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A Web-based Application for Screening Alzheimer's Disease in the Preclinical Phase

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***Abstract*—As a result of an increasing elderly population, the number of people with age-related diseases is increasing worldwide. Alzheimer's disease is thus becoming an emergency health and social problem. Neuropsychological evaluation and biomarker identification represent the two main approaches to identifying subjects with Alzheimer's. In this paper, we propose a web application designed to be sensitive to the cognitive changes distinctive of the early Mild Cognitive Impairment, which is a condition in which someone experiences minor cognitive problems, and the preclinical phase of Alzheimer's disease. The application is conceived to be self-administered in a comfortable and non-stressful environment. It was designed to be quick to administer, automatic to score, and able to preserve privacy because of the highly sensitive data collected. The preliminary evaluation of the application was done by enrolling 518 subjects characterised by several risk factors and the presence of a family history, which underwent standard neuropsychological screening.**

***Index Terms*—Digital cognitive assessment tool, Early screening, Cognitive screening, Alzheimer's disease, eHealth**

I. Introduction

In recent years, life expectancy has increased significantly in all developed countries, increasing attention to all age-related and mental health conditions. In the 2022 report, Alzheimer's Disease International estimates that the number of people living with Dementia is expected to rise to 139 million in 2050. Moreover, they believe that 75% of people with Dementia are not diagnosed globally, with that rate estimated to rise as high as 90% in some lower/middle-income countries [1]. At different levels of severity, cognitive impairment and Dementia affect individuals, their families and the wider economy. In 2019, the World Health Organisation estimated the global cost of Dementia at about US$1.3 trillion, with an expectation of growth to US$2 trillion by 2030 [2]. Dementia is a general term for a decline in mental ability leading to a loss of self-sufficiency in daily life, while Alzheimer's is a specific disease and the most common cause of Dementia.

In this scenario, the emergency is exacerbated by the fact that no cure for Alzheimer's disease is available. Thus, health-monitoring technologies and methods for detecting the early signs of cognitive decline have become extremely important, especially at preclinical or prodromal stages (*e.g.*, Mild Cognitive Impairment). Early diagnostic tools are of utmost importance since there are numerous works in the literature suggesting that modifying risk factors could prevent or delay the onset of Dementia including Alzheimer's disease [3]–[5]. Typically, there are two main approaches to screening subjects looking for early signs of Alzheimer's disease, that is biomarker identification and neuropsychological evaluation. The first represents a costly, invasive, and unsustainable method on a large scale [6], while the latter is cheaper, less invasive, and easier to administer for large-scale population screening [7], [8].

A recent review of the preclinical stage of Alzheimer's disease on a neuropsychological evaluation basis focuses on the fact that the earliest cognitive changes concern episodic memory, semantic memory, and executive functions [9]. In particular, a decline in episodic memory can arise 6-10 years before the onset of the symptomatic phase, and both immediate and delayed measure analysis is recommended [9], [10]. The elderly with associative memory deficits have been shown to be at increased risk of Dementia [11]. Furthermore, there is evidence of deficits in short-term memory binding in older adults with Alzheimer's disease and familial Alzheimer's disease. The evaluation of executive functioning is often missed in cognitive screening tools, whereas the two "hot" and "cold" components, which can be affected many years before the clinical phase and seem to accelerate 2-3 years before, are crucial in the early

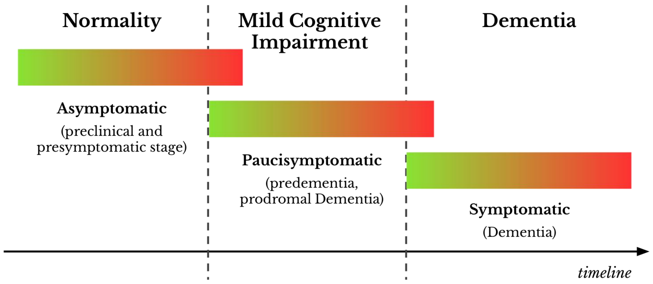


Fig. 1: The degenerative process of Dementia: features and speeds of progression can be variable. The aim is to identify the cognitive symptoms before the onset of the clinical ones (*i.e.*, the leftmost side of the graph).

assessment of cognitive decline. The hot component involves the experiences of reward and punishment, regulation of social behaviour and decision-making, while the cold component is the coordination mechanism and inhibition and shifting [12].

Since diagnostic coverage remains low even in high-income countries, researchers have recently focused on digital and non-invasive automated tools, which offer several advantages over traditional paper-and-pencil screening tests [8], [13]. However, most of the proposed tests accurately discriminate between Mild Cognitive Impairment/Dementia and healthy subjects [9], but they are not sensitive to micro changes that are characteristic of the preclinical phase (Figure 1). This is the rationale behind the development of a more cognitively demanding and sensitive digital tool.

In this paper, we propose a web application conceived to be self-administered in approximately 30 minutes using a tablet in a comfortable and non-stressful environment, such as the general practitioner's office. The idea is that primary care is the most appropriate place for early cognitive decline detection and managing the risk to develop Dementia. For this reason, the web application is designed to be quick to administer, automatic to score -to provide a basic assessment of the subject's cognitive performance-, and able to preserve privacy because of the highly sensitive data collected. In particular, the web application implements a client-server architectural pattern and consists of ten subtests that assess cognitive domains found to be early compromised preclinical Dementia, such as temporal orientation, episodic and semantic memory, visuo-constructive, visuospatial abilities, divided attention, shifting, verbal fluency, perceptual speed, and inhibition/switching. The subtests were inspired by traditional paper-and-pencil tests and adapted to the digital tool. Moreover, to propose a more cognitively demanding evaluation tool, the exposure time was reduced and different cognitive functions were examined in parallel. The web application automatically computes the partial and total scores and records the time taken for a comprehensive assessment of cognitive performance. For the preliminary evaluation of the web application, we enrolled 518 subjects (*i.e.*, 231 males and 287 females) aged between 45 and 75 years with different levels of education. Each participant was classified according to two categories: acquired risk factors (*i.e.*, high/low) and the presence of a family history of Dementia (*i.e.*, yes/no). Moreover, all subjects were requested to complete an anamnestic interview and were assessed with the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), which are two tests widely used in clinical practice.

The main contributions of this work are as follows:

- the web application is conceived to be self-administered in a comfortable and non-stressful environment;
- the test battery assesses several cognitive domains found to be early compromised preclinical Dementia;
- the web application is designed to be quick to administer and automatically score;
- the preliminary assessment includes 518 subjects assessed through a standard battery of cognitive tests.

II. Related Works

Digital tools are becoming increasingly popular for screening and diagnosing various medical conditions, including Alzheimer's disease and Dementia. The development of web-based and mobile applications for mental health screening has the potential to improve the early detection and management of mental diseases. In this section, we review some of the relevant studies that have investigated the use of digital tools for mental health screening.

The approach of using a tablet-based application that records a person's spoken responses to questions about their daily activities and experiences could be a valuable tool for detecting Alzheimer's disease in its early stages [14]. The results demonstrated that the tablet-based approach could accurately differentiate between healthy individuals and those with Mild Cognitive Impairment or early-stage Alzheimer's disease with a high level of sensitivity and specificity. Several mobile applications are available for dementia screening that focus on assisting patients with brain training, improving their memory power, and preventing negative incidents associated with cognitive impairment [13]. In [15], the authors present MOBI-COG, which is a mobile application able to identify Dementia through three different tasks. The application is based on the Mini-Cog Dementia Screening Test [16] and it has proven accurate in screening for Dementia. BrainTest is a mobile application that uses the Self-Administered Gerocognitive Exam [17] and can be completed by either the patient or caregiver. The ACE application was created for healthcare professionals and employs Addenbrooke's Cognitive Examination-3 Medical Exam [18]. It measures the individual's cognitive abilities such as attention, memory, fluency, and language [19]. In [20], the authors propose the CAIDE-DRS application, which runs only on Apple devices and assesses an individual's cognition condition using their biographic information, physical measurements, and lifestyle factors. It is based on the CAIDE risk score and can predict, with high sensitivity and specificity values, the user's risk of developing Alzheimer's disease [21]. The MoCA application is designed to assess various cognitive functions like attention, language, memory, and executive functions, along with time and place awareness, to diagnose brain and memory-related conditions like Alzheimer's disease [22]. The eSLUMS application is a digital adaptation of the Saint Louis University Mental Status Examination (SLUMS) that can be conducted by healthcare professionals [19]. It measures brain health in a short time frame of 7-10 minutes, and the SLUMS test can detect Alzheimer's disease characteristics with a high level of sensitivity and specificity [23]. In [24], the authors proposed DementiaScreener, which is an Android application using the Symptoms of Dementia Screener (SDS) [25] and AD8 Dementia Screening Interview [26] medical tests to evaluate the likelihood of an individual developing Alzheimer's disease. The SDS assesses memory, emotions, attention, problem-solving abilities, and repetitive behaviours, while the AD8 evaluates changes in behaviour.

One of the main limitations of the currently available solutions is that they are limited to screening paucisymptomatic and symptomatic stages of Dementia, while we propose a tool for the preclinical (*i.e.*, asymptomatic) phase.

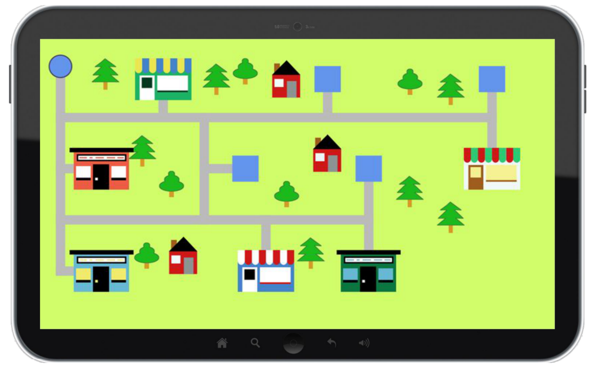
III. The Proposed Screening Application

The rationale behind this work includes the development of a more cognitively demanding screening tool for the preclinical phase of Alzheimer's disease, easy to administer and inexpensive. In this section, we present the proposed web application discussing the assessed cognitive domains, structure and design.

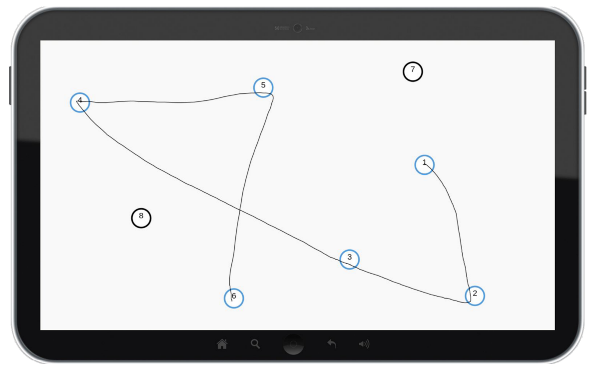
A. Cognitive Tests

The proposed web application consists of ten subtests that assess the most influencing cognitive domains in terms of preclinical screening of Alzheimer's disease.

1) *Personal and Temporal Orientation Test* - The subject is asked for her/his gender and date of birth, and temporal information regarding the day, month, year, and day of the week of today's date. This first test helps the subject to become familiar with the tool.
2) *Immediate Complex Learning Test* - This test assesses memory involved in normal daily life tasks. The subject is asked to repeat a path previously simulated on a map that visits several shops; to select items previously purchased in the various shops of the simulated itinerary; and, finally, to provide some information about the character of the simulation (*i.e.*, face, name, and surname).
3) *Trail Making Test* - This is a standard cognitive test that requires the subject to connect items (*i.e.*, letters, numbers and both) in the right order, to assess executive functions, visual search speed, spatial exploration, processing speed and mental flexibility.
4) *Constructional Praxis Test* - This test requires the subject to complete a simple geometric figure previously displayed in its entirety to which certain parts are omitted. This assesses visual-spatial memory and constructive praxis ability.



(a)



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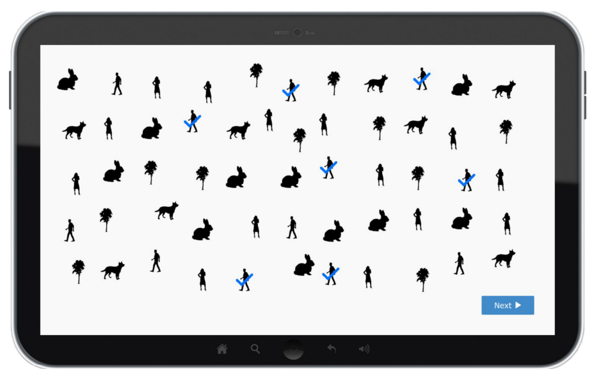

(c)

Fig. 2: Screenshots of the web application representing three subtests administered to the subject: the itinerary map of the *Complex Learning Test* (a), the *Trail Making Test* (b), the *Attentional Matrices Test* and (c).

5) *Attentional Matrices Test* - This test assesses the ability to detect stimuli characterised by a conjunction of features, evaluating visual-spatial exploration, selective and divided attention, psychomotor speed and inhibition ability. On a board full of various black silhouettes, the subject is asked to mark all the ones equal to a given target.
6) *Visual Fluency Test* - When drawings of various objects appear, the subject must select those that begin with a certain letter or pair of letters. This allows for assessing

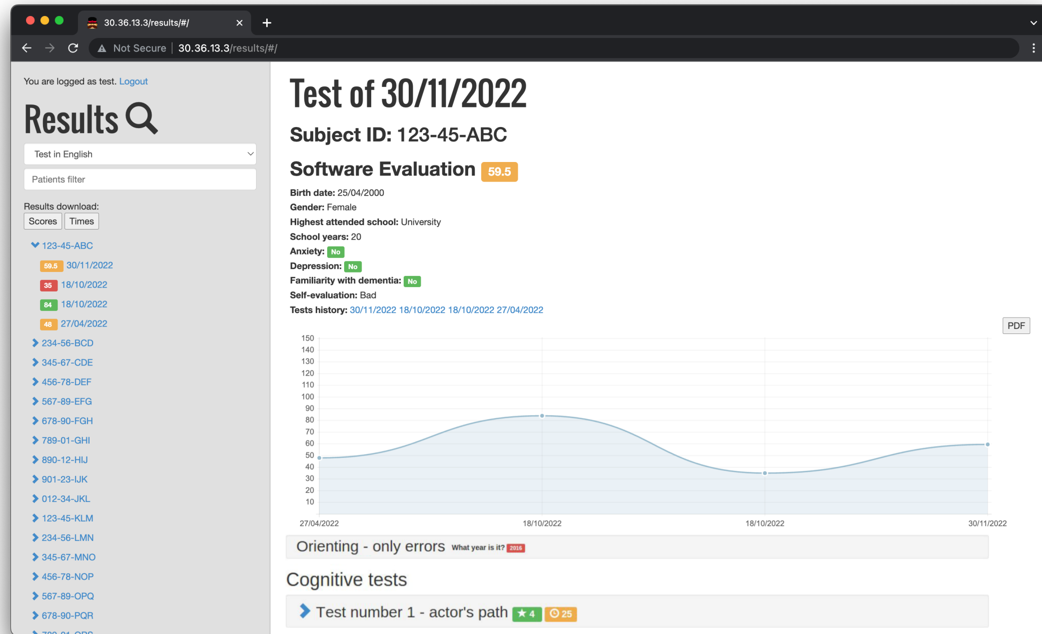

Fig. 3: Results web interface: the evaluator can quickly consult all the subjects' results -identified by a generic alphanumeric code-, obtain a summary of the performance trend, explore qualitative and quantitative details about each subtest, and download all scores/times or the individual subject report.

divided and selective attention, visual recognition, executive functions, and phonemic access verbal fluency at once.

7) *Stroop Test* - The subject is asked to choose the semantically wrong answer to a simple question from the two available options. This test assesses semantic memory and the ability to inhibit interference.
8) *Delayed Complex Learning Test* - This test repeats the task of the second subtest about 15/20 minutes later.
9) *Benton Judgment of Line Orientation Test* - This test assesses visual-spatial skills and iconic memory. The subject is presented with two lines that form a specific angle. When the stimulus disappears, the subject must choose between the 10 lines, shown to him in a different position, the two that form the same angle.
10) *Anosognosia Test* - The subject is asked to self-evaluate his/her cognitive performance, testing meta-cognitive skills which are predictive of disease progression.

At the beginning of each test, the instructions are available as text and via audio to the subject. Moreover, to propose a more cognitively demanding tool, the exposure time is restricted, and different cognitive functions are examined in parallel. The evaluation of the tests involves both a partial and a total score, moreover, each subtest is enriched with quantitative (*e.g.*, number of errors, reaction times) and qualitative details (*e.g.*, type of errors, screenshots of the drawing tasks).

B. Web Application Architecture

The web application was designed by adopting a client-server architectural pattern. This solution allows running the web application on multiple platforms (*e.g.*, browsers and devices) regardless of the operating system and the underlying hardware. Moreover, intending to provide a screening service in the future, all users access the same version, updates can be deployed easily just by updating the server, and, even more important, all the results are encrypted, stored and protected in a central database using high-level solutions. In addition, on the server side, the tests are organised in a modular manner, which allows new tests to be added in the future or dynamically configured to study specific deficits in a particular cognitive domain.

The client module includes the user interfaces and the logic of each subtest. It can run on any web browser and it is conceived for at least a 10-inch screen (Figure 2). The rationale behind this choice is the fact that smaller screens could introduce an additional disturbance and stress factor for the subjects to be tested, thus distorting the cognitive assessment. Moreover, the client caches the final results before encrypting and sending them to the server, also solving any network failures. Since no other personal data is collected by the client, this preserves the privacy of the subjects, who are identified by a generic alphanumeric code. The server module provides the cognitive tests, safely stores the results and provides authorised users with a report of the outcomes for each subject. In particular, the evaluator may rapidly review the results for all the subjects, and,

TABLE I: Final scores distribution according to risk and family history factors.

Risk & Family history	# cases	min	max	μ	σ	median	skewness
Risk = *low* & Family history = *no*	271	38	127	80.46	14.12	80.00	0.04
Risk = *high* & Family history = *no*	71	48	96	74.24	11.52	74.50	-0.20
Risk = *low* & Family history = *yes*	129	44	108	79.17	11.13	80.00	-0.29
Risk = *high* & Family history = *yes*	47	36	102	74.23	14.26	74.00	-0.36
All	518	36	127	78.72	13.30	79.00	-0.04

for each subject, she/he can get an overview of the performance trend, study the qualitative and quantitative details of each subtest, and download the report. Moreover, all scores/times can be downloaded in bulk, making possible temporal and comparative analysis and advanced epidemiological studies (Figure 3).

The two modules use state-of-the-art and open-source web technologies, such as the Angular framework version 8.3.23, HTML version 5, CSS version 3, and JavaScript version 5 for the client side; and the Django framework version 4.0, Python version 3.9.5, and PostgreSQL version 14.1 for the server side. The communication protocol between the client and server also provides a caching mechanism during the tests loading and results sending from and to the server. This makes it possible to compensate for any connection problems that could lead to data loss.

IV. Preliminary Results

The preliminary assessment of the web application involved a cohort of 518 subjects[1] aged between 45-75 years (μ=59.26 and σ=8.22), with different levels of education (years range=[5-18], μ=12.63 and σ=3.88) from two centres in Emilia Romagna and Lombardy, that is two regions of northern Italy. These characteristics were balanced in the two subgroups consisting of 231 males and 287 females, with no significant statistical differences.

The inclusion criteria were Italian first language, absence of current or previous disabling neurological pathologies, blindness, deafness or other serious sensory impairment, intellectual or cognitive disability, and serious psychiatric diseases. Each participant was classified according to two categories: acquired risk factors (*i.e.*, high/low) and the presence of a family history of Dementia (*i.e.*, yes/no). According to the standard cognitive screening guidelines, the risk factor was determined based on the presence of two out of three health, lifestyle and psychological risk factors, while the family history of the disease was based on the presence of first-third-degree relatives with a neurodegenerative pathology [27].

All subjects were requested to complete an anamnestic interview and were assessed with the MMSE and the MoCA, which are two tests widely used in clinical practice. In addition, each subject was administered the proposed cognitive test lasting approximately 30 minutes, at the end of which the examiner has access to the total execution time and the total score in the range of 0-150, which is computed considering correct answers, errors, and reaction times, and different quantitative and qualitative details.

[1]The trial was approved by the local research ethics committees and informed written consent was obtained.

TABLE II: Equivalent scores with the five-classes stratification and the distribution of evaluated subjects.

Class	Range	Frequency
0	$score \leq 59.0$	18
1	$59.0 < score \leq 67.2$	41
2	$67.2 < score \leq 73.8$	82
3	$73.8 < score \leq 79.9$	118
4	$score > 79.9$	259

All the subjects performed normally at the conventional cognitive tests, that is μ=29 and σ=1.24 for the MMSE, μ=25.23 and σ=2.46 for the MoCA. Table I describes the distribution of the final scores of the proposed web application w.r.t. risk and family history factors, neither factor has an impact on the final score. These descriptive values have been crucial to compute the equivalent score, which is an adjusted score through an estimate correction factor to make it comparable as gender, age and educational level change. In particular, this analysis estimates the relationship between the final score and sex, age and education through a linear regression model. Only age and education level proved to be significantly associated with the final score, and the model yielded the equivalent score values shown in Table II. Moreover, the equivalent scores were stratified into five classes, where class 0 indicates an abnormal situation and the other classes suggest an increasing level of performance.

The early detection of cognitive decline is crucial for preventing cognitive deterioration and for aiding in therapeutic intervention. The preliminary evaluation of the proposed web application shows the potential screening accuracy of the tool in this direction. In particular, the statistical analysis shows that the results are normally distributed without ceiling and floor effects, and are not significantly influenced by either the family history of dementia or the acquired risk factors.

V. Conclusions

As the world's elderly population increases, the number of people living with Dementia is increasing rapidly and digital tools for automatically detecting the early signs of cognitive decline have become increasingly important. In particular, the neuropsychological-based evaluation tools represent less invasive and easier-to-perform solutions for cost-effective large-scale early population screening.

The proposed web-based application is conceived for an accessible and brief evaluation of those cognitive domains found to be early compromised in Mild Cognitive Impairment and the preclinical phase of Alzheimer's disease. In this paper, we presented the idea behind the design of the application and the cognitive domains assessed by the tool. Moreover, we discussed the preliminary results of the normative data in a sample of cognitively healthy subjects, which are crucial for future validation. To evaluate the application, we used a cohort of 518 subjects. The results showed that the final score is normally distributed, without ceiling and floor effects. Moreover, the well-educated and younger subjects achieved better results than the less educated and/or older ones.

In future works, we plan to repeat the administration to the same cohort to assess the screening capabilities of the proposed tool over time. Furthermore, we plan to integrate machine learning and deep learning techniques to extract other potential screening features, such as the *Trail Making Test* hand shaking, and automatically evaluate complex drawing tests, such as the *Constructional Praxis Test*.

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