Welcome

I am delighted to welcome our Dementia in Europe magazine readers to this special supplement about the research project “From Patient Data to Clinical Diagnosis in Neurodegenerative Diseases” – PredictND.

Alzheimer Europe (AE) is a partner in the dissemination and outreach activities of this four-year project (2014–2018), co-funded under the European Seventh Framework Programme (FP7).

Neurodegenerative diseases (NDs), such as Alzheimer’s and other dementias, are hard to diagnose and many of them are known to progress years or even decades before the symptoms appear. PredictND, coordinated by VTT Technical Research Centre of Finland, aims to develop and validate new, more efficient procedures for the earlier diagnosis and for detecting individuals at high risk. If successful, this would be a major step forward in the challenge posed by dementia.

Since the kick-off meeting at the Haltia Nature Centre in Espoo, Finland in March 2014, there has been great progress made in all areas of the project. The baseline data collection, consisting of around 800 suspected neurodegenerative disease cases from four memory clinics in Kuopio (Finland), Copenhagen (Denmark), Amsterdam (Netherlands) and Perugia (Italy), was completed in mid-2016. The PredictND project will continue until January 2018 and will collect follow-up data with these same volunteers. Project partners report very promising preliminary findings regarding the efficacy of their low-cost approach to detection and already have an impressive number of scientific publications in peer-reviewed journals, with many more in the pipeline.

The high standard of the work happening in PredictND was reflected in a recent interim review meeting with the European Commission and review board, at which reviewers rated PredictND’s progress as “excellent”. The strong project leadership, together with great cooperation between the participating centres and researchers are to thank for this progress and I am personally excited to be involved in such a promising project.

I am also pleased that AE was able to provide the project with one of the most valuable resources it has to offer – the input of the European Working Group of People with Dementia (EWGPWD). Members of the working group were involved in a consultation in December 2015, during which they were able to give constructive feedback on the usability of the PredictND Citizen Portal, which will contain information about dementia, as well as memory tests and games designed to detect possible signs of neurodegenerative diseases before the appearance of symptoms. Involving people with dementia in projects like this is so important, to help researchers get it right. I am proud that we were able to support the project in such a practical manner from the outset.

This special supplement includes a general overview of the PredictND project, along with interviews with each of the project leaders, as well as some information about each of the project’s work packages and their remits. We have also included a report about the participation of PredictND at the Alzheimer’s Association International Conference (AAIC) in both 2016 and 2017, a report on the project’s interim review result this year, and a list of scientific publications in peer-reviewed journals.

I would like to personally thank Jyrki Lötjönen, Mark van Gils, Juha Pärkkä, Wiesje van der Flier and Steen Gregers Hasselbalch for their contributions and I hope you will enjoy the resulting supplement.

Finally, if you are reading this at our 27th Alzheimer Europe Conference (#27AEC) in Berlin, I invite you to attend Parallel Session P20, an interactive and educational session organised by the PredictND Consortium, on Wednesday 4 October from 8.30 to 10.00 am.

See you there!

Jean Georges
Executive Director, Alzheimer Europe
About PredictND (2014–2018)

We talk to the project leaders about the project, its aims, and how things are progressing, as the project approaches its final year

PredictND (Patient Data to Clinical Diagnosis in Neurodegenerative Diseases) is a four-year, EUR 4.2 million project that began in January 2014 and will come to a close in 2018. The primary aim of PredictND is to develop tools and means for earlier, evidence-based and data-driven diagnosis of a range of neurodegenerative diseases (NDs) such as Alzheimer’s disease, vascular dementia and fronto-temporal dementia. This novel approach is being tested on 800 patients in four hospitals in Finland, Denmark, the Netherlands and Italy. The PredictND project is coordinated by VTT Technical Research Centre of Finland.

Mark van Gils, PredictND Scientific Coordinator (VTT, Finland)

Q: What are the main issues the PredictND project aims to address?

Neurodegenerative diseases, such as Alzheimer’s disease (AD) and other forms of dementia, are difficult to diagnose. Moreover, many of them have progressed years, or even decades, before symptoms appear. When the first memory problems manifest themselves, there is no single test, which immediately gives conclusive information to make the correct diagnosis. Instead, several tests need to be done to collect possible indicators of the actual cause and rule out other possibilities. This causes a delay in diagnosis. Being able to provide an efficient diagnosis in an earlier phase would mean tremendous cost-saving and would increase the quality of life of patients and their close family members. Over the past years, a vast amount of data from patients with memory problems, combined with knowledge about outcomes and diagnoses, has been collected by healthcare providers. These data can be used for improved diagnostics.

Our main scientific aim is the development of a clinical protocol to enable earlier and objective differential diagnostics of neurodegenerative diseases, using the principles of data-driven evidence-based medicine. The ultimate objective in the management of neurodegenerative diseases is to identify patients that could benefit from treatment at a very early phase, preferably before symptoms occur. Although sensitive measurements exist (e.g. via imaging methods), these are generally expensive. There is a clear need for cost-friendly tests which can be used for initial diagnostic testing on a wide scale to detect persons at high risk, who could benefit from more extensive testing.

Our second aim is thus to develop affordable tests and protocols for early detection, to enable cost-efficient diagnostics.

Diagnosis is typically done via consensus of several experts who have thoroughly examined the patient background and the collected data and interpret information based on guidelines and experience. Objective data obtained from previous patients can help in making decisions, when utilised in an intuitive and easy-to-use form.
A more technical objective is thus to develop a decision support software application for improved diagnostics in clinical settings.

Use of computerised approaches in this area is still rare. One of the main challenges is that the methods currently used need reliable integration of very diverse measurements – measurements in clinical settings, but also, more measurements during daily living. In order to address this, we come to our final technical objective:

To develop an ICT ecosystem for early and objective diagnostics of neurodegenerative diseases.

Q: How is the PredictND consortium uniquely composed to address this issue?

The consortium consists of a carefully selected multi-disciplinary team of nine partners. Clinical relevance, advanced data analysis, exploitation and uptake of results, involvement of citizens, advanced data analysis and software development are the cornerstones of the project. These components are all represented by high-profile partners. Since proving the clinical relevance on a European-wide scale is essential, we have no less than four clinical partners on board, all of whom have a very strong international reputation in the field of dementia. These are:

- University of Eastern Finland (Finland)
- Rigshospitalet/Region Hovedstaden (Denmark)
- VUmc (The Netherlands)
- University of Perugia (Italy)

The methods and solutions themselves are developed by technological research and development partners; VTT Technical Research Centre of Finland Ltd. (Finland, co-ordinator) and Imperial College London (UK), together with industry partners Combinotics Ltd. (Finland) and GE Healthcare Ltd. (UK) who also have a strong interest in the exploitation of developed methods. Finally, the partnership with Alzheimer Europe (Luxembourg) provides the all-important link with patients and wider society, as well as policy makers.

All partners have long-standing experience in developing approaches (clinical, or ICT-based) for improving diagnostics in Alzheimer’s and other dementias. The EU project PredictAD (2008–2011) laid the first foundations of the work in PredictND, and part of the consortium was already formed at this time. Furthermore, PredictND partners are actively co-operating in, and linking to, other actions, such as IMI EMIF-AD and VPH-DARE@IT in order to create as much synergy as possible.

Juha Pärkkä, PredictND Project Manager (VTT, Finland)

Q: What are the concrete objectives and actions being undertaken?

The main technical objective of the project is to create a computer application that can present the collected data to the clinician in a useful manner to support clinical decision making. The main clinical objective is to evaluate this software tool in a clinical environment by running a prospective study with about 800 memory clinic patients.

When a patient has memory problems, he/she normally visits a memory clinic. As part of the first visit to a memory clinic, the project collected data from the patients. This so-called “baseline data collection” included clinical and neuropsychological tests, walking tests, MRI images, blood and CSF tests. After

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Mark van Gils
performing clinical diagnosis using the procedures of each clinic, the software tool was used and we evaluated whether it would help in the interpretation. To confirm the diagnosis or see possible progression, the patients were followed up after either 12 or 18 months. The PredictND project completed the baseline data collection in summer 2016 and the project is now collecting the follow-up data, analysing the collected data and focusing on dissemination and exploitation of the results.

Q: Has the project met or even exceeded your expectations during its lifetime so far?

The project consortium consists of people who are professionals in their roles and this creates a fruitful atmosphere for a research project. The PredictND consortium members work very well together and the collaboration is warm and inspiring.

Progress with the project so far has been excellent, which has also been recognised by the EC technical review board in the yearly reviews. The project is creating a valuable scientific contribution to support dementia care, but also commercialising the results actively to bring the results into clinical practice as soon as possible.

The project and the consortium were formed by Jyrki Löjtjönen at the VTT Technical Research Centre of Finland Ltd in 2013. In 2015, a spin-off company called Combinostics was formed from VTT to commercialise the PredictND technologies with Jyrki Löjtjönen as the Chief Scientific Officer. Combinostics joined the PredictND consortium and the work towards better decision support in dementia diagnostics in PredictND project continues together. The exploitation of the PredictND results by Combinostics and other partners has clearly exceeded my expectations.

Q: What impact do you hope PredictND will have after the project life ends next year?

There is clearly a gap between the great promise surrounding machine learning and clinical practice. One key goal of PredictND is to find ways to build a bridge across this gap, by wrapping machine learning techniques in a clinically useful and easy-to-understand form. After all, it is the clinician who carries the responsibility of her/his decisions, and “black box” solutions are therefore not appreciated.

The difficulties related to black box solutions are also discussed among EU officers, making the laws in this new area. We hope, in PredictND, that we have been able to close the gap and find ways to make modern technologies more useful and acceptable to clinicians.

Q: What are the plans regarding exploitation of the results?

One key component of EU projects is impact; our society, including citizens as tax payers but also as possible patients, professional, companies and even countries, should benefit from the results. Healthcare projects are, however, in a special position because they are acting on the sensitive and regulated area affecting individuals’ health.

The main technical objective of the project is to create a computer application that can present the collected data to the clinician in a useful manner to support clinical decision making. The main clinical objective is to evaluate this software tool in a clinical environment.

Juha Pärkkä

Jyrki Löjtjönen, PredictND Scientific Director (Combinostics, Finland)

Q: What are the plans regarding exploitation of the results?
Therefore, it is often challenging to show exploitation and further the tangible impact during the project. I remember that the reviewers of the previous PredictAD project were asking, at the beginning of 2012, when real patients will benefit from the project results. We answered that, probably in five years for such novel technology, which left the reviewers a bit disappointed. Now, however, after those five years, we can see that at least two companies have made the technologies developed in PredictAD available to the public. Due to the solid basis built in the previous projects, we don’t expect such a long time-span in PredictND.

Actually, some of the tools and methods developed in PredictND have recently become available, to help with earlier diagnosis in memory diseases. Both commercial partners of the project, GE Healthcare and Combinostics, are actively seeking ways to use the project outcomes.

Wiesje van der Flier (VUmc Alzheimer Center, Netherlands) and Steen Gregers Hasselbalch (Rigshospitalet – Region Hovedstaden, Denmark)

Q: What are the current challenges in diagnostics of cognitive disorders?

The major challenge in cognitive disorders is how to provide an accurate and timely diagnosis. Diagnosis of dementia is difficult. Various disciplines need to collaborate to arrive at a diagnosis and treatment plan. Among the most important challenges for the clinician is how to weigh and combine the results of the different diagnostic tests. In some cases, all tests are either clearly positive, or clearly negative. In these situations, diagnosis is not that difficult. More often however, results are conflicting, or borderline (ab)normal. There is not one test that, on its own, has perfect sensitivity and specificity. In addition, some tests, such as an MRI, contain more information than visible to the human eye. A computer tool can help to extract as much information from all available data as possible, thereby supporting human decision making.

From the patient’s point of view, one of the main issues is to reduce the delay between initial symptoms and the diagnosis. Improved diagnostic methods can help to achieve this.

Q: What does the future of diagnostics look like and what is the role of ICT technology?

Diagnostic tests will improve over time, and this implies that an increasing amount of information needs to be weighed, combined and integrated to come to a meaningful conclusion. ICT and computer tools can support the clinician to come to a balanced conclusion. Ultimately, the clinician with the human eye will always be the expert in diagnosis of dementia. Nonetheless, it will be helpful to have a computer tool to carefully arrange and visualise all the available data, to make sure that the clinician takes into account all the available information. PredictND might be just such a tool!

Looking to the future, we hope there will be treatments for Alzheimer’s and other types of dementia. These treatments will target specific aspects of the disease, such as amyloid or tau, but might also target other aspects, including vascular disease, neuronal repair systems or immune processes. In this future world, a diagnosis of dementia will have to be just as specific – we like to call this molecular diagnosis. ICT may have an increasingly large role here, where diagnosis of dementia goes beyond simply deciding on Alzheimer’s – “yes” or “no”, but might really provide support in defining the presence and extent of different types of pathologies.

“There is clearly a gap between the great promise surrounding machine learning and clinical practice. One key goal of PredictND is to find ways to build a bridge across this gap.”

Jyrki Lötjönen
The PredictND clinical decision support tool

The PredictND clinical decision support tool is based on comparing the data of the patient being studied to data from a high number of previously-diagnosed subjects. The tool measures quantitatively how similar the patient is to subjects previously diagnosed with Alzheimer’s disease (AD), frontotemporal lobar degeneration (FTLD), vascular dementia and Lewy-body dementia, as well as to cognitively normal subjects. The comparison is based on the disease-state fingerprint technology, which visualises, graphically, why the patient is more similar to AD and not FTLD, for instance. In other words, the tool aims to make the underlying machine-learning techniques as transparent and understandable to the user as possible, instead of being a black box.

Another strength of the PredictND tool is that it enables the user to view data from multiple sources, such as from clinical and neuropsychological tests, imaging studies and cerebrospinal fluid biomarkers. This reflects the clinical reality, where doctors need to interpret complex data when making differential diagnoses. The PredictND tool also contains methods for characterising imaging data, using a rich set of imaging biomarkers. Today, medical images are interpreted still largely by visual inspection in clinical practice, but quantitative imaging biomarkers are clearly coming to support this decision-making process.

Main image: A screenshot from the main view of the PredictND tool: The left panel shows a summary of different data acquired from a patient. The middle panel gives more detailed information about a specific data point selected on the left panel, in this case magnetic resonance images (MRI) of the patient. The right panel shows the similarities between all this patient data and a large number of previously-diagnosed subjects, using the disease-state fingerprint technology. The tool shows that this particular patient’s data shares the most similarities with others diagnosed with Alzheimer’s disease, and presents reasons for this. The user can interactively explore the data and view how different patient data compares with data from different diagnostic groups. The follow-up indicated that this particular patient does indeed have Alzheimer’s disease.

Above: Screenshot from the image quantification tool visualising the grey matter concentration in different regions of the brain.
The PredictND work packages and their objectives

**WP1: Project Management**

**WP Leader:** VTT Technical Research Centre of Finland Ltd., FI

All the work packages are supported by the project management, to make sure that expected project outcomes are delivered timely.

**WP1 Objectives:**

- Day-to-day project management and operating rigour of the consortium
- Guarantee smooth collaboration among project participants
- Provide effective internal and external communication

**WP2: Clinical data acquisition and management**

**WP Leader:** University of Eastern Finland, FI

One challenge in clinical practice is how to differentiate Alzheimer’s disease from other dementia diseases. A second challenge is whether it is possible to predict dementia in its very early stages when patients present with subjective complaints only. Third, there is the challenge of different availability of diagnostic tools in different settings (e.g. GP, specialised memory clinic). To address these challenges, this work package focuses on acquiring and management of:

1. Retrospective data from cohorts of patients along the spectrum of cognitive decline from subjective memory complaints to dementia, including also other dementia diseases than Alzheimer’s
2. Prospective data from mixed patient cohorts in the memory clinic, to facilitate further development, refinement and validation of the software tool. In the prospective data acquisition, both standard clinical data and non-standard low-cost test data are acquired

**WP2 Objectives:**

- Design a plan for data acquisition (prospective) and data management (prospective and retrospective)
- Acquire prospective data (standard and low-cost) in mixed memory clinic population
- Manage prospective and retrospective data and provide it for WP3–WP5
- Oversee the ethical and legal aspects of the project

**WP3: Biomarker discovery tools**

**WP Leader:** Imperial College London, UK

This work-package focuses on biomarker discovery tools, i.e. tools for extracting useful measures (biomarkers) from imaging, low-cost test data and blood samples. In earlier work we developed several tools for quantifying imaging data. In PredictND, these tools are modified for clinical use and also extended to the analysis of computerised tomography images. In addition, quantification of low-cost and blood sample data is performed.

**WP3 Objectives:**

- Develop optimised versions of software tools for imaging biomarker extraction to enable their routine use in clinical practice
- Develop accelerated versions of earlier developed imaging biomarker software tools to perform near-real time image analysis
- Further develop the software tools for the analysis of CT images
- Quantify low-cost measurement data.
- Extract metabolomics biomarkers from blood samples using earlier developed methodologies developed in the PredictAD project
**WP4: Deployment in clinical practice**

**WP Leader:** VTT Technical Research Centre of Finland Ltd., FI

The software tool was originally developed as a platform for analysing locally available, predefined patient datasets. Integration into clinical environments was not yet a priority at that moment. This work package is responsible for translating the software package into a deployable version that addresses the issues that hinder the tool’s practicality in clinical settings. It also ensures that the tools can be deployed at various memory clinics with minimal overhead from configuration and installation tasks.

**WP4 Objectives:**

- Plan and carry out risk analysis to prepare the way for successful implementation of the software solution
- Develop new features that allow the tool to reach its potential in clinical use
- Deploy and integrate improvements that simplify installation of the software tool and allow it to communicate with selected hospital information systems
- Develop support tools communicating with the main PredictND tool to improve the user experience in clinical tasks where access to a desktop workstation or laptop PC is impractical

**WP5: Clinical validation**

**WP Leader:** Rigshospitalet/Region Hovedstaden, DK

The PredictND software tool is refined on the basis of prospective and retrospective data from cohorts provided in WP2 and developed in WP3 and WP4. This work package focuses on validations studies using the refined tool, as it is developed in the first half of the project. The major focus is on validation studies in prospective data from mixed patient cohorts in the memory clinic setting as well as using low-cost measures suitable for the general practitioner setting. In addition, various studies with retrospective data are performed.

**WP5 Objectives**

- Design the validation plan and strategy
- Validate the software tool in prospective mixed memory clinic populations and clinical setting
- Validate the software tool in different studies using retrospective data
- Evaluate the usability of the tool

**WP6: Requirement and Business, Development and Dissemination**

**WP Leader:** Combinostics Ltd., FI

The focus of this work-package is on outreach. First, this work-package defines the requirements of the ICT ecosystem from the functional point of view taking into account clinical needs, market needs and ethical and legal needs. Second, exploitation strategies are considered. Third, strategies for dissemination are planned and its implementation co-ordinated.

**WP6 Objectives**

- Define clinical needs
- Develop user requirements for the ICT ecosystem
- Develop business cases and exploitation strategy
- Actively disseminate the knowledge generated in the project within and beyond the consortium
- Jointly plan high-level scientific activities
PredictND showcases its findings at key scientific conference in 2016 and 2017

The PredictND team is delighted to have been actively involved in the Alzheimer's Association International Conference in both 2016 and 2017

The Alzheimer's Association International Conference (AAIC) is the world's largest forum for the dementia research community, bringing together global research leaders, next generation investigators, clinicians and the care research community to share discoveries in basic and translational research, with the aim of supporting the search for methods of prevention and treatment, as well as improvements in diagnosis for Alzheimer's disease and other dementias.

The PredictND team was delighted to have been actively involved in such an important global event as AAIC with two project abstracts accepted in 2016 and four in 2017. As well as the presenters themselves, the project was also represented by several consortium members and project partners in attendance, including Alzheimer Europe at both events.

Alzheimer's Association International Conference 2016 (AAIC16)

The 2016 Alzheimer's Association International Conference (AAIC16) meeting was held from 23 to 28 July in Toronto, Canada and Lennart Thurfjell, CEO of Combinostics Ltd. (Finland), one of the PredictND partners, reported on the conference:

Such a large conference covers many different topics but research around how to effectively treat Alzheimer's disease (AD) and how to better diagnose people were amongst the key topics. With this in mind it is clear, that the work in PredictND is essential as finding the right patient at the right disease stage will become more and more important. There were several PredictND researchers present at AAIC and two papers were presented:
1. An oral presentation with the title “Towards data-driven medicine in differential diagnostics of neurodegenerative diseases”, by Jyrki Lötjönen et al.

2. A poster on the topic of “Cost effective differential diagnostics of neurodegenerative diseases using a stratified approach” by Wiesje van der Flier et al.

Both presentations were well received and are perfectly aligned with the problem of early diagnostics outlined above.

The AAIC conference is also a great place for networking and PredictND partners had several meetings around potential exploitation of the PredictND technology. Meetings were held with two pharma companies and with several medical device/biomarkers companies. The main point was to raise awareness of the PredictND technology but there will be follow-up discussions based on some of these initial meetings.

### Alzheimer’s Association International Conference 2017 (AAIC17)

The 2017 Alzheimer’s Association International Conference (AAIC17) meeting was held from 16–20 July in London, UK.

A lot of attention was given to the potential of biomarkers to identify people at risk of developing Alzheimer’s dementia and of preventative approaches (both pharmacological and lifestyle interventions) to halt or delay the progression to Alzheimer’s dementia in persons with positive biomarkers for Alzheimer’s pathology.

Again, the PredictND achievements were well received and centred on four key presentations:

2. A poster on the topic of “Data-Driven Diagnosis of Dementia Disorders: The PredictND Validation Study” by Marie Bruun et al. (Rigshospitalet)
3. A poster on the topic of “Detecting Cognitive Disorders Using Muistikko Web-Based Cognitive Test Battery – Validation in Three Cohorts” by Teemu Paajanen et al. (University of Easter Finland – UEF)
4. A poster on the topic of “Computed Rating Scales for Cognitive Disorders from MRI” by Jyrki Lötjönen et al.

During the conference, project partner Combinostics was represented with a booth and demonstrated some of the tools to which the PredictND project has contributed. The project was discussed multiple times with conference delegates visiting the booth and increased the visibility of the PredictND consortium at this key conference in the Alzheimer’s and related disorders field.

AAIC18 will be held from 22 to 26 July 2018, in Chicago.
Reviewers rate progress as excellent

On 14 March 2017, the PredictND team attended an interim review meeting with the European Commission and the review board to present the progress and achievements of the project.

The representatives of the different work packages updated the European Commission and the reviewers about the progress since the last review and gave updates on the overall progress (Mark van Gils, VTT, Finland), the clinical data acquisition and management (Hilkka Soininen, University of Eastern Finland, Finland), the decision support tool requirements (Timo Urhemaa, VTT, Finland and Jan Wolber, GE Healthcare, UK), the biomarker discovery tools (Daniel Rueckert, Imperial College, UK), the clinical validation studies (Steen Hasselbalch, Rigshospitalet, Denmark) and the business development and dissemination activities (Lennart Thurfjell, Combinostics, Finland). Hanneke Rhodius-Meester (VUMC, Netherlands) gave a demonstration of the developed decision support tool to show how the tool can be used by clinicians and Jyrki Lötjönen (Combinostics, Finland) updated the reviewers on how the team had addressed the comments of the reviewers from the last meeting. All of these presentations had been prepared and rehearsed at a project team meeting in Copenhagen, Denmark on 6 and 7 March 2017.

The reviewers showed a lot of interest in the different achievements, with a number of lively question and answer sessions following the different presentations. All in all, the reviewers were impressed by the progress to date which they rated as “excellent”.

NDs are typically diagnosed with a consensus of several experts that have examined the patient and the collected data. The diagnosis will be based on the current guidelines and expertise of the participating specialists. Objective exploitation of data collected from previous patients with similar symptoms is hard. Knowledge of these patients, their tests and outcome should be collected and documented in an intuitive and easy to use form.

Following the meeting, the European Commission sent its written interim report to the project coordinators, stating:

“The Consortium has made excellent progress and the work performed during this reporting period is impressive. The demonstrations presented during the review meeting provided a very good demonstration of the benefit that the system could provide.”

The PredictND consortium is very grateful to the Commission for its support.
PredictND peer-reviewed Journal articles


Peer-reviewed Conferences and Workshops


PredictND in action: Snapshots from project meetings
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