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Name of the scientific representative of the project’s co-ordinator, Title and Organisation: Jyrki Lötjönen, Principal Scientist, VTT Technical Research Centre of Finland

Tel: + 358 20 722 3378

Fax: + 358 20 722 3499

E-mail: jyrki.lotjonen@vtt.fi

Project website address: http://www.predictad.eu
4.1 Final publishable summary report

Executive summary

Alzheimer’s disease (AD), the most common cause of dementia, alone accounts for costs equivalent to about 1% of the gross domestic product (GDP) of the whole world. The number of persons affected currently is about 36 million but the number is expected to double in the next 20 years. Many approaches are now under investigation targeting either treatments for pathology directly, such as anti-amyloid plaque agents, or prevention strategies, such as lifestyle changes. Especially when new drugs or prevention strategies become available, early diagnosis is essential to detect patients, to start medication and/or preventative treatments and to stop plaque forming as early as possible.

PredictAD was an EU-funded research project (6/2008-11/2011) that developed objective and efficient methods for earlier diagnosis of Alzheimer’s disease. Diagnosis requires a holistic view of the patient combining information from several sources, such as clinical tests, imaging and blood samples. Blood samples are a highly interesting source for biomarker discovery due to their ease of acquisition. Metabolomic and proteomic biomarker signatures were detected from blood samples showing a good accuracy in detecting Alzheimer’s disease. Imaging has established its role in current diagnostic guidelines. Several efficient image analysis methods were developed for the analysis of magnetic resonance images (MRI) and positron emission tomography (PET) images. The tools quantify the volume or the atrophy rate of the hippocampus, define modern morphometric measures from MRI and detect pathologic patterns from PET images. A novel technology for detecting the disease based on quantification of electrophysiologic signals (TMS/EEG, transcranial magnetic stimulation combined with electroencephalography) was studied with good results.

Currently, clinicians make the final diagnosis by combining heterogeneous measurements with information from interviews of the patient and relatives. This process involves subjective reasoning and requires strong expertise from the clinicians. PredictAD designed a totally novel approach for measuring objectively the state of the patient. This decision support system, developed in close collaboration with clinicians, compares patient measurements with measurements of other patients in large databases and provides an index and graphical representation reflecting the state of the patient. The PredictAD tool was validated in several studies showing that it improves the diagnostic accuracy and clinician’s confidence of making the diagnosis, both factors allowing earlier diagnosis.

PredictAD took several steps towards more objective and efficient diagnostics in Alzheimer’s disease on different fronts. The project results have been widely disseminated in scientific forums as well as in public media. The exploitation of the project results was started during the project and some tools developed have already been licensed to companies.
**Project context and objectives**

Dementia has been recently identified as a health priority both in Europe and in the USA\(^1\). Alzheimer’s disease (AD), the most common cause of dementia, alone accounts for costs equivalent to about 1% of the gross domestic product (GDP) of the whole world\(^2\). The number of persons affected currently is about 36 million but the number is expected to double in the next 20 years. When this is combined with the fact that we have four working-age people per every elderly citizen and that ratio will soon change to 2:1 in Europe, we are going towards serious challenges – both human and economical ones\(^3,4\).

No cure exists for Alzheimer’s disease: available treatments provide only symptomatic relief to this neurodegenerative disease. Many approaches are now under investigation targeting either treatments for pathology directly, such as, anti-amyloid plaque agents, or prevention strategies, such as lifestyle changes\(^5\). When new drugs or prevention strategies become available, early diagnosis is essential to detect patients, to start medication and/or preventative treatments and to stop plaque forming as early as possible. Even only modest improvements in delaying the disease have dramatic effects in the population level. If onset of the disease could be delayed by five years, the number of cases worldwide would be halved\(^6\).

No single test, prior to post mortem pathology, proves that a person suffers from AD. AD is diagnosed clinically by physical and neurological exams, and checking for signs of intellectual impairment through standard tests of mental functions. In addition to these clinical measures, the current guidelines for the diagnostics of Alzheimer’s disease emphasize the role of various biomarkers. These biomarkers include measures from magnetic resonance imaging (MRI), positron emission tomography (PET), biomarkers from cerebrospinal fluid (CSF) and genetic biomarkers.

A skilled specialist physician can diagnose AD with more than 90% accuracy at the later stages but this accuracy decreases at the early stages of dementia. The delay from symptoms to diagnosis is currently 20 months on average in Europe\(^7\). With regard to prevention, the disease is thought to progress pathologically for 5–8 years prior to symptom development, based on some reports this can be even decades. 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 the memory problems and detect persons already at non-symptomatic phase.

The current diagnostic process involves subjective reasoning and requires strong expertise from the clinicians. The diagnosis of a patient may depend on country, on hospital, on clinician or even on the weekday when the clinician is doing the diagnosis although the only variable should be the patient. In modern society, such subjective reasoning should be minimised as it potentially exposes humans to unequal situations and affects the efficacy and quality of our healthcare system.

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5 IDdb3 database (Thomson Scientific), February 2007.
6 Alzheimer’s Association: Generation Alzheimer’s – the defining disease of the baby boomers.
The EU-funded research project PredictAD (www.predictad.eu, period: 6/2008-11/2011, budget: 3.9 M€), consisting of eight partners, was established to address the challenge of early and objective diagnostics in Alzheimer’s disease. The project consortium consisted of eight beneficiaries: VTT Technical Research Centre of Finland (Finland), GE Healthcare Ltd (UK), Nexstim Oy (Finland), University of Eastern Finland (Finland), Imperial College London (UK), Karolinska Institutet (Sweden), University of Milan (Italy) and Rigshospitalet (Denmark).

The first scientific objective of the project was
to find efficient biomarkers from heterogeneous patient data and integrate them for making early diagnosis and progress monitoring of AD more efficient, reliable and objective.

The development of efficient and objective therapeutic approaches to AD requires improved use of already known biomarkers and extraction of novel biomarkers, i.e., there is a need for biomarkers that enable early detection of pathophysiology and serve as markers for treatment benefit. In addition to discovery of novel biomarkers, more efficient methods to extract previously known biomarkers, e.g., from imaging data, are essential. In clinical trials, biomarkers can be used to enrich populations and monitor therapy. In clinical practice a diagnosis, before onset of symptoms, enables early intervention and the diagnostic test can serve as the baseline for monitoring of treatment. In addition to improved biomarkers, methods are needed for combining systematically the comprehensive information from biomarkers. Forming a holistic and objective view about the status of the patient requires the use of modern information analysis technologies. Only efficient biomarkers and their integration may finally enable early diagnosis.

The second scientific objective of PredictAD was
to improve the cost-effectiveness of AD diagnostics by optimizing diagnostic protocols.

Even if the optimal combination of biomarkers for AD were known, it does not mean necessarily that all of these biomarkers could or should be used each time in clinical practice due to several reasons. First, all the modalities are not available in all hospitals. Second, even if the modality existed in the hospital, considering the economical aspects it may be desirable to utilise only a limited range of modalities for a required accuracy. Third, all the data cannot be acquired from all the subjects (for example, obtaining MRI is not possible for subjects with metal implants). The final aspect is the order in which different modalities are used, called the stepwise scoring approach. Low-cost methods can be used to stratify risk populations, or may be accurate enough for detecting clear AD cases, but additional more profound and high-cost studies will be needed for borderline cases. There is a clear need to define the most cost-efficient clinical diagnostic protocols, for example, for given clinical environments or even for a given patient.

To implement these scientific objectives three technical objectives were defined:
A widely accepted software solution for computer-assisted diagnosis of AD is not available as even the type of data that should be used as a basis for diagnostics is unclear. The lack of effective and reliable tools for AD diagnostics has been identified as one major challenge with high impact by Frost & Sullivan. They made a strategic recommendation: ‘Simple tools have to be developed to assist physicians in identifying the signs and symptoms of the disease’. In order to enter clinical practice, the tool must be simple and clinical user requirements must be central to its design. Being simple includes also that continuous increase in clinical data production is addressed appropriately by developing intuitive yet highly informative visualisation techniques.

If the evidence-based practise is followed, diagnostics should be based on the most recent and valid research results. Traditionally this means the results from literature. A more flexible way would be to store and utilize directly the data from which the results are computed because it allows computing new research results and the use of different statistical modelling approaches.

Modern hospitals have huge data reserves containing information that nobody has extracted but could be utilized in diagnostics by systematic modelling. The databases contain information about biomarker values and their variability due to normal variation in humans or due to different diseases. If the measurements of a patient are compared with measurements from many database cases with known diagnosis, i.e., containing information about the mentioned variabilities, the disease-related state of the patient can be inferred and a probability of having a disease computed. This approach follows the principles of evidence-based medicine.

Lots of interest has been recently focused on personalized healthcare or medicine, where the population is divided into sub-groups based on some personal factors, and the diagnosis and/or treatment is decided using the information tailored specifically to each sub-group. Typically, the sub-groups are determined based on age, gender, or genome. Considering the diagnosis of AD, demographic information of a patient, such as age, gender, education and weight have been reported to interact with the results of neuropsychological tests and biomarkers. The statistical framework for diagnostics must, therefore, be able to take into account the personalized healthcare aspect.

One major bottleneck for exploitation of computer-assisted or decision support system-based diagnostics is the difficulty in quantifying measured data automatically. For example, the reliable and fast enough segmentation of images, a necessary step usually in quantifying images, is currently probably the most challenging problem in image processing. Therefore,

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methods are typically developed only for specific applications. The usability of the tools and their fit to current clinical work-flows is also a central issue. The computation time needed for image segmentation can be hours instead of minutes or seconds thereby considerably reducing clinical acceptability. The tools should be also intuitive and the results understandable. AD diagnostics requires a solution that allows accurate quantification of clinical data while fulfilling simultaneously other clinical requirements, such as acceptable computation time.

Results

The first scientific objective of the PredictAD project “To find efficient biomarkers from heterogeneous patient data and integrate them for making early diagnosis and progress monitoring of AD more efficient, reliable and objective” is still relevant although it was written more than four years ago. Biomarker discovery is a hot topic in Alzheimer’s disease research but no real breakthrough has been published. The extraction of CSF-based biomarkers is being standardized world-wide and discoveries on blood-based biomarkers have been reported. PredictAD has published two studies about blood-based markers, one from metabolomics and one from proteomics. The promising results produced with the blood-based biomarkers may open new avenues for early diagnostics and screening. Although magnetic resonance imaging (MRI) has progressed rapidly, no real breakthrough has been published related to diagnostics of Alzheimer’s disease. However, MRI has established its position in current diagnostic guidelines. Novel state-of-the-art image analysis methods allow automated extraction of efficient MRI-based biomarkers. PredictAD has been active in developing such techniques. PET imaging, especially using novel amyloid imaging tracers, are showing great potential for the diagnosis of Alzheimer’s disease. These tracers provide in-vivo information about amyloid depositions in the brain, one of the hallmarks for the disease. Results are promising and efforts are ongoing to bring these tracers to the market. However, it is still unclear whether all amyloid positive subjects will develop AD especially in pre-symptomatic subjects and information from other biomarkers complement PET amyloid biomarkers. Another obstacle in the spread of this technique is a relatively high price of acquisition. PredictAD has been active also in developing tools for quantification of PET images. In addition to these more standard techniques, there are several other innovative approaches under development for the diagnostics, such as, analysis of the fundus of the eye and the use of TMS/EEG (transcranial magnetic stimulation combined with electroencephalography), the latter being studied in PredictAD. In summary, there is currently no single biomarker that could predict Alzheimer’s disease but the diagnosis is based on the integration of the evidence from different biomarkers. This has been indicated also in current diagnostic guidelines. PredictAD has been in the front line in developing clinically useful techniques for integrating the biomarker information. We have shown in our studies that combination of information indeed improves the diagnostic accuracy.

PredictAD had three work-packages focusing on biomarker discovery from different patient measurements: molecular data, electrophysiological data and imaging data. The third technical objective “to develop data quantification methods for AD meeting various critical clinical requirements, including accuracy and computation time” reflects the work done in these work-packages. New quantification methods were developed in the all three fronts: extraction of metabolomics and proteomics compounds from blood samples, quantification of TMS/EEG measurement data and development of image analysis tools for MRI and PET data. The accuracy of these methods represents the state-of-the-art. In addition to accuracy, the clinical usability was an issue. The work done in these work-packages is summarised next.
Quantification of molecular data

Molecular level biomarkers are currently under extensive studies in Alzheimer's research. Many biomarkers, such as tau proteins and β-amyloid 42, measured from the cerebrospinal fluid (CSF), the liquid surrounding the cerebral cortex, have been found to be strongly related with the disease. One major challenge of these biomarkers is that taking samples from CSF requires an invasive measurement limiting their usability in early diagnostics. Blood samples would be an excellent source for detecting Alzheimer's disease, as blood sampling is not considered an invasive technique. PredictAD has studied the role of metabolomic and protein compounds in Alzheimer's disease when defined from blood samples.

PredictAD used metabolomics, a high-throughput method for detecting small metabolites, to produce profiles of the serum metabolites associated with progression to AD. Serum samples were collected at baseline when the patients were diagnosed as AD, mild cognitive impairment (MCI), or healthy controls. 52 out of 143 MCI patients progressed to AD during the follow-up of 27 months in average. A molecular signature comprising three metabolites measured at baseline was derived which was predictive of progression to AD. Furthermore, analysis of data in the context of metabolic pathways revealed that pentose phosphate pathway was associated with progression to AD, also implicating the role of hypoxia and oxidative stress as early disease processes. The elucidation of early metabolic pathways associated with progression to Alzheimer’s disease may also help identifying new therapeutic avenues.

In proteomics, the analytical platform used was a combination of state-of-the art mass spectrometers. At the same time, an in-house written label-free quantification program was further developed, to become about 2-3 times more accurate than respective commercial algorithms. The main improvement was to account for the electrospray current fluctuations by statistical analysis of the abundances of simultaneously eluting peptides.

The same samples used in the metabolomics analysis were used also in proteomics. We performed label-free quantification and found proteins that correlate with the AD degree separately for two genders using the new platform. IsoAsp analysis, as an example, verifies the previous literature hypothesis that there is gender related difference of isoAsp levels in blood proteins and the isoAsp-AD link is consistent with the previous finding for AD brains.

Quantification of TMS/EEG data

Alzheimer's disease is known to affect the electromagnetic activity of the brain. Transcranial magnetic stimulation combined with electroencephalography (TMS/EEG) is a novel, non-invasive tool for measuring the electrophysiological brain responses to direct cortical stimulation, unbiased by the cognitive impairment and subjective functional performance of patients with AD. In summary, a stimulating coil delivers brief magnetic pulses on the scalp.

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10 Mild cognitive impairment is a condition in which a patient has memory impairment but activities of daily living are preserved. It is a risk factor for AD, but not every MCI patient develops into AD. Typically, the MCI cases converting to AD are called progressive MCI (P-MCI) or converters and the cases not converting are called stable MCI (S-MCI) or non-converters.

that are able to induce an electric field on the cortical surface; simultaneous recording of electroencephalographic (EEG) activity allows to measure with good spatiotemporal resolution the response of the entire brain to this direct perturbation. The additional integration of TMS/EEG with a neuronavigation system (NBS) provides a real-time precise control over the stimulation parameters that is crucial for reproducibility of experimental conditions across subjects\textsuperscript{12}.

Compared to other methodologies, TMS/EEG provides a reliable and objective measure of cortical excitability and effective connectivity, which are key parameters of the pathophysiology of AD. Moreover, TMS/EEG can be used to track, longitudinally and in any cortical region, the changes occurring in the brain during disease progression and treatment, thus representing a useful tool to extract reliable biomarkers of AD. However, unlike traditional peripherally-evoked potentials and metabolic activations, an established data analysis procedure is not currently available to extract synthetic and quantitative indices of brain responsiveness to TMS. PredictAD developed a standardized, data-driven procedure to extract from TMS/EEG data synthetic and early markers of the neuropathological processes occurring in AD.

A unified mathematical approach to analyse TMS/EEG data and to extract synthetic indices of cortical excitability and effective connectivity from TMS-evoked potentials was developed\textsuperscript{13}. The following general indices were defined: Significant Current Density (SCD), that sums up the amplitude of all significant currents induced by TMS; broad-band and narrow-band Phase-Locking (bPL and nPL), that reflect the ability of TMS to reset the phase of ongoing cortical oscillations; and Significant Current Scattering (SCS), that measures the average distance of significantly activated sources from the stimulated site. All these indices can be integrated either in time or space domains, thus obtaining synthetic measures of brain activity cumulated over specific temporal windows or cortical areas of interest.

PredictAD recorded TMS/EEG from 41 subjects, including 15 healthy elderly controls (CTR), 15 MCI patients, and 11 patients with Alzheimer’s disease (AD). TMS was delivered on the left prefrontal cortex, Brodmann’s area 6/8, using a Navigated Brain Stimulation system, with intensity about 110 V/m and inter-pulse interval randomly jittering between 1.5-1.8 s (Nexstim Ltd., Helsinki, Finland); EEG was simultaneously recorded with a TMS-compatible 60-channel amplifier. Due to the low signal-to-noise ratio of TMS/EEG data, some patients were not included into subsequent group analysis. In order to additionally evaluate brain responsiveness to TMS in healthy elderly per se, 9 healthy young subjects were enrolled and recorded.

The effects of physiological and pathological aging on TMS-evoked potentials were investigated by comparing TMS/EEG data recorded from elderly and young healthy subjects and AD patients\textsuperscript{14,15}. The local and early cortical response to TMS was comparable between

elderly and young healthy subjects, while it was significantly reduced in AD patients. Significant differentiation among elderly healthy subjects, AD patients, and MCI patients was obtained by looking at the late EEG response to TMS cumulated over the whole brain. Results show that whole-brain SCD as well SCS are impaired in AD and MCI patients as compared to CTR at latencies between 45-100 ms. The TMS/EEG results were compared with MRI findings in\textsuperscript{16}.

Results obtained during this project suggest that TMS/EEG can be successfully exploited to accurately capture the modulation of cortical excitability and connectivity parameters during disease progression in order to early identify AD biomarkers and bring forward therapeutic interventions. In particular, we observed that the local and early SCD provided the best performance in discriminating controls, either young or elderly, and AD patients, compared to other indices developed for this purpose. This index can be computed without making specific \textit{a priori} assumptions and can be easily interpreted in terms of local cortical excitability in response to direct stimulation.

\textbf{Quantification of imaging data}

Neurodegenerative brain diseases mark the brain with morphological and functional signatures; detection of these signs may be useful to improve diagnosis, particularly in diseases for which there are few other diagnostic tools. For example, early and disproportionate hippocampal atrophy in people who have memory complaints points to a probable diagnosis of Alzheimer's disease. Brain volume loss, as measured with MRI structural imaging, is accepted as a sensitive and objective marker of disease progression in various pathologies such as multiple sclerosis (MS) and AD. Atrophy has been measured with a variety of methods, some of which are longitudinal (measuring atrophy rate, for example, percentage brain volume change, using two or more temporally separated scans per subject) and others being cross-sectional (measuring atrophy state, for example, brain volume normalized for head size, with a single scan per subject). In addition to structural imaging, functional imaging offers complementary information about the disease status. For example, FDG-PET (fluorodeoxyglucose) images show glucose metabolism in the brain, which is highly correlated with the loss of neurons due to AD and is hence useful for monitoring progression and for determining the severity of the disease. For early detection of AD it has been shown that changes in metabolism in the posterior cingulate cortex are a useful marker. MRI and FDG-PET both show secondary effects of the disease process. It is hypothesized that AD is caused by accumulation of amyloid plaques in the brain and because of this there has been an increased interest in in-vivo imaging of amyloid deposits. One of the most promising methods is PET imaging using a tracer that binds to amyloid plaques and the most frequently used tracer is PIB (Pittsburgh compound B).

PredictAD developed and studied several tools for quantifying imaging data: hippocampus segmentation, atrophy rate analysis, manifold learning, tensor-based morphometry, cortical thickness using MRI images and detection of pathological patterns using PET images. In


medial temporal lobe (MTL), the volume loss of hippocampi, entorhinal cortex and amygdala is a hallmark indicating towards AD. Current guidelines suggest that the volume loss is “evidenced on MRI with qualitative ratings using visual scoring”. Qualitative and subjective ratings may, however, lead to different results between interpreters and the diagnosis made by even a single interpreter may vary considerably when re-examining images. Therefore, there is a clear need for objective methods. Although automated tools are developed actively in many research groups, the development of robust, accurate and fast automatic methods has appeared to be a highly challenging problem and automatic methods are still very much lacking in clinical practice.

The methods developed are shortly summarized next. The validation and their comparison are presented after the summaries. Detailed documentation of results can be found either from the related journal publications.

**Segmentation of the hippocampus.** Atlas-based segmentation is a commonly used technique to segment image data. In atlas-based segmentation, an intensity template is registered non-rigidly to an unseen image and the resulting transformation is used to propagate tissue class or anatomical structure labels of the template into the space of the unseen image. The segmentation accuracy can be improved considerably by combining basic atlas-based segmentation with techniques from machine learning, e.g. classifier fusion. In this approach, several atlases from different subjects are registered to unseen data. The label that the majority of all warped labels predict for each voxel is used for the final segmentation of the unseen image. This multi-atlas segmentation has become very popular in the image analysis community. PredictAD developed two different methods based on multi-atlas segmentation concept. In the LEAP technology\(^{18}\), the atlases are propagated in waves in large databases allowing the segmentation of very heterogeneous data. In the other method\(^{19,20}\) two extensions to the standard multi-atlas segmentation were made: atlas-selection was performed, i.e., not all but the atlases similar to the patient image were used, and intensity distributions of the patient image were utilized in segmentation. In addition to the volumes of the hippocampus, the shape of the hippocampus was studied as a biomarker. Although some publications have reported good results, the performance of the shape in diagnostics was much worse than that of the volume in our studies.

**Atrophy rate measurement.** The consistent segmentation of several time points taken from longitudinal image data is a prerequisite for an accurate measurement of atrophy – an established biomarker for AD. In practice, atrophy rate measures the change of the brain volume per given time period, usually a year. In PredictAD, the methods developed for the

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segmentation of the hippocampus were extended for images from multiple time points. The resulting segmentations are more robust to spurious intensity differences between follow-up scans and therefore are more sensible to the measurement of atrophy.

**Manifold learning.** A novel machine-learning framework was developed in which a low-dimensional manifold representation of a set of brain images is learned from pair-wise image similarities. In contrast to classical approaches, \textit{no a priori} hypothesis about the biomarker itself is used in this learning step. In the learned anatomical manifold space, images that are similar according to a chosen similarity measure (based on the whole brain or a region of interest) are close and more different images are further apart. The developed framework also allows considering follow-up images of a given subject allowing incorporating additional information about a subject’s state into the manifold learning process.

**Tensor-based morphometry.** Voxel- and tensor-based morphometry (VBM and TBM) methods are widely applied in neurosciences for detecting differences in various populations. In TBM, a reference image is registered non-rigidly, i.e., deformed or warped, to images of a database, and the deformations obtained are analysed. As, for example, AD cases have typically larger brain ventricles than healthy controls, the deformations from the reference image to the AD cases are different than to the healthy controls in the ventricle area. If TBM is applied for diagnostics, not just for population based analysis as usually, the deformation field is computed also from the reference to the patient image and compared with the deformations to other database cases to which the diagnosis is known. In PredictAD, a novel more accurate approach for TBM was developed based on multiple reference images. In addition, we have developed a method that combines the VBM and TBM methods at voxel-level combining the strengths of the both approaches.

**Cortical thickness analysis.** Cortical thickness is a well-known method for evaluating the brain atrophy. The performance of cortical thickness in AD diagnostics has been studied in PredictAD. The focus has been in applying an existing tool than developing new methodology as such. A third-party measurement tool was used.

**Comparison of developed image analysis methods.** The role of structural brain magnetic resonance imaging (MRI) is becoming more emphasized in the early diagnostics of Alzheimer’s disease (AD). Although the image analysis methods presented above were

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24. J. Koikkalainen, J. Lötjönen, D. Rueckert, L. Thurfjell, G. Waldemar and H. Soininen. Voxel-level Combination of VBM and TBM Analyses, non-published manuscript.


validated using the ADNI cohort (www.loni.ucla.edu/adni), their direct comparison is impossible as different subsets of the ADNI cohort have been used. In this section, several methods for image analysis are compared using exactly the same ADNI cases. It is also shown that combining features extracted using different methods gives better results when classifying cases of different disease states. A detailed description of the study can be found from 27.

Altogether 477 subjects (dataset I: 152 healthy controls (HC), 112 stable mild cognitive impairment (S-MCI), 110 cases that progressed from MCI to AD (P-MCI), 103 AD) from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database for which Baseline, Month 12 and Month 24 MRI scans were available. Classification into the diagnostic groups was done with automatic MRI methods including hippocampal volume, tensor-based morphometry and manifold-based learning. Furthermore, an extended feature set (dataset II) including automatically derived cortical thickness measurements was applied to a subset of 364 baseline images. Selecting this sub-set was necessary because reliable cortical thickness values were not available for all cases. Tables 1 and 2 show results for the dataset I and dataset II, respectively.

When applied separately to baseline features, TBM provided the overall best results, closely followed by MBL. Combining all baseline methods improved the results in all study experiments. The results show how a combination of different MRI-based features can improve results based on only one measurement, resulting in a more stable classifier. The use of follow-up images further enhanced classification accuracy in all experiments. It shall, however, be noted that all features apart from hippocampal atrophy do not consider actual intra-subject development. The reported improvements with follow-up data can therefore be mainly attributed to the pathomorphologically more advanced differences between the different subject groups. Such a development can be expected to be of particular interest for the S-MCI vs. P-MCI comparison.

| ADNI (N=477) | BL M12 M24 HV HA12 HA24 MBLBL MBL12 MBL24 TBMBL TBM12 TBM24 |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| HC vs AD    | 0.89 0.90 0.91 0.82 0.80 0.86 0.84 0.86 0.88 0.88 0.89 0.89 |
| P-MCI vs S-MCI | 0.68 0.72 0.74 0.66 0.61 0.66 0.67 0.68 0.69 0.64 0.66 0.68 |
| HC vs P-MCI | 0.86 0.87 0.88 0.77 0.68 0.77 0.81 0.83 0.84 0.83 0.84 0.86 |

Table 2. Classification accuracies using linear discriminant analysis for the ADNI cohort (N=364). The following abbreviations are used: healthy controls (HC), Alzheimer’s disease (AD), progressive mild-cognitive impairment cases (P-MCI), stable mild-cognitive impairment cases (S-MCI), baseline (BL), 12 months follow-up data (M12), 24 months follow-up data (M24), hippocampus volume (HV), hippocampal atrophy (HA), manifold-based learning (MBL), tensor-based morphometry (TBM).

<table>
<thead>
<tr>
<th>ADNI (N=364)</th>
<th>ALL</th>
<th>CTH</th>
<th>HV</th>
<th>MBL</th>
<th>TBM</th>
<th>MBL+HV</th>
<th>MBL+TBM</th>
<th>MBL+CTH</th>
<th>HV+TBM</th>
<th>HV+CTH</th>
<th>TBM+CTH</th>
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<tbody>
<tr>
<td>HC vs AD</td>
<td>0.90</td>
<td>0.81</td>
<td>0.80</td>
<td>0.87</td>
<td>0.89</td>
<td>0.88</td>
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<td>0.87</td>
<td>0.86</td>
<td>0.90</td>
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<tr>
<td>P-MCI vs S-MCI</td>
<td>0.65</td>
<td>0.64</td>
<td>0.64</td>
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<td>0.63</td>
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<td>0.62</td>
<td>0.65</td>
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<tr>
<td>HC vs P-MCI</td>
<td>0.86</td>
<td>0.78</td>
<td>0.76</td>
<td>0.81</td>
<td>0.81</td>
<td>0.81</td>
<td>0.85</td>
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In conclusion, none of the five methods for MRI images was clearly superior compared to the other methods tested. The combination of multiple features improved the accuracy and predictive power in detecting early AD. Obtaining repeated follow-up scans does not necessarily provide significant improvement over the baseline measurement.

In addition to the ADNI cohort (N=776), the methods were applied to several other cohorts: Kuopio (N=106), GE Healthcare (N=72), Descripa (www.descripa.eu, N=352), AddNeuroMed (http://www.innomed-addneuromed.com, N=312) and AIBL (http://www.aibl.csiro.au, N=226). In other words, data from almost 2000 cases have been used in validation. The results with other cohorts have been corresponding to the results obtained with the ADNI cohort.

In addition to accuracy, the clinical usability has been an issue, e.g., the computation time of the hippocampus segmentation from MRI images can be performed only in two minutes making the exploitation in the clinical practise straightforward.

**PET image analysis.** The revised NIA-Alzheimer’s Association criteria\(^28\) divide the biomarkers into two major categories: 1) biomarkers of Aβ accumulation, which include tracer retention on amyloid PET imaging and low CSFAβ42, and 2) biomarkers of neuronal degeneration or injury which include FDG-PET and atrophy measured with structural MRI. In this section, we focus on biomarkers derived from amyloid PET alone and combined with MR-based markers of neuronal degeneration. As well as structural biomarkers from MRI, PredictAD has extracted functional biomarkers from both amyloid-PET and FDG-PET imaging.

**Amyloid-PET.** \(^{11}\)C-Pittsburgh Compound B (\(^{11}\)C-PIB) is a widely used compound for in vivo detection of Aβ amyloid plaques. However, the short half-life of the \(^{11}\)C tracer limits access to \(^{11}\)C-PIB to centres with an on-site cyclotron. Following \(^{11}\)C-PIB, a small number of other amyloid PET tracers have been developed, most of which are \(^{18}\)F labelled hence making them more suitable for distribution. One of these new \(^{18}\)F labelled tracers is \(^{18}\)F–flutemetamol and one of the cohorts studied in PredictAD is the \(^{18}\)F–flutemetamol phase II data. PredictAD used also PIB and MR data from the AIBL (Australian ADNI) trial.

\(^{28}\) G McKhann, D Knopman, H Chertkow et al., The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup. Alzheimer’s & Dementia. 7(3), 263-269, 2011.
One focus area for the Amyloid-PET work in PredictAD has been on the development of robust methods for extraction of PET-based biomarkers from amyloid PET images. Automated quantification typically requires spatial normalization of the data to standard space. However, spatial normalization of PET amyloid imaging data is challenging because of the different uptake patterns in negative (Aβ-) and positive (Aβ+) scans and there is a risk for systematic bias if a standard method is used. To overcome this problem, we developed a novel method based on the use of a so-called adaptive template registration method. Linear regression of voxel intensities on the standard uptake value ratio (SUVR) in a neocortical composite region for all scans gave an intercept image and a slope image. We devised a method where an adaptive template image spanning the range corresponding to the most Aβ- to the most Aβ+ image can be generated through a linear combination of these two images, and where the optimal template is selected as part of the registration process. We applied the method to the [18F]flutemetamol Phase II data. Validation was performed in several steps. The PET-based adaptive template registration method and SPM’s MR-based method was used to spatial normalize PET and MR scans. Resulting transformations were applied to co-registered gray matter probability maps and correlations of amounts of gray matter were computed. For comparison, FreeSurfer was used to segment each subject’s MRI scan and the parcellations were applied to the co-registered PET scans. Furthermore, to investigate whether the [18F]flutemetamol model could be generalized to [11C]PIB, we applied the method to AIBL [11C]PIB scans downloaded from ADNI (n=285). Results showed that the new PET-based method and SPM’s MR-based method had almost identical results in the cortical regions. Pearson’s correlation coefficient of amount of grey matter contained by atlas regions (Pearson’s r=0.996). The comparison of [18F]flutemetamol quantification results between the new PET-based method and FreeSurfer showed strong correlation for SUVR values (Pearson’s r=0.98). We obtained a similar correlation for the AIBL data (Pearson’s r=0.98).

Another focus area has been to study timing and combination of PET and MRI biomarkers. PIB and the other amyloid imaging agents have been evaluated as markers of early AD related changes. The general conclusion in the research community is that Aβ plaques form very early in the disease process, possible many years before the first clinical signs. What is less understood is why some individuals seem to stay cognitively intact for several years despite lots of amyloid deposits while others progress more rapidly. Because of this it is important to combine information from multiple sources. In summary, PIB and other PET amyloid ligands give a very early indication of AD related changes while other markers (e.g. MRI or FDG-PET) are needed to predict the time course of the disease. We have studied combination of biomarkers both in the [18F]flutemetamol cohort and in the AIBL cohort. Both studies show similar results. Healthy subjects with subjective memory complaints (SMC) showed a small non-significant increase in SUVR and decrease in hippocampus volume compared to healthy controls. A larger and significant increase in SUVR and decrease in hippocampus volume was observed in progressive MCI subjects when compared to stable MCI. When both measures were combined, most P-MCI subjects clustered in the area with high SUVR and low

31 L Thurfjell, J. Lötjönen, R. Lundqvist, J. Koikkalainen, V Villemagne, C. Rowe, Combination of biomarkers: amyloid imaging and structural MRI in dementia and MCI, accepted for presentation at the Human Amyloid Imaging conference, Miami Jan 2012.
hippocampus volumes indicating that these subjects were in different stages of neurodegeneration as compared to the S-MCI subjects.

**FDG-PET.** Numerous studies have shown that both MCI and AD are associated with significant reductions in the cerebral metabolic rate of glucose in brain regions preferentially affected by the disease. AD patients typically display reductions of greater magnitude and spatial extent than MCI patients. Reduced metabolic activity in AD patients can predict both their cognitive decline and histopathological diagnosis, and in MCI patients it can predict their conversion to AD. FDG-PET is mentioned in the revised AD diagnostic criteria as a potentially useful tool for early diagnosis and monitoring of disease progression.

In PredictAD, both region-based and voxel-based analyses were used in FDG-PET image analysis. In the region-based analysis, an 83-structure brain atlas was used to define the regions. First, corresponding MRI images were segmented using multi-atlas segmentation, the segmentations were transformed into PET images and SUVR values were defined. In the voxel-based approach, all images were transformed into a common coordinate system, in this case to the MNI space, similarities between all images were defined using the random forest classifier, the data were transformed into the manifold space converting intensity values to new features and finally these features were used in the random forest classifier.

The ADNI cohort was used in the FDG-PET analysis (N=287 for FDG-PET). The classification accuracy between healthy controls and AD cases was 82 % and between S-MCI and P-MCI groups 56 % when using the region-based analysis. The use of 12-month follow-up data improved the accuracies to 88 % and 63 %, respectively. The voxel-based approach produced the classification accuracy 88 % for the baseline data between healthy controls and AD cases. When MRI features were combined, the accuracy increased to 90 %, while region-based MRI features alone produced 87 % accuracy.

**Development of statistical framework for decision support**

The integration of heterogeneous biomarker data in a clinically useful way is a challenge as such. In addition, the biomarkers from blood, electrophysiology and imaging described above do not represent the whole spectrum of data used in diagnostics because demographic data and clinical data, such as, neuropsychological test results as well as interviews of patient and relatives affect the decision making. Forming a holistic, truthful and objective view of the state of the patient is not straightforward. This challenge of data integration was formulated in the second technical objective of PredictAD “to develop a strictly evidence-based statistical framework, via precise modeling of heterogeneous data, which allows objective AD diagnostics”.

Information sciences have developed a wealth of methods for processing and analyzing multi-dimensional heterogeneous data. Most publications reporting the detection of Alzheimer’s disease using multiple patient measurements are based on the use of classifiers. The classifiers define the most probable class label for a given patient using a decision model derived from


training data. The problem of most classifiers is that they provide only classification and not an estimate about the reliability of the result for each case separately. If a clinician knows that the accuracy of the classification is, e.g., 70%, as shown in the prediction of the converters to AD using the ADNI cohort, the result of the classification will not affect largely the decision. Therefore, if the overall classification accuracy has not been shown to be high, e.g., 95% or 99%, an estimate about the reliability of the classification should be provided to each individual separately.

In PredictAD, a disease state index (DSI) was developed based on comparing the patient measurements with measurements of other subjects (healthy and diseased) from large databases. DSI is a risk score, a value in the interval [0,1], indicating a patient’s disease state, i.e., the location or rank based on data, in relation to previously known control (healthy) and positive (disease) populations. It is intended to be used mainly with quantitative features, such as standardized questionnaire answers, laboratory analysis results, automatically quantified biomedical data, and outputs of personalized disease model simulations. It can be considered a supervised classifier, where patient data are compared to previously diagnosed data. In addition to DSI, a disease state fingerprint (DSF), a graphical counterpart of DSI, was developed. It visualises the relevance of each biomarker or measure in diagnosing the disease (the size of the box in DSF) and the fitness of the patient measurements against the study populations (the color of the box in DSF). The use of DSF keeps the computation of the index transparent and a clinician can find reasons and understand why the index is high or low. This is not the case with many existing classifiers, and they remain more or less black-boxes for the user. The basic principles of DSF and DSI are described in Panel 1.

The use of a continuous risk score like DSI, allows detecting the clear cases from the whole patient population. Although the accuracy for the whole population would be only around 70%, the accuracy for the patients with a high or low DSI value is much higher. Our preliminary results with the ADNI cohort show that the diagnostic decision could be made with the accuracy of 87% for 50% of MCI patients about 16 months earlier than using current diagnostic protocols. The value of 87% represents the maximum accuracy that was possible to obtain using the data from the moment when the diagnosis was made for these patients using current diagnostic protocols, i.e., data 16 months later than used in our test to select those 50% of cases. As the ADNI cohort provides only clinical diagnosis, not based on pathological confirmations, the real diagnostic accuracy cannot be defined. A recent study showed 85% concordance between clinical and neuropathologic diagnosis. In other words, if a method is validated against clinical diagnosis, the accuracies higher than 85% do not necessarily reflect the real diagnosis but only method’s ability to mimic current clinical decision making or the higher values are obtained only by chance.

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Panel 1. Disease State Fingerprint (DSF) and Disease State Index (DSI). The red and blue distributions on the right show the probability density distributions of the hippocampus volume in AD patients and healthy controls, respectively, computed from a database of several hundreds of cases. The more separated the peaks are the better and more relevant the biomarker is in diagnostics. The relevance of the biomarker is indicated by the size of the box in DSF (on the left). The black vertical line on the right shows the value measured from the patient studied, i.e., the total volume of the hippocampus in the patient is about 2900 mm$^3$. When compared with the distributions, it can be seen that the probability of belonging to the AD population is much higher than to the healthy control population. This is indicated by the color of the box and the DSI value (deep red and DSI values close to one indicate high probability of AD and blue shades and DSI values close to zero indicate high probability of healthy). In addition to single biomarkers, DSF contains a hierarchical representation showing the relevance and fitness for combined measures, such as, MRI imaging and CSF biomarkers. The total DSI value 0.56 indicates that data do not support strongly making the diagnosis for this patient although the probability of belonging to the AD population is higher: MRI shows indications of AD but CSF biomarkers and ADAS neuropsychological test are pointing more towards healthy population.

The concepts of personalized healthcare can be easily incorporated into the DSI framework. Different methods for building personalized models were studied in\textsuperscript{38}. Decent improvements were observed thanks to personalization: a maximum improvement of 6% units in the classification accuracy was obtained with MRI image-based features.

In addition to diagnostics, the follow-up of disease progression or treatment efficacy is possible as the DSI value is a real number. In\textsuperscript{33}, it was shown that DSI maps healthy controls, stable MCIs, progressive MCIs and AD cases more or less linearly on the scale $[0,1]$. In standard classifiers, the mapping was more biased to the both ends of the scale. PredictAD studied the behavior of DSI with longitudinal data. It showed clearly that the DSI changes much more slowly in stable than in progressive MCI cases.

Development of decision support software tool

One of the key objectives of PredictAD (first technical objective) was “to develop an efficient and reliable software solution that a physician can use to assess the risk, to diagnose and to monitor the progress of AD in real clinical conditions using heterogeneous patient data”. The tool was developed in a close collaboration with clinicians, starting from application

requirements and modifying the tool based on several meetings with clinicians. PredictAD
made also a survey among the members of the European Alzheimer’s Disease Consortium
(EADC\textsuperscript{39}). The answers were obtained from 33 centres. The study showed that 85 \% of
experts “would like to use a tool that combines all the available information (clinical, imaging
and other biomarker data) and provides some kind of risk score for the diagnosis”. The need
for such clinically useful tool is clear.

The PredictAD software tool was developed in the Microsoft Windows environment (Panel
2). The database and semantics related to the medical terms have been kept separate from the
software tool. This means that the tool is generic and can be used also in other diseases by
changing the database and the semantics. The tool serves as a basis for the development for
example in the TBIcare EU-project (\texttt{www.tbicare.eu}). The tool has been used to study data
also from various public databases. The results using diabetes, cardiac diseases and hepatitis
data were showing a good performance\textsuperscript{35}.

The tool has been validated in several ways (publication of these results is in progress).

Three clinicians (two from Copenhagen, Denmark and one from Kuopio, Finland) predicted
the conversion from the baseline MCI data of 140 cases each\textsuperscript{40}. The clinicians used first the
tool and about one week later the patient measurements the task was repeated using a
structured paper report. In both cases, the clinicians predicted the conversion and the
confidence about the decision with six categories: clear, probable and subtle indication of AD
or non-AD. It is worth noting that the clinicians did not see the patients in person. When using
all available data (neuropsychology, MRI and CSF), the prediction accuracy using the tool
was 70 \% while it was 63 \% when the information was given on paper. If the results for the
clear cases are studied, they covered 33 \% of cases and the prediction accuracy was 86 \%
when the tool was used. The corresponding numbers were 26 \% and 82 \% when using the
structured paper reports.

In another study, the use of the PredictAD tool was compared with the current diagnostic
guidelines for prodromal Alzheimer’s disease. Altogether 391 MCI subjects from ADNI were
studied. The prediction accuracy reached by the PredictAD tool was 71 \% while the best
accuracy 66 \% for the current guidelines was obtained with neuropsychological tests and CSF
biomarkers.

\textsuperscript{39} http://www.eadc.info/sito/pagine/home.php
\textsuperscript{40} A. Simonsen, J. Mattila, A. Hejl, K.S. Frederiksen, S-K. Herukka, M. Hallikainen, M. van Gils, J. Lötjönen,
H. Soininen, G. Waldemar, for the Alzheimer’s Disease Neurodegenerative Initiative. Application of the
PredictAD software tool to patients with mild cognitive impairment. \textit{Dementia and Geriatric Cognitive
Disorders} 34: 344-450, 2012.
Panel 2. Screenshot from the PredictAD tool. Top-Left: Patient Details-window contains basic information about the patient. Bottom-Left: Timeline of Entries-window shows an overview of all patient measurement in function of time. It shows also if the measured value points towards a disease or healthy state. The window is interactive and pressing any of the measurements provides details in the Entry Preview-window. Top-Centre: Entry-Preview-window provides details of different patient measurements. The ‘Analyze’-button directs the user to detailed analysis of data, e.g., image segmentation. Top-Right: Disease State Fingerprint-window shows the DSF of the patient. DSF is interactive and the user can study freely different hierarchical levels of the tree. Detailed analysis of DSF can be entered by the ‘Explore’-button. Bottom-Right: Disease State Index-window shows the DSI of the patient. This window is linked to the DSF window. As user selects any of the items in the DSF, the details of the item are shown, i.e., probability density distributions with the patient measurement overlaid, number of cases used for computing the distributions and contributions of different measures at the lower hierarchical levels to the selected item.

Cost-efficiency analysis
The second scientific objective of PredictAD concerns cost-effectiveness in diagnostics: “to improve the cost-effectiveness of AD diagnostics by optimizing diagnostic protocols”. As PredictAD was a research project using retrospective data, the cost-effectiveness was based on simulation models. The major work on this topic was done by analyzing the costs in five European countries. The cost-efficiency of diagnostic tests for AD was analysed using two different approaches; a discrete state approach and a continuous disease severity index. We applied them to two scenarios: screening of an entire population, and more advanced diagnosis for MCI subjects. The continuous state approach addresses several limitations that exist with the discrete state approach and thus provides a good basis for future cost-effectiveness studies. The models proved to be robust against parameter variations. The most important factor in determining cost-effectiveness outcome is related to country-specific cost structure definitions. In the current study we used the ADNI data as primary source for many
model parameter estimations and used only drug administration as intervention. Future studies give us a chance to refine the model and make it more generally valid.

In addition to the results reported in the simulation study, the PredictAD tool includes properties that make the cost-efficiency analysis possible on the level of a single patient. The tool shows the performance of different diagnostic tests and the improvements in diagnostic accuracy and increased costs if a certain test would be performed.
Potential impact & Dissemination & Exploitation

Potential Impact

The challenge of dementia is enormous both from human and economic point of views. There are 36 million people living with dementia worldwide in 2010 but the number is expected to increase to 115 million by 2050. In addition, it is not a disease of the patient only but of the whole family. The number of persons suffering from the disease is therefore much higher. The worldwide costs are also staggering: 604 billion USD annually. These costs combined with rapidly growing prevalence explain why dementia has been identified as a health priority both in Europe and in the USA.

Early diagnostics is essential for efficient treatments, either pharmacological or psychosocial care. The role of early diagnostics becomes highly important especially in the future when efficient treatments affecting the disease progression become available. At the moment, dementias are clearly the most studied neurological disease in the pharmaceutical industry: more than 100 drug candidates are at phase I-III trials. The current consensus is that prevention should be started early to be efficient, emphasizing the importance of early diagnosis. In Europe, the diagnosis of Alzheimer’s disease is made about 20 months after the appearance of memory problems but it is known to progress several years or even decades before the memory problems occur. The challenge of early diagnostics is still far from being solved.

Although the numbers in dementia are alarming, relatively small improvements can have a high impact. Delaying both the onset and progression only by one year would reduce the number of AD cases by 10%. We believe that the challenge of dementia will be solved gradually with consecutive innovations. PredictAD has taken in several fronts steps towards more accurate and efficient diagnostics.

Several studies performed in PredictAD show that the tools developed indeed allow earlier diagnosis. The preliminary results of PredictAD show that the diagnosis could be done with high accuracy for 50% of the cases about 16 months earlier than currently. One of the innovations in PredictAD is the stratification of populations, i.e., patients can be categorized to clear and less-clear cases based on the continuous disease state index. It is worth noting that the preliminary estimate of making diagnosis earlier includes data only from clinical tests, MRI and CSF biomarkers. If PIB-PET data and our novel blood or TMS/EEG based markers were utilized, the numbers could be clearly better.

Although PredictAD has been developing a holistic solution to the challenge of diagnostics, the project made several innovations that have future also independently. Several image analysis tools were developed that can be utilized as such in improving and automating clinical work-flows. The findings in metabolomics and proteomics have attracted very much interest and provide potentially solutions for very early diagnostics. The proof-of-concept was accomplished for a novel technology TMS/EEG with promising results. In addition, a unique framework for decision support was developed. The PredictAD team is certain that these innovations separately or together will impact the challenge of Alzheimer’s disease.

In addition to diagnostics, the use of the disease state index makes possible also the follow-up of disease progression and treatment efficacy. Both stratification of populations and follow-up

of treatment efficacy are interesting properties when new treatments are developed for Alzheimer’s disease. Another component affecting potentially to the development of treatments is the findings made from blood samples. For example, the elucidation of early metabolic pathways associated with progression to Alzheimer’s disease may also help identifying new therapeutic avenues.

PredictAD has identified several lead users for the innovations: 1) clinicians responsible for patients, 2) industry commercialising the results, 3) administrative officers and politicians responsible for the economy, and 4) citizens.

Clinicians are currently facing an enormous challenge in diagnostics of dementia. Earlier diagnosis enables doctors to provide medical care at an earlier stage, at a time when clinical diagnosis using only signs and symptoms of disease is challenging. The PredictAD survey and several discussions with various clinicians have shown a great need for objective tools for diagnostics. A high number of clinicians aware of PredictAD’s achievements have been enthusiastic in starting to exploit the results of PredictAD.

An obvious way to measure the impact to industry is to consider interests for licensing the innovations. PredictAD has already closed licensing deals with industry and there are deals under negotiations. The achievements in science, novel methods and biomarkers, help the field to progress in general and stimulate industry for new products and innovations. PredictAD has produced 34 peer reviewed publications by 1/2012 increasing the scientific knowledge.

Due to its enormous costs dementia is of great interest to administrative and political decision makers. PredictAD demonstrated that the decision support tool developed has tendency to improve the diagnostic accuracy and clinicians’ confidence about their decisions, both factors leading to earlier diagnosis. It is a well-known fact that diseases in general should be treated at early phase. This is especially true in dementias where it has been shown that very little can be done if treatments are started at late phase. Early diagnosis has an extremely important role in the early interference. In addition to economic challenges, systematic and objective approaches for diagnostics improve the safety and overall the quality of healthcare. We are living in a modern information technology society but quite often the systematic exploitation of huge data reserves in healthcare is not modern. PredictAD provides a straightforward but modern approach for shifting the diagnostic decision making into the new level.

Finally, PredictAD will affect the citizen in three aspects. First, having diagnosis earlier and hence also treatments earlier during the disease process will mean reduced suffering for the individual and their relatives. Second, it reduces the burden of the citizen as a taxpayer. The most expensive period of the disease is at the late phase when patients are under institutional care, paid by taxpayers. Third, systematic and objective approaches bring equality between citizens. Unfortunately, still now the quality of healthcare depends on where you are living and if the neighbouring hospital has the best experts available. PredictAD is removing this inequality.

Reliable quantification of the impact in euros is impossible in research projects where the central results are typically obtained when the projects are ending. Especially in medical sciences, various regulations delay and limit the piloting and testing of innovations in real environments; the burden of proof for validations is high with medical devices. Estimating even potential impact is especially difficult in dementia as diagnostics and treatments are
under continuous evolution. When efficient treatments become available, the whole picture changes dramatically. However, even now early started treatments can delay hospitalisation up to one year.

In overall, we can conclude that PredictAD has met its objectives and taken steps towards more objective and efficient diagnostics in Alzheimer’s disease in several fronts. As PredictAD is dealing with medical solutions including high reliability and safety standards, some innovations require more validations in the future before entering the market. PredictAD is, however, going towards exploitation of these results in the clinical practise. Another strength of the methods developed, e.g., image analysis algorithms and the PredictAD tool, is that they are generic and can be applied in other application domains as well. This opens new possibilities for the exploitation.

**Dissemination and Exploitation**

The project produced 25 peer reviewed journal and 9 peer conference papers, numerous other papers and four patent applications by 1/2012. The journal papers include publications in high-quality journals, such as, NeuroImage, Journal of Neuroscience, Journal of Alzheimer’s Disease, Translational Psychiatry, PLoS One, Medical Image Analysis and IEEE Transactions on Medical Imaging. Several manuscripts are still either submitted or under preparation.

The project has been visible in about 150 events and in public media via five press-releases and other contacts. The audience in the events include scientists (technology & medicine), business people (a high number of companies), politicians (up to royal persons), patient organisations and general public. PredictAD has been several times in TV, radio and newspapers. The PredictAD team receives continuously invitations for speaking about the innovations made in the project.

The project website (www.predictad.eu) has been updated regularly. In addition, dissemination material, including the project logo, templates for presentations and newsletters have been prepared.

The exploitation of the project results was started during the project. Some tools developed have been already licensed to companies and negotiations are on-going for multiple other licensing deals. There are tools which are mature for commercialisation in a short term period, such as, tools for image processing but the commercialization pathway is longer for other results. The blood based markers require further validations in other cohorts. As a simple and cheap blood-based test is of great interest, efforts are needed to develop simple kits for detecting the defined molecular signatures. This area contains huge potential. The results produced were very positive for TMS/EEG but it needs also further validations in larger cohorts to confirm the findings. The PredictAD decision support tool is a unique approach and requires piloting in real clinical conditions as a part of the commercialisation path. The commercialisation actions have already been started on several fronts.

The project team considers the project successful and believes that several fruits of the project will end up to the markets in a form or another.
Contact information

The project web-site:

www.predictad.eu

Contact information of the co-ordinator:

Jyrki Lötjönen, Scientific co-ordinator
VTT Technical Research Centre of Finland
P.O.Box 1300
33101 Tampere, Finland
email. jyrki.lotjonen@vtt.fi
web: www.vtt.fi