DELIVERABLE 9.1

VPH-DARE@IT Health Technology
Assessment conceptual framework

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2. INTRODUCTION

This introductory chapter will briefly explore the background and context of the VPH-DARE@IT project and the VPH Initiative as such. It reports on the overriding goal of the work to be presented and to be undertaken further on in Work Package 9, and states concrete objectives of the tasks to be performed.

2.1. BACKGROUND

Health Technology Assessment (HTA) is a multidisciplinary field of policy analysis that examines the medical, economic, social, and ethical implications of the incremental value, associated to diffusion, and use of a medical technology in healthcare. As VPH technologies usually do not constitute an incremental or marginal improvement of health technologies, but rather a leap forward towards more predictive, personalised, integrative, and efficient healthcare provision, a critical reflection of HTA approaches is a necessary pre-condition to any impact assessment in the world of biomedical simulation. This includes reviewing and developing a VPH-focused evaluation approach and meaningful indicator development.

Certainly VPH technologies can be wrapped in such tools and results to the end-user as to integrate well with clinical workflows, rendering the adoption of the technology so as not to result in disruptive, major leaps. Clinical utility will be the central guideline during development. VPH-DARE@IT’s exploitations strategy will follow this goal; nonetheless, our impact assessment methodology must be readily designed to allow us to understand costs and benefits for a variety of scenarios, including broader levels of impacts.

All of this has to be seen and put into the context of the global VPH and Physiome Projects. Globally, there is a growing interest for computational technologies in the area of medicine. Whereas ICT already plays a decisive role in medical informatics, bioinformatics or telemedicine, the use of ICT as a support for prevention, screening, diagnosis, treatment, and monitoring in computer-aided medicine remains limited. Yet it is evident by now that this is the area of medical technology that is most likely to revolutionise the practice of medicine. Computer models that simulate physiopathological processes can be employed to help in taking clinical decisions on the basis of “what-if” analyses (predictive medicine), to tailor the delivery of care to the specific needs of individual patients (personalised medicine), and to explore pathological scenarios for systemic interactions between multiple physiological processes (integrative medicine). Furthermore, the use of multidisciplinary approaches and in-silico computer models is seen by many in the scientific community as the only way forward to embrace the complexity of the human body, push the boundaries of our understanding of the human physiology and pathology, and therefore improve clinical practice1.

The VPH initiative and similar innovative health technology initiatives have been marked by a demand for measurable evidence that such complex technology is actually worth the cost. This concerns how to quantitatively assess such technologies in terms of safety, efficacy, and socioeconomic impact. This involves, for example, how the transformative impact on clinical guidelines can be assessed and how evidence can be generated to have VPH-DARE@IT technologies enter the guidelines in the future.

1 http://www.vph-institute.org/
2.2. GOAL

The overall goal of the tasks in WP9, Technology Assessment, Market Analysis and Exploitation is to develop—at the early phase of the project—a socioeconomic and technology assessment method (HTA) that also includes a scenario-based clinical impact analysis approach, forecasting potential impact on clinical outcomes.

From a user, stakeholder and market perspective, these tasks will a) develop upon and adapt in the VPH and other contexts proven approaches, methods and tools to the specific environment and objectives of this work package, b) establish a set of meaningful criteria and their measurement instruments, and processes that are robust to demonstrate socioeconomic cost-benefit impacts, and c) incorporate health economic considerations underlying the onset and the progression of dementia in a European context.

2.3. OBJECTIVES

The overall goal of this deliverable is to develop a VPH-DARE@IT Health Technology Assessment conceptual framework, i.e. a first outline of an assessment method. A final and ultimate method to be applied in the economic assessment of the technologies will only be available once the exploitation strategy of the project has been specified in more detail. This exploitation and business strategy should inform the direction of the socioeconomic assessment; hence, the methodological framework as developed in this deliverable needs to be adaptive enough to tailor the measuring process.

For the first task in WP9 and this deliverable, these specific objectives need to be pursued:

- Review the literature on conventional HTA research & achievements and prepare for a dynamic VPH approach, including:
  - Critically revisiting conventional health technology assessment procedures and approaches
  - Developing upon and adapting in the VPH and other contexts proven approaches, methods, and tools
  - Establishing a set of meaningful criteria and their measurement process that are robust to demonstrate socioeconomic cost/benefit impacts.
- Prepare for clinical impact assessment and cost-benefit scenarios.

These specific assessment objectives are informed by the medical and clinical objectives of the project, such as:

- Achieving earlier differential diagnostics of dementia by
  - Using MRI-based features in differential diagnostics
  - Combining heterogeneous data from patients
  - Taking into account lifestyle related risk factors
  - Incorporating novel features from modern VPH modelling approaches?
- Improving early differential diagnosis of dementias (from the accuracy and usability point of views) through data-driven decision support tools
- Improving the prediction of dementia through modelling of genetic and metabolomic risk profile and lifestyle-based/cardiovascular risk factors
- Link the properties of biomechanistic brain models of AD with the pathophysiology of neurodegenerative diseases:
  - Amyloid load
  - Brain pathology (reflected by CSF Aβ42, tau and P-tau levels)
  - Regional brain atrophy
  - Ischaemic changes of the brain
The health technology assessment (HTA) that is developed and applied by this work package will serve as a support tool that delivers information useful for health system actors and decision makers in order to allow them to arrive at more factual, evidence-based decisions and policy measures, and, in turn, support the RTD work packages in developing business cases when implementing the VPH-DARE@IT models, tools, and decision support systems.

2.4. POLICY BACKGROUND

Dementia is the most frequent form of degenerative condition in old people:

- The total cost associated to dementia in the EU 27 in 2008 was estimated to be €160 billion (€22,000 per person with dementia per year)
- The corresponding cost associated to dementia for the whole of the Europe was estimated to be €177 billion.
- In northern Europe, direct costs associated to sufferers were estimated to be considerable, while the cost of informal care was found to be the major cost component in southern Europe [1]

The VPH-DARE@IT project responds to the European Parliament’s 2011 resolution for a European Initiative on Alzheimer’s disease and other dementias. The resolution explicitly underlines the optimality of prevention and relevance of early diagnosis for effective interventions, and stresses the need to strengthen research and improve access to diagnostic services.

The basis for the resolution was the 2009 EC communication that explicitly highlighted four key areas of action:

- Prevention, including measures to promote mental well-being and support early diagnosis
- Co-ordinating research across Europe
- Spreading best practice for treatment and care
- Developing a common approach to ethical questions – rights, autonomy, and dignity of people with dementia

Addressing dementia and helping citizens cope with this condition constitutes an EU health priority for action, in particular in the context of the Europe’s ageing population and current estimates that the number of European affected by dementia will double by 2040 [2]. In 2001, the European Commission launched the Joint Action “Alzheimer Co-operative Valuation in Europe (ALCOVE)" with the aim of improving knowledge and promoting the exchange of information on dementia among EU member states. 2014 was declared the EU Year of the Brain; an initiative urging member states to develop dedicated national plans and strategies to combat Alzheimer’s disease and other forms of dementia.

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3. **Generic HTA Framework**

This chapter briefly analyses a) core HTA methodological challenges with respect to VPH technologies, establishing a more precise and well-defined terminological framework for generic HTA work as a base for further discussions and b) disease-specific challenges relating to introducing and evaluating clinical application in dementia diagnosis. Specific VPH aspects will then be discussed and determined in the next chapter.

3.1. **Methodological Challenges: Biocomputational Modelling**

HTA is a multi-disciplinary field of policy analysis that examines the medical, economic, social and/or ethical implications of the incremental value, diffusion, and use of a medical technology in healthcare provision. Conventional (HTA) methods look at existing, "mature" technology; they provide information on consequences and implications of use in clinical routine (and are accordingly not used as an aid in research guidance, product or service development). As a consequence, these methods are not sufficiently well adjusted and useful when applied to the relatively more complex nature of multi-scale simulation technologies. The insufficiency here does not only reside with lower level of maturity but also with the unclear definition of where exactly the intervention to be assessed sets in, given that biocomputational modelling, *i.e.* VPH technologies are composed of components and probably impact a broader range of clinical endpoints and workflow steps.

Consequently, the impact of simulation models and computer-aided medicine on clinical decision making and practice may be far-reaching, causing organisational, management, cultural – disruptive – impacts, which have a potential to:

- Revolutionise prevention and diagnosis
- Predict disease progression and outcomes related to treatment options
- Generate new knowledge from patient and other health data (learning, adaptive decision support systems, which are different from conventional, static decision-support systems).

To move towards a better understanding of the role of HTA and to further develop the HTA concept to better suit VPH-specific purposes, the following subsection provides for a more comprehensive, detailed definition of terms applied and used in our further HTA work.

3.2. **Methodological Challenges: Clinical Applications in Dementia**

Methodological challenges relating to the application-specific nature of dementia disease domain can be summarised in the following, to list but a few examples:

- Diagnostics procedures vary extensively between countries, hospitals and even among clinicians
  - In addition, the question is the assessment should focus on the procedures of a few selected countries, the simplified generic procedure or the procedures presented in the most recent research guidelines (but not implemented yet in practice in many countries),
- The care models and tools for financing the care vary greatly between countries,
- The ground-truth (neuropathological) diagnosis is seldom available (based typically on less-accurate clinical diagnosis with 60 – 90% agreement with neuropathological diagnosis) complicating the analysis
- the situation will change dramatically when disease modifying interventions become available
Subsequently, the question arises if, for the assessment, VPH-DARE@IT should focus on the current, more symptomatic treatments which have been shown to delay hospitalisation several months when started early enough, or, on the pharmaceutical treatments of the future, which could delay the disease’s progression much further).

- Very little information exists about the efficacy of psychosocial interventions

Given the above challenges, and considering the lack of data and robust comparative variables, a plethora of assumptions has to be made. The development of our HTA approach from a dementia and application-specific challenge as briefly outlined in this sub-section will be further discussed in sections 5 and 6.

3.3. Defining Health Technology Assessment

3.3.1. Basic definitions

In building upon commonly used health technology assessment (HTA) definitions (such as in [3]), we understand HTA to be:

the transparent, purpose-driven assessment - based on explicit assumptions - of the impact of developing or newly developed health technologies on issues of relevance for health policy decision making.

The following table, Table 1 expands on the precise meaning of this definition:

<table>
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<th>Term</th>
<th>Definition</th>
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<tr>
<td>Transparency/ Falsifiability</td>
<td>Scientific method-based, therefore transparent, making assumptions explicit, and in principle repeatable and falsifiable by others, i.e. open to scrutiny by-and in need of validation by the (HTA) community.</td>
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<tr>
<td>Purpose-driven; issues of relevance for health policy decisions</td>
<td>Any HTA exercise will always have a distinct purpose, which usually will be informing decision-makers in the context of a specific health policy issue for a specific stakeholder, several stakeholders, a stakeholder group, or groups of stakeholders. Policy is understood to also concern issues at the concrete implementation level of an individual person or organisation, not only at the societal level. The pending decision may either be directly related or indirectly related to health such as a technology development intended to be of benefit to health.</td>
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<td>Assessment</td>
<td>In principle, the assessment may concern only the technology under consideration. However, given that health service provision constitutes one of the oldest services we have (since the early years of Egyptian culture) and given that it demonstrates a certain maturity, it is common practice and it will also be assumed here that the assessment will usually concern two (or more) competing technologies. Assessment feasibility alludes to the availability of relevant evidence, time and resources required to complete a meaningful assessment.</td>
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<tr>
<td>Impact</td>
<td>To observe an impact, a direct or indirect causal relationship must exist between an input (validated simulation model; research effort; medical</td>
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intervention; etc.) and an output (new simulation model; improvement of health; etc.) or result, facilitated by the technology and its property(ies), e.g. usability. One should distinguish between:

- Intended impacts and
- Unintended impacts

Furthermore, one should distinguish between

- Primary impact(s) like on the health of an individual person, and
- Secondary (tertiary, etc.) impacts like on the labour market or tax income of the government when, for instance, due to better health a person is employed for a longer period of time, etc.

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<th>Developing or already developed</th>
<th>The health policy issue may concern not only an already-existing, usually proven technology (as with conventional HTA), but also a technology on the drawing board or at the research and/or development stage.</th>
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<tr>
<td>Health</td>
<td>According to the WHO, “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”</td>
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| Technology                    | Technology means “the application of scientific knowledge for practical purposes, especially in industry.”  
Three basic types of technology – the first two of which in reality mark endpoints of a scale rather than clearly distinct entities - need to be distinguished:

- Simple technologies, like a drug containing only one active ingredient, which may not disturb or change established clinical processes
- Complex technologies, which may combine different technical components thus requiring more complex assessment methods; and
- Transformative technologies that may lead to a disruptive change in clinical practice

Given this basic definition and initial explication of the meaning of HTA, we will now further explore this concept and discuss its key dimensions, thereby explicating this further and helping us operationalise the various HTA dimensions in a way amenable to application in the VPH-DARE@IT project and other dynamic contexts.

### 3.3.2. Common HTA assessment perspectives

Generally, the following HTA assessment perspectives can be distinguished, depending on the specific decision support context within which an HTA study is being undertaken:

**a) Assessment of effectiveness and safety of technology**

- Clinical benefits, clinical effectiveness, generalisability of results for healthcare provision,
- Risk (with patient safety being a judgment of the acceptability of risk)

**b) Assessment of organisational, legal, ethical, and socio-cultural impacts**

- Organisational implications (impacts on structures, processes; groups of stakeholders, acceptability)

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- legal (legal frameworks), ethical, socio-cultural implications
- Assessment of socio-economic consequences
- Socio-economic analysis, e.g. cost-effectiveness, benefit-cost analysis
- Return-on-investment analysis, business case development

### 3.3.3. Definitions of HTA socio-economic concepts

Since a focus of future work will be on the socioeconomic impact of the developing VPH-DARE@IT technologies, and so that exploitation considerations and business planning can be supported, some core concepts in this context are further explored and identified in the following table.

**Table 2: HTA socio-economic concepts**

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<th>Socioeconomic impact:</th>
<th>The potential aspects of impact for each stakeholder – benefits and costs to citizens, healthcare professionals and healthcare providers, and third-party payers. Costs encompass negative impacts, whereas benefits reflect positive impacts. The resulting quantitative measures, although presented in Euros, do not reflect financial flows or only the economic aspects of impact. They are merely a comparative representation, i.e. an index of the impact, including economic as well as social, cultural, and organisational aspects.</th>
</tr>
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</table>
| Microeconomic impact: | a) Refers to costs, prices, charges, and payment levels associated with individual technologies;  
                          b) Concerns comparisons of resource requirements and outcomes (or benefits) of technologies for particular applications, such as cost-effectiveness, cost utility, and cost-benefit. |
| Macroeconomic impact: | The impact of new technologies on national healthcare costs, resource allocation among different health programs or among health and other sectors, and shifts in the site of care, such as from inpatient to outpatient settings. Other macroeconomic issues that pertain to health technologies include the effects of intellectual property policies (e.g. for patent protection), regulation, third-party payment, and other policy changes on technological innovation, investment, competitiveness, technology transfer, and employment. |
| Efficacy: | Experimental effectiveness; efficacy refers to the benefit of using a technology for a particular problem under ideal clinical conditions, e.g. within the protocol of a carefully managed, randomised, controlled trial, involving patients meeting narrowly-defined criteria, or conducted at a "centre of excellence". |
| Effectiveness: | Effectiveness refers to the benefit of using a technology for a particular problem under general or routine conditions, e.g. by a physician in a community hospital for various types of patients; thus, outcomes/effectiveness research emphasises health problem-oriented assessments of care delivered in general or routine settings. |
| Comparative effectiveness: | Comparative evaluation of effectiveness. For example, evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver healthcare. |
| Efficiency: | Efficiency measures whether resources get the best value for money. Relation between resource inputs (costs, in the form of labour, capital, or equipment) and either intermediate outputs |
Benefit: Benefits – as positive impacts – but also costs are conceptual categories that go beyond merely prices of goods and profits from investments, and includes a variety of issues such as quality of life and efficiency of workflows. Costs, on the other hand, can usually be defined as negative impacts.

Stakeholder perspective: As the perspective of any evaluation is central to understanding the aim of the analysis, it is important to clarify whose perspective is taken in the analysis. Because the interconnections of stakeholders in a health technology environment can be complex, it is important to define and record the stakeholder perspective taken in the evaluation.

Stakeholders: In a healthcare setting, the five main stakeholder groups are (1) society, (2) citizens, (3) healthcare professionals, (4) healthcare providers, and (5) third-party payers.

Health outcome variables: Used to measure the safety, efficacy, and effectiveness of healthcare technologies. Health outcomes have been measured primarily in terms of changes in mortality (death rate) or morbidity (disease rate). Of course, a wide variety of further measures are to be found in the literature.

Unit of outcome: E.g. cost per quality-adjusted life year (QALY)\(^7\).

The above mentioned five stakeholder groups can be characterised as follows:

1) Society can be seen as a surrogate for the health system level and serves as a macro-level perspective for a given political system, which has legislative power over health regulation and policy – be it a region, nation-state, or international organisation. This ‘aggregate’ stakeholder perspective is most useful for policymakers/regulators to advise or inform technology-related policymaking.

2) Citizens also include people who are not patients yet have an interest in services being available for their family now, or for themselves in the future – carers and patients.

3) Healthcare professionals include various types of doctors, nurses, medical technicians, and administrative staff. Other categories can be added for staff whose working practices and arrangements are affected by the technology, but who are not users. These healthcare professionals and other workers can work in a wide variety of healthcare settings including primary care and hospitals, and then in various roles including emergency care, out-of-hours care, general and acute hospital care, and other services to citizens.

4) Health service provider organisations can include General Practitioner (GP) practices, general hospitals, specialised hospitals, teaching and university hospitals, and social care organisations.

5) Third parties include health insurance companies and other payer bodies, as well as authorities or government organisations that could be affected without having the explicit role of reimbursing health care professionals HPOs for health services.

\(^7\) However, measuring quality of life in dementia is, at best, challenging. The calculation of cost per QALY in, for example, Alzheimer's disease, relies on the measurement of health-related quality of life (HRQL) in different disease states. “Although key symptoms such as functional ability strongly correlate with quality of life and could be used as a proxy measure, there are currently no validated methods of measuring HRQL in Alzheimer's disease, an inquiry into the NHS England’s National Institute for Health and Care Excellence (NICE) cites (http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=476).
Their perspective of the assessment, i.e. those offered by the stakeholders above, must not be confused with the ultimate recipient or sponsor of HTA: usually the policymaker or a regulatory agency – as the goal of technology assessment is to provide policymakers with information on policy alternatives.

3.4. MEASURING BENEFITS AND COSTS

This chapter starts with a presentation of cost-benefit analysis and a discussion of some core concepts and challenges upon considering how to measure benefits and costs of a health technology such as VPH models. It then explores some concrete measures and tools to indeed identify and measure such benefits and costs.

3.4.1. Cost-benefit analysis

The UK Treasury ‘Green Book’ [4] provides a useful definition of cost-benefit analysis (CBA) as:

“Analysis which quantifies in monetary terms as many of the costs and benefits of a proposal as feasible, including items for which the market does not provide a satisfactory measure of economic value.”

CBA aims to determine whether and to what extent a planned (ex-ante) or completed (ex-post) project or programme has been worthwhile. The CBA’s aim of reflecting reality in practice means to define a unit of analysis and separate it into distinguishable impacts (see the Figure below). These impacts can be observed when they show a positive or negative effect on a stakeholder. Impacts are operationalised through a set of associated techniques.

Figure 1: Types of costs, benefits, and returns

Applying clinical use cases and concrete application scenarios as detailed descriptions of potential futures allows for the identification of core:
- health system actors,
- technologies,
- workflows and steps, and
- any other factor or variable

impacting on or being impacted by benefits and costs to be recorded or estimated. To realise this, it will be necessary to develop a realistic process model of the currently implemented pathway(s) and measure (or estimate) the related outcomes/benefits as well as inputs and their costs.

This needs to be compared with a newly-developed process model reflecting the envisaged implementation of the VPH-DARE@IT technology components. Then, their potential benefits as well as their implementation and service costs need to be estimated. This new pathway (model) must be aligned with the foreseeable optimal use of VPH-DARE@IT technologies, databases and instruments.

3.4.2. Operationalisation of measures

3.4.2.1. Simple and complex measures

Positive impacts are sometimes easy, yet also sometimes very difficult to measure. Depending on the RTD workflow stage of the technology under scrutiny, key aspects of the assessment may relate to the verification and validation of the simulation models like the capability or accuracy of models – which is not our concern here, and at later stages e.g. improved health outcomes for individual patients or populations, costs saved for the health system, reduction of hospital admissions, avoidance of medications to take, or also monetised benefits like waiting time or travel time.

The same applies to negative impacts, which may be higher financial costs, more complex interventions, inconvenience to users, loss of hierarchical power among healthcare professionals due to new clinical pathways (often specialists possess so called “veto” power, by resisting and blocking change, an indicator often overlooked in healthcare management), time lost, etc.

Complex measures (or also sometimes termed as “indicators”) establish a specific relationship between single measures such as quality of life years (QALYs). It is a measure of disease burden, including both the quality and the quantity of life lived. This measure is, e.g., often used in cost-utility analysis to calculate the ratio of cost to QALYs saved for a particular healthcare intervention. This is then used to allocate healthcare resources, with an intervention with a lower cost to QALY saved (incremental cost effectiveness) ratio (“ICER”) being preferred over an intervention with a higher ratio.

Another example of measurement indicators is efficiency, which, in its generic form, is an empty concept of an output/input relationship. Principal efficiency concepts concern economic/financial and technical efficiency measures; others may concern energy or pollution. Concerning e.g. health outcomes, a certain technology is deemed to be more cost efficient than another if it either achieves the same health outcome with a less costly (in monetary terms) input (or a better outcome with the same input costs), or if it achieves comparatively higher health outcomes with relatively little higher costs. A cost/benefit analysis compares the ratio of the monetised positive impacts (benefits) to the monetised negative impacts (costs), and the technology with the higher ratio is the one to be preferred.
3.4.2.2. Context dependency of measures

It must be noted that all impact measures are not neutral, but, rather, context dependent. What is e.g. a benefit to one stakeholder (like income) may be a cost to another. Or what is regarded by one person as a highly negative impact (like a shorter life from smoking) may be regarded by another as a negligible negative impact compared to the pleasure derived from smoking.

Another aspect is that a decision towards, e.g., an option with a higher benefit/cost ratio may not be feasible due to affordability constrains, i.e. the financial means to secure the inputs needed to achieve the desired result may not become available to the stakeholder.

3.4.3. Benefits

Conventional HTA is usually restricted to look at a given point in time (or short period) at just a single, newly intervening variable, and then measure the benefits and costs related to it – compared to the “old” or standard technology, respectively, intervention serving as benchmark or “comparator” (see also “comparative effectiveness”). Quite often this involves estimating the benefits for “the patient”, for the healthcare system as such, or for society at large only.

In more complex change situations such as introducing a new VPH-based decision support system or a computer-aided medicine intervention, such an approach is not sufficient to assess the eventual success perspective. There are two critical dimensions towards estimating future benefits:

1) The temporal or RTD workflow stage as outlined above must be taken into account, which requires both evaluation approaches adjusted to the respective stage achieved and a dynamic perspective covering several years.

A similarly critical aspect is that such new interventions as developed by VPH projects like VPH-DARE@IT tend not just to change a single variable, but, rather, lead to more fundamental changes like an entirely different clinical pathway, which needs to be compared to the standard diagnostic and/or treatment path prevailing so far. This implies looking at a multitude of variables, which leads to much more complex methodological issues as discussed in this report. A core aspect is that such a change usually will impact various stakeholder groups, from which it follows that:

2) All stakeholders involved must have a business case

i.e. we need to examine whether and how a “3W”, that is, a “win-win-win” situation can be achieved such that all relevant stakeholders are on board and support – or at least will not block – the introduction and diffusion of the new technology. This concerns particularly:

- Patients
- Medical professionals
- Healthcare provider organisations (hospitals, community centres, etc.)
- Third-party Payers
- (Health), local/regional politicians

Operationalised and measured tangible benefits that are to be considered, involve items like:

- Higher income/turnover (from more or new patients)
- Improved reimbursement/charging of newly introduced DRGs (diagnosis-related groups)
• Direct costs saved (e.g. hospital bed capacity, travel, lab examinations, drugs avoided, etc.)
• Improved outcomes (death, disease, days in hospital or in rehabilitation, Sol score, QALYs, etc.)

Intangible benefits include:

• Improved patient safety (e.g. fewer serious drug interactions recorded)
• Convenience (higher work satisfaction, more professional contacts, faster learning)
• Competitive position (more patients served; more privately paying patients among the clients; extension of catchment region)
• Staff satisfaction (fewer complaints, easier agreement to substitute or exchange work time, staff retention rate improved, etc.)

Measurement tools and data gathering approaches for the assessment of benefits include reading data from paper and electronic records such as accounting systems, reports, management information systems. Others involve data-gathering and obtaining estimates from administration, clinicians, staff, other experts, and other stakeholders. Regarding assessment of clinical outcomes with medical data, medicine literature very often provides detailed and well-researched data. Interviews or even focus group discussions may also become useful procedures.

Estimating the monetary value of intangible impacts may involve further data-gathering techniques. Revealed preference can be used to estimate time savings of professionals. An average salary is used as a proxy to attach a monetary value to it. For the valuation of others a stated preference approach can be used. Willingness to pay and willingness to accept are further options.

3.4.4. Costs

The cost model applied in a concrete assessment situation should not be based only on a singular intervention or factor, but rather on a comprehensive use case or workflow presenting the present standard of care together with the (future) new patient pathway. Such a clinical use case will then reflect and gather data on the total cost of running such workflow or use case.

Cost items to be considered include:

• Investment expenditure/depreciation costs
• Labour (wages, fringe benefits, etc.)
• Instrumentation/medical device and other operating/maintenance costs
• Treatment costs
• Work productivity loss by patients and by informal caregivers
• General overhead

Wherever possible, costs should be based on real costs; however, quite often healthcare provider organisations and other health system actors do not avail themselves of professional cost accounting systems. Then professional or expert estimates and other data gathering methods as outlined earlier will need to be applied.

8 Revealed preference theory is an economic method of understanding and analyzing choices made by individuals. These models assume that the preferences of consumers can be revealed by their purchasing habits or by indications as conceptualised by “willingness to pay”.

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Table 3 and Table 4 below represent the proposed schema to collect basic cost data for a present standard of care pathway, and a future care pathway supported and facilitated by VPH-DARE@IT technology, respectively.

**Table 3: Schema for basic cost data collection: standard of care pathway (usual care)**

<table>
<thead>
<tr>
<th>Pathway Step</th>
<th>Clinical Use Case</th>
<th>Service Use Case</th>
<th>Deployable Component / Unit</th>
<th>Instrumentation</th>
<th>Labour costs</th>
<th>Comments and sources</th>
<th>Sums [€]</th>
<th>Patient Distribution / Pathway</th>
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<tr>
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<tr>
<td>Standard of Care</td>
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<td>Visit</td>
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</table>

<table>
<thead>
<tr>
<th>Max Cost Pathway [€] (Total sum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per Cohort [€]</td>
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</table>

**Table 4: Schema for basic cost data collection: VPH-DARE@IT care pathway**

<table>
<thead>
<tr>
<th>Pathway Step</th>
<th>Clinical Use Case</th>
<th>VPHOP Service Use Case</th>
<th>Deployable Component / Unit</th>
<th>Instrumentation</th>
<th>Labour costs</th>
<th>Comments and sources</th>
<th>Sums [€]</th>
<th>Patient Distribution / Pathway</th>
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<tr>
<td>Now</td>
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</table>

<table>
<thead>
<tr>
<th>Cost per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per subset of cohort (100 - 1)</td>
</tr>
</tbody>
</table>
3.4.5. Stakeholder perspectives and costs

Societal perspective

The societal perspective is the broadest and most recommended perspective for economic evaluations as it considers the costs of all resources used or lost due to the disease, irrespective of who the payer is. This perspective is the most relevant for decision makers whose main interest is the welfare of the society as a whole [11]. The societal perspective thus includes costs falling not only on direct health service provision, but also those falling on other public sector budgets.

Under a societal perspective, costs are usually divided into direct medical costs, direct non-medical costs and indirect costs. Depending on the healthcare system and with reference to a providers perspective (explained below), direct medical costs can further be classified into direct reimbursable medical costs of all social insurance providers and the direct non-reimbursable medical costs [12].

a) direct healthcare costs (i.e. all goods and services related to the prevention, diagnosis and treatment of a disorder; e.g. physician visits, hospitalisations and pharmaceuticals)

Direct healthcare costs include hospital inpatient, physician inpatient, physician outpatient, emergency department outpatient, nursing home care, hospice care, rehabilitation care, specialists’ and other health professionals’ care, diagnostic tests, prescription drugs and drug sundries, and medical supplies.

b) direct non-medical costs (i.e. other goods and services related to the disorder; e.g. social services, special accommodation and informal care)

c) indirect costs (i.e. lost production due to work absence or early retirement).

Indirect costs usually denote the production losses due to incapacity for work (in the case of illness), occupational disability (in the case of long-term illness or disability) and premature death [12].

Provider Perspective

Only direct medical costs are included. From the payer's perspective, economic analyses involve the series of medical expenses incurred and avoided as a result of the health care intervention under scrutiny. The perspective of social insurance schemes considers only the costs directly involved, in other words, not the costs that the SHI insurance have to pay themselves nor any indirect costs resulting from productivity losses [12].

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9 is sometimes defined as an indirect cost, see explanation following.

10 http://painconsortium.nih.gov/symptomresearch/chapter_12/Part_1/sec4/ckspt1s4pg1.htm

11 Statutory health insurance
Table 5: Cost categories by stakeholder perspective

<table>
<thead>
<tr>
<th>Cost category</th>
<th>direct reimbursable medical costs</th>
<th>direct non-reimbursable medical costs</th>
<th>direct non-medical costs</th>
<th>costs of other social insurance schemes</th>
<th>transfer payments</th>
<th>indirect costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>society</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>social insurance</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>SHI insurants</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHI</td>
<td></td>
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<td></td>
<td>x</td>
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</tbody>
</table>

Source: adapted from [12]

**Cost (general)**

The economic definition of cost (also known as opportunity cost) is the value of opportunity foregone, strictly the best opportunity foregone, as a result of engaging resources in an activity.

**Unit Cost (diagnosis)**

Cost that refers to components of diagnostic procedures. E.g. costs per lab battery, per investigation (CT, MRI, EEG, etc.), per visit.

**Cost of Illness**

The personal cost of acute or chronic disease. The cost to the patient may be an economic, social, or psychological cost or personal loss to self, family, or immediate community. Cost of illness studies typically employ cost of illness: A large proportion of economic studies in health completed to date employ some variant of the 'cost-of-illness' methodology which combines the ‘direct’ costs of medical care, travel costs etc. with the ‘indirect’ cost of lost production because of reduced working time.

**3.4.6. Indirect costs and informal care**

One of the biggest challenges in estimating indirect costs under a societal perspective is routinely attributed to informal care.

Different methodological perspectives exist when estimating informal care costs [13]. The opportunity cost method and the replacement cost method are most commonly used in cost-of-illness studies. The opportunity cost method values the informal carer’s benefits foregone due to time spent by providing informal care, in general, approximated by the individual’s market wage. The replacement cost method in turn values time spent on informal care at the market price of a close market substitute (e.g. the wage of a home carer), regardless of whether informal care by relatives leads to restraints on their working time or their leisure time. In other words, this method puts a price on the time spent on informal care by considering the actual cost that would arise if relatives could no longer take care of the person with dementia [14].
However, methodological difficulties remain when estimating informal care costs. Identifying the best alternative use of time is not always easy, especially if a family carer already has been responsible for an individual, e.g. a spousal carer already undertaking a range of activities that benefit the whole household. This has led to a considerable variation in estimates of informal care for Alzheimer’s Disease and other dementias ranging from 36 to 85 per cent of total costs in one review [15]. Informal care is often classified as indirect costs; however, several caveats remain and the classification remains dependent on the economic valuation approach and the respective health care system. The Cost of disorders of the brain in Europe 2010 study, Gustavsson et al. puts informal care under direct non-medical costs because “it replaces formal services that would have fallen into this category” [11]. Other studies delineate that costs of long term nursing or home care can be regarded as both medical and non-medical direct costs. In countries with substantial sickness benefits, such as Germany or Sweden, incapacity for work is associated with only partial income losses, which means that consideration of income losses due to incapacity for work would only have a minor impact on quality-of-life estimates. Sweden has further seen a transfer of indirect costs to direct non-medical costs which accounts for lower indirect cost in a cross country comparison [16].

### 3.4.7. Cost analysis methods

#### Cost effectiveness analysis

Cost effectiveness is the point at which the minimum amount of input (and therefore cost) is used to achieve a given output. Cost effectiveness analysis is a measure of technical efficiency. It identifies and measures the costs of different options for achieving a required outcome. Alternatively, this is the same as the option that delivers maximum output at a given cost. In contrast to a CBA, one part of the input/output ratio has to be fixed.

#### Cost utility analysis

Cost utility is a measure of technical and allocative efficiency. It measures the cost of a particular treatment or type of care and compares it to the effects, expressed in additional utility to the patient. Utility can include anything from a subjective feeling of satisfaction to objective factors such as being alive and not suffering illness. Often, Quality Adjusted Life Years (QALY) is used as a unit of utility. Comparing the costs per additional QALY allows decision makers to identify the investment option that increases patient’s utility the most, given the resources available.

### 3.4.7.1. Economic evaluation and budget impact: concept of affordability

When introducing a new health technology, the economic effects are of paramount importance to the healthcare system. Yet the assessment of budget impact has to be distinguished from economic evaluation. While the latter depicts the relative economic value of two alternative technologies, a budget impact analysis addresses the affordability in predicting the impact of the introduction of a new technology on a particular budget holder’s budget. It serves additional informational needs as decision makers in healthcare often have to operate within given budgets.

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12 Technical efficiency is the physical relation between resources (capital and labour) and health outcome. Allocative efficiency takes account not only of the productive efficiency with which healthcare resources are used to produce health outcomes but also the efficiency with which these outcomes are distributed among a given community.
Even if the cost-effectiveness of a technology is favourable, it can still be not affordable without overspending, and a reallocation of resources, however socially beneficial, is often politically difficult.

Budget impact analysis enables health policymakers to identify potential conflicts between a comprehensive societal assessment and an assessment from the perspective of a particular third party payer or health care provider and to recognise the need for additional intervention, research or testing. In order to ensure the successful diffusion and deployment of a new technology, e.g. healthcare financing arrangements can be changed or research grant making and policy can be readjusted or adapted accordingly.

Budget impact analysis also varies in methodology as it has to meet the needs of the targeted decision-maker which can differ from what is customarily provided in efficiency analysis. Instead of the societal perspective for example, decision-makers are rather interested in the relevant costs that will incur to their particular budget, as mostly they cannot profit from savings occurring in any other area. Similarly, the time horizon might be inapt, as compensating for overspending in the short term with savings occurring at some time in the future may not be a feasible option. Besides the estimated market diffusion of a new technology and the impact its implementation has on service delivery, a budget impact analysis should address whether it has a substitution potential or would require additional funding, and imply what this means for the decision-maker, accounting not only for the acquisition cost but also for the financial consequences over time.

4. FRAMEWORK AND DIRECTION OF VPH-DARE@IT ASSESSMENT

This section develops the assessment method further with a specific focus VPH-related aspects.

4.1. INTRODUCTION

The complexity of data gathered from dementia research allows it to be at a critical juncture to benefit from technologies such as computational modelling. For instance, biomarker-based screening measures are under development as are therapies that may modify the underlying neuropathological disease process. Thanks to the computational power available today, the underlying mechanisms of the disease can be simulated, and the vast amounts of complex data gathered can be analysed holistically to identify new findings or set forth new hypotheses. Despite the improbability that modelling can simulate the complete human brain in detail, it is still a possible solution to increase the chances of clinical success especially since modelling and simulation techniques allow clinicians and researchers “to establish the appropriate population to treat or narrow the efficacy range needed for a drug in early stages of development to be commercially viable.” [5] However, understanding and accepting such computational technology would require “investments in infrastructures and a new generation of scientists and data analysts with a broad understanding of network physiology, pharmacology, biology, and drug discovery.” [5]

VPH technology is radically different from anything else used in hospitals that a systematic assessment is required already in the phase where specific tentative clinical indications are being searched. Due to its extremely innovative nature the medical professionals have no general understanding of the potential of VPH technology, and thus have difficulties in driving the process that associated the result of some basic technological research to the solution of a concrete clinical problem.

A large number of important clinical questions could be answered even by moderately accurate predictive technology that allow earlier diagnosis: but this becomes evident only if
the current standard of care is reviewed in the light of a predictive technology, so as to provide a baseline for performance that can be used to decide if and when a VPH technology can be used to solve a given clinical problem. Thus, we need to measure safety, efficacy and impact of the current standards of care, and use this as a reference already in the very early stages of technology development.

Furthermore, predictive technology is a radical departure from any current type of medical technology. Although many other human activities now rely on predictive technology, in medicine there is a clear cultural resistance to the idea that a computer may provide predictive information that may be usable in the healthcare process. This cultural resistance is different from a separate problem in clinical uptake of new technologies: lack of validation and integration with existing workflows. The best way to fight these resistances is to provide early measurable evidences that the use of VPH technologies is safe, effective, and convenient. Once successfully validated and implemented, VPH-DARE@IT will gradually transform dementia diagnosis. It will deliver more objective and accurate differential diagnosis than what is available thus far in Europe.

Transformation will happen via:

- Novel biomedical dementia biomarkers
- Personalised, multi-factorial, predictive brain models, taking into account genetics, metabolism, biophysics, physiology and environmental influences
- Advanced brain image analysis tools
- An integrative and personalised modelling platform to support clinical research in dementia
- A clinical platform for personalised diagnosis of dementia and assessment of treatment efficacy

The structure behind the socioeconomic assessment model is similar to a dual-arm trial set-up, comparing the “standard of care” with VPH-DARE@IT as a candidate representing an alternate approach. The VPH-DARE@IT arm aims to replace not only the risk assessment per se, but moreover, once employed, will detect high-risk patients and channel them to detailed diagnostic analyses from an early phase. This requires a structured approach that differentiates between those levels.

Table 6: Salient arms of the assessment model

<table>
<thead>
<tr>
<th>Current standard of care</th>
<th>VPH DARE@IT Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently dementia diagnosed clinically by physical and neurological exams/formal cognitive testing using a standardised instrument, such as:</td>
<td>- Improved differential diagnosis using existing technologies and careful exploitation of large databases</td>
</tr>
<tr>
<td>- Mini Mental State Examination (MMSE)</td>
<td>- New biomarkers from VPH-modelling</td>
</tr>
<tr>
<td>- 6-Item Cognitive Impairment Test (6-CIT)</td>
<td>- Risk-scoring by a portal for citizens</td>
</tr>
<tr>
<td>- General Practitioner Assessment of Cognition (GPCOG)</td>
<td></td>
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<tr>
<td>- 7-Minute Screen.</td>
<td></td>
</tr>
<tr>
<td>In general, standard routine use of:</td>
<td></td>
</tr>
<tr>
<td>- History taking</td>
<td></td>
</tr>
<tr>
<td>- Cognitive Assessment</td>
<td></td>
</tr>
<tr>
<td>- Haematology and biochemistry: laboratory tests</td>
<td></td>
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<tr>
<td>- Cerebral Imaging</td>
<td></td>
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</tbody>
</table>
Subtype dementia diagnosis with help of conventional MRI/CT imaging

- Novel MRI sequences will be developed for improved characterisation of dementia & the development of computational imaging tools for mechanistic model personalisation and extraction of novel biomarkers for dementia quantification. These data and methods will be added to conventional MR

Standard of care – TIME

- Tools for pre-clinical screening allowing earlier detection – shortening the current average 20-month time lapse between the onset of cognitive and memory deficits and its first diagnosis

4.2. **BEYOND STANDARD COST-BENEFIT ANALYSIS AND HTA: TOWARDS A MORE DYNAMIC HEALTH TECHNOLOGY IMPACT ASSESSMENT**

4.2.1. **The Need for a More Dynamic Approach**

In addition to the traditional HTA elements, there is need for a more dynamic approach to the impact assessment of medical technologies, and, in particular, of VPH-based health technology. The purpose of many impact assessments involving clinical assessment of medical technologies is to measure the change of cost-benefit ratio during the development and during the early phases of innovation, often for each stage of development and prototype, and dynamically per each year.

Therefore we need an approach that also takes into account the technology dynamics by emphasising socio-dynamic processes. Similar to the so called *constructive technology assessment* (CTA) [6], first described in the 1980s, a comprehensive assessment can be combined with an intentional influence in a favourable direction to improve quality (related to so-called formative evaluation)

Early assessments (including feedback into ongoing developments – “action-oriented assessments”) occur, but choices will be primarily about promises: the role of expectations and promises (and concerns), and the need to understand their role in ongoing developments.

**Clinical evaluation models** and research methodologies used for clinical trials have been applied to some forms of e-Health, especially where electronic data is embedded in medical equipment. The results are rigorous. Extending this as a methodology to HER, but also to modelling technologies is limited because:

- Control groups for the placebo equivalent will know that they are not using decision-support systems based on the technologies, so will not be statistically effective
- Cause and effect of EHR and VPH technologies on benefits is neither singular nor direct, so cannot be easily measured using a clinical evaluation methodology

Measures to deal with these limitations, however, must be included in the selected methodology.

True experiments such as randomised controlled trials (RCTs) are neither the best design for questions about impact assessment. While RCTs are the “gold standard” of internal validity for causal relationships, they are not necessarily the best method for answering all questions
of relevance to an HTA. As noted by Eisenberg [7], “Those who conduct technology assessments should be as innovative in their evaluations as the technologies themselves… The randomised trial is unlikely to be replaced, but it should be complemented by other designs that address questions about technology from different perspectives.”

In this multidisciplinary and multi-method approach, the classical methodologies underlying classical HTA form just one element of the method mix that is required to deliver informed decision-making in VPH research (see Figure 2).

**Figure 2: Multidisciplinary approach to informed decision-making**

### 4.2.2. Configuration and Components of the framework

In a preclinical preliminary assessment, the analytical framework encompasses the investigation of disease state, target population, and epidemiological factors as well as associated costs and current treatments to formulate the disease impact and therapeutic benchmarks. Costs and effectiveness of available therapies need to be assessed, with the understanding that the less effective current treatments are, the higher the potential for a new therapy to be cost-effective [8,9].

Information from the clinical assessment will be used to model the expected utilisation, that is, the benefits, and cost impacts. The model should be able to project the expected impacts on healthcare benefits and costs. In measuring the cost impacts of dementia, the most common clinical pathways for a cohort of dementia patients must first be identified. From there it can be projected how those care paths would be altered by the introduction of the VPH-DARE@IT technologies. Each clinical care pathway should have an associated probability of occurrence, costs, duration of activity and care, and other measures.

Once clinically applied, the new VPH-DARE@IT technologies will first of all affect care providers and patients. In order to assess the technology’s impact on these two stakeholders, two correspondingly different objects of analysis will need to be investigated – they present the constituting elements of the clinical impact:

1) the clinical management of the patient and, consequently, its change management;
2) the disease states and health of the patient
For generating the financial and non-financial data necessary to conduct a cost benefit analysis, a method-mix has been designed. This mix serves as the tool-box for extracting, generating and interpolating data (clinical and non-clinical; tangible and non-tangible). The results that the tools are assumed to deliver will be embedded inside a broad and encompassing CBA. The tools for feeding the CBA consist of two approaches:

- clinical pathway analysis deriving from clinical management and evidence-based medicine (cost-effectiveness of care paths);
- and disease simulation models based on health economic evaluation methodologies

Figure 3 depicts how the two tools are integrated and how the flow of work constitutes the overall assessment framework.

**Figure 3**: Components of the Assessment Framework

The aim of the socioeconomic impact analysis is to dynamically translate the health states of patients, the clinical data and the running costs of the healthcare process into estimates of socioeconomic benefits, costs, and related risks, allowing for a balanced overall assessment. The developed innovative assessment method allows identifying relevant costs and benefits for all stakeholders, from patient over healthcare provider to policy decision-maker, and, thereby, provides a tool to appraise the overall value of multi-scale modelling for society.
5. ASSESSMENT TARGET: THE NEED FOR AN EARLY DIAGNOSIS

5.1. THE CLINICAL AND ECONOMIC DIMENSION OF DEMENTIA

Dementia is a syndrome characterised by progressive cognitive malfunction that is severe enough to affect one’s daily life and activities. Symptoms include a malfunction in at least two of the following: memory; orientation; communication and language; calculation, focus/attention; and reasoning/judgement. A decline in emotional control, social behaviour, and motivation are also commonly observed.

Alzheimer’s Disease is found to be the most common or prevalent type, covering 60 – 80% of all dementia cases. There are still debates on which types are next prevalent after AD, but it is generally agreed that Vascular Dementia, Dementia with Lewy Bodies (DLB), and Mixed Dementia are all relatively more common dementia types. Acquiring precise prevalence rates for a certain dementia type is difficult not only because of the differences in age range and region measured by each study, but also because differentiating between different dementia types has proved to be particularly challenging.

The 2012 report by the World Health Organisation describes dementia as a public health issue due to its high global prevalence and economic impact. It was estimated that 35.6 million people worldwide were living with dementia in 2010, with the majority (7.0 million) from Western Europe. Germany is the country with the 5th largest dementia population (1.5 million) after China (5.4 million), the USA (3.9 million), India (3.7 million) and Japan (2.5 million). The total number of people with dementia is expected to double every 20 years. In 2010, global costs for dementia were estimated to be 1.0% of aggregated worldwide GDP, which is US $604 billion. 70% of this total is spent in North America and Western Europe only [11]. The latest report on the economic costs of dementia in Europe was provided by the European Collaboration on Dementia, who estimated costs to be €177 billion in 2008 [1].

5.2. ADVANCING EARLY DIAGNOSIS

Dementia is conventionally diagnosed only when discernible signs of progressive cognitive decline have been displayed by an individual. This cognitive decline is characterised by severe memory impairment that is coupled with noticeable impacts upon the person’s ability to carry out important everyday activities. And yet the neuropathological changes that eventually lead to severe memory impairment are believed to have formed well in advance – for example, in Alzheimer’s Disease as much as 20 - 30 years – prior to the onset of symptoms [11]. The World Alzheimer Report of 2011 has summarised the timeline of disease progression and current treatment in Figure 4 on the following page.
Figure 4: Current diagnosis (T4) is done during the “late-stage” of the disease, well after the onset of pathological changes in the brain. Source: taken from [11]

The figure depicts how current diagnosis is delayed, being made when symptoms are quite marked if it is being made at all (T4). Therefore, the aim of “early diagnosis” is to advance the time at which the diagnosis is made, especially before the onset of cognitive decline and disability (T1 and T2). The use of biomarkers would advance diagnosis even further than currently available technology when they have been developed enough to become a valid predictor and indicator of progression towards the disease.

Early diagnosis is also believed to have an economic impact. In high-income countries, the direct costs of social care and the indirect costs of family care are similar, each accounting for around 40% of total costs. In these settings, the costs of institutional care account for a large proportion of direct social care costs, since, according to some estimates, between a third and a half of people with dementia live in care homes. Given patterns of demographic ageing, it is likely that the largest increases will be among frail, older people with more severe dementia, who for those reasons, and because they are more likely to be widowed, are most likely to require residential or nursing home care.[11]

In its 2007 report [12], the UK National Audit Office recommended to Parliament “an ‘invest to save’ approach, asserting that earlier diagnosis and intervention could reduce costs for both families and the taxpayer by delaying entry to care homes. This delay was hypothesised as possible through the prevention of harm and crises from early rather than late or no diagnosis, by providing support, respite and psychological therapies to carers to prevent or treat psychological stress” [11].

Moreover, according to the Alzheimer’s Association and the Organisation for Economic Co-operation and Development (OECD), “research modelled on United States prevalence and cost of care suggests that a disease-altering therapy that would delay onset of 5 years would decrease the total number of Americans age 65 and older with AD from 5.6 million in 2010 to 4 million by 2020. Within this scenario, by 2020, five years after the introduction of the treatment in 2015, total costs to all payers for the care of people with the condition would be US $50 billion less than would be expected without the breakthrough (Figure 5). By 2050, the reduction in total costs to all payers would be US $447 billion; decreasing from an expected US $1.078 trillion to US $631 billion with the breakthrough [5,13].”
Figure 5. Impact of a 5-Year Delay in Onset on Costs for Americans Age 65 and Older with Alzheimer’s Disease. *Source: taken from [13]*

There have also been specific researchers who performed economic analyses that had attempted to model the impact of implementing earlier diagnosis on future costs on health and social care system and/or societal costs. Apart from cost-benefit analyses and cost-effectiveness analyses, cost comparison analyses were also done to compare the total costs involved in a particular intervention (e.g. pharmacological interventions: acetyl cholinesterase inhibitors and memantine) between groups receiving and not receiving this intervention. The introduction of the intervention is said to be favourable if the overall costs are lower in the intervention group [11].

One study stated that pharmacological treatments and carer interventions can delay entry into nursing homes and potentially reduce costs, but these cost savings are not being realised because many AD patients are either not diagnosed or diagnosed at later stages when they have no access to carer support programs that are funded by a social insurance (Medicaid). The researchers conducted a Monte-Carlo cost-benefit analysis that is based on estimates of parameters in medical literature, and that suggests that “the early identification and treatment of AD have the potential to result in large, positive net social benefits as well as positive net savings for states and the federal government”. The study was conducted by first, estimating the net social benefits and net fiscal savings to the particular state (Wisconsin) and the federal government assuming that a drug treatment and/or a carer programme has intervened in the progress of AD. The progress of AD was measured by a yearly cognitive decline (concretised by a drop in MMSE score) that was randomly and appropriately distributed to each patient, and that was assumed to correlate with the probability of being sent to a nursing home (institutionalised). This meant that a bigger drop in MMSE was assumed to point to a higher risk of being sent into a nursing home, wherein the annual nursing home costs of US $46,355 were defined by the state’s Bureau of Health Information. In short, the Monte-Carlo analysis provided a distribution of the values of net social benefits and fiscal savings from interventions occurring at different stages of the disease, as defined by the MMSE. Next, the
cost of identifying an AD patient were also estimated based on a study by Boustaní et al. [14], wherein a screening and diagnosis programme was implemented. All in all, the predictions of the benefits of early intervention plus the predicted costs of the screening diagnostic programme permitted an estimate of the overall net social benefits and fiscal savings that would result from the implementation of an early-stage diagnostic and treatment program. This Monte-Carlo analysis produced positive net social and fiscal benefits, which suggest that the early recognition and management of persons with AD would generate cost savings [15]. At least two other studies using economic analyses support the implementation of early diagnosis, having results that, for example, point to potential net savings of US $12,400 per patient [16, 17].

5.3. PURPOSE OF EARLY DIFFERENTIAL DIAGNOSIS

Early diagnosis has been suggested as possible upon observing that amyloid deposits were already found in 50% of people who are around 75 years old, yet the prevalence of Alzheimer’s Disease only reaches 50% in people who are 85 years old and above. This points toward the concept that a “preclinical Alzheimer’s Disease” exists wherein plaques and tangles accumulate for years before mental decline of the individual is manifested [18].

Differential diagnosis achieved only at the later phases of the disease is insufficient, as it is only early diagnosis that can help postpone the actual onset of the disease. It can transform care pathways and care relationships for people with a dementing disease [19–21]; for instance, by making possible timely referral for dementia-related education, carer counselling, and referral to social services or support. Above all, missed and delayed dementia diagnosis leads to lost opportunities for treatment and increases patient and caregiver burden [22].

Only through timely diagnosis can patients get access to available drug and non-drug therapies that can improve their cognition and enhance their quality of life. It also allows people with a dementing disease to plan ahead while they still have the capacity to make important decisions about their future care [11]. Thus, early and accurate diagnosis of dementia is considered critical to best practice in dementia care and is consistent with the overall goal of high-quality health care. The performance of clinical pathways is an important quality parameter that needs to be factored in when developing care and support services for people with dementia and their families [21].

Accurate differential diagnosis at an early stage of the disease also suggests a decrease in the need for institutionalisation or specialist care treatment, including the costs they involve. In one study based on a Cox proportional hazard model, the annual risk of institutionalisation is about 1% when the MMSE score falls to 24 points (30 being a perfect score i.e. the patient is healthy) and increases to over 90% when the MMSE score falls to 2 points, averaging across all demographic categories. For single older males and females, the probabilities reach 100% at MMSE scores of around 11. An untreated AD patient will typically decline, on average, about 3 to 4 MMSE points per year. Studies suggest that between 40% and 80% of individuals affected with dementia are untreated as a result of being undiagnosed in primary care. The failure to diagnose and treat persons with AD was attributed to the lack of physicians’ knowledge about dementing illnesses, the absence of cognitive screening, and the public perception that nothing can be done about the disease [15].

It has recently been shown that treatments are not effective if started at the later phases. Currently, the delay of diagnosis is on average 20 months after symptoms occur, and yet the disease is thought to progress up to decades prior to symptom development. The first objective in the earlier diagnostics is to shorten the 20-month delay in making the clinical
diagnosis. However, the real challenge is to go beyond the onset of severe memory problems and detect subjects already at non-symptomatic phase.\textsuperscript{13}

5.4. **BIOMARKERS AS A DIAGNOSTIC TOOL FOR EARLY DIFFERENTIAL DIAGNOSIS**

5.4.1. **Definition and Classifications of Biomarkers**

The Biomarkers Definitions Working Group of the National Institutes of Health [23] defined a biomarker, as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’’. When classified according to the mode of collecting information, biomarkers may be distinguished as either biochemical parameters that are detected from tissue samples (\textit{e.g.} from biopsies or surgeries), biochemical parameters or cells that are obtained from bodily fluids (\textit{e.g.} blood, spinal fluid, urine), and anatomical, functional or molecular parameters that are found through imaging techniques [24].

Imaging techniques may thus be divided into three categories: (1) Structural Imaging, which measures changes in brain structure; (2) Functional Imaging, which assesses brain function or malfunction; and (3) Molecular Imaging, which takes a look at cellular biochemical processes in the brain. The imaging techniques are useful in different circumstances, and some of the advantages and disadvantages of each are listed in the table on the following page:

\textsuperscript{13} Taken from the Description of Work
### Table 7: Examples of modalities used to collect information on dementia biomarkers.

<table>
<thead>
<tr>
<th>Biomarker/Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Duration of process</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural Imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| CT scan | - Wide availability  
- Compared to MRI, lower costs and shorter acquisition time  
- Can be used for patients with metal devices (e.g. pacemakers)  
- Useful for restless patients (duration of scan is short) | - Limited access to different parts of the brain  
- Radiation exposure | Under 30 seconds using modern scanners |
| MRI | | Higher costs than CT scan | ~ 45 minutes |
| fMRI | - Higher resolution (spatial and anatomical)  
- Better contrast and sensitivity when detecting certain brain parts e.g. soft tissue, white matter  
- Non-ionising radiation is used | - Not suitable for patients with pacemakers, implanted electronic hearing devices, and other foreign metallic body | |
| **Functional and Molecular Imaging** | | | |
| PET | Compared to SPECT:  
- Better spatial resolution  
- Changes can be quantified | - Not favourable for restless patients (lying down still during the scan is necessary or blurry images/errors may occur!)  
- Tracer injected needs to settle into the tissues and organs for 1 hour before scanning!  
- Expensive | 90 – 135 minutes total (waiting for the tracer plus scan) |
| SPECT | - shorter duration than PET | Compared to PET:  
- Poor resolution, sometimes additional CT scan is required!  
- Radiation exposure | 10 – 40 minutes |
| MRS | | | 45 – 60 minutes |
| **Other Biomarkers** | | | |
| CSF | - So far, CSF measures of tau and Aβ have advanced to the latest stage of biomarker validation, having high sensitivity and specificity especially in differentiating between AD and other dementia types | - May cause discomfort or headaches  
- Invasive  
- People with brain tumours, blood clotting problems and low platelet count must not take this test | ~ 30 minutes overall (allowing the patient to rest for a while is included here) |
5.4.2. General Potential Value of Biomarkers

A key role of the biomarker is to give information about the disease. Ideally, a biomarker for e.g. dementia should be able to:

1) Conduct a risk assessment for healthy persons
2) Screen for affected persons well before the onset of severe memory decline
3) Differentiate between different types in order to deliver a proper diagnosis
4) Predict the likely course of the disease in order to deliver the best possible therapy,
5) Monitor the course of the disease
6) Assess the response of therapy in order to predict outcomes and establish the populations most likely to respond to certain treatment [25]

The underlying value of biomarkers is not only recognised in the possible clinical impact, but also in the according economic considerations.

Table 8: Use and potential economic value of biomarkers in patient care

<table>
<thead>
<tr>
<th>Biomarker use</th>
<th>Clinical objective(s)</th>
<th>Economic consideration(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predisposition</strong></td>
<td>• Identify people at risk of developing dementia</td>
<td>• Potential savings if total costs of preventing disease onset or progress are less than costs of current treatment (i.e. after symptoms show)</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>• Detect and treat asymptomatic dementia;</td>
<td>• Potential savings if total costs of early treatment are less than costs of current treatment</td>
</tr>
<tr>
<td></td>
<td>• Accurately distinguish MCI patients from healthy aging patients</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis and Prognosis</strong></td>
<td>• Accurately establish which type of dementia is present;</td>
<td>• Potential savings from optimising treatment approach and timing</td>
</tr>
<tr>
<td></td>
<td>• Predict the likely course and accordingly find the best treatment approach</td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>• Determine whether treatment is having intended effect;</td>
<td>• Potential savings from optimising treatment approach and facilitating timely second-line treatment</td>
</tr>
<tr>
<td></td>
<td>• Enable timely detection of post-treatment recurrence</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Optimisation</strong></td>
<td>• Predict outcomes;</td>
<td>• Potential savings from optimising treatment approach leading to improved outcomes, and minimising costs of adverse events</td>
</tr>
<tr>
<td></td>
<td>• Establish populations most likely to respond to certain treatment;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Determine aggressiveness of treatment</td>
<td></td>
</tr>
</tbody>
</table>

Different biomarkers such as genomics, molecular imaging, or CSF levels will each be useful in a diagnostic flow, depicted in Figure 6 from an article by [26]
Figure 6: Different biomarkers can identify different populations, the largest being those who may benefit from low-cost and safe primary prevention strategies (base of pyramid). We primarily focus on the use of biomarkers for early differential diagnosis, here boxed in red. Source: adapted from [26]

The article also states that “biomarkers can identify a large population of individuals (see Figure 6, base of pyramid) who may benefit from low-cost and safe primary prevention strategies”. The role of biomarkers for diagnostics is also enabled by information technology known as a “clinical decision support” that starts from risk assessment (predisposition biomarker) and ends with the monitoring of treatment effect to enable true individualisation of therapy.

“This flow starts from tests with high sensitivity but low specificity and low cost to those with increasing specificity and value” [26], leading ultimately to treatment optimisation and individualisation. Patients will enter at different points (from the bottom to the top of the pyramid) according to their respective status in relation to the disease i.e. whether they are healthy, at risk, asymptomatic, or symptomatic. Aiming for early differential diagnosis would make use of biomarkers with relatively low specificity but high sensitivity, and would target a large proportion of the affected population as depicted in the red box of Figure 6.

5.4.3. Potential Value of Imaging Biomarkers

Imaging biomarkers detect and analyse electromagnetic, photonic or acoustic signals that are emitted by the patient and are afterwards translated into images. Compared with biochemical and histological biomarkers, they have the advantage of remaining non-invasive, being spatially and temporally resolved, and repeatable. Conventional structural neuroimaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), has long played a supportive role in the diagnosis of memory disorders and is today recommended for the routine evaluation of AD. However, structural changes are undetectable until in the later course of the disease and thus, other more contemporary imaging techniques have emerged. These imaging techniques are able to detect even the subtle changes in the brain that are not readily apparent on routine images obtained at a single time point. These include positron emission tomography (PET), single photon emission CT (SPECT), and functional MR imaging (fMRI). fMRI, for example, “measures brain activity by detecting changes in blood flow and blood oxygen levels (the ratio of oxygenated haemoglobin to deoxygenated haemoglobin in the blood with respect to a control baseline), at many individual locations within the brain. It is widely believed that blood oxygen level is influenced by local neural activity, and hence it is generally taken as an indicator of neural activity [5].” An fMRI scan of one human produces a series of 3D brain images each containing approximately 15,000...
volume-pixels (voxels), wherein each voxel contains hundreds of thousands of neurons. These data are collected once per second within a twenty-minute session, yielding tens of millions of data observations. Yet accurate quantification of regional brain volumes is time- and labour-intensive. fMRI would be a promising approach for the study human cognitive processes or for the early detection and monitoring of e.g. Alzheimer’s Disease in patients if there are appropriate data analysis methods that are developed to assess and make sense of the huge volumes of data acquired [5].

Imaging biomarkers are also useful because they may be applied to fulfil any of the clinical objectives listed in Table 8, which means they may be used as a predisposition, screening, diagnostic, prognostic, or predictive biomarker.

One area where imaging biomarkers have a critical role is new drug development, which is currently a process that begins with identification and validation of a target in the body, moving on to lead identification and optimisation, and ending with preclinical and clinical trials of the drug candidates [24]. Discovery and identification of possible new drugs or interventions have recently been successful due to the progresses in understanding molecular biological processes in a healthy or affected human body, but nevertheless there is a general concern on the slow arrival and increasing cost on the development of these possible therapies. One reason for the slow development of new therapies is the fact that the most reliable way to assess the clinical impact of a therapeutic intervention is through its effect on a clinical endpoint such as survival or disease-free survival.

Under a dementia setting, this means that the clinical impact of the new therapeutic intervention is assessed by taking note of any improvements on cognitive abilities of the patients (e.g. better MMSE score) or checking if memories were restored or even, whether the lesions were eradicated or improved. Such an assessment requires long periods of time and a large number of patients, rendering it impractical especially for dementia patients, who are diagnosed very late. The developments in quantitative medical imaging offer the opportunity of using imaging biomarkers to speed up the drug development process [24]. Another possible use of imaging biomarkers is if they can be used to overcome the limitations of the established histological “gold standards” [27] (in Alzheimer’s Disease, the “gold standard” has been the identification of plaques and tangles in the brain through biopsy). Invasive reference examinations in cases such as dementia would require that the patient be long-affected by the disease, which, as explained, would be insufficient to attain a positive clinical and economic impact. As a gold standard, imaging biomarkers would theoretically detect and diagnose dementia patients in a non-invasive manner, ideally before the late stages of the disease occur.

Nevertheless, imaging biomarkers that would be used in drug development studies or clinical trials must be validated, for which several points must be considered. “First, the imaging biomarker should bring new information on top of existing diagnostic tools or existing risk factors and have the potential to modify the patient management. Second, the imaging biomarker should be completely non-invasive, for not losing the advantage of safe imaging methods over invasive reference examinations. Third, the imaging biomarker should be cost-effective. If the biomarker is to be added as part of the clinical routine examination, and not to further burden the public health system with increased costs of care, its diagnostic advantages have to offset its cost. The imaging biomarker also should be easy to implement in the clinic, meaning that the machinery must already exist or be easily available, that there should not be the need for specific expertise from hospital employees, and that the parameter must be easy to measure and interpret” [27].
5.4.4. Current Progress of Biomarkers

To consider a biomarker as a valid diagnostic tool, it must undergo a series of stages of assessment, ultimately leading it to become a surrogate end point. Once surrogacy is reached, it means that the biomarker is expected to predict clinical benefit, harm or lack of benefit or harm. As of today, no biomarker in Alzheimer’s Disease has been shown to reliably predict clinical outcome [28].

![Current development stages of AD biomarkers]

Figure 7: Current development stages of AD biomarkers. Source: Taken from [29]

In addition to achieving the clinical objectives described previously (Section 4.4.2 and Table 8), biomarkers would ideally “be validated in autopsy-confirmed subjects; show > 80% high sensitivity and specificity; and be reliable, non-invasive, easy to perform and inexpensive” [30]. Sensitivity and specificity are measures of the ability of the biomarker to correctly identify patients with the disease and the ability of the biomarker to correctly identify patients without the disease respectively. Both are common values used to evaluate the performance and accuracy of a particular biomarker. Data on the sensitivity and specificity of all biomarkers is currently incomplete due to insufficient studies.
Table 9: The sensitivity and specificity of the main AD diagnostic methodologies is currently limited.\textsuperscript{14}

\textit{Source: Taken from [19]}

5.5. CLINICAL DIMENSION SUMMARY

Dementia is currently described as a public health issue due to the high number of affected individuals all over the world and its large economic impact. Its current diagnosis is considered “late-stage”, which means that patients are only being diagnosed when cognitive decline and mental disability are already pronounced. Differential diagnosis at such a late stage is both challenging and insufficient as it is early diagnosis that can help postpone the onset of disease and possibly differentiate from overlapping symptoms. There have been studies stating that the neuropathological changes believed to cause the mental disability already appear as much as decades before the actual onset of dementia. As there is currently no cure for dementia diagnosed at a late stage, an early diagnosis is believed to provide more effective treatment as well as efficient healthcare planning and cost reduction. Differential diagnosis at an early stage of the disease also suggests a decrease in the need for institutionalisation or specialist care treatment, but such an accurate diagnosis is prevented by the failure to diagnose even in primary care. This failure is attributed to the lack of physicians' knowledge about dementia, and the public perception that nothing can be done about the disease. These shortcomings will be addressed by VPH-DARE@IT.

Reliable biomarkers are possible tools to put this early differential diagnosis into effect, but, so far, each individual biomarker is still at a certain stage in its validation process. Furthermore, there is limited information on the accuracy (sensitivity and specificity values) of current biomarkers and little research has been done exploring the effects of combining biomarkers in order to improve the mentioned values. At such a standpoint, the establishment of an early dementia diagnosis is delayed and – given the consequences of late diagnosis – needs to be addressed.

From the clinical perspective, VPH-DARE@IT will deliver more objective and accurate differential diagnosis than what is available thus far in Europe, shortening the current average 20-month time lapse between the onset of cognitive and memory deficits and its first diagnosis. The ultimate objective of early differential diagnosis is to predict the onset of dementia when a patient does not yet even have severe memory disorders.

\textsuperscript{14} Description of Work
6. **Towards a VPH-DARE@IT Care Pathway**

6.1. **Comparing Current Standard of Care with Expected Impacts**

We plan to supplement a commonly-agreed clinical pathway reflecting the current standard of optimal diagnosis and care with a cost-benefit dimension. The description and conceptualisation of the clinical care pathway serves as a tool for collecting the required, basic clinical, economic and organisational data. In practical terms, the current pathway *i.e.* the current standard of care can be disaggregated into three levels:

- Diagnosis
- Prognosis and pharmacological treatment
- Interventional treatment planning.

For the purpose of this assessment, we focus on diagnosis since the main clinical target is to improve early differential diagnosis.

Conceptually, at each junction in the pathway tree, the human and instrumental resources involved, the duration, and the costs associated, will be attached. Once the new technology has been validated in a clinical context, a new modified pathway will evolve. The comparison between the old and the new pathways represents the initial tool for estimating the expected overall impact of the new clinical technology for clinical management. At this stage, relevant factors specific to the clinical roll-out of the new technologies will be integrated.

Assessing socioeconomic and technology impact is mainly a comparative exercise. Therefore, in a later step, a clinical pathway will be developed with activities reflecting the path that patients would be taking with the technologies evolving from VPH-DARE@IT. This would allow for a better comparison between (1) costs incurred and benefits generated by the conventional path to diagnose dementia, and (2) the costs incurred and benefits generated by the path of the VPH-DARE@IT supplemented technologies.

6.2. **Current Standard of Care Dementia Diagnosis**

Currently, there are no common guidelines for Alzheimer’s diagnosis within the EU. Some countries like England and its NHS pathways (of which an outline scheme can be seen in Figure 8), have very detailed ones; whilst others are still developing pathways; a few countries seem to have no pathway at all [31].
When dealing with the official national guidelines, it has become obvious that it will be necessary to establish a least common denominator guideline, which is depicted in Figure 9.

This algorithm incorporates information on medical guidelines from different organisations and countries as well as interviews with health professionals from Finland, the Netherlands and NHS England that were conducted for Deliverable 8.1. Whilst a consensus exists in literature that the diagnosis of dementia is the responsibility of General Practitioners (GPs), it is noted from the review work undertaken for this report that the Welsh, French, and the English Strategies/Plans emphasise the importance of specialist memory clinic services for the assessment and diagnosis of dementia with a complementary role for GPs and other secondary services [32].
Figure 9: Proposal for least common denominator guidelines Germany, Finland, NHS England
6.3. **INTERNAL VALIDATION PROCESS AND NATIONAL CARE PATHWAY**

Viable input on the common denominator model came from cross-work-package meetings with WP1 and WP8. During these meetings, it became clear that the pathways differ starkly from country to country, and that there are not only additional regional differences within each country itself but, moreover, from clinic to clinic the care and diagnostic pathway can vary. To make things even more complicated, memory clinics in the NHS can be specialist-led in one trust, and nurse-led in another.

The common denominator model was hence discussed with the General Assembly and reviewed again. There was very little disagreement concerning the current steps towards a diagnosis, except for sonography (where it was noted that MRI is used more often in vascular dementia) and PET/SPECT. The crux of the matter again is how to reduce and capture the various care pathways in different countries into one overarching model sufficiently complex and meaningful for the impact assessment: whilst in Germany, most of the diagnostic work is done in primary care, it is almost completely done in secondary care in Italy\(^\text{15}\) and other countries.

For the CBA to show realistic values in a real-world scenario, we hence decided to use existing, streamlined national pathways from particular countries. At the time of writing, and considering this deliverable serves as an analytic framework foremost and requires us to remain dynamic to some degree, we outline below a care pathway based on German guidelines.

The German pathway employed in Figure 10 is outlined in the guidelines of *Deutsche Gesellschaft für Neurologie* (German Association for Neurology) and the *Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde* (German Association for Psychiatry, Psychotherapy and Psychosomatics). When developing their guidelines, these associations assessed numerous international guidelines and applied the evidence-based *Deutsches Instrument zur methodischen Leitlinien-Entwicklung* (German guideline assessment tool) in order to adapt to high-quality standards. The guidelines from the NHS England NICE-SCIE and SIGN scored highest in this assessment and are hence quoted as primary source guidelines. Our developed algorithm as depicted below, in turn, is based on the understanding and merging of the two societies’ diagnostic and treatment guidelines.

Figure 10 below depicts that the General Practitioner (GP) is the first point of care for patients, as the GP is usually familiar with a patient’s personal situation and his or her surroundings. Following medical history taking and a basic physical exam, the GP performs quick memory tests (a maximum of three basic tests such as MMSE, FTDD or DemTect is reimbursed by EBM\(^\text{16}\)). The results of these two first steps should already enable well trained GPs to diagnose dementia\(^\text{17}\). It remains fuzzy on which care level the following steps (haematology/biochemistry and cerebral imaging) are being performed. Both levels are possible, yet it seems possible, for example, to have cerebral imaging being conducted in secondary care.

The sub-type diagnosis is being performed entirely on the secondary care level and consists of (a combination of) specific tests chosen by a specialist.

\(^\text{15}\) Italy installed specialised Alzheimer’s Evaluation Units (*Unità di Valutazione Alzheimer – UVA*); in the Netherlands the number of specialised Memory Clinics quintupled from 1998 to 2009[41]

\(^\text{16}\) Statutory Health Insurance Scheme (*Einheitlicher Bewertungsmaßstab EBM*), see section 6.6.

\(^\text{17}\) However, the rate of diagnosis done in this setting seems to not have been sufficient in the past, according to [2, 3]. This shows the imminent misery comparing guidelines and clinical reality.
6.4. **Routine Tests Used in Present Dementia Diagnosis**

Dementia is not diagnosed by a single test. Primary care practitioners, such as a General Practitioner (GP), usually perform a range of assessments and tests to rule out other possible causes for a patient’s symptoms. The primary care practitioner may either refer the patient to a specialised consultant such as a geriatrician, or to a Memory Clinic.\(^{18}\)

6.4.1. **History taking**

“Conversation with the patient may be as important as any formal cognitive assessment”[33]: History taking is usually the first step in a new patient appointment and is done by a GP. In order to substantiate the patient’s history, it is useful to have a second person (a relative or close friend) interviewed separately; ADCS-ADL (Alzheimer’s Disease Co-operative Study - Activities of Daily Living Inventory) seems to be a reliable guideline in this context [34]. Pseudodementia caused by stress, sleeping problems and depression may show the same symptoms as a neurodegenerative dementia, and hence should be ruled out.

6.4.2. **Cognitive Assessment**

Quite important in the diagnosis process are mental functioning tests. Quick memory tests like MMSE, DemTect, ACE, etc. are used to obtain an overview on the patient’s actual impairment. Those tests can also be used to monitor the patient’s mental abilities over time and are mainly suitable for patients aged 65 and older. For younger patients, more thorough neuropsychological tests are performed. As these tests examine different areas of function (calculation, memory, language, reasoning, etc.), they can help distinguish the type of dementia present.

The differentiation between MCI and dementia is “inherently a clinical judgement made by a skilled clinician” [35].

6.4.3. **Haematology and biochemistry: laboratory tests**

At this stage, if dementia is diagnosed, it may be appropriate to conduct further tests in order to (a) exclude other reasons such as thyroid abnormalities, HIV, Huntington’s disease, anaemia, and infection or metabolic disease amongst others, and (b) determine the sort of dementia – this usually induces haematology and clinical chemistry. There is a basic testing of Complete Blood Count (CBC: to exclude anaemia and infection), electrolytes, blood glucose, and Vitamin B12; whereas other substances like fT3, fT4 or HbA1c are mostly tested only if no clear results could be drawn from the basic testing. An electroencephalography (EEG) may be indicated in particular cases to rule out treatable systemic diseases [36].

6.4.4. **Cerebral Imaging**

The next step is cerebral imaging. This can be used to rule out other causes for dementia like brain tumours, prior stroke, fluid build-up or head trauma. MRI is the first choice; CT gives no detailed information about brain soft tissue and is mainly used if no MRI is available or if patients have pacemakers or claustrophobia. According to the interviews done for D8.1, in the Netherlands, MRI is used for approximately 70% of patients, CT for 25% and no brain imaging for the remaining 5%.

6.5. **NON-ROUTINE TESTS IN DEMENTIA DIAGNOSIS**

6.5.1. **Extended Diagnostics**

If no aetiology differentiation is possible after image analysis, additional tests can be performed. The clinician has to decide on which of these tests is recommended. If dementia is diagnosed within a hospital context, then it is rarely a primary diagnosis. Dementia as secondary diagnosis is quite common with elderly people.

6.5.2. **CSF Diagnostics**

CSF biomarkers have been shown to have a high diagnostic performance (T-tau, P-tau 181 and Amyloid Beta 42 peptide) and can be used in order to help differentiate AD from other types of dementia. While this type of diagnostics in the Netherlands is routine for patients younger than 65 years, it is not standard in NHS England, where CSF is taken only if other test methods do not lead to a reliable diagnosis.

6.5.3. **Nuclear Medicine**

Expensive and thus rarely used, except for research purposes; it consists of functional brain imaging with PET or SPECT [37,38].
6.5.4. **Sonography**

For ruling out vascular dementia, extra- and intracranial Doppler sonography of blood vessels can be employed.

6.5.5. **Genotyping**

Apolipoprotein e4 or PSEN1 is possible, but rather rarely used when testing blood. It tends to be used when there is a known familiar tendency towards early-onset dementia.

6.6. **Costs for the Diagnosis**

Generally, there are limited data available on the use and costs of the diagnostic procedures in clinical reality and on which factors determine the complexity of the work up [39]. Below are figures for Sweden in Table 10, based on results from SveDem [40], and for Germany in
Table 11, based on its Statutory Health Insurance Scheme (*Einheitlicher Bewertungsmaßstab EBM*).

This Statutory Health Insurance Scheme is for outpatient services only; the cost in a hospital context will be higher, but no reliable data were available at the time of writing.

Table 10: Example from Sweden: Unit costs of diagnostic services (adopted from [40])

<table>
<thead>
<tr>
<th>Resource Item</th>
<th>Unit</th>
<th>Unit cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic lab tests</td>
<td>Per lab battery</td>
<td>33</td>
</tr>
<tr>
<td>CT</td>
<td>Per investigation</td>
<td>200</td>
</tr>
<tr>
<td>MR</td>
<td>Per investigation</td>
<td>290</td>
</tr>
<tr>
<td>CSF</td>
<td>Per investigation</td>
<td>624</td>
</tr>
<tr>
<td>SPECT</td>
<td>Per investigation</td>
<td>379</td>
</tr>
<tr>
<td>EEG</td>
<td>Per investigation</td>
<td>100</td>
</tr>
<tr>
<td>Neuropsychologist</td>
<td>Per visit</td>
<td>423</td>
</tr>
<tr>
<td>Physical/occupational therapist</td>
<td>Per visit</td>
<td>145</td>
</tr>
<tr>
<td>Speech therapist</td>
<td>Per visit</td>
<td>145</td>
</tr>
<tr>
<td>Family physician</td>
<td>Per visit</td>
<td>123</td>
</tr>
<tr>
<td>Specialist care</td>
<td>Per visit</td>
<td>368</td>
</tr>
</tbody>
</table>
Table 11: Costs of diagnostic items based on German EBM, primary care only

<table>
<thead>
<tr>
<th>Action</th>
<th>Item</th>
<th>Cost EBM DE [€]</th>
<th>EBM#</th>
</tr>
</thead>
<tbody>
<tr>
<td>History taking</td>
<td>Base lump sum</td>
<td>15.7 (55y –75y), 21 (76y+)</td>
<td>03000</td>
</tr>
<tr>
<td></td>
<td>Medical interview</td>
<td>9 every 10m</td>
<td>03230</td>
</tr>
<tr>
<td>Cognitive Assessment</td>
<td>Memory Tests</td>
<td>1.9 per test (max. 3 tests)</td>
<td>32424</td>
</tr>
<tr>
<td>Haematology</td>
<td>CBC</td>
<td>1.1</td>
<td>32122</td>
</tr>
<tr>
<td></td>
<td>fT3</td>
<td>3.7</td>
<td>32321</td>
</tr>
<tr>
<td></td>
<td>fT4</td>
<td>3.7</td>
<td>32320</td>
</tr>
<tr>
<td></td>
<td>Blood glucose</td>
<td>0.25</td>
<td>32057</td>
</tr>
<tr>
<td></td>
<td>HbA1c</td>
<td>4</td>
<td>32094</td>
</tr>
<tr>
<td></td>
<td>Electrolytes</td>
<td>0.25 per test</td>
<td>32056-32079, 32081-32087</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>27.5</td>
<td>32783</td>
</tr>
<tr>
<td></td>
<td>Max value</td>
<td>27.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI of neurocranium (no contrast material)</td>
<td>121.3</td>
<td>34410</td>
</tr>
<tr>
<td></td>
<td>min 2 further sequences</td>
<td>44.6</td>
<td>34452</td>
</tr>
<tr>
<td></td>
<td>Gadobutrol (contrast material)</td>
<td>7.5 ml</td>
<td>NA, SNR 91064</td>
</tr>
<tr>
<td>MRI (radiologists only)</td>
<td>CT of neurocranium</td>
<td>61.4</td>
<td>34310</td>
</tr>
<tr>
<td></td>
<td>Contrast material injection</td>
<td>42.6</td>
<td>34312</td>
</tr>
<tr>
<td></td>
<td>2 further series</td>
<td>50.9</td>
<td>34344</td>
</tr>
<tr>
<td></td>
<td>Spinal tap</td>
<td>39.3</td>
<td>02342</td>
</tr>
<tr>
<td></td>
<td>Phosphorylated Tau Protein</td>
<td>24.9</td>
<td>32416</td>
</tr>
<tr>
<td></td>
<td>Total Tau</td>
<td>24.9</td>
<td>32416</td>
</tr>
<tr>
<td></td>
<td>Beta-Amyloid</td>
<td>24.9</td>
<td>32416</td>
</tr>
<tr>
<td></td>
<td>CSF diagnostics</td>
<td>Scintigraphy of parts of the body</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td>Additional fee for two- or multi-head SPECT</td>
<td>104.5</td>
<td>17363</td>
</tr>
<tr>
<td></td>
<td>Additional fee for single head SPECT</td>
<td>67.2</td>
<td>17362</td>
</tr>
</tbody>
</table>

19 An aftercare of two about two hours is indicated after a spinal tap, which is not yet represented in the costs here.
In order to get an overview of the overall costs, additional data are needed, especially when considering the commonness of diagnostic tests. Table 12 on the following page relies heavily on Swedish data from the results from SveDem. As shown by the table, CT is more common than MR in Sweden, which again shows the difficulty of stitching together a common pathway.

Table 12: Example from Sweden: Diagnostic tests (percentage) used in primary and specialist care
(adopted from [40])

<table>
<thead>
<tr>
<th>Diagnostic tests</th>
<th>Primary care</th>
<th>Specialist Care</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>93</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>94</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>80</td>
<td>87</td>
<td>5 – 10</td>
</tr>
<tr>
<td>MR</td>
<td>1</td>
<td>16</td>
<td>15 – 90</td>
</tr>
<tr>
<td>SPECT</td>
<td>&lt;1</td>
<td>13</td>
<td>10 – 40</td>
</tr>
<tr>
<td>CSF</td>
<td>3</td>
<td>43</td>
<td>30 – 45</td>
</tr>
<tr>
<td>EEG</td>
<td>&lt;1</td>
<td>27</td>
<td>30 – 45</td>
</tr>
<tr>
<td>Neuropsychological tests</td>
<td>1</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Assessment by occupation therapist</td>
<td>27</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Assessment by physiotherapist</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Assessment by speech therapist</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total number of tests</td>
<td>2,8</td>
<td>4,6</td>
<td></td>
</tr>
</tbody>
</table>

[23] http://apt.rcpsych.org/content/6/2/109.full

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7. CONCLUSION AND SUMMARY

While there is a growing interest for computational technologies in the area of medicine, the use of ICT as a support for prevention, screening, diagnosis, and treatment in computer aided medicine remains limited despite its large likelihood to revolutionise the current practice of medicine into that which the VPH technologies envision: a more integrative, predictive, and personalised healthcare provision. Such technologies would particularly benefit a condition such as dementia, wherein its current late-stage diagnosis prevents accurate differentiation between its types; proper prediction of its course and direction of treatment; the possibility to find an actual cure; better patient planning, care and support; and cost savings. Addressing dementia and helping citizens cope with this condition constitutes an EU health priority for action due to its prominently rising prevalence and economic impact.

VPH-DARE @IT will deliver the early and accurate differential diagnosis needed to shorten the time lapse between the onset of cognitive deficits and its first diagnosis through the construction of an integrative platform to support clinical research and enable personalised medicines, along with tools such as novel biomarkers and advanced brain image analysis.

Within VPH-DARE@IT, WP 9 Technology Assessment, Market Analysis and Exploitation aims to develop a socioeconomic and technology assessment method (HTA) and a prospective clinical impact analysis approach that are especially suitable for VPH purposes (integrative predictive personalised instead of incremental value.)

The socioeconomic assessment’s model structure focuses on the diagnosis being done in the current “standard of care”, and compares this with VPH-DARE@IT as a candidate representing an alternate approach. There are currently no common guidelines for dementia diagnosis within the EU and therefore the guidelines of two/three countries were targeted. In this deliverable, clinical pathways of the current dementia diagnosis of Germany and the NHS England were constructed, including (very initial) information on the investigation of the disease state, target population, epidemiological factors, associated costs and current treatments that are used to model the expected utilisation, that is, expected impacts on healthcare benefits and costs.

In a later step, another clinical pathway that reflects the path that dementia patients would be taking with the VPH-DARE@IT technologies will be developed. A comparison of the old and new pathways would then constitute the initial tool for estimating the overall expected impact of the new clinical technology for clinical management.

In the next step, this deliverable – conceptualised as a pragmatic, dynamic project work document – will elaborate more in detail the method and main scenarios for cost-benefit analysis. Initial discussion and planning, for example, could lead into the following direction to underpin the “framework” as presented in this deliverable to result in the final method and data collection tool:

- Diagnostics - showing how improved accuracy and a potential improved stratification patients might lead to earlier diagnosis and fewer follow-up visits
- Diagnostics and interventions – in addition to “diagnostics”, less effort and costs for institutional care and other related costs should be included; one key issue is whether interventions affecting pathological processes (= future interventions) or only symptomatic interventions (= current interventions) are expected, or
- Screening: the complexities (both clinical, economic, and institutional) of including health screening in assessment scenarios
Finally, then upcoming tasks regarding exploitation activities will be based on work in this deliverable, and research and activities from the market analysis will, vice versa, be reflected in any updates and revision of the VPH-DARE@IT health technology assessment.
References


8. GLOSSARY

Dementia
- A condition characterised by a decline in mental ability that is severe enough to affect one’s daily life, causing the individuals to eventually depend on others to assist in their daily activities.
- Symptoms of dementia include a malfunction in at least two of the following: memory; orientation; communication and language; calculation; focus/attention; and reasoning/judgment. A decline in emotional control, social behaviour, and motivation is also commonly observed.

Common Types of Dementia:
Alzheimer’s Disease (AD)
- The most prevalent type of dementia, covering 60–80% of all cases. It is an irreversible brain disease that slowly and progressively destroys memory and thinking skills. Alzheimer’s Disease is characterised by tangles and plaques in the brain called neurofibrillary tangles and beta-amyloid plaques.

Dementia with Lewy Bodies (DLB)
- A type of dementia characterised the formation of tiny clumps of abnormal protein (called Lewy Bodies) in the brain. Apart from problems in memory, judgment and movement (similar to movement problems in patients with Parkinson’s Disease), DLB patients also experience hallucinations, sleep disturbances, and fainting/unsteadiness.

Frontotemporal Dementia (FTD or FTLD)
[past name: Pick’s Disease]
- This term is used to describe non-Alzheimer’s dementias that are characterised by loss of brain cells, gliosis (the accumulation of star-shaped cells called glial cells in the brain thereby forming scars), and brain damage in the frontal and anterior temporal regions.
- Three major types or variants are termed as (1) frontal or behavioural variant (FvFTD), (2) aphasic variant or semantic dementia (SD), and (3) progressive aphasia (PA). Patients having the latter two types have language abnormalities as initial symptoms as compared to the personality changes seen in FvFTD.

Vascular Dementia (VaD)
[also: Vascular Cognitive Impairment and Vascular Cognitive Disorder. Past names: Multi-infarct or Post-stroke dementia]
- Dementia that is associated with cardiovascular or vessel disorders such as atherosclerosis of cerebral arteries (AS), arteriosclerosis or cerebral small vessel disease (SVD), and cerebral amyloid angiopathy (CAA).

Other Types of Dementia:
Mixed Dementia
- This term is used when characteristics of two types of dementia are present in an individual. The usual combination is Alzheimer’s disease and Vascular dementia.

Creutzfeld-Jakob Disease
- A rapidly fatal disorder caused by an infectious misfolded protein (prion) that causes other proteins in the brain to also misfold and malfunction. Common symptoms are behavioural changes and impairment in memory and co-ordination.

Parkinson’s Disease (PD)
- A disease caused by the loss of nerve cells in the part of the brain that produces dopamine, which normally regulates the movement of the body. Thus, besides progressive brain damage PD patients also have symptoms related to movement i.e.
involuntary shaking, muscle stiffness, and very slow physical movements. Other symptoms are depression, sleepiness during the day, and difficulties in swallowing.

- Lewy Bodies (see Dementia with Lewy Bodies) are also found in the brains of people with PD.

Normal Pressure Hydrocephalus
- A condition wherein cerebrospinal fluid abnormally builds up in spaces in the brain. Symptoms are similar to those in Alzheimer’s, Parkinson’s, and Creutzfeld-Jakob (slow movement, problems with walking, mental impairment) along with loss of bladder control.

Cognitive Tests:
MMSE or Mini-Mental State Exam
- A series of questions and tests used by both general practitioners and specialists to help diagnose dementia and assess its progression or severity.
- Most common test for screening of dementia.
- Although it may help in distinguishing demented patients from non-demented patients, people who have hearing/seeing impairments or people who are poorly educated may score low and be misdiagnosed.

ADAS-Cog or Cognitive Subscale of the Alzheimer’s Disease Assessment
- A test consisting of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities.
- Considered the best short examination of memory and language skills. Duration is ~30 minutes.

Other Tests:
Neuropsychological Testing
- A number of tests administered by a psychologist specialising in assessing brain disorders. The tests may be conducted in more than one visit and all in all would comprise around 2 hours.

Haematology Test
- Blood is collected and examined to investigate vitamin deficiencies, liver function, drug interactions, and possible infections.

X-ray
- This is performed to rule out lung cancer as it may cause brain tumours.

ECG or Electrocardiogram
- A recording of the heart’s electrical activity.
- Results show heart rate and rhythm, and if applicable decreased blood flow and increased heart size.

EEG or Electroencephalography
- A measurement of brain functionality by analysing electrical activity generated by the brain.

Important Terms:
Biomarker or Biological Marker
- A change in the components of tissues or body fluids that is significant enough to point out and classify a particular disease and its risk factors.
- Biomarkers must enable scientists and clinicians to increase their knowledge on how the disease develops. Ideally, they would be inexpensive and easy to perform, and show at least 80% sensitivity and specificity.
- Biomarkers may be changes that are found through imaging techniques or samples taken from the blood and spinal fluid.

Sensitivity
The ability of a test to correctly classify an individual as 'diseased'.

Calculated as the amount of true positive results divided by the total amount of true positive and false negative results.

For example: 80% sensitivity means that 8/10 individuals were correctly identified (by the test or biomarker) as those with the disease.

Specificity

The ability of a test to correctly classify an individual as disease-free.

The statistical probability that an individual who does not have the particular disease being tested for will be correctly identified as negative, expressed as the proportion of true negative results to the total of true negative and false positive results.

For example: 80% specificity means that 8/10 individuals were correctly identified (by the test or biomarker) as those without the disease.

**Structural Imaging:**

**CT / CAT Scan or Computerised (Axial) Tomography**
- Brain imaging involving X-ray transmission readings taken through the head at many different angles. Data are processed by a computer and presented as a series of pictures.
- When compared to MRI, it has lower costs and shorter acquisition time, but limited access to different parts of the brain. It can also be used for patients with metal devices (e.g. pacemakers). CT is useful for restless and unco-operative patients as the scan itself does not take very long.

**MRI or Magnetic Resonance Imaging**
- Imaging that constructs a spatial representation of (brain) tissue through utilising the electromagnetic properties of protons.
- Image resolution is improved enabling the examination of soft tissue, brain white matter, and vascular parts such as blood vessels.
- 3D images may be generated and the structure of the brain may be imagined in any plane.

**Functional Imaging / Molecular Imaging:**

**SPECT or Single Photon Emission Computed Tomography**
- Imaging that involves injecting a substance that distributes in the brain in proportion to blood flow, and emits gamma rays that are detected by gamma cameras for viewing. SPECT provides a “snapshot” of blood flow in the brain a few minutes after the injection. Different brain functions can also be demonstrated.
- Disadvantages include poor resolution, imaging not done in “real time”, and the necessity to be exposed to radiation. This imaging technique can take 10 – 40 minutes, making it unfavourable for restless and unco-operative patients.

**PET or Positron Emission Tomography**
- An imaging technique involving the injection of an individual with a radioactive substance that would spread and collect in tissues and organs. Signals from the tracer will be detected by a tunnel-shaped scanner, and these signals will be translated into 3D images by a computer.
- A PET scan can reveal the size, shape, position, and some function of organs.
- The tracer needs to settle into the tissues and organs for 1 hour before scanning can begin. Lying down still during the scan is a must, otherwise blurry images or errors may occur.

**Functional MRI**
- Instead of just measuring brain structure, fMRI is able to measure brain function by detecting changes in the blood flow. These changes are present upon neural activity, and thus they (the changes) are used as indicators of brain reaction towards a specific stimulus.
FDG- PET or F-18 fluorodeoxyglucose PET
- A PET scan wherein FDG is used as an agent to reflect glucose metabolism that is happening in the brain.

MRS or Magnetic Resonance Spectroscopy
- An imaging technique similar to MRI. The interaction of radio waves and chemical in the brain is measured and translated into a graph or spectrum.
- In neuroscience, MRS using the hydrogen proton, or $^1$H MRS, can show data on concentrations of N-acetylaspartic acid (NAA), which is commonly found in the brain. When NAA concentrations are low compared to other molecules (choline, creatine, and phosphocreatine), it is an indicator of neuronal loss and dysfunction.

Other Biomarkers:
CSF or Cerebrospinal Fluid
- A clear fluid that cushions the brain and spinal cord to protect them from injury.
- Normal values of indicators such as CSF pressure, appearance, total protein amount, glucose amount, and blood cell amount have already been defined and thus when values appear outside of this defined range, some diseases are able to be pointed out.