutations and treatment with reducing-risk (prophylactic) surgery. The estimation uses a Markov decision model which consider the available incidence tables and parameters of uptake of genetic testing and prophylactic surgery from the literature. The cost-effectiveness model also considers the cost of death, including palliative care, which is significantly higher for cancer-related death (£4,134) than for non-cancer death (£110).

At the current 10% carrier probability threshold, the estimated incremental cost effectiveness ratio is lower than £20,000 in the three populations considered for adults aged 40-49: ICER of £18,114 for affected individuals, ICER of £12,108 for unaffected individuals with available affected relative tested with 10% carrier probability, and for unaffected individuals with no relative tested, undertaking the genetic test is a costs saving strategy, or dominant as compared to no testing. The ICER increases with age but it remains below the acceptable £30,000 threshold for affected individuals under 60. Genetic testing is always cost-effective (ICER below £20,000) when applied to unaffected individuals who undergo genetic testing based on the prior result of testing in an affected relative. This positive effect on relatives should be taken into account when considering testing affected individuals even if the test present higher ICERs for affected patients. Moreover, the threshold could be lowered to 5% carrier probability and remain under ICER levels considered cost-effective.

3.1.3. COMMUNICATING CANCER RISK AND CARRIER PROBABILITY BEFORE GENETIC TEST

Even though familial breast cancer is not a public health programme, NHS Choices informs on the options for people concerned with the risk[4]. NHS Choices raises some issues beyond the NICE clinical guidelines and the Institute of Cancer Research (ICR) protocols. In particular, there is mention of the present policy where it is not compulsory to communicate carrier status to insurers. NHS Choices also presents several options on planning a family including prenatal testing. It clarifies that telling close relatives about the results is the patient's responsibility, and it advises on the services, information offered, and prices if the patient decides to pay for private testing.

[4] http://www.nhs.uk/conditions/predictive-genetic-tests-cancer/pages/introduction.aspx

When an unaffected patient is referred from primary to secondary care for assessment of breast cancer risk is due to the family history of breast cancer. The assessment of risk given in primary care does not communicate carrier probability of high risk-predisposition risk mutation. The assessment tools such as BODICEA and Manchester score are used in secondary care to determine the carrier probability and apply the protocol depending of the 10% threshold (The Institute of Cancer Research, 2015).

The communication of risk status in probability terms is difficult and patients do not always remember or understand the information given. The full guideline by NICE (2013d) summarises a literature review of studies which have assessed the process of risk communication for familial cancer with inconclusive advice on effective communication. Nonetheless, NICE has a protocol on the standard written information which should be given in all cases.

But before explaining the result on carrier probability, the patient should understand the risk assessment exercise and the tool (BOADICEA or Manchester score), and how to obtain a comprehensive family history. Also, the patient must be informed on the potential outcomes, taking into account that the protocol only considers three possible treatments and follow-up: (1) surveillance in either primary or secondary care (enhanced surveillance includes MRI only offered in cases of identification of the mutation in genetic testing), (2) chemoprevention using drugs such as tamoxifen and raloxifene for which there is no European marketing authorisation for preventive use at present, and (3) risk-reducing surgery of breast or ovaries (mastectomy or bilateral salpingo-oophorectomy).

If the patient agrees to completing the risk assessment tool, there is a guideline to summarise in a written document and to explain orally to the patient both the numeric information on absolute carrier probability risk and on the level of uncertainty. The information must also include qualitative information on risk such as the availability and side effects of potential treatments. This is important since the treatment choice can target either early diagnosis (surveillance) or avoidance of cancer (chemoprevention and prophylactic surgery). The clinical effects in terms of survival and quality of life vary and depend of the age of patient who must be advised in genetic counselling on the decision about the type and when to undergo the treatment depending on the result.

The health economic model assumes the patient should be offered two or three genetic counselling sessions, one more than for unaffected relatives. The model only considers the costs of genetic counselling for the patients undergoing the genetic test. Then, it implicitly assumes that genetic counselling is only offered after genetic testing to inform on the results and the treatment options. However, NHS Choices specifies that “if your doctor thinks genetic testing may be appropriate in your case, you will usually be referred for genetic counselling as well.”

3.1.4. COMMUNICATING CANCER RISK AND CARRIER PROBABILITY AFTER GENETIC TEST

The Institute of Cancer Research (ICR) has issued a protocol to guide patients and professionals on the optimal pathway before and after genetic testing. “Protocol 3. BRCA mutation carrier guidelines” clearly explains the clinical pathway after obtaining the genetic test results. In the case of a negative result (no mutation identified) the patient should be monitored through the national surveillance plan in primary care, but there are other options which can be discussed in case of strong familial history. There are cases where the test identifies variants of uncertain significance which are derived to the Institute of Cancer Research.

For positive results of either BRCA1, BRCA2 or both, the protocol establishes the numeric information which should be communicated on breast cancer risk according to tables obtained from BOADICEA data. This numeric information includes lifetime risk and approximate 5 year risk, depending on the age and sex of the patient.

Also, the protocol establishes to inform the patient with positive result on “carrier management” by (1) surveillance, granting access to annual MRI for women aged 30-50, (2) chemoprevention for BRCA2 carriers, and (3) risk-reducing surgery or breast and/or ovary.

The breast cancer risk reduction after treatment is only available for risk-reducing surgery which achieves a 90-95% reduction of breast cancer risk after bilateral mastectomy.

3.1.5. STORING PATIENT DATA

Every patient undertaking genetic test in the NHS and resulting in positive results must be registered in the "Carrier Register" as specified in Protocol 3 of the ICR. We only found a mention of this Carrier Register in this protocol. The register is not mentioned in the NICE clinical guidelines and there is no additional information in the ICR site about the management of this "Cancer Register".

3.2. FRENCH HAS GUIDELINES AND INCA EXPERT ADVICE

Incidence of breast cancer in France is among the world highest, with 48,763 new cases in 2012 which amounts more than one-third of new cancer cases for women[5]. In a study by Molinie et al. (2014) from data issued from nine population-based cancer registries in France, the incidence of invasive breast cancer increased annually by 0.8 % from 1990 to 1996 and more markedly by 3.2 % from 1996 to 2003, and then sharply decreased until 2006 (-2.3 % per year), especially among women aged 50-69 years (-4.9 % per year).

Since 2003, France has launched three National Cancer Plans for 2003-2007, 2009-2013 and 2014-2019. These are public health programmes for screening and prevention of cancer. Familial breast cancer is included, where women classified at high risk of breast cancer follow personalised screening outside of the public health program targeted to all French women aged 50 to 74. The first diagnostic instrument used is a mammogram. The programme has the objective of early treatment with proven lower mortality rates. The Plan 2009-2013 has detected almost 16,000 new cases each year and the participation in the programme achieved a 52.7% by 2012.

In particular, the Cancer Plan 2009-2013 includes "Action 23.3. Monitor people at high genetic risk of cancer" which considers expanding prescription criteria for BRCA1/2 genetic tests. Following INCa demand under this Cancer Plan, HAS prepared a clinic-economic study and recommendations for personalised screening women at high risk of breast cancer, including familial breast cancer (Haute Autorité de Santé, 2014). The evaluation of screening on women carrying the BRCA1/2 mutations includes INCa recommendations which were being actualised for these cases but there is not any update of the HAS report since 2014. Also, INCa completed a guideline for the medical profession on "Prophylactic surgery of cancers with genetic predisposition" (Institut National du Cancer, 2009) addressed to the treatment of women carriers of BRCA1/2 mutations. The guidelines distinguish the treatment for unaffected women and women with a confirmed diagnostic of breast cancer.

The HAS recommendations provide an indication giving the right to a visit to the genetic clinic for women classified at high risk of breast cancer, after which a genetic test for the BRCA1/2 mutation can be recommended or not. The guidelines for the treatment with prophylactic surgery of women are clearer for women already diagnosed with breast cancer.

3.2.1. INFORMATION CONTENT

The screening for familial cancer is assessed according Eisinger's score (Eisinger et al., 2004) ranked from 1 to 5, with a maximum risk of five only in cases where the BRCA1/2 mutation has been identified in a relative. A high risk score (between 3 and 5) indicates a referral to genetic consultation. A score of 3 is assigned to women with antecedents of breast cancer in a female relative younger than 40; the score of 4 is assigned for any antecedents of ovarian cancer, or for breast cancer in male relatives.

[5] Les traitements des cancer du sein. Collection Guides Patients. October 2013. Institut National du Cancer

According to the population survey "Baromètre santé 2005 INPES", 12.2% of women screened with mammogram requested the test due to family history of breast cancer, with a majority being younger than 50 which is the threshold age for the general screening programme.

The study by Haute Autorité de Santé (2014) summarises French and International recommendations, in particular from INCa and from the Belgian Centre of Expertise of Health Care (KCE). In particular, when the mutation has been identified in a relative, the genetic consultation is recommended to apply a risk score: BOADICEA in the case of INCa and Gail or Tirer-Cuzick in the KCE case. A score above an agreed threshold should be followed by surveillance at the same level than for carriers. However, at this point of the recommendation for women classified at maximum risk, HAS recommendations are limited to imaging diagnostics, including mammogram, ultrasound, and MRI. The study by Haute Autorité de Santé (2014) reviews the clinical outcomes of these three imaging diagnostics in terms of specificity and sensitivity, with consequences on mortality. The report does not include any recommendation relative to treatments through chemoprevention or risk-reducing surgery of breast and/or ovary.

A key objective of the Cancer Plan is the coverage of cancer through clinical trials. In 2013, more than 25,000 cancer patients of all types were included in clinical trials. There is a register of clinical trials in the INCa with several trials on breast cancer. Regarding the mutations BRCA1/2, there are registered trials in the Cancer Centres Marseille and Caen. The largest clinical trial was launched in April 2015 by the cancer reference centres on Lyon, Montpellier, Nancy, Nantes and Paris, in collaboration with the American Quest Diagnostics, l'Inserm, and UNICANCER. The research focuses on sharing a large database on anonymised clinical information from carriers of the mutations BRCA1/2 (BRCA Share)[6]. Another ongoing clinical trial (LIBER trial) is testing a medical preventive therapy with aromatase inhibitor letrozole versus placebo in menopausal women carrying BRCA1/2, involving 30 centres in France. The number of patients expected is 724 with 5 year treatment and 5 year follow-up.

3.2.2. HEALTH ECONOMIC EVALUATION MODEL

HAS does not include an economic evaluation of the screening on women at high risk of breast cancer. The first study realised in 2011 (Haute Autorité de Santé, 2011) includes an estimation of costs from treatment of breast cancer and from losses of productivity. The treatment cost average €19,000 per patient without including recurrence. The productivity loss in terms of absenteeism due to breast cancer accounts for 50% of the total productivity loss.

3.3. ELEMENTS OF VALUE

This subsection is a summary of the elements of value discussed above relative to our value framework. The NHS Choices site "Predictive genetic test for cancer risk genes" is a good summary of the different elements of value of knowing offered to the patient, with explicit "pros" and "cons" for undertaking predictive genetic testing. In the value framework presented in this project (Phase I Report), these pros and cons, classified according to the value framework seven elements, are as follows:

1. **Health gain [Life Years gained (LYs) and Improvement in quality of life (QoL)].** The knowledge of the carrier probability, as prognostic information, allows to manage the medical risks, including: undertaking prophylactic surgery, by enhanced surveillance and breast screening in the form of mammograms and MRI, by lifetime preventive changes such as suspending oral contraceptive pill or hormone replacement therapy for patients carrying the mutation, and by preventive chemoprevention which can reduce the risk of breast cancer for up to 20 years from five years of taking them, and by risk-reducing surgery of breast and/or ovaries. Moreover, this information is predictive to the accuracy of the chemotherapy treatment in women affected as

[6] http://www.umd.be/BRCA1/

analysed in the second case study, since familial breast cancers are basal-like cancers with poor prognosis. As summarised above, NICE has presented some data on survival and QALY gains from the interventions of genetic testing for familial breast cancer to support genetic testing as a cost-effective diagnostic. The QALY data presented discount survival according to disutility from prophylactic surgery and health state associated to cancer. The expected QALY gains vary with the threshold and the probability and type of prophylactic surgery. NICE illustrates many examples, from expected QALY gains ranging from 0.5 to 0.8.

2. **Cost-savings [within and outside health system].** Some data from the NICE Costing report have been summarised above, remarking the unique consideration of direct costs for the NHS, including genetic counselling, testing costs, and cancer treatment costs. Many direct costs are ignored assuming they cancel out in the process of redistribution of patients within the health system. Besides it is almost impossible to impute overhead costs accrued from referral genetic testing as part of the clinical practice associated to primary and secondary care.

3. **Value from reduced uncertainty.** Knowing the result, independently of the outcome, may reduce stress and anxiety, as suggested by surveys conducted for other tests (Phase I Report). This part of prognostic information can be either valued or avoided by the patient due to this psychic value. In fact, the lower uptake to genetic testing for unaffected women versus women with personal history of breast or ovarian cancer, hints that this prognostic information is avoided and many women prefer to live without knowing their risk of suffering cancer, even if they are concerned given their family history. Even though the well-being value of information does not account for planning value, the case of testing germline DNA is linked with the value of reproductive planning. In fact, NHS Choices highlights the value of family planning as how to avoid passing faulty genes to children, including embryo selection, and prenatal testing with option to terminate pregnancy. Besides family planning, people knowing the risk of the onset of future diseases can use this information for planning finances and future care.

4. **Value of hope.** The policy of participation in clinical trials considers the voluntary participation, including written consent, of patients. Participation of patients in research trials like the “Breast and Ovarian Cancer Study” can be motivated by the “value of hope” in innovative medicines, available in the present or in the future, with more uncertainty but with a window of hope from the unknown.

5. **Option value.** This element is neither considered in NICE nor in HAS evaluation of screening tests for familial breast cancer. The response or uptake for the diagnostic, a mammogram in this case, can be driven by advertising the public health programmes. According to the French Baromètre Santé 2005 INPES, 2% of women undertaking a mammogram are driven solely by the advertisement of the public health programme without having any other health concern from symptoms or relatives suffering the disease – this uptake could relate to option value.

6. **Productivity.** Only the HAS guidelines for screening of women at high risk of breast cancer illustrate the potential effect of reducing the incidence of breast cancer in terms of productivity. HAS report (Haute Autorité de Santé, 2011) signals two sources of loses due to breast cancer: absenteeism during the disease, and lifetime earnings lost due to death.

7. **Scientific spillovers.** This case study has illustrated an important point in the economics of scope and scale from research in family breast cancer. The NICE and HAS guidelines feed from international evidence and the most important current research is based on shared databases such as from the Breast and Ovarian Cancer Susceptibility Genes Study and BRCA Share.

   Equity and privacy considerations. NICE economic evaluation has demonstrated a lower cost-effectiveness ratio for BRCA1/2 testing in unaffected women with a relative being confirmed BRCA1/2 carrier. The fact that the genomic information of a relative facilitates the diagnostic for a patient generates social value for the diagnostic but this

does not mean that women without affected living relatives should be excluded from the test. Regarding to privacy, the communication policy states that the carrier status is patient information and the doctor cannot inform relatives. Telling the family about carrier status and being available for providing a blood sample for testing if required by a relative is a personal decision that should not block access to the diagnostic by relatives. Nonetheless, Phase I report has shown that this rule of patient privacy may reduce the amount of genetic testing.

4 GENE EXPRESSION PROFILING FOR BREAST CANCER

Microarray-based gene expression profiling is a genetic diagnostic made from tumour cells of breast cancer which allow a classification of the type of cancer for prognostic and predictive purposes. Gene expression profiling studies have shown that oestrogen-receptor (ER)-positive and ER-negative breast cancer are distinct diseases at the transcriptomic level, that additional molecular subtypes might exist within these groups, and that the prognosis with ER-positive disease is largely determined by the expression proliferation of these genes (Reis-Filho and Pusztai, 2011).

These diagnostics are being applied in clinical practice for optimising the treatment of early stage breast cancer. The cases considered in this study are the ones assessed by NICE as per the diagnostic guidance 10 (NICE, 2013e), and the ones reviewed by a group of experts that were commissioned by the INCa (Institut National du Cancer, 2013) in France. The diagnostic tests based on gene expression profiling Oncotype DX (by Genomic Health) and MammaPrint (by Agendia) are analysed in both countries. Two different tests based on immunohistochemistry (protein expression profiling) are analysed in England: IHC4 (by Royal Marsden Hospital and Queen Mary University, London) and Mammostrat (by Clarient, GE Healthcare). The report commissioned by the INCa also reviews evidence on a different immunohistochemistry test of two proteins: uPA/PAI-1 (ELISA test Femtelle d'Amarican Diagnostica).

4.1. INFORMATION CONTENT

Even though breast cancer is the most common cancer for women, it is the second cause of cancer-related mortality for women after lung cancer. In 2011, 11,716 women died in the UK from breast cancer. Around two-thirds (65%) of women diagnosed with breast cancer in England and Wales survive their disease for 20 years or more (2010-11 Cancer Research UK Statistics). The absolute incidence and mortality of breast cancer in France is similar with 48,763 new cases in 2012 and 11,886 deaths (Institut National du Cancer[7]). With almost 2 million more inhabitants in France than in the UK, this means a slight larger incidence and mortality in the UK than in France.

Until recently, the prognosis in terms of survival and companion treatment was based on predictions by NPI and Adjuvant! Online. These indexes classify the type of gene profiling in the cancer cells based solely on the sign of oestrogen receptor (ER), progesterone receptor (PR), and HER2. Other clinic-chemistry data are also considered, in particular the size of the tumour and the proliferation of tumour cells in the lymph-nodes (LN-, or LN+). According to the signs of ER, PR and HER2, breast cancer can be clustered in subtypes which are different diseases at molecular level. Reis-Filho and Pusztai (2011) present seven subtypes, three of them with poor prognosis, three with intermediate prognosis, and only one (luminal A) with good prognosis which is HER2+, ER+, PR+ and does not have basal markers. On the contrary, the triple negative cancer (molecular apocrine and basal-like), which characterise cancers in women carriers of BRCA1/2 mutations and other germline mutations, presents the worst prognosis. This approach has been successful for reducing breast cancer mortality but they resulted in an excess of adjuvant chemotherapy for patients with early-stage breast cancer, of which only a small proportion, 2-15% of patients will benefit as responders (Reis-Filho and Pusztai, 2011).

[7] http://www.e-cancer.fr/Patients-et-proches/Les-cancers/Cancer-du-sein/Quelques-chiffres

4.2. HEALTH ECONOMIC EVALUATION

The Institut National du Cancer presented a systematic literature review of clinical trials related to the selection of gene expression profiling in Oncotype DX, MammaPrint, and the proteomic tests uPA/PAI-1 (Institut National du Cancer, 2013). This literature review covered health economic evaluations realised between 2005 and 2012, including 13 studies for Oncotype DX, and six studies for Mammaprint. These health economic evaluations conclude in general on the added value of the gene expression profiling tests. However, the INCa questions the general favourable conclusions given the following limitations: (1) the large heterogeneity of comparators, (2) the high uncertainty of the clinical evidence used, (3) the costs of the adjuvant chemotherapy, (4) the utility weighting used to measure QALYs, and (5) the conflict of interests declared by some authors. NICE based its recommendation (NICE, 2013e) on the economic model submitted by the manufacturers, and on the systematic review and de novo economic model undertaken by the External Assessment Group.

Comparators. There is neither a consensus on the type of patients which should be covered nor on the type of optimal treatment, especially if the patient is at intermediate risk according to traditional clinical and pathological criteria. The External Assessment Group model concluded it was clear that these diagnostics where complementary. For instance, one study assumed that the new test was given to women with a NPI score above 3.4 indicating intermediate risk of distant recurrence.

Clinical evidence. The success of the diagnostic is measured following a 10-year survival period in most of clinical trials, which is extrapolated to life time horizon in the health economic evaluation models. The uncertainty around long term survival is high with frequent recurrence after 10 years.The economic models have extrapolated the survival and the follow up to the remaining life expectancy which may overestimate the years of life gained from the diagnostic. Moreover, all the economic studies reviews but one (Hall et al., 2012) use aggregated data instead of patient level data, and the data sources are not always transparent. NICE recommendations are based on clinical outcomes simulated by Markov modelling under the assumption that all women were treated with endocrine therapy in the baseline with the possible addition of chemotherapy after the predictive result of the new test.

Cost of adjuvant chemotherapy. Several studies include the costs of trastuzumab, and two French studies consider the costs of docetaxel. These costs depend of the type of cancer profile, effects on recurrence, costs of adverse events, and inclusion of hospital-related costs. For example, by considering the costs of chemotherapy drugs, there are more expensive for HER+ than for HER- type, and for metastatic node-positive than for node-negative disease. The annual costs including chemotherapy drugs, supportive care, and toxicity for node-negative cancers patients, as reported in the study by Hall et al. (2012) for the UK, ranges between £5,876-£9,121, depending on the chemotherapy regime from the three considered (FEC100 with fluorouracil, epirubicin, and cyclophosphamide; FEC100-T with FEC100, then docetaxel; TC=docetaxel and cyclophosphamide). The economic model used by NICE applies to HER- and node-negative women and includes costs of both endocrine therapy and chemotherapy. The chemotherapy drugs and administration costs associated with these patients is reported at £3,931 per patient and year.

QALY measure. The French report commissioned by the INCa (Institut National du Cancer, 2013) criticises the application of the utility weights used to link years of life gained and quality of life, as used in the standard QALY measure (based on EQ-5D weighting). They argue that these standard values do not reflect the quality of life for patients under chemotherapy and after recurrence of cancer. Moreover, the utility weights are not subject to sensitivity tests in most of the cases. However, the study by Hall et al. (2012) uses health state valuations from a survey of Swedish patients at different stages of breast cancer, and also accounts for disease specific states. They do not present sensitivity analysis for the health state valuations. Even though it can be argued that Swedish subjective health status can differ from UK population, which is their case study for patients on Oncotype DX, this utility weighting is deemed appropriate to approach the quality of life of women suffering breast cancer.

Conflict of interest. The French report criticises that "there are few studies without funding from the private commercial sector". They do not explicitly mention any interested party as funding possibly biased studies. Nevertheless, the most robust study, in the sense of being based in patient level data receiving Oncotype DX in the UK (Hall et al., 2012) is an academic study with no external funding. Also, NICE has commissioned the evaluation within his group of External Experts. Rouzier et al. (2013) present a more recent systematic review and they include publications recognised as of high quality, as assessed by the QHES instrument. The authors state that "Evidence suggests that multigene assays are likely cost saving or cost-effective relative to current approaches to adjuvant therapy."

As already mentioned, the economic evaluation models support Oncotype DX as a cost-effectiveness diagnostics instrument. The results of the study by Hall et al. (2012) show an ICER of £5,529 per QALY, demonstrating the cost-effectiveness in favour of Oncotype DX with 61% probability of ICER under £30,000 per QALY. The only value included was the use of Oncotype DX as a "companion diagnostic" or test-directed chemotherapy. There are more recent papers analysing the cost-effectiveness of Oncotype-DX (Bargallo-Rocha et al., 2015; Fischer et al., 2015; Hannouf et al., 2014; Kip et al., 2015; Paulden et al., 2013; Yamauchi et al., 2014). Importantly, the study by Fischer et al. (2015) finds that the cost-effectiveness for patients lymph-node negative (LIN-) (group for which the treatment is targeted by NICE) is similar to the range of ICER found in studies for LIN+ patients. NICE's economic model was used considering a discounted price for Oncotype DX (offered under a managed entry agreement to the NHS) and a pure prognostic value of the test, which leads to a conservative cost-effectiveness result. Under these assumptions, they estimated an ICER of £22,600 per QALY gained compared with current clinical practice for patients with a NPI score above 3.4.

All in all, the value included in these economic evaluations is only the medical value conferred by the use of Oncotype DX and MammaPrint as companion diagnostics based on gene profiling. That is, they are considered for its predictive value to stratify responders to chemotherapy and/or endocrine therapy. On the other hand, these diagnostics are powerful prognostic tools informing about survival and risk of recurrence of breast cancer. This value of prognostic information has been partly considered by the External Assessment Group when evaluating Oncotype DX for NICE as the key value for optimising treatment since the chemotherapy treatment depends on a prognostic information score: cancer of intermediate prognosis. The remaining value of prognostic information from the patient's side in terms of planning and psychic value is ignored.

There is a recent study from Japanese women on Oncotype DX (Yamauchi et al., 2014) which claims a calculation of "societal cost-effectiveness" for Oncotype DX. The only new societal value added in this study comes from the consideration of indirect costs in terms of patient time and transport, and by imputing health care costs linked to the management of adverse events. Their results reinforce the cost-effectiveness of Oncotype DX but cannot fully capture the "value of knowing". Therefore, the health economic evaluation of gene expression profiling accounted neither for the value of knowing used by the medical profession for prognostic purposes nor for the planning and well-being value as used by the patient.

4.3. NICE DIAGNOSTIC GUIDELINE

NICE has recommended the use of Oncotype DX as diagnostic tools for patients with early breast cancer and some levels in specific biomarkers. Surprisingly, the NICE clinical guidance 80 of "Early and locally advanced breast cancer" (NICE, 2014), issued in 2009 and modified in 2014, does not mention any gene expression profiling diagnostics, and only recommends Adjuvant! Online to guide prognosis and treatment. The recommendations on the use of gene expression profiling diagnostics is contained in a diagnostic guidance issued in 2013 (NICE, 2013e). Therefore, it is not clear whether clinical practice should only use Adjuvant! Online as prognostic and predictive tool, or complement the diagnostic with the new gene expression profiling and immunohistochemistry tests recommended in Diagnostic Guidance 10. This Guidance states "In the UK, local guidance based on the NPI and Adjuvant! Online has been developed to help clinicians decide about the benefits of adjuvant chemotherapy for a particular patient. However, it has been suggested that these tools may

be imperfect and different local approaches to the use and interpretation of these tools leads to a proportion of people with early stage breast cancer being over- or under-treated. This may result in unnecessary use of expensive chemotherapy with its associated adverse effects for people who derive little or no benefit. In addition, there may be avoidable deaths in people who would have benefitted from chemotherapy had it been offered." In particular, the NICE Quality standard on breast cancer (NICE, 2011) included patient involvement in the decisions about adjuvant chemotherapy after surgery, and opens the use of appropriate models to support estimates of prognosis and the benefit of adjuvant treatment beyond Adjuvant! Online and NPI.

The final recommendation of NICE is to offer a new test (Oncotype DX) to women for whom the decision to offer chemotherapy is uncertain based on the score of Adjuvant! Online or NPI (NPI above 3.4). These women have a prognosis of intermediate risk of distant recurrence. Even though the well-being or psychic value for these woman has not been accounted for in the evaluation model on which this decision is based, the Diagnostic Advisory Committee acknowledged that these test can help to alleviate emotional and psychological strain (higher for women uncertain about whether having or not chemotherapy) and promote consistency of practice within the NHS.

Of the four tests analysed, Oncotype DX is the only one recommended on the basis of its analytical validity and clinical validity: prognostic ability in the short and medium term (ability to predict the risk of distant recurrence). In terms of clinical utility for the choice of medical treatment, the Committee concluded that the existing evidence is not robust enough to support the predictive value of Oncotype DX to the response of chemotherapy depending on the level of risk, for LN- patients, and recommended that further evidence should be collected to support the clinical utility of the test. The manufacturer offered the NHS a confidential access scheme that included a different price which allowed the test to be cost-effective and be recommended by NICE for use in clinical practice. The recommendation extends to be applied to men and women over 70 even though the evidence is mostly based on younger women.

4.4. POSITION OF INCA "PLAN CANCER"

The ongoing "Cancer Plan 2014-2019" includes "Objective 6: Reinforce the advancement of France in Personalised Medicine". This makes reference to the diagnostics based on germline DNA, tumour DNA and other immunohistochemistry biomarkers. Section 1 covers the Cancer Plan for genetic services offering susceptibility tests BRCA1/2 from germline DNA. This subsection summarises the actions for pharmacogenomics and diagnostics based on tumour cells. We have mentioned above the INCa study of four diagnostics: Oncotype DX, MammaPrint and uPA/PAI-1 (Institut National du Cancer, 2013) whose conclusions do not recommend the new diagnostic instruments in the clinical practice. Even for Oncotype DX, which has been recommended for clinical practice in the UK and which presents more robust evidence in the INCa study, the INCa position only recommends further research on biomarkers. It seems that the trend in France, under the scientific leadership of INCa, is proposing next generation sequencing (NGS) approaches with panels for most of the cancers, thus making the assumption that the current available commercial gene signature tests are insufficient in their ability to demonstrate clinical utility and actionable information for targeted medicine. The INCa is not habilitated to conduct health technology assessment of new technologies, as this is the role of the HAS. We understand HAS recently announced on its website that it will be reviewing breast cancer genomic tests in 2016.

The most important actions relate to interventions linked to clinical research trials covering large number of patients. In 2013, 60,000 patients have participated in research involving genetic tests of cancer cells. The deployment at national level in 2014 includes (1) the institutionalisation of all genetic tests for which there is a companion medicine - the Plan Action 6.4 states there are around 100 companion diagnostics; (2) the use of genetics diagnostics on 10,000 cancers in 2015, and on 60,000 cancers in 2018; (3) the use of whole genome sequencing in 3,000 cancer patients in 2015, 10,000-15,000 patients in 2017, and 50,000 patients in 2019.

This policy is in line with the large involvement of France in the International Cancer Research Consortium since 2008. The target is to produce an extensive review of mutations in 50 types of cancers. The program for a sub-type of breast cancer has already been implemented, coordinated by INCa and ITMO Cancer. The previous Cancer Plan 2009-2013 stated that all cancer patients should have access to innovative molecular tests conducted by regional platforms at no cost for patients (Action 21.2).

French research has also participated in the clinical validation of Oncotype DX through the different waves of the PACS trial, with participation of 1,999 patients enrolled in the PACS 01 parent trial, and 3,010 patients enrolled in the PACS 04 trial between February 2001 and August 2005 (Jacquemier et al., 2011; Roche et al., 2006; Spielmann et al., 2009).

4.5. COMMUNICATING RESULTS

Gene expression profiling tests are performed on patients who voluntarily participate in clinical trials, and as new diagnostics for NHS patients after having received the results of the recurrence score from Adjuvant! Online or NPI. In these cases, these test do not imply any new ethical or legal requirement regarding the communication with patients. These requirements should be discussed on a case-basis for patients treated under private insurance of out-of-pocket funding.

The French HAS includes the communication guidelines of participation in cancer research trials in the report published by Institut National du Cancer (2015). First, there is a requirement to pass ethical and legal conditions in the design of a clinical research trial, which must be authorised by the National Agency of Security for Medicines and Health Products and the Committee of Protection of People. The patient must agree by written consent and also for allowing the use of her clinical data. The patient should know the phase or phases in which will participate, especially whether phase II will have double blind randomisation, in which case, the patient will not know the treatment received. Importantly, the patient must be given a written information about the content and schedule of the trial, including possible benefits and risk, and the possibility of withdrawing from the trial with no damage. After the trial, the patient must be informed about the result and publications. However, if the treatment has been given according to the rules of blind randomisations, the patient only has the right of knowing the treatment received in case of medical emergency or medical justification.

NICE regulates most of the communication guidelines in the code of “Patient experience in adult NHS services” (NICE, 2012). This guideline is organised in five different actions. There are two actions governing the communication with patients: “continuity of care and relationships”, and “enabling patients to actively participate in their care”. Regarding the continuity of care, the communication concerns with the right of the patient to know the professionals in charge of her care, including contacts for the family in different situations. The second action of communication contains the principles to discuss risks and benefits, which are important to discuss the decisions of genetic testing and results, especially linked to different choice of treatment. The patient is a decision maker so that the doctor must be very consistent when communicating risk information, which is difficult to understand (the guideline enumerates nine principles to discuss risks and benefits).

4.6. STORING PATIENT DATA

The data from patients diagnosed by using gene expression profiling are governed by the same legal and ethical guidelines that any patient level data obtained in clinical practice and clinical research trials, both in France and UK. In general, researchers work with anonymised data, as it is the case of BRCA Share database under management led by French INCa and the regional cancer centres. Equally, clinical data such as hospital register data (HES data in the UK) follow strict rules of confidentiality and safe storage. If they are transferred for research purposes, they are anonymised and released under strict rules of not publishing individual level data and safe storage.

4.7. ELEMENTS OF VALUE

The discussions on the evaluation of gene expression profiling diagnostics, as considered by NICE and the French HAS, are solely based on the medical value of the information provided by these diagnostics, either prognostic or predictive value.

Within the value framework considered in the Phase I Report, the components of value are considered as follows.

1. **Health gain [Life Years gained (LYs) and Improvement in quality of life (QoL)].** We have summarised above the economic evaluation of INCa and NICE, including the QALYs gains derived from genetic profiling testing. The range of incremental QALY estimated for Oncopype DX is 0.1-0.2. This clinical benefit derived from the optimisation of chemotherapy treatments is assumed to be derived from avoiding more distant recurrences than in standard clinical practice and from gaining quality of life in those patients that avoid un-necessary chemotherapies . In clinical effectiveness terms, the most accurate classification of response to chemotherapy and endocrine therapy is obtained for patients with good prognosis. However, NICE only recommends the use of Oncoptype DX in clinical practice for patients at intermediate risk according to traditional tools. In terms of subjective valuation by the patients, there are some studies on willingness to pay for avoiding chemotherapy side effects in breast cancer treatments (Lalla et al., 2014; Miller et al., 2013) obtaining WTP above $3,000.
2. **Cost-saving [within and outside health system].** In terms of cost considered, the only computed costs considered are direct costs, mainly those of the diagnostic tests, the adjuvant chemotherapy, the concomitant medications, the outpatient fee, the hospitalisation, the side effects, and including follow up costs and palliative care which is very costly for cancer patients. Again, the costs for families is widely ignored except in the case cited for Japanese patients treated with Oncotype DX (Yamauchi et al., 2014).
3. **Value from reduced uncertainty.** The NICE Committee has acknowledged the psychic value for the patient, especially under high uncertainty regarding a treatment by chemotherapy, which has severe adverse effects. Nonetheless, this value is not accounted for in the costs of counselling, which are not included into the treatment of these patients. In this regard, it is important to remark here the difference with the case of eligibility for genetic testing of germline mutations BRCA1/2 since these patients are offered genetic counselling under NHS coverage.
4. **Value of hope.** We do not have data on the participation rate in clinical trials, but the large participation on trials as in the Breast and Ovarian Cancer Susceptibility study implies that there are patients willing to analyse their genetic profile to search for causes of having had cancer or risk to suffer cancer. In the case of cancer patients, they are asking for a reassessment of their disease records and cancer samples to search innovative treatments in the hope of better outcomes than the resulted from the prior therapy. Moreover, many of the innovative diagnostics like Oncotype DX are only offered in clinical trials even though they are already authorised for commercial use so that the patient is informed on their clinical effectiveness and the possibility of access through a clinical trial.
5. **Option value.** There is no acknowledgement of the element of option value in the HTA evaluation of gene expression profiling. However, the principal manufacturer of gene expression profiling tests, with Oncoptype DX as the landmark product, is a publicly-traded company: Genomic Health, Inc. Among its shareholders and investors there are citizens participating via pension funds and others. It might be argued that the value perceived by the average citizen as option value and future success of the company is reflected in the stock prices.
6. **Productivity.** Neither INCa nor NICE has included an analysis of productivity loss or gains for patients receiving some type of gene signature diagnostics. As already cited, Yamauchi et al. (2014) illustrates the productivity gain associated to Oncotype DX on Japanese patients.

7. **Scientific spillovers.** 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 available therapies when treating their patients'. This aspect of scientific spillovers over time have been especially important for the commercial and research development of Oncotype DX, whose first coverage by Medicare was achieved in 2006 for breast cancer. Indeed, wealth of evidence has been published since then and recently, the first results from prospective studies were published confirming the previously published prospective-retrospective results (Shak S et al., 2015; Sparano et al., 2015; Stemmer SM M et al., 2015).

Equity considerations. The burden of disease of breast cancer is widely documented and has been mentioned above. The severity and mortality of the disease at relative young ages implies large societal costs, including the effect on direct and indirect costs on children care and education when their mothers are diagnosed with breast cancer.

5 PROCALCITONIN

"Procalcitonin is involved in maintaining calcium levels in the blood and is an indirect biomarker of infection. It is released into the circulation in response to pro-inflammatory stimuli, especially those originating from bacteria. Procalcitonin testing can be used to help clinicians to diagnose bacterial infection (that can cause sepsis) and guide decisions on starting antibiotic treatment. Procalcitonin levels are usually low in people with viral infections, chronic inflammatory disorders or autoimmune processes" (NICE, 2015).

Procalcitonin levels have been used in clinical practice as a biomarker for acute infections (sepsis). Their role as a good biomarker depend on its value used as (1) diagnostic test for predictive purposes to monitor antibiotic treatment, (2) prognostic test for predicting the course of severe infections and mortality likelihood, (3) therapeutic test to follow up the efficacy of the therapy (e.g. the reaction to antibiotics), and the accessibility in terms of application in routine clinical practice, good acceptability for patients, and cost-effectiveness.

Procalcitonin is not the only biomarker found in the serum of septic patients. However, according to an expert panel in the management of antibiotic therapy (Dupuy et al., 2013), there are only two proper biomarkers for acute infections which are routinely available: procalcitonin and C-reactive protein.

Procalcitonin tests are being used in clinical practice in some hospitals in the UK for monitoring sepsis in intensive care units and in emergency admissions. The French HAS mentions the use of procalcitonin tests for monitoring acute infections in newborns. However, this clinical practice is not the standard practice in these countries. In particular, NICE has published the first technical assessment of the available diagnostic tests based on procalcitonin in October 2015 (NICE, 2015). The position of HAS regarding the use of procalcitonin for monitoring sepsis in newborns was stated in 2002 (Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES), 2002), restricting the use of the diagnostic for research purposes.

The French clinical guideline only contains some analytical evidence on the test levels regarding the uncertainty of procalcitonin levels in newborns. The procalcitonin test is not included in the HAS guideline for antimicrobial resistance (Haute Autorité de Santé, 2008). Therefore, we only analyse the arguments provided by NICE in the diagnostics guidance, which contains the clinical and economic evidence supporting NICE's decision against the recommendation of the diagnostics tests for clinical practice. NICE limits the recommendation for continuing the clinical practice in the few hospitals currently using these diagnostics tests so as to strengthen the research evidence in the UK.

A possible channel to include the use of procalcitonin tests in clinical practice is through the policy of antimicrobial resistance. NICE mentions the overlapping of risk assessment protocols and the use of biomarkers for infections. The Committee discussed the potential contribution that procalcitonin testing could make to improving antimicrobial stewardship by reducing the incidence of antibiotic-resistant infections. However, this outcome has not been measured and a complete protocol of antimicrobial stewardship includes several actions. Whether procalcitonin testing may add value or not to the package of actions has still to be demonstrated.

5.1. HEALTH ECONOMIC EVALUATION

The evidence analysed by NICE includes data from the five commercial diagnostics based on procalcitonin under consideration: ADVIA Centaur BRAHMS PCT (by Siemens Healthcare Diagnostics), BRAHMS PCT Sensitive Kryptor (by Thermo Fisher Scientific), Elecsys BRAHMS PCT (by Roche Diagnostics), The LIAISON BRAHMS PCT (by DiaSorin), and VIDAS BRAHMS PCT (by bioMérieux UK). Their performance is evaluated as compared with standard clinical practice. That is, the intervention is to use antibiotic therapy plus the procalcitonin tests and the comparator is to use antibiotic therapy without procalcitonin testing (and assumedly without any other biomarker-based test like C-reactive protein used in the main economic model). Nonetheless, although the main comparator is "antibiotic

therapy alone", the evidence reviewed allowed the Committee to state: "procalcitonin is a more specific biomarker for bacterial infection than other biomarkers that are currently widely used for diagnosing and monitoring bacterial infection and sepsis. Other biomarkers, such as C-reactive protein and white blood cell count are inflammatory markers that have low specificity for the diagnosis of bacterial infection."

The procalcitonin diagnostic is indicated for two common cases of acute infection:

1. Patients with confirmed or highly suspected sepsis in intensive care settings;
2. People admitted to the emergency department with suspected bacterial infection.

The result of the diagnostic should be used for (clinical utility or predictive value):

1. Decide when to stop the antibiotic therapy for patients in intensive care settings;
2. Decide when to start and stop the antibiotic therapy in patients admitted to the emergency department with suspected bacterial infection.

The performance of the diagnostic is evaluated according to the following outcomes:

1. Duration of the antibiotic therapy, with shorter durations indicating better performance;
2. Resource use in terms of hospitalisation: length of stay, costs;
3. Adverse clinical outcomes, mainly mortality, condition-specific outcomes (e.g. readmission, multiple organ dysfunction syndrome), and antibiotic-related adverse events (e.g. multi-drug resistant infection, antibiotic side effects).

NICE uses systematic review methods and de novo economic modelling to assess the available evidence. First, they present a systematic review of published studies; eight deemed relevant for the evaluation of the clinical efficacy of the test in intensive care settings, and 10 deemed relevant for the evaluation of clinical efficacy in patients admitted in emergency care. Secondly, the External Assessment Group present the economic evaluation based both on a systematic review and a de novo economic model based on a decision-tree model calibrated with some parameters taken from the literature and other parameters assumed stochastic. A scenario analysis was run over this decision-tree model to assess the impact of assumptions on the estimated outcomes, and one-way sensitivity analysis was run over the stochastic input parameters.

Clinical efficacy. The studies from intensive care settings did not cover children. Most of the studies covered Swiss patients and European countries, but there was no UK-specific data. In the case of emergency settings, only two studies were done in children, and the infections affected the respiratory system. Therefore, the representatives of the studies is questioned for children treatment, as well as for assessing costs in the UK and the use of the test in emergency departments for general infections. The clinical performance of procalcitonin tests is better supported for its effects on reduction on antibiotic therapy and reduction on hospital resources, either in total length of stay or in in intensive care, for both intensive care treatment and in emergency departments. However, the clinical effect on adverse events is not demonstrated. The effect on reduction in mortality and reduction in readmission to hospital was not statistically significant in any study. Among other adverse events, the evidence on reduction in antibiotic-related adverse events was found significant in a study for adult patients admitted in emergency departments.

Costs. The External Assessment Group considered cost-effectiveness ratios reported from two research studies, both for adults in outpatient clinic and in hospitals. In the novo economic analysis, the costs considered are computed for a 6-month horizon, split in 28 days for short term plus 155 days for monitoring. Costs were computed according to parameters from the previous literature review on hospital length of stay and duration of antibiotic treatment, which was computed at antibiotic prices without adding costs of adverse events in the baseline model. The unit costs of hospital day, antibiotic therapy were drawn from routine NHS resources (NHS reference costs) and the manufacturers provided the price of the five procalcitonin diagnostics. Neither indirect costs nor societal cost derived for instance from the contribution to anti-microbial resistance were considered. Since the clinical effects found in the literature derive in a reduction in hospital stay and antibiotic therapy, the model

estimated costs savings, which are important for adults in intensive care settings (£3,268 per patient).

QALY measure. The gains in life expectancy were modelled according to the baseline probabilities and relative risks for all-cause mortality parameters taken from the literature review. Antibiotic-related adverse events were also considered with occurrence associated to the estimated duration of antibiotic therapy. The estimated survival gains and health states were weighted according to health state utilities. The disutility of intensive treatment was considered larger than in emergency treatment, almost halving the survival time in full health. Also, the disutility of adverse events from antibiotic treatment was added as in the range found in one of the reviewed studies. All these parameters were applied to adult population while for the simulation on children admitted in emergency departments, the model assumed a baseline utility of 0.99.

Even though the estimated gains in terms of QALY were very small (0.001 for adults in intensive care setting), the ICER was estimated below a £20,000 threshold with 95% probability for adults in intensive care setting, and with 88% probability in emergency setting. The cost-effectiveness result for adults in both settings was robust to scenario changes, mainly to removing non-significant differences in mortality. However, the ICER increased when the mortality differences were considered in the upper bound interval for adults in emergency department. Nonetheless, the economic case based on ICER results is demonstrated. The weakness of the case is derived from the heterogeneity and inconclusive evidence on clinical effectiveness as reported from the systematic review.

Besides the doubts on the representativeness of the systematic review and the non-significant effects on mortality and other adverse events, other key factors tilted NICE's decision toward the non-recommended outcome. Importantly, the consideration of new results from a large trial run on 1,800 patients in the Netherlands and a study from Australia did not add new evidence on clinical effectiveness. Moreover, the antibiotic stewardship practices in hospitals, for instance the use of protocols and C-reactive biomarkers must be considered. The effect of procalcitonin diagnostic can be confounded with the use of these protocols, and it is not expected that the procalcitonin test will displace C-reactive test which are largely used by laboratories in emergency department settings. This would result in costs of unnecessary tests which were not considered in the model.

5.2. ELEMENTS OF VALUE

According to the value framework considered in Phase I, the value of knowledge considered in the economic evaluation model considers the costs and benefits of reducing uncertainty in the medical condition for a better treatment. It is then a value linked to the clinical utility of the test. The components considered as well as those that have not been considered and may remain implicit in the discussion are listed below.

1. **Health gain.** The health gain measures for the patients treated has been measured in life of years gained which in turn have been discounted according to the disutility caused by the illness and treatments, to result in aggregate QALYs. The range of QALYs gained is between 0.001 to 0.005 per patient. In terms of life years gained this range translates into several hours of life, or between less than one day to a maximum of around 2 days. Yet, considering the length of treatment of an episode of infection and the epidemiology of sepsis, this may account for saving many lives and less hospital stay, since the disutility of time is accounted for during the stay in intensive care.
2. **Cost-saving.** The hospital resources and medicines are direct cost of the treatment. Other treatments downstream the health care sector, such as a primary care from community-related infections are not considered in the model. Also not included in the unit cost per hospital day is an overhead of joint costs from services, such as ambulance. Nonetheless, since the costs of hospitalisation in intensive care and emergency admission are high, the cost savings derived from a shorter stay and taking less antibiotic treatment are higher than the costs of procalcitonine. This

results in cost savings of more than £3,268 per adult patient treated in intensive care settings.

3. **Value from reduced uncertainty.** The patient treated in intensive care or emergency care does not participate in the decision of undertaking the diagnostic tests. In this sense, the "value of knowing for the sake of knowing" does not apply in this context since the patient may know about suffering an infection and even about receiving antibiotic treatment, but she does not know about the hospital protocol of treating infections. However, for the infectious disease clinicians, the information from using the test will be valuable, as highlighted already.
4. **Value of hope.** Sepsis is a life-threatening condition. Severe sepsis cause multiple organ dysfunction with high mortality rate. However, the condition is so acute and short in time, that the patient is a passive subject who is not being informed on alternative possibilities of treatment. This component of value does not apply for acute infections as compared for cases of cancer or other severe conditions where the patient is conscious and can live during enough time to make risky decisions.
5. **Productivity, option value, and scientific spillovers.** The effects on population health and productivity derived from this diagnostic can be important. The epidemiology is important, with sepsis causing between 5.1% and 7.7% deaths in England in 2010 (McPherson et al., 2013). Therefore, the potential social externalities in terms of epidemiology, productivity, option value, and scientific spillovers from reduced hospitalisation time and health gain can be large. Moreover, the cost of antimicrobial resistance are very high, and the availability of a better diagnostic of sepsis as a part of a protocol to reduce antibiotic treatments could contribute to large savings in the fight against antimicrobial resistance.

6 CONCLUSION: SUMMARY AND NEXT STEPS

This Phase II report outlines the evaluation approaches for diagnostics in England and Wales and France, and discusses three case studies: familial breast cancer (BRCA1/2 tests), gene expression profiling for breast cancer, and procalcitonin tests. We have explored how our extended value framework, as presented in our White Paper "The Value of Knowing and Knowing the Value: Improving the Health Technology Assessment of Complementary Diagnostics" (OHE/EPEMED, 2016) could be applied to these three case studies. This Phase II report was preceded by our Phase I report "Complementary Diagnostics: A Literature Review on the Value of Knowing".

The Phase I and Phase II 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 summarises the key findings from these two reports, and offers policy recommendations.

REFERENCES

Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES), 2002. Diagnostic et traitement curatif de l,infection bactérienne précoce du nouveau-né. Recommandations pour la pratique clinique.

Bargallo-Rocha, J. E., F. Lara-Medina, V. Perez-Sanchez, R. Vazquez-Romo, C. Villarreal-Garza, H. Martinez-Said, R. J. Shaw-Dulin, A. Mohar-Betancourt, B. Hunt, J. Plun-Favreau, and W. J. Valentine, 2015. Cost-effectiveness of the 21-gene breast cancer assay in Mexico, *Adv Ther* 32(3), pp. 239-253.

BIVDA, 2015. 'Robust, fair and sustainable: our visoin for the future access and provision of molecualr diagnostics in England. Pre-launch draft.'.

Boulenger, S. and P. Ulmann, 2004. French Guidelines for the Economic Evaluation of Health Care Technologies, *Paris: College des economistes de la sante.*

Cook, J. P., J. H. Golec, J. A. Vernon, and G. H. Pink, 2011. Real option value and path dependence in oncology innovation, *International Journal of the Economics of Business* 18(2), pp. 225-238.

Dupuy, A. M., F. Philippart, Y. Pean, S. Lasocki, P. E. Charles, M. Chalumeau, Y. E. Claessens, J. P. Quenot, C. G. Guen, S. Ruiz, C. E. Luyt, N. Roche, J. P. Stahl, J. P. Bedos, J. Pugin, R. Gauzit, B. Misset, C. Brun-Buisson, and G. Maurice Rapin Institute Biomarkers, 2013. Role of biomarkers in the management of antibiotic therapy: an expert panel review: I - currently available biomarkers for clinical use in acute infections, *Ann Intensive Care* 3(1), pp. 22.

Eisinger, F., B. Bressac, D. Castaigne, P. H. Cottu, J. Lansac, J. P. Lefranc, A. Lesur, C. Noguès, J. Pierret, and S. Puy-Pernias, 2004. Identification et prise en charge des prédispositions héréditaires aux cancers du sein et de l'ovaire (mise à jour 2004), *Bulletin du cancer* 91(3), pp. 219-237.

Fischer, L., M. Arnold, F. Kirsch, and R. Leidl, 2015. [Cost-Effectiveness of the 21 Gene Assay in Patients with Node-Positive Breast Cancer], *Gesundheitswesen*.

Frank, T. S., A. M. Deffenbaugh, J. E. Reid, M. Hulick, B. E. Ward, B. Lingenfelter, K. L. Gumpper, T. Scholl, S. V. Tavtigian, and D. R. Pruss, 2002. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals, *Journal of Clinical Oncology* 20(6), pp. 1480-1490.

Garau, M., A. Towse, L. Garrison, L. Housman, and D. Ossa, 2013. Can and should value-based pricing be applied to molecular diagnostics?, *Personalized Medicine* 10(1), pp. 61-72.

Garrison, L. and M. Austin, 2007. The economics of personalized medicine: a model of incentives for value creation and capture, *Drug Information Journal* 41, pp. 501–509.

Garrison, L. and A. Towse, 2014. Personalized Medicine: Pricing and Reimbursement Policies as a Potential Barrier to Development and Adoption, Economics of, *Encyclopedia of Health Economics*, pp. 484-490.

Hall, P. S., C. McCabe, R. C. Stein, and D. Cameron, 2012. Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer, *J Natl Cancer Inst* 104(1), pp. 56-66.

Hannouf, M. B., B. Xie, M. Brackstone, and G. S. Zaric, 2014. Cost effectiveness of a 21-gene recurrence score assay versus Canadian clinical practice in post-menopausal women with early-stage estrogen or progesterone-receptor-positive, axillary lymph-node positive breast cancer, *Pharmacoeconomics* 32(2), pp. 135-147.

Haute Autorité de Santé, 2011. 'Dépistage du cancer du sein en France : identification des femmes à haut risque et modalités de dépistage', *Note de cadrage*.

----, 2014. 'Dépistage du cancer du sein en France : identification des femmes à haut risque et modalités de dépistage. Volet 2', *Recommandations de Santé Publique*.

----, 2008. ‚Stratégie d'antibiothérapie et prévention des résistances bactériennes en établissement de santé'.

Institut National du Cancer, 2009. ‚Chirurgie prophylactique des cancers avec predicposition genetique'.

----, 2015. 'Participer a un essay clinique en cancerologie'.

----, 2013. 'uPA/PAI-1, Oncoptype DX, MammaPrint. Valeur pronostique et predictive pour une utilite clinique dans la prise en charge du cancer du sein'.

Jacquemier, J., J. M. Boher, H. Roche, B. Esterni, D. Serin, P. Kerbrat, F. Andre, P. Finetti, E. Charafe-Jauffret, A. L. Martin, M. Campone, P. Viens, D. Birnbaum, F. Penault-Llorca, and F. Bertucci, 2011. Protein expression, survival and docetaxel benefit in node-positive breast cancer treated with adjuvant chemotherapy in the FNCLCC-PACS 01 randomized trial, *Breast Cancer Res* 13(6), pp. R109.

Kip, M., H. Monteban, and L. Steuten, 2015. Long-term cost-effectiveness of Oncotype DX((R)) versus current clinical practice from a Dutch cost perspective, *J Comp Eff Res* 4(5), pp. 433-445.

Lkdawalla, D. N., J. A. Romley, Y. Sanchez, J. R. Maclean, J. R. Penrod, and T. Philipson, 2012. How cancer patients value hope and the implications for cost-effectiveness assessments of high-cost cancer therapies, *Health Aff (Millwood)* 31(4), pp. 676-682.

Lalla, D., R. Carlton, E. Santos, T. Bramley, and A. D'Souza, 2014. Willingness to pay to avoid metastatic breast cancer treatment side effects: results from a conjoint analysis, *Springerplus 3*, pp. 350.

Lee, A. J., A. P. Cunningham, K. B. Kuchenbaecker, N. Mavaddat, D. F. Easton, and A. C. Antoniou, 2014. BOADICEA breast cancer risk prediction model: updates to cancer incidences, tumour pathology and web interface, *Br J Cancer* 110(2), pp. 535-545.

Lee, D., P. Neumann, and J. Rizzo, 2010. Understanding the medical and nonmedical value of diagnostic testing, *Value in Health* 13(2), pp. 310-314.

McPherson, D., C. Griffiths, M. Williams, A. Baker, E. Klodawski, B. Jacobson, and L. Donaldson, 2013. Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010, *BMJ Open* 3(8).

Miller, P. J., S. Balu, D. Buchner, M. S. Walker, E. J. Stepanski, and L. S. Schwartzberg, 2013. Willingness to pay to prevent chemotherapy induced nausea and vomiting among patients with breast, lung, or colorectal cancer, J Med Econ 16(10), pp. 1179-1189.

Myriad Genetic Laboratories, 2010. 'Mutation Prevalence Tables'.

NICE, 2011. ‚Breast cancer. Quality standard', *Guidance QS12*, National Institute of Health and Care Excellence.

----, 2013a. 'Clinical evidence review. Familial breast cancer. Clinical evidence reviews, 2004, 2006 & 2013'.

----, 2013b. 'Cost-effectiveness evidence review. Familial breast cancer. Health economics evidence reviews & full reports 2004, 2006 & 2013'.

----, 2014. 'Early and localy advanced breast cancer. Diagnosos and treatment'.

----, 2013c. 'Familial breast cancer. Costing report'.

----, 2013d. 'Familial breast cancer: Clasification and care of people at risk of familial breast cancer and related risks in people with a family history of breast cancer'.

----, 2013e. Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer managemnt: mammaPrint, Oncotype DX, IHC4 and Mammostrat, NICE diagnostics guidance 10.

----, 2012. 'Patient experience in adult NHS services: improving the experience of care for people using adult NHS services'.

----, 2015. ‘Procalcitonin testing for diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay). NICE diagnostic guidance 18.’.

Paulden, M., J. Franek, B. Pham, P. L. Bedard, M. Trudeau, and M. Krahn, 2013. Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer, *Value Health* 16(5), pp. 729-739.

Reis-Filho, J. S. and L. Pusztai, 2011. Gene expression profiling in breast cancer: classification, prognostication, and prediction, *Lancet* 378(9805), pp. 1812-1823.

Roche, H., P. Fumoleau, M. Spielmann, J. L. Canon, T. Delozier, D. Serin, M. Symann, P. Kerbrat, P. Soulie, F. Eichler, P. Viens, A. Monnier, A. Vindevoghel, M. Campone, M. J. Goudier, J. Bonneterre, J. M. Ferrero, A. L. Martin, J. Geneve, and B. Asselain, 2006. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial, *J Clin Oncol* 24(36), pp. 5664-5671.

Rouzier, R., P. Pronzato, E. Chereau, J. Carlson, B. Hunt, and W. J. Valentine, 2013. Multigene assays and molecular markers in breast cancer: systematic review of health economic analyses, *Breast Cancer Res Treat* 139(3), pp. 621-637.

Shak S, Petkov VI I, Miller DP P, Howlader N, Gliner N, Howe W, Schussler N, B. F. Cronin K, and Penberthy L., 2015. ‘Breast cancer specific survival in 38,568 patients with node negative hormone receptor positive invasive breast cancer and oncotype DX recurrence score results in the SEER database’, *2015 San Antonio Breast Cancer Symposium*.

Solomons, J., 2013. ‘Familial breast cancer. Full needs assessment report’.

Sparano, J. A., R. J. Gray, D. F. Makower, K. I. Pritchard, K. S. Albain, D. F. Hayes, C. E. Geyer, Jr., E. C. Dees, E. A. Perez, J. A. Olson, Jr., J. Zujewski, T. Lively, S. S. Badve, T. J. Saphner, L. I. Wagner, T. J. Whelan, M. J. Ellis, S. Paik, W. C. Wood, P. Ravdin, M. M. Keane, H. L. Gomez Moreno, P. S. Reddy, T. F. Goggins, I. A. Mayer, A. M. Brufsky, D. L. Toppmeyer, V. G. Kaklamani, J. N. Atkins, J. L. Berenberg, and G. W. Sledge, 2015. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer, *N Engl J Med* 373(21), pp. 2005-2014.

Spielmann, M., H. Roche, T. Delozier, J. L. Canon, G. Romieu, H. Bourgeois, J. M. Extra, D. Serin, P. Kerbrat, J. P. Machiels, A. Lortholary, H. Orfeuvre, M. Campone, A. C. Hardy-Bessard, B. Coudert, M. Maerevoet, G. Piot, A. Kramar, A. L. Martin, and F. Penault-Llorca, 2009. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial, *J Clin Oncol* 27(36), pp. 6129-6134.

Stemmer SM M, Steiner M, S.-G. L. Rizel S, N. B. Geffen DB B, I. K. Ben-Baruch N, Fried G, Rosengarten O, S. C. Uziely B, Rothney M, Klang SH H, Ryvo L, Kaufman B, Evron E, Zidan J, Shak S, and Liebermann N, 2015. ‚Real-life analysis evaluating 1594 N0/Nmic breast cancer patients for whom treatment decisions incorporated the 21-gene recurrence score result: 5-year KM estimate for breast cancer specific survival with recurrence score results £30 is >98%’, *2015 San Antonio Breast Cancer Symposium*.

The Institute of Cancer Research, 2015. ‘Protocol 2. BRCA1 and BRCA2 mutation testing guidelines. Frquently asked questions’.

Torre, L. A., F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, 2015. Global cancer statistics, 2012, *CA Cancer J Clin* 65(2), pp. 87-108.

Yamauchi, H., C. Nakagawa, S. Yamashige, H. Takei, H. Yagata, A. Yoshida, N. Hayashi, J. Hornberger, T. Yu, C. Chao, C. Yoshizawa, and S. Nakamura, 2014. Societal cost-effectiveness analysis of the 21-gene assay in estrogen-receptor-positive, lymph-node-negative early-stage breast cancer in Japan, *BMC Health Serv Res* 14, pp. 372.