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TESI DI LAUREA

Validation of the Italian consensus recommendations for the biomarker-based diagnosis of neurocognitive disorders

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TABLE OF CONTENTS

ABSTRACT

Background. Several recommendations for a biological diagnosis of neurocognitive disorders have been published, but adherence to these guidelines has been poorly tested. One of the main candidate for a biological diagnosis is the young-onset cognitive decline (YOCD), defined as cognitive decline with symptoms onset before age 65. Increased awareness of YOCD in clinical and research settings may have contributed to make this diagnosis more frequent in the last years.

Objectives. The present study will aim to compare the most frequent diagnostic workups before and after the release of the Italian recommendations for the biological diagnosis of mild neurocognitive disorders. The project aims to evaluate: i) the adherence of Italian specialists to the consensus recommendations for the diagnosis of patients with MCI and dementia (primary outcome); ii) changes of patient management and following the adoption of the recommendations (co-primary outcome). In addition (iii), the present work also aimed to assess the incidence of YOCD in the province of Padova, to describe factors that could delay diagnosis and to identify how many diagnostic resources are dedicated to these patients.

Methods. In three Italian memory clinics (CDCD), the medical charts of two sets of consecutive patients with mild neurocognitive disorders and dementia have been retrospectively reviewed during two periods: 1) pre-consensus and 2) post-consensus. In addition, patients were included among those referring to two CDCD based at the University-Hospital of Padova: the Neurology clinic and the CRIC centre. We retrospectively collected all patients aged <65 years with a first visit for cognitive decline between January and December in 2022. Over 204 patients with young-onset cognitive decline (YOCD), 97 (47,55%) had their first neurological visit in 2022. Adherence to recommendations, standard diagnostic pathway, type of deviations from the ideal pathway based on recommendations, and the impact of deviations on diagnosis times and prescription of drugs are calculated through process mining.

Results. 1. From 2018 to 2019, a total of 235 patients were collected: 70 non-diagnostic follow-up patients, 108 patients with clinical diagnosis without biomarkers and 57 diagnostic patients with biomarkers. Biomarker-based diagnoses

of retrospective patients with Alzheimer's disease, frontotemporal dementia, and non-neurodegenerative diseases were commonly based on FDG-PET (AD: 85,7%, FTLD: 77,8%, non-neurodegenerative: 66,7%) and CSF (71,4%, 66,7%, and 55,6%, respectively). In dementia with Lewy bodies (DLB), the first-line biomarkers were FDG-PET (42,9%), and DaT-SPECT (39%). **2.** About the comparison of biomarkers between pre and post-consensus, CSF analysis was more frequent in post-consensus group than in the pre-consensus one, although the distribution of different diagnoses was comparable. FDG-PET and DaT Scan were performed less in the prospective cohort. **3.** The incidence rate of YOCD was 17.25/100,000 PY (95% CI, 13,99–21,04), while the age–sex standardized incidence rate was 16.93 per 100,000 PY (95% CI, 13,72-20,65). This incidence would yield an estimated 5987 (95% CI, 4852–7303) of YOCD new cases in the whole Italian population ignoring mortality. Incidence increased with age, in both sexes, reaching its peak after 60 years. Mean age is 58.6±8.2 years, F=60%, mean time to disease diagnosis: 2 years. In this subgroup, the most frequent diagnoses were mild neurocognitive disorder (N= 30; 31,6%), Alzheimer's disease (N=21; 22,1%) and frontotemporal dementia (N=13; 13,7%), followed by other neurodegenerative diseases (N=9; 9,5%). The most used investigation after cognitive testing and brain MRI were PET-FDG (N=37; 38,1%), CSF (N=28; 28,9%), Apo-E (N=38; 39,2%) and dementia-oriented genetic study (N=23; 23,7%). In regression models, none of demographic variables was significantly associated with time-lapse from first symptoms until diagnosis ($p > 0.05$). By making a comparison between the tests carried out for YOCD in 2020, 2021, 2022, we obtained a significant increase in frequencies for CSF, PET-FDG, genetic analyses and genetic counseling.

Conclusions. This preliminary analysis outlines the most frequent diagnostic pathways and confirm partial adherence to the raccomandation as regard as second line biological markers for AD, FTD and DLB. Moreover, our data underline the alarm that young onset dementia can represent. This is the first epidemiological study about YOCD in North East Italy region and it could be a starting point for social and health-related programs dedicated to intercepting and caring of this specific population. Improved knowledge on YOCD epidemiology is essential to organize health services.

RIASSUNTO

Introduzione. Sono state pubblicate numerose raccomandazioni per la diagnosi biologica di disturbi neurocognitivi, ma l'aderenza a queste linee guida è stata scarsamente testata. Tra i migliori candidati per la diagnosi biologica ci sono i disturbi neurocognitivi giovanili (YOCD), definiti come deficit cognitivi con esordio prima dei 65 anni. Una maggiore consapevolezza di essi in contesti clinici e di ricerca ha contribuito a rendere questa diagnosi più frequente negli ultimi anni.
Obiettivi. Il presente studio mirerà a confrontare gli accertamenti diagnostici più frequenti prima e dopo il rilascio delle raccomandazioni Italiane per la diagnosi di disturbi neurocognitivi. Il progetto si propone di valutare: i) l'adesione degli specialisti italiani alle consensus recommendations per la diagnosi di pazienti con MCI e demenza (esito primario); ii) cambiamenti nella gestione dei pazienti e in seguito all'adozione delle raccomandazioni (esito co-primario). Inoltre (iii), il presente lavoro ha come scopo anche quello di valutare l'incidenza di YOCD nella provincia di Padova, di descrivere i fattori che potrebbero ritardare la diagnosi e di identificare quante risorse diagnostiche sono dedicate a questi pazienti.
Metodi. In tre cliniche italiane della memoria (CDCD), le cartelle cliniche di due gruppi consecutivi di pazienti con MCI e demenza sono state riviste retrospettivamente durante due periodi: 1) pre-consenso e 2) post-consenso. Inoltre, considerando due CDCD con sede presso l'Ospedale Universitario di Padova (Clinica Neurologica e CRIC), son stati raccolti retrospettivamente tutti i pazienti di età <65 anni con una prima visita tra gennaio e dicembre nel 2022 per declino cognitivo. Su 204 pazienti con declino cognitivo a esordio giovanile (YOCD), 97 (47,55%) hanno avuto la prima visita neurologica nel 2022. L'aderenza alle raccomandazioni, il tipo di deviazioni dal percorso ideale basato sulle raccomandazioni e l'impatto delle deviazioni sui tempi di diagnosi e sulla prescrizione dei farmaci saranno calcolati attraverso il process mining.
Risultati. 1. Dal 2018 al 2019 sono stati raccolti in totale 235 pazienti: 70 pazienti di follow-up non diagnostici, 108 pazienti con diagnosi clinica senza biomarcatori e 57 pazienti diagnostici con biomarcatori. Le diagnosi retrospettive basate sui biomarcatori di pazienti con malattia di Alzheimer (AD), demenza frontotemporale

(FTLD) e malattie non neurodegenerative erano comunemente basate su FDG-PET (AD: 85,7%, FTLD: 77,8%, non neurodegenerative: 66,7%) e rachicentesi (71,4 %, 66,7% e 55,6%, rispettivamente). Nella demenza a corpi di Lewy (LBD), i biomarcatori di prima linea erano FDG-PET (42,9%) e DaT SPECT (39%). **2.** Per quanto riguarda il confronto dei biomarcatori tra pre e post-consenso, PET-FDG e DaT Scan sono stati eseguiti maggiormente nella coorte retrospettiva, mentre l'analisi del liquido cerebrospinale è stata eseguita maggiormente nella coorte prospettica. **3.** Il tasso di incidenza di YOCD era 17,25/100.000 PY (95% CI, 13,99-21,04), mentre il tasso di incidenza standardizzato per età-sesso era 16,93 per 100.000 PY (95% CI, 13,72-20,65). Questa incidenza produrrebbe una stima di 5987 (95% CI, 4852-7303) nuovi casi YOCD nell'intera popolazione italiana, ignorando la mortalità. L'incidenza aumenta con l'età, in entrambi i sessi, raggiungendo il picco dopo i 60 anni. L'età media è 58,6±8,2 anni, F=60%, tempo medio alla diagnosi della malattia: 2 anni. In questo sottogruppo, le diagnosi più frequenti sono state mild cognitive impairment (MCI) (N= 30; 31,6%), malattia di Alzheimer (N=21; 22,1%) e demenza frontotemporale (N=13; 13,7%), seguite da altre malattie neurodegenerative (N=9; 9,5%). Gli esami più utilizzati dopo i test cognitivi e la risonanza magnetica cerebrale sono stati PET-FDG (N=37; 38,1%), analisi del liquor (N=28; 28,9%), Apo-E (N=38; 39,2%) e studio genetico orientato alla demenza (N=23; 23,7%). Nei modelli di regressione, nessuna delle variabili anamnestiche era significativamente associata al time-lapse dai primi sintomi fino alla diagnosi ($p > 0,05$). Effettuando un confronto tra i test effettuati per YOCD nel 2020, 2021, 2022, è stato ottenuto un aumento significativo delle frequenze per CSF, PET-FDG, analisi genetiche e consulenza genetica.

Conclusioni. Questa analisi preliminare delinea i percorsi diagnostici più frequenti. Questi dati sottolineano inoltre l'allarme che la demenza ad esordio giovanile può rappresentare e confermano la parziale adesione alle raccomandazionii per quanto riguarda la seconda linea di marcatori biologici per AD, FTD e DLB. Questo è il primo studio epidemiologico su YOCD nel Nord Est d'Italia e potrebbe essere un punto di partenza per programmi socio-sanitari dedicati all'intercettazione e alla cura di questa specifica popolazione. Una migliore conoscenza dell'epidemiologia di YOCD è essenziale per l'organizzazione dei servizi sanitari.

INTRODUCTION

Definitions, classification and epidemiology

Dementia, or major neurocognitive disorder, is an acquired clinical syndrome with organic nature, and usually with a progressive course, characterized by deficits in at least two cognitive domains (amnesia, aphasia, apraxia, agnosia, disorders of critical capacity and abstract thinking) and or behavioral, of such severity as to significantly compromise working, social or relational activities, with a worsening compared to the previous functional level, with no alterations in the state of consciousness. (1)

Considering the preservation or loss of function is the key to classify a neurocognitive disorder (NCD). Neurologists face three diagnostic levels. The first level corresponds to the diagnosis of a major or minor neurocognitive disorder, without specifying the etiology. The second level is a clinical syndrome diagnosis and finally in the third, more accurate, a clinical-biological diagnosis is made. (2)

Mild NCD or MCI (mild cognitive impairment) refers to cognitive decline in which, however, daily functions are maintained. MCI is very common in the population, 10-20% of patients < 65 years have (or report) memory problems; of these, 10% per year will develop NCDs. The diagnosis of MCI is reached through a series of steps.

First of all, the subject's cognitive functioning is not within the limits of the norm but, at the same time, the patient does not meet the requirements for the diagnosis of dementia. Secondly, functional skills must be substantially intact or minimally compromised. In addition, the patient could have cognitive decline recognized by himself or other people: this decrease must be studied to identify objective performance's deficit in cognitive tasks or evidence of decline in neuropsychological tests.

Dementia affects 4-5% of the population over 65, reaching a percentage higher than 20-30% of those over eighty. The prevalence of dementia is very low, but not negligible, before the age of 60 and subsequently increases exponentially, doubling every five years with age.

Dementia can be classified into primary and secondary. Degenerative diseases with dementia as primary symptom are: Alzheimer's disease (40-55% of late onset disease [LOD] cases), Frontotemporal dementia FTD (10-15%) and Lewy body

dementia (10-25%). There is dementia also in other CNS degenerative diseases: Parkinson's disease, Huntington's chorea, progressive supranuclear palsy, amyotrophic lateral sclerosis, and spinocerebellar degenerations.

On the other side, in the secondary ones, patients have cognitive deficits that are caused by other pathological processes. They could be CNS diseases: vascular dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, tumors, trauma, infections, and multiple sclerosis. Other systemic pathologies can be: Wilson's disease, metabolic disorders, deficiency disorders, organ pathologies, intoxications, and immune-mediated diseases.

It is important to know how to distinguish them because in case of secondary dementia, it is possible to treat the primary cause and consequently treat the patient. (2)

Classical diagnosis and clinical course

The diagnosis of dementia is a clinical diagnosis based on an accurate anamnesis, a scrupulous neurological and neuropsychological evaluation, biohumoral and neuroimaging tests. The diagnostic path of a patient with cognitive impairment is based on a multi-stage assessment. We must answer two questions: i) whether we are facing with cognitive impairment which meets the diagnostic criteria of dementia; ii) if it is dementia, what is the most likely cause. (2)

In Padua, we are using techniques for studying eye movement and trying to understand if patterns of movements can be used to differentiate the various stages of the disease, evaluating the "internal activity" of the SNC and therefore the "rigidity" of the brain. In patients with MCI there is less variability in eye movements and even less with dementia.

As an axiom, in Alzheimer's disease, changes are progressive: first the biochemical change occurs (changes in tau and amyloid), then imaging changes (macroscopic degeneration from neuronal and glial atrophy) and then clinical changes.

When patients start presenting symptoms, it means that damage to the brain with progressive neurodegeneration began a long time before. (3)

Amyloid alterations at the CSF level are the first to be detected, followed by amyloid-PET, CSF Tau alterations and finally the markers of neurodegeneration.

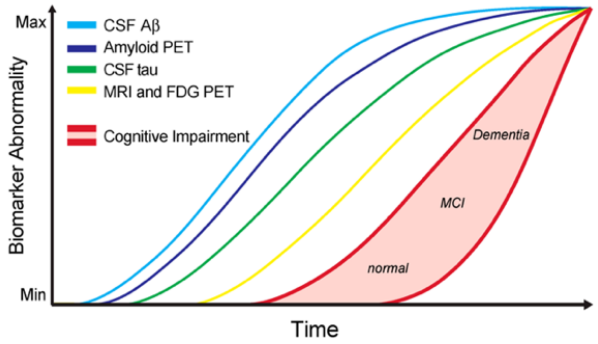
In particular, it is known that the disease develops over time through moderate and severe stages. The progression of Alzheimer's disease is characterized by the

deposition of amyloid plaques that are visible on imaging and in the CSF. Then there is neurodegeneration which is consistent with the increase in tau in the CSF and with degeneration visible on both PET and MRI. The diagnosis is no longer just clinical but clinical-biological and it can be made in vivo with specific biomarkers. Actually we are in the era of biomarkers.

We need to stress the fact that initially the clinic is characterized by mild cognitive symptoms, then behavioral disorders appear (visual hallucinations, obsessions, compulsions, psychomotor agitation, aggressive behavior) until the loss of self-sufficiency and hospitalization in healthcare facilities. (4)

Death, which occurs approximately ten years after the development of the disease, occurs from aspiration pneumonia in the most frequent cases. (2)

It is also crucial to remember that there are many decades in which amyloid accumulates.



I: Biomarkers in Alzheimer's Disease (3).

With a patient with cognitive impairment, we need to focus on the patient's residual abilities, not on the skills that he or she progressively continues to lose. Interaction is also important, especially when there is a diagnosis to communicate that can be difficult to accept. These pathologies have to be treated with a good dose of placebo effect. The white coat effect is very relevant, therefore these patients need to be reassured. They are patients who have a lot of awareness, a lot of anguish, a lot of fear.

Pharmacological therapy is represented by anticholinesterases which are donepezil, rivastigmine and galantamine, and an antagonist of NMDA receptor, which is memantine. (5)

In addition to pharmacological therapy, aerobic exercise, maintaining an active social life, and maintaining a cultural life by "keeping the brain trained" should be

recommended. It is therefore important to give the patient all this "healthy aging package" information. Another important resource is cognitive training therapy. Maintaining a very active mental life is fundamental, so beyond to the biological section there is a very important behavioral part that must be emphasized.
Considering the pathogenetic mechanism's progression from a health condition to MCI and then to dementia, the idea of preventively acting with population's screening appears coherent. One of the main future neurology goals is to refine the diagnoses of MCI by studying effective biomarkers, from CSF to the use of imaging.

Innovation in dementia's pathophysiology

The most suggestive pathogenesis among dementias is certainly that of Alzheimer's disease. Its current conceptualization is therefore guided by the amyloid hypothesis, in which a deterministic chain of events leads from amyloid deposition and then tau deposition to neurodegeneration and progressive cognitive impairment.
In pathological anatomy the following are observed: cerebral atrophy, synaptic rarefaction with neuronal loss, involvement of Meyern's nucleus, neuritic plaques, neurofibrillary tangles, and congophilic angiopathy. (2)
This model fits autosomal dominant AD but is less applicable to sporadic AD. Due to emerging information regarding the complex biology of AD and the challenges of developing amyloid-targeted drugs, we could consider to propose a probabilistic model of AD in which three AD variants (autosomal dominant AD, APOE ε4-related sporadic AD, and APOE ε4-related sporadic AD) show decreasing penetrance of the amyloid pathophysiological cascade and increasing burden of stochastic AD factors (environmental exposures and low-risk genes). Implementation of this model in research can lead to a better understanding of the pathophysiology of the disease, a revision of the current taxonomy, and an accelerated development of strategies to treat AD. (4)
As a personal view of dementia research, we recognize the importance of emphasizing pathophysiology. In particular, continuing to refer to the well-known pathology of AD, a goal could be trying to act on prevention as a temporal bridge until the discovery of the primary, and perhaps unique, origin of what is microscopically and metabolically at its basis. If quantum physics has shown that

everything is energy, this can be applied also to the mathematical laws that rule the brain.

We know that the energy center of the body, brain and cells is the mitochondrion. (6)

AD is characterized by progressive neuronal dysfunction in which mitochondria play a key role in the maintenance of optimal neuronal function and neuronal vitality-longevity. Mitochondrial dysfunction may be the primary cause of AD, causing findings like Aβ and tau pathology. There is both metabolic defects and oxidative damage in AD. Further research is needed to elucidate the mechanisms underlying AD pathology and gain a robust understanding of mitochondrial dysfunction (as either a primary cause or secondary event) to facilitate the development of optimal therapeutic interventions. (7)

Neuronal dysfunction, the core feature of neurodegenerative disorders, is therefore closely linked with mitochondrial dysfunction. The brain can regulate its energy supply through neurovascular coupling and neurons signal to dilate local blood vessels to increase its oxygen and glucose supply. (7)

The long-standing Amyloid Cascade Hypothesis claims that AD pathogenesis is due to early production or reduced clearance of Aβ, the primary component of amyloid plaques, leading to intracellular accumulation and initiation of a multistep cascade culminating in neuronal damage. This hypothesis appears to be, as previously stressed, most relevant in cases of early-onset of familiar AD, as some of the strongest evidence favoring this hypothesis comes from genetic studies. On the other side, Apolipoprotein E, involved in regulating amyloid plaque deposition, is also associated with an increased genetic risk for sporadic AD. (7)

There is a rationale for a re-evaluation of the amyloid cascade hypothesis, caused by the evidence that Aβ does not correlate well with disease severity and may not drive alone AD pathology. This is especially evident in the oldest-old (age > 85), where clinicopathological studies reveal a weak correlation between cognitive decline and the level of Aβ plaque deposition: the accumulation of Aβ is common in the oldest-old without any clear clinical impact. Interventions that target Aβ have largely failed or are at best equivocal. (8)

Emerging evidence suggests that mitochondrial dysfunction is closely linked with AD pathology. Many investigators currently consider the possibility that a secondary mitochondrial cascade may prove essential to AD.

The primary Mitochondrial Cascade Hypothesis, subsequently referred to simply as the Mitochondrial Cascade Hypothesis, does not assume Aβ or tau drive the pathogenesis of AD, but it proposes that mitochondria drive the pathogenesis of AD. Changes in mitochondria that occur with age are thought to play a key role in determining the development of AD pathology. (7)

Both baseline function and environmental factors (which affect mitochondrial change rates) affect progression to AD and AD progression itself. Changes in bioenergetic hypermetabolism are thought to affect these Aβ levels. Epidemiology and endophenotypes reveal that mothers contribute more than fathers to their offspring's AD risk, implicating a role for mitochondrial DNA (mtDNA), which is maternally inherited. (7)

Haplogroups (sets of similar mtDNA polymorphisms inherited from a common ancestor) were analyzed from two longitudinal cohorts of AD and cognitively normal participants with high apolipoprotein E (APOE) ε4 carrier rates. mtDNA haplogroup J frequency was higher in AD, suggesting a possible mtDNA haplotype-AD risk association. (9)

AD cytoplasmic hybrid (“cybrid”) cell line models can be used to investigate the functional consequences of defective mtDNA in AD. Cells are depleted of endogenous genetic information, fused with platelet cytoplasm from AD patients, and repopulated with the mtDNA contained within the platelet mitochondria. AD hybrid cells exhibit increased oxidative stress, reduced adenosine triphosphate (ATP) levels, reduced Complex I and IV activity, and diminished mitochondrial movement. (10) Collectively, these data suggest that mtDNA can contribute to the pathogenesis of AD. Middle-aged individuals with AD-affected mothers are also shown to have lower activity of platelet mitochondria cytochrome c oxidase (COX) activity, which suggests that inherited energy metabolism set-points may help determine an individual's lifetime AD risk. (7)

Summing up, interactions between mitochondrial dysfunction and classical Alzheimer's disease (AD) pathology (amyloid beta plaque and tau deposition) lead to neuronal loss and dysfunction, the most proximal neurobiological event to account for clinical dementia.

Biomarkers' Era

A diagnostic biomarker is a characteristic that distinguishes a patient, based on the presence or absence of a specific physiological, pathophysiological, or disease state. The appropriate use of biomarkers in the diagnostic process is supported by guidelines and recommendations specific to disease. Despite their immense significance, there is a pronounced ambiguity surrounding their definitions and the intricacies of their application in both research and clinical settings. (11)

The concept of "biomarker", derives from the amalgamation of "biological" and "marker". Medical signs provide objective evidence of patient's health condition and can be consistently and accurately quantified. This is different from medical symptoms, which are subjective sensations reported by the patient. Biomarkers represent the pinnacle of objective and quantifiable indicators that contemporary lab sciences can consistently measure. In the reality of drug innovation and biomedical investigations, biomarkers hold a transformative role. For biomarkers, to be efficacious as replacements for clinically relevant endpoints, there are prerequisites to thoroughly grasp the standard biological mechanisms, the alterations in disease conditions, and the impacts of varied interventions. (12)

For many biomarkers, validation is incomplete, although they are routine in clinical practice. At the moment, current guidelines and recommendations focus especially on the diagnostic performance of individual markers and their role in specific disorders. There is limited evidence comparing biomarkers or their diagnostic utility when combined or used sequentially.

Choice and use of biomarkers are often guided by experience and local availability rather than by rational use based on efficacy data and cost-benefit ratio. There is a need for a shared algorithm for the choice of biomarkers in initial cognitive disorders.

Contemporary demographic studies indicate that the category of old people is expanding more rapidly than its counterparts. Epidemiological data from 2019 show that 703 million individuals globally were aged 65 or older, which is a figure that is projected to grow to 1.5 billion by 2050. The escalating aging trend is the cause of the rise of age-related health challenges. Recent analyses have emphasized that neurological disorders stand as the primary contributors to DALYs (disability-adjusted life-years), accounting for 276 million cases, and are the second

predominant cause of mortality, with 90 million cases. There was a great overtaking of neurological pathologies over cardiovascular ones. (13)

Looking for consistent biomarkers holds promise in advancing the early detection of neurodegenerative diseases, paving the way for the initiation of tailored therapeutic regimens. Research in dementia's field has apparently been static for a long, but now it's time to act applying new discoveries.

Therefore, it is noteworthy that parameters such as DNA methylation levels, SIRT activity, and BDNF expression witness a marked decline in individuals diagnosed with dementia or Parkinson's disease. Hence, the concurrent assessment of these epi-biomarkers might enhance the diagnostic accuracy for neurodegenerative diseases, thanks to the reversibility of epigenetic alterations.

Biomarkers have been categorized into two main types: "dry" markers, which encompass imaging parameters, and "wet" markers, which refer to genetic and biochemical elements detectable in fluids such as blood, serum, urine, and tissue samples. (14)

There are also surrogate markers (or surrogate endpoints), which are markers that are used as a distant relationship between an action and a clinical endpoint. Picking surrogate endpoints and demonstrating their efficacy represents a challenging task, because this action requires an excellent knowledge of the disease's pathophysiology.

Actually, the categorization of most biomarkers hinges on the pathogenic processes they signify. For conditions like Alzheimer's disease and frontotemporal degeneration spectrum, the primary focus is on biomarkers indicative of amyloid-β (Aβ) and tau pathologies. These biomarkers are predominantly evaluated through CSF examinations, blood tests, and positron emission tomography scans. (15)

As previously written, in the preclinical stages of AD, while there are detectable biomarkers signaling brain alterations, clinical manifestations remain absent. Conversely, in Parkinson's disease (PD), the onset of classic motor symptoms is observed only after a significant proportion, over half, of neurons in the substantia nigra (SN) have already degenerated. Consequently, discovering these conditions early is important for implementing strategies geared toward preventing neuronal loss.

In addition, neuroinflammation is a key factor that is both result and cause of neurodegeneration. There is a growing demand for biomarkers that can elucidate

additional aspects of AD pathogenesis, highlighting areas like neuroinflammation and early neuronal dysfunction preceding overt cell death. (16)

Also carotid intima-media thickness (cIMT) has been long debated as a surrogate endpoint of neurodegenerative disease; however, actually, it is a relevant influence in neurodegenerative disease. (17)

Over the past decade, neurofilament light chain has garnered attention as a potential biomarker for FTLD due to its sensitivity. Moreover, its levels demonstrate a correlation with clinical progression, providing prognostic insights. (18)

Progranulin (GRN) can be quantified in both blood and CSF, although the preponderance of research has been conducted on blood samples. Preliminary investigations reported remarkable sensitivity and specificity (both exceeding 95%) with a threshold of 61.5 ng/mL in plasma. However, subsequent research has proposed an elevated threshold of 71.0 ng/mL, boasting a sensitivity of 98.1% and specificity of 98.5%. Furthermore, these levels manifest stability over extended periods, remaining relatively unaltered for up to four years as evidenced in one study. (19)

The REST protein has emerged as a potential novel biomarker for AD, even if its exclusive detection in the central nervous system and in vitro models limits its application in translational research. Repressor element 1-silencing transcription factor (REST, also known as neuron-restrictive silencer factor, NRSF) is a universal feature of normal aging in human cortical and hippocampal neurons. REST is lost, however, in MCI and AD. Chromatin immunoprecipitation with deep sequencing and expression analysis show that REST represses genes that promote cell death and Alzheimer's disease pathology, and induces the expression of stress response genes. Moreover, REST potently protects neurons from oxidative stress and amyloid β-protein toxicity, and conditional deletion of REST in the mouse brain leads to age-related neurodegeneration. (20)

A trend in REST levels has been observed with declining levels corresponding to increasing clinical severity of the disease.

DNA genotyping, DNA microarray techniques and sequencing facilitated numerous genome-wide association studies (GWASs) in AD. The APOE ε4 allele stands out as a significant genetic determinant for AD susceptibility with carriers exhibiting distinct pathological traits, including a higher prevalence of amyloid plaques. (21)

Not only genomics but also metabolomics, with its diverse analytical platforms, offers powerful diagnostic tools and insights into disease mechanisms. Metabolic pathways, that are disrupted in conditions like AD and MCI, have been studied, for example a notable discovery is the reduced plasma levels of desmosterol, a cholesterol precursor, in AD patients; this decrease correlates with cognitive changes. DNA microarray techniques have also been employed to delve into neurobiology and neurodegeneration. Recent publications have emphasized the significance and appropriate utilization of this technology while exploring neurodegenerative mechanisms. (22)

Innovative imaging technologies, such as PET, hold promise for enhancing early diagnostic precision in AD's prodromal states, especially in patients with MCI, potentially fast tracking the evolution of disease-altering treatments. (23)

The arena of stem cell technology is witnessing rapid advancements. Many patients are opting to have their stem cells collected and reprogrammed. One advantage is the creation of cellular models representing "aged" cells, but there is caution to exercise, as reprogrammed cells may not perfectly replicate native neurons. (24)

Advancing our comprehension of the intricate interplay between oxidation, antioxidants, and neurodegenerative maladies will necessitate a multidisciplinary approach. Among the array of neuroimaging modalities, three techniques stand out in specialized clinical contexts due to their advanced validation stages relative to other biomarkers. These are structural MRI for atrophy detection, FDG-PET for hypometabolism assessment, and amyloid-PET for amyloid deposition quantification. The sequential application of these tools, as recommended by a consortium of multidisciplinary experts, draws upon their individual merits and limitations. (25)

Validation of consensus recommendations

In 2019, five Italian scientific societies (SINdem, AINR, SiBioC, AIP, AIMN) developed consensus recommendations for the biomarker-based diagnosis of neurocognitive disorders (Boccardi et al., Eur J Neurol, 2020(26)). The effort led to the definition of a diagnostic workflow with three waves of assessment, based on the rational use of the most established biomarkers for the etiological diagnosis of neurocognitive disorders at the prodromal stage.

As previously written, biomarkers support the aetiological diagnosis of Alzheimer's disease (AD) and other neurocognitive disorders, even at the prodromal clinical stage of mild cognitive impairment (MCI). An early accurate diagnosis allows the disease to be tackled with available or experimental intervention, lifestyle changes or logistical arrangements before disability has developed. Early intervention is expected to have greater clinical impact, extend independent and active life, improve its quality, and decrease the burden and costs of the disease.

Guidance for biomarkers' use is included in consensus appropriate use criteria specific to single biomarkers or in disease-specific research diagnostic criteria.

Considering the 2019 Boccardi et Al. guidelines (27), at the first visit to the memory clinic, patients should undergo a general clinical, neurological and cognitive examination, blood test and structural neuroimaging. It is recommended to do an in-depth clinical evaluation to highlight any non-neurodegenerative forms that may not have been detected as significant causes of cognitive disorders.

According to the Italian guidelines the kidney should be evaluated with also liver function and possible infectious causes. Global cognitive state should be assessed with the Montreal Cognitive assessment. (28) (29)

Magnetic brain resonance imaging (MRI) should be performed as a baseline exam to evaluate atrophy or other abnormalities. MRI should be ordered by a dementia expert, acquired with a standard acquisition protocol and evaluated in expert centers or by properly trained specialists. This exam could provide accurate results information, even in the prodromal phase, on the degeneration, vascularity or typical features of less common disorders, as Creutzfeldt-Jakob disease and should be preferred to computed tomography (CT) scan to age 85. (30)

If the clinical data are coherent with a possible neurodegenerative disorder, a more detailed clinical examination provides an etiological diagnostic hypothesis direct to the prescription of biomarkers. In addition to medical items like nutrition, sleep, medications, the cognitive assessment should cover all the main areas and networks and ideally be standard across all centres. We shouldn't forget the fundamental role of the glylymphatic system during sleep time. The evaluation of functional autonomy should be designed for the current era and avoid gender bias. Depression and anxiety should be assessed with common validated scales. (31)

There are different combinations of the information acquired through direct investigation.

With dementia with Lewy bodies (DLB) as primary diagnostic hypothesis, dopamine transporter single-photon emission CT (DaT-SPECT) can exclude AD when parkinsonism is absent or unclear. Myocardial metaiodobenzylguanidine (123I-MIBG) scintigraphy has a higher diagnostic specificity (32) (33) although not yet reimbursed for this diagnostic purpose. In patients with evident parkinsonism, both 123I-MIBG and 18F-fluorodeoxyglucose positron emission tomography hypometabolic bast models (FDG-PET) are greater informative compared to DaT-SPECT. (34) (35)

If frontotemporal lobar degeneration (FTLD) is the primary diagnostic hypothesis, the differential frontal or temporoparietal hypometabolic patterns in FDG-PET help the differential diagnosis with AD in most cases (34) (36).

About a third of frontotemporal dementia (FTD) patients may present with parkinsonism, often associated with altered DaT-SPECT. In these cases, a careful search to exclude other associated physical or dysautonomic signs and the pattern of hypometabolism on FDG-PET could help differentiate FTD with parkinsonism due to Parkinson's disease, multiple system atrophy (MSA), progressive supranuclear palsy and cortico-basal degeneration.

With suspicion of AD, different clinical scenarios address the investigation of biomarkers. Negative MRI requires FDG-PET to look for evidence of this early neuronal damage. With positive MRI or FDG-PET, amyloid and tau in cerebrospinal fluid (CSF) are the first choice examination to investigate etiology up to age 75. (37) (38)

The clinical impact of additional tests should be evaluated with patients between 75 and 85 years old and can be limited beyond 85 years. Only with contraindicated or rejected lumbar puncture, amyloid-PET is recommended at this level of investigation. (39)

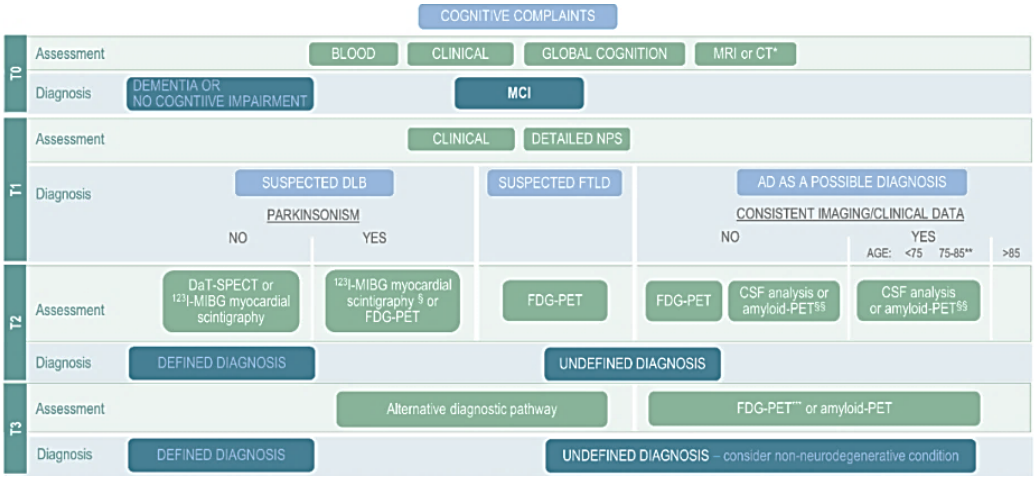
If not already performed, FDG-PET can disambiguate cases still undefined after investigations for AD.

Cases still undefined at T2 may benefit from the assessment of a different diagnostic path. For example, unusual cases with atypical parkinsonisms presenting with MCI but lacking other typical neurological signs or symptoms may be clarified by FDG-PET, if not yet performed, and confirmed by DaT-SPECT. (40)

Cases undefined at the end of the diagnostic procedure may be due to psychiatric causes or non-pathological aging, and may require assessment by other specialists.

Biomarkers are thus used variably in clinics, depending on clinicians' expertise or logistical issues (laboratories' proximity, waiting lists, perceived acceptability).

Until this year the available recommendations and guidelines have been disease or biomarker-focused. A European multidisciplinary task force composed of 22 experts from 11 European scientific societies worked to define the first patient-centric diagnostic workflow that aims to prioritize testing for available biomarkers in subjects attending memory clinics. They used a consensus procedure to identify clinical syndromes, based on clinical history and examination, neuropsychology, blood tests, structural imaging, and EEG. It is recommended first-line and, if necessary, second-line biomarker testing based on the patient's clinical profile and previous biomarker results. That workflow promotes consistency in the diagnosis of neurocognitive disorders across European countries. (41)



II: Consensus recommendations for the aetiological diagnosis of neurocognitive disorders (MCI specifically) in Italian memory clinics (modified from Boccardi et al., 2020)(26).
T0: baseline general assessment. T1: baseline detailed assessment. T2: biomarker assessment. T3: disambiguation of undefined diagnoses.
** CT should be performed only if MRI is unavailable or contraindicated. Moreover, it is acceptable over age 85 due to the lower impact of imaging biomarkers on diagnosis at older ages.*
*** Due to wide individual variability, over age 75 additional examination should be prescribed based on the potential clinical impact for the individual patient.*
**** If not yet performed, FDG-PET is the first-choice exam for possible AD patients whose diagnosis is still undefined at T2. Despite greater validation and current authorization and reimbursement, DaT-SPECT provides limited added value if the patient presents with clear parkinsonism. If CSF analysis is not possible, prescribe amyloid-PET to assess brain amyloidosis at T2.*
CSF: cerebro-spinal fluid. CT: computerized tomography. DaT: dopamine transporter. FDG:18F-fluorodeoxyglucose. MCI: mild cognitive impairment. MRI: magnetic resonance imaging. NPS: neuropsychology. PET: positron emission tomography. SPECT: single-photon emission computed tomography. 123I-MIBG: metaiodobenzylguanidine.

White text continuation of diagnostic procedure; blue text: conclusion or interruption of this consensus diagnostic procedure.

Summing up, several diagnostic recommendations have been published in the field of dementia by a number of national and international authorities.

In all previous efforts the impact of guidelines onto clinical practice is evaluated with a retrospective and detailed review of medical charts.

Innovations make healthcare better, more convenient and more efficient. Developments such as new technologies and business models help advance healthcare. Furthermore, healthcare systems around the world are facing unprecedented challenges, including rapidly and permanently adapting clinical processes based on emerging scientific evidence and providing high-quality care with limited resources. Typically, healthcare organizations make intensive use of Healthcare Information Systems (HIS), such as hospital information system. It can support clinicians, healthcare organization managers, and other decision makers with a wide range of process-related questions in the medical field.

Process execution data is a valuable source of information to support the management and improvement of healthcare processes.

REFERENCE	EVALUATED GUIDELINES OR RECOMMENDATIONS	METHODS	OUTCOME	RESULTS
Chui & Zhang. Neurology, 1997	- Practice Parameter (1994)	Retrospective study design. Medical chart assessment (n=119). Comparison between standard dementia work-up and comprehensive work-up (including laboratory and neuroimaging studies).	Incremental diagnostic value of laboratory and neuroimaging studies. Sensitivity and specificity of 4 clinical indicators (early symptom onset, no insidious course, focal neurological signs, and gait disturbance).	Diagnostic accuracy was improved by laboratory and neuroimaging studies. Clinical indicators were 82% sensitive and 40% specific in predicting that neuroimaging studies would change the diagnosis.
Phung et al., Dement Geriatr Cogn Disord. 2009	- The Italian Neurological Society Guidelines (Sorbi et al., 2000). - Practice parameter (Knopman et al., 2001). - Conclusion from the Canadian Consensus Conference (Patterson, 2001). - EFNS Recommendations (Waldemar et al., 2000)	Retrospective study design. Medical chart assessment (n=200). Reference standards: evidence-based dementia guidelines.	Completeness of the work-up on which the dementia diagnosis was based. Positive predictive value (PPV) of clinical dementia diagnosis.	Satisfactory or acceptable completion of the basic dementia workup was documented in 51.3% of the patients. The PPV of a clinical diagnosis of dementia syndrome was 88.5% (95% CI = 84.0–93.0), but correct subtypes were diagnosed in only 35.1%
Turró-Garriga et al., J Alzheimers Dis, 2017	- NICE-SCIE guideline, 2006. - EFNS-ENS guidelines (Sorbi et al., 2012). - Practice parameter (Knopman et al., 2001). - Conclusion from the Canadian Consensus Conference (Patterson, 2001). - EFNS Recommendations (Waldemar et al., 2007). - Spanish clinical practice guideline (2010)	Retrospective study design. Medical chart assessment (n=475). Reference standard: basic dementia work-up.	Index of Adherence (AI; Range 0-10; higher values state for greater adherence). Drug prescriptions and supplementary tests ordered.	AI (mean±SD) =8.2±1.3; for severe cases of dementia, AI=7.8±1.8.

1: Previous initiatives aiming at validating guidelines and recommendations for the diagnosis of dementia and MCI in clinical practice.

The future of medicine

To answer process-related questions, process mining techniques can be a great value. Process Mining is a set of techniques used by many domains, including healthcare, to retrieve valuable information from an event log. Various process mining techniques have been developed in industries, and enable healthcare stakeholders to identify the actual order of activities in a process, to determine the conformity between an existing model and reality and to provide information on the involvement of regulators sources in a process.

Compared to alternative approaches, process mining takes data from real-life behavior of a process as a starting point. In this way, process mining can support healthcare institutions in achieving each of this quadruple objective for improving healthcare: (i) improvement population health, for example, by supporting the analysis and improvement of care paths; (ii) improve the patient experience, for example by highlighting how a process can be optimized from the patient's point of view; (iii) reduce costs; and (iv) improve the work-life balance of healthcare workers. In addition to supporting data-driven management and improvement of healthcare processes, process mining also has the potential power to support health system resilience by providing detailed insights into how processes are executed within a particular context. (42)

To induce widespread and systematic adoption of process mining in the healthcare sector, targeted methods and techniques that explicitly domain-specific characteristics must be taken into account.

Recent advances in machine learning allow us to develop predictive models of neurodegenerative disease by mining multimodal datasets that include measurements of cognition and neuropathology from large patient cohorts. Machine learning models have been shown to help in the prediction if individuals diagnosed with MCI will decline or remain stable. Fewer models have achieved prediction of individual variability in disease progression focusing primarily on some models estimating exact time to conversion. (43)

Novel modeling approaches that predict individualized trajectories of cognitive decline based on continuous measures need to be developed to enhance clinical validity and guide effective clinical interventions and drug discovery trials (43). Process mining has been used not only for modelling prognostic trajectories of cognitive decline due to Alzheimer's disease, but also in the domain of chronic

diseases(44), COVID-19 management for cancer patients (45) and to explore Type 2 diabetes evolution (46).

Young onset dementia

Young onset dementia (YOD) refers to the onset of dementia before the age of 65 years. Diagnosis of YOD is challenging compared to LOD (late-onset dementia), because it affects individuals in the middle of their careers, taking care of their families, and often with financial burdens. The costs of YOD involve not only the direct costs but also the indirect economic burden due to loss of employment and income. YOD diagnosis is usually delayed primarily because patients are not referred to dementia centers soon enough, and because health-care professionals may not initially take into consideration the fact that the cause may be a neurodegenerative disorder. The focus of most dementia services is primarily upon the needs of older people, and as a consequence, these services are frequently not able to respond to the specific needs of patients with YOD. From this perspective, understanding the epidemiology of YOD is the first step in addressing this challenge. (47).

The increased use of biological and imaging markers in routine clinical practice has further improved diagnostic accuracy of atypical clinical presentations. Concomitantly, the revision of the clinical criteria for Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) spectrum, and dementia with Lewy bodies (DLB) has prompted a wider recognition of these disorders in experienced clinical settings.

Therefore, up-to-date epidemiological studies with register-based approaches and with the involvement of specific clinical experts could improve knowledge in terms of numbers and impact of YOD.

Administrative setting and ethical therapy

Alzheimer's disease represents the third cause of death for the over 65s in Western Europe, considering also complications related to the development of the disease. It is necessary to promote better patient care, starting from the early diagnosis of the disease, followed by a personalized approach and the strengthening of an integrated healthcare network present in the area. It could facilitate access to

continuity of care and the development of research pathways. There is a strong, but never enough, awareness by institutions about the importance of considering these pathologies as a primary public health problem, structurally facing most critical issues. (48) (49)

Research has been working on anti-amyloid drugs for thirty years and in recent years it is more evident that working on this mechanism can be one of the strategies to slow down or stop the disease. While waiting for new effective therapies, it is important to not wait for starting therapy. (8) (49)

The importance of continuity of care is reiterated, to be pursued through integration between all territorial facilities but starting from the idea of home as the first place of care. These are some of the concepts that emerged during the conference "Alzheimer's and neuroscience: a priority for the country", held last July 14th at the Italian Chamber of Deputies, following the birth of the Parliamentary Intergroup for Neuroscience and Alzheimer's. The Government and institutions should try to work to consider these pathologies as a primary public health problem. (50)

Advance is essential to fight dementia. With this purpose the Interceptor project was created, coordinated by the "Agostino Gemelli" Polyclinic Foundation of Rome, by the Italian Alzheimer's Disease Association (AIMA), by the IRCCS-INRCA of Ancona, by Istituto Superiore di Sanità and sponsored by AIFA and the Ministry of Health. Scientific research has shown that for many years the disease can "work in the dark", destroying cells and nerve circuits. This can happen thanks to the plastic reorganization capabilities of the brain which uses resources from the "neural reserve" to replace damaged circuits. There is, therefore, a prodromal stage of the disease in which the symptoms are absent or very subtle. The Interceptor project focuses specifically on the diagnosis of this stage. (51)

In recent years, as previously written, the most frequent research approach is to develop a very early pharmacological intervention in the first stages of the disease, when the symptoms are minimal. This is why greater attention has been paid to identify biomarkers that allow us to predict the conversion from MCI to Alzheimer's disease. Neuropsychological tests, remain one of the main pillars of diagnosis.

This is the scenario where the Italian Medicines Agency and a group of dementia experts have launched a series of activities with two objectives. (50)

The first: be ready to start all treatments and counteractions currently available as soon as possible.

The second: managing the eventuality of the arrival on the market of one or more drugs potentially capable of preventing or treating Alzheimer's disease.

About the use of cholinesterase inhibitors, the problem is that the mean change is relatively small and may be difficult to discern in individual patients with a fluctuating course of disease, and after six to twelve months progression resumes.

In contrast to the position with statins and blood lipids, for example, there is no biomarker of efficacy. If we could monitor a clinical measure of cholinergic activity, we would have greater faith in treatment. From recent studies, also non-invasive brain stimulation with transcranial alternating current stimulation at gamma-frequency (γ-tACS), applied over the precuneus, can improve episodic memory and modulate cholinergic transmission by modulating cerebral rhythms in early Alzheimer's disease. (52)

Many people come to memory clinics with mild cognitive problems. There is so much discussion about whether it is ethical to diagnose dementia in such people when we lack more effective means of intervention. Very careful consideration must be given assessing the patient’s true wishes about disclosure of any biomarker-based diagnosis, the uncertainties surrounding such an important diagnosis, the potential involvement of family members and close friends, and the provision of counselling. (49)

However, there is the main principle that the patient has the right to know. Knowledge also brings the possibility to plan for the future and perhaps take all possible preventive measures.

Recent data show a lower age-adjusted incidence of dementia in the cohort recruited in the 2000s than among people recruited in the 1990s. The brain is healthier and brain volumes are larger. The factors thought to be responsible include a reduction in cardiovascular risk factors, supported by MRI evidence of less vascular change, and higher levels of education.

Turning to AD specifically, around a third of the condition worldwide is attributable to risk factors such as midlife hypertension and obesity, diabetes, physical inactivity and depression.

Randomized controlled trials of primary prevention have reported some encouraging results. The Finnish FINGER study involved 1260 people aged sixty and above and used a two-year intervention including advice on nutrition, exercise, cognitive training and social activity. The intervention group showed a significant

enhancement of cognitive performance and lower risk of cognitive decline, but longer follow-up is needed to assess incidence of dementia in general. (53) (49)

The art of memory

The word dementia derives from the Latin “dèmens”, which literally means "out of mind". The first author to adopt the word "dementia" was Aulus Cornelius Celsus, who in De Medicina used this expression to generically designate "alterations of intelligence and behavior". In the past, the clinical use of "demented" remained restricted to the social sphere with a derogatory meaning. The French psychiatrist Jean Etienne Esquirol, in 1838, was the first to emphasize memory disorder and define dementia as a clinical picture characterized by loss of memory, judgment and attention. In 1906 Alois Alzheimer, and in 1909 Gaetano Perusini, described the case of a 51-year-old woman with progressive cognitive decline, associated with delusions of jealousy and restlessness. The autopsy findings showed a picture of cerebral atrophy and the presence of characteristic alterations, senile plaques and neurofibrillary balls, which still constitute the diagnostic neuropathological substrate of this pathology, which is called Alzheimer's Disease. (2)

We must remember Giordano Bruno's concept of the human mind and memory, expressed in "De Umbris Idearum" and "Ars memoriae". (54) In the philosophical vision, the universe is a single body, with a precise order of structure and connection. The starting points are ideas, immutable principles in the mind, but these ideas are overshadowed and separated in the act of wanting to understand them. By reflecting the structure of the universe, the human mind, which has within itself not ideas but the shadows of ideas, can achieve true knowledge. We must try to obtain a cognitive method that captures the complexity of reality, up to the ideal structure that supports everything.

This method is based on the art of memory, whose task is to avoid the confusion generated by the multiplicity of images.

The logic, mathematical and rational laws that govern the mind can drown in the sea of emotions and confusion, erasing personal identity. Therefore, as a personal view, the art of memory is a system that clarifies reality.

The iconography at the end of each paragraph has been chosen because it is inherent to the project's deep purpose.

William Charles Utermohlen (South Philadelphia, 1933 – London, 2007) was an artist who after his diagnosis of AD decided to begin producing a series of self-portraits to describe in an artistic way what he would have experienced with this illness. In 1996 he drew pencil portraits where anger can be seen, with the visual prevalence of his forehead. A saw also began to appear, as a reference to autopsy and anatomopathological diagnosis. (55)

In 1997 his face began to become more schematic; he began to dominate the color black and red. Since 1998 he began to have loss of motor skills and retired from art and by 2002 he could no longer work. Taken to a clinic in 2004, he died there in March 2007. (56)

In this work the self-portraits are listed from the most recent to the oldest one. The motivation is allegorical, as an expression of the will to prevent and regress degeneration and a return to the origin of the painter's identity, consistent with the purpose of this study. The product of his art reflects what we see through patients we welcome weekly in the clinic; the interest in dementia and cognitive deficits does not only aim to save lives, like every other branch of medicine, but also to preserve their souls.

III: "Head I", 2000. One of Utermohlen's last self-portraits.

OBJECTIVES

The present study is part of an ongoing project (the VALICO study) that aims to compare the most frequent diagnostic workups in three academic memory clinics before (retrospective data, pre-recommendations: January 2018 - December 2019) and after (prospective data, post-recommendations: October 2022 - October 2023) the release of the Boccardi et al. recommendations to assess their applicability in clinical routine. The project aims to evaluate: i) the adherence of Italian specialists to the Italian consensus recommendations for the diagnosis of patients with MCI and dementia (primary outcome); ii) changes of patient management and following the adoption of the recommendations (co-primary outcome).

The innovative engineering and computed methods used could be pioneering in creating a standardized model for establishing guidelines. The process mining systems used will be explored in depth in the following chapters.

Until now, just a few studies have specifically assessed the incident rates of neurodegenerative YOCD, mainly in small population settings and using past clinical criteria. Usually AD is reported as the most frequent form of YOCD, followed by frontotemporal dementia (FTD), but different etiological diagnoses need to be investigated further. (47)

In addition (iii), the present work, based on the Padova register, also aimed to assess the incidence of YOCD in Padova County, to describe factors that could delay diagnosis and to identify how many diagnostic resources are dedicated to these patients.

IV: "Erased Self Portrait",1999, Utermohlen's self-portrait.

MATERIALS AND METHODS

Recruitment

This study is part of a complete validation of the Italian consensus recommendations for the biomarker-based diagnosis of neurocognitive disorders (VALICO).

In three Italian memory clinics (CDCD), the medical charts of consecutive MCI or dementia patients have been retrospectively reviewed during two periods: 1) preconsensus (January-December 2019 and in addition January-December 2018, referring to Boccardi et Al. (26)) and 2) post-consensus (October 2022-October 2023).

Patients' pathways, plotted against medical records and mapped onto the consensus workflow, will allow assessment of adherence to the present recommendations and changes in diagnostic work-up.

Three expert memory clinics took part to the project. These were chosen based on a survey about the clinical use of biomarkers among members of SINdem and AIP scientific societies who are in charge of a Centre for Cognitive Disorders and Dementia (CDCD). The selection was based on availability, frequent use of all biomarkers and geographical representation (one in the north, one in the centre and one in the south of Italy).

To identify CDCD centers it was developed a brief structured questionnaire that was emailed to all members of SINdem and AIP scientific societies in charge of a CDCD. For each CDCD the important info was on: routine clinical work-up of MCI or dementia patients, availability and frequency of use of molecular and imaging biomarkers, time and number of visits required to achieve a diagnosis, other diagnostic tests, logistic factors involved in biomarker selection (costs, availability of instrumental examination in the centre), estimated number of new patients with MCI or dementia per year, willingness to allocate personnel to the retrospective data collection of this study. Analysis of the collected data allowed to identify the three CDCD that took part to the study.

An information session on the content of the Italian consensus recommendations was organized for clinicians in the selected CDCD centres. For the retrospective section we considered eligible all consecutive patients with MCI or dementia that came for the first time to observation and entered a diagnostic path between January 2018 and December 2019 (period 1: pre-consensus. This part of the study could be

considered a retrospective longitudinal systematic chart review) and ii) between October 2022 and October 2023 (period 2: post-consensus). Hypothetically, the medical charts of 600 patients should be reviewed (100 per center per period, 200 per CDCD). The sample size was calculated using the statistical techniques for estimating sample size in descriptive studies with dichotomous variables. The width of the 95% confidence interval was set at 0.15, yielding a minimum sample size of 171 medical records per center.

Patients' journeys were tracked by dedicated researchers, based on medical charts and mapped onto the consensus workflow.

Adherence is the primary outcome, so we will calculate an Index of Adherence (AI) (26) using prespecified items in the medical charts. The number and type of deviations per patient from the consensus recommendation in period 2 will be analysed in the whole sample and after stratification by memory clinic. The same data in period 1 will be used as the control.

Changes in patient management is the co-primary outcome, so we will estimate whether the adoption of the recommendations may significantly affect the clinical management of patients. To this end, data concerning the change in diagnosis and treatment (medication and/or non-pharmacological interventions) will be collected from medical charts.

We will assess whether a-priori determined demographic and/or clinical features lead to systematic changes in diagnostic workup. We hypothesized that early age at onset, atypical presentations and rapid progression may impact the diagnostic work-up in both period 1 and 2.

Data analysis: process mining

Through computer engineering work it was possible to create a process mining platform. This allows to carry out Process Discovery: starting from real data it can derive the process that generated them.

Process mining is a family of techniques focused on gaining valuable insights from data that processes generate. It works as a bridge between process science (which includes areas such as business process management and operations research) and data science (which includes areas such as data mining and predictive analytics), resulting in methods to analyze processes through data.

Process mining is domain-agnostic, and it can be applied in any industry where processes are present and data is available. Healthcare, the topic of this work, is a domain where the use of process mining is growing.

Processes can be represented using a model as a sequence of steps and the different paths a process can take. Nowadays, many healthcare processes are supported by Health Information Systems (HIS). This process execution data can be used to create an event log.

Event logs containing process execution data are the primary input for process mining algorithms, and they are composed of cases. Each case is composed of a sequence of events, and they refer to the completion of a particular activity in the treatment process. The key components of an event log are:

- case id: a process instance contained in the data, which could be a patient being treated in the hospital in a clinical process;
- activity: a step of the process, which could be “check vital signs”;
- timestamp: time at which the event took place;
- transaction type: the state when the event was recorded;
- resource: refers to the resource associated to the event. This could refer to a healthcare professional or medical device;
- other attributes: additional case or event attributes may also be recorded in an event log, such as the hospital unit where the patient has received care, the patient’s vital signs, etc.

Using the event log, various process mining types can be performed in order to generate valuable process-related insights. Three prominent types of process mining are:

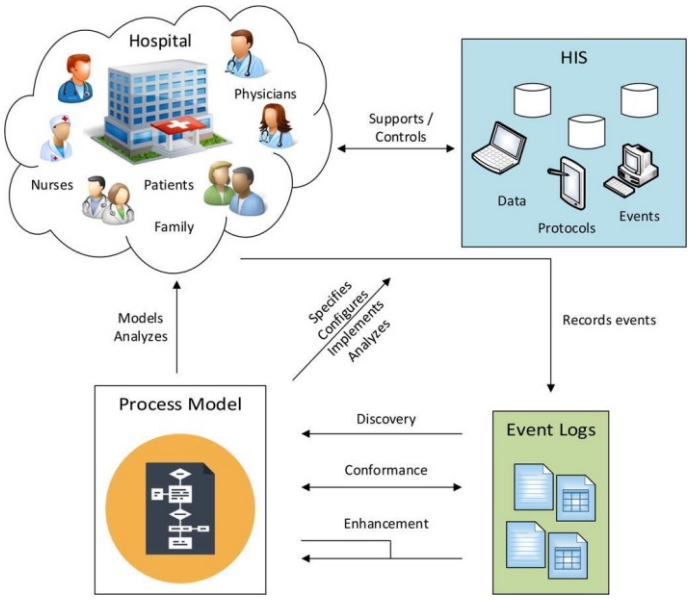
1. discovery: these algorithms are useful to obtain process models reflecting process behavior from an event log;
2. conformance checking: these algorithms require a process model and aim to compare the behaviour in the event log with the behaviour in that process model. Conformance algorithms help to detect deviations between the observed behaviour in the event log and the process model;
3. enhancement: these algorithms help to enrich and extend an existing process model using process data. (42) (57)

In this work, data analysis were conducted in R. The pMineR structure has been specifically designed to support the evolution and extensibility of the system and to privilege improvements oriented to real-world issues in medicine.
The main collections of pMineR are:

- Data Loader: it includes classes handling the loading of event logs and data pre-processing. It provides tools to translate and/or group event log terms by a given dictionary, used for storing structured information extracted from raw data for creating different views;
- LOG Inspection: this collection is a set of classes aiming to provide some descriptive statistics on event log data, useful for a preliminary exploration of the data;
- Process Discovery: this collection implements one or more algorithms. In the current version of pMineR there are two classes implementing, respectively, first and second order Markov Models-based algorithms. Classes in this package interact by a set of standard methods, in order to increase the possibility of interaction among objects of different classes;
- Conformance Checking: there is a set of classes specialized in Conformance Checking.

Even if also the Process Discovery classes have methods to check how a set of given processes can flow through the models, normally, the formalism for representing clinical guidelines has no algorithms to automatically generate an interpretable guideline starting from real world data. pMineR allows to work with an internal formalism for representing WorkFlow-like diagrams: such formalism is called Pseudo-WorkFlow (PWF) and was designed to represent a set of needed guidelines. The current version of pMineR implements two algorithms referring to the first one (FOMM). The pMineR can calculate the differences between the generated models and reproduce them in the form of diagrams, which can then be analyzed by human experts.
These items are specifically designed to support Conformance Checking, proposing schemes and diagrams close to the language adopted by the doctors. At the moment pMineR implements an engine capable of analyzing guidelines written in the previously introduced PWF language, which is based on three main constructs: events, states and triggers. Given an event log, the engine reads the list of events and, for each event, checks if one or more triggers can be fired. A trigger is an

element composed of two main sections: condition and effects. The condition part can check just read event log items or other patient states. Using this approach, states are automatically updated as events and processed, sequentially, from first to last. (58)



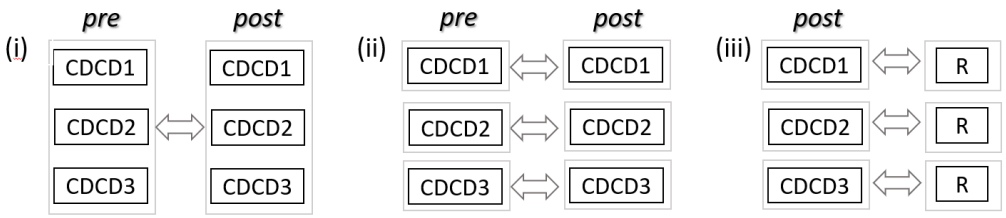
V: Process mining for healthcare.

It also allows Conformance Checking, allowing you to measure how closely patient paths adhere to a given process. The analysis method used is:

(i) comparison of the pre-and post-adoption paths of the recommendations (R) between the various centers;

(ii) measurement for each center of the pathways in place pre- and post-introduction of recommendations;

(iii) compliance monitoring to measure adherence to given recommendations.

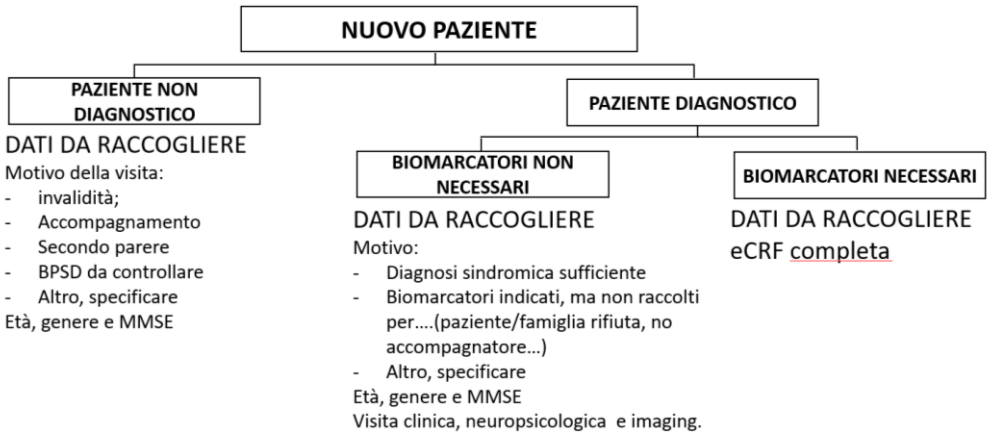


VI: Analytical method.

Data collection

Patients for each of the two selected periods were divided into three categories: non-diagnostic, diagnostic without use of biomarkers, diagnostic with use of biomarkers. The last category is the one on which we mostly focused our attention. To define a patient as "diagnostic" it is necessary that the diagnosis of neurocognitive disorder was carried out with the first visit just in our neurological clinic.

For each category, the data in the image below was collected.



VII: Patients' classification. For each category, the data contained in each bullet point was collected.

Basically, structural images (CT and MRI) are not considered biomarkers. CSF analysis, FDG- and amyloid-PET, PET/MRI, DaT SPECT and myocardial scintigraphy with MIBG are all biomarkers.

As previously written, a good biomarker must have high prognostic and predictive value, it is able to predict a disease and direct it towards those treatments that could be more successful. The characteristics required of a good biological marker are: a specific correlation with the disease, adequate predictability on the type of treatment and response, the possibility of carrying out the determination precisely in a short time and to be relatively insensitive to sampling errors.

In neurology, biomarkers represented by imaging tests are as important as biohumoral tests. The most obvious example is that of Alzheimer's disease, in

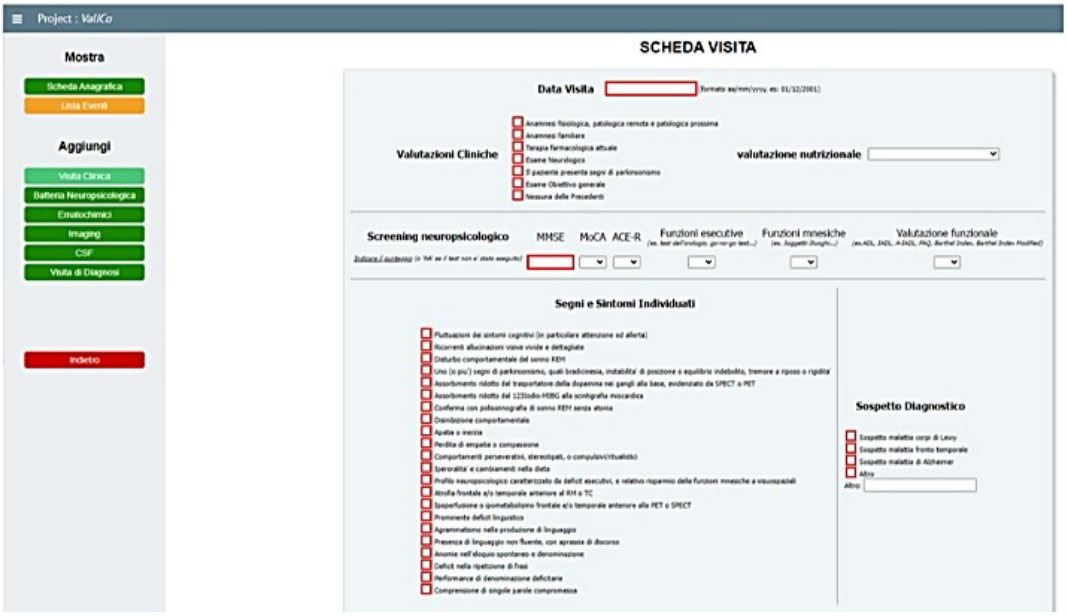
which genetic investigation from blood sampling, CSF analysis and MRI and PET examinations go hand in hand.

The diagnostic investigation, as this work demonstrates, must be a chain of tests. The most modern diagnostic technology techniques base their foundations on the oldest tests, starting from anamnesis and physical examination. No biomarker alone can overturn the diagnostic history of a pathology, but underlining the importance of research and the advancement of each technique is essential for progress in the future.

The platform we used was the result of an elaborate engineering study.

For each patient, the data entered initially are:

1. ID: progressive number automatically assigned by the system for each patient;
2. randomization code: alphanumeric code assigned by the compiler to each subject;
3. gender of the patient;
4. age of the patient at first visit;
5. patient type: “non-diagnostic patient”, “diagnostic patient - markers NOT necessary”, “diagnostic patient – necessary markers”.



VIII: Example of a screen for entering clinical visit data.

The data collected for “non-diagnostic patient" are:

1. MMSE: the raw score on the patient's Mini Mental State Examination at the first visit or the first available MMSE;
2. reason for visit: the reason why the patient comes to the center for the first visit. The available options were: disability, accompaniment, second opinion, BPSD to be checked, other to specify.

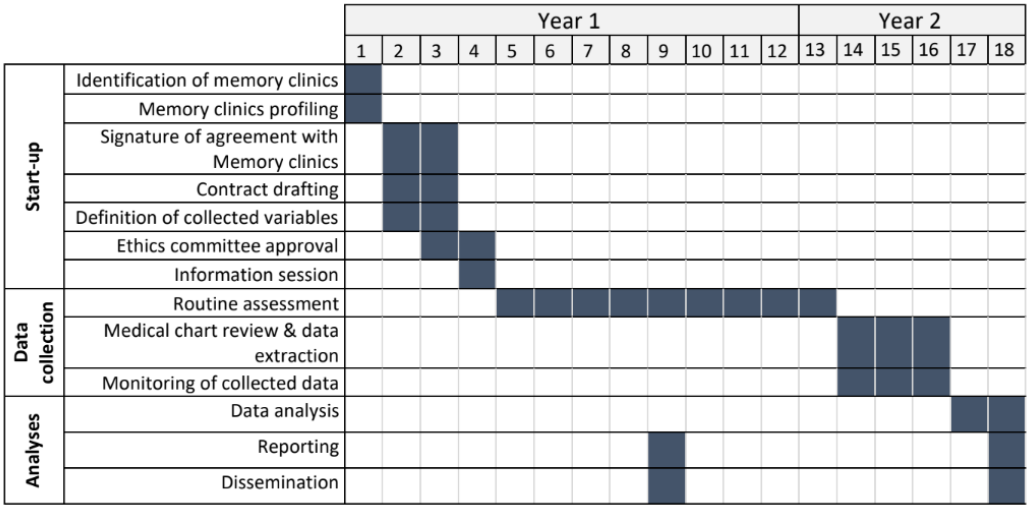
The data necessary for «Diagnostic patient – markers not necessary" are:

3. MRI exam: whether the subject underwent an MRI during the diagnostic process, remembering that MRI is not considered a biomarker;
4. neuropsychological examination: whether the subject underwent a neuropsychological examination during the diagnostic process;
5. blood chemistry tests: whether the subject underwent blood chemistry tests during the diagnostic process;
6. MMSE: the raw score on the patient's Mini Mental State Examination at the first visit or the first available MMSE;
7. main diagnoses: the patient's main diagnosis at the end of the diagnostic process by selecting one of the available options;
8. reason for missing biomarkers: the main reason why biomarkers are not present for the patient and the options are: sufficient syndromic diagnosis, biomarkers impossible/not prescribable;

For the "diagnostic with biomarkers" patient, the data to be entered for the first visit to the clinic are:

1. visit date: enter the date of the patient's first visit.
2. clinical assessments: the various assessments/information collected on the patient;
3. nutritional assessment: the nutritional assessment performed. The available options were: None, BMI, Clinical Scale (MUST, MNA);
4. neuropsychological screening: the only score to enter was the raw MMSE score;
5. signs and symptoms identified: signs and symptoms reported in the report from the first visit.

For the diagnostic suspicion, we indicated the diagnostic suspicion inferred from the Data Entry, aided by the symptoms highlighted in the previous field.
Then any additional ones needed to be added ongoing clinical visits, carried out before arriving at the diagnosis second level neuropsychological battery, blood chemistry tests, imaging tests, liquor tests.



IX: Timelines. Start date: the project started after the contract was signed. The total project duration was 18 months at the beginning. Start-up phase: M0-M5. Data collection phase: M6-M16. Data analysis and dissemination phase: M16-M18. Actually total duration has been extended.

Young onset dementia

This epidemiological part of the study was conducted retrospectively by analyzing patients from January 1, 2020, to December 31, 2022 in Padua province, located in Veneto, northern Italy. (59)
We considered all new cases of YOD confirmed in the study period, for people living in the reference geographical area, and reviewed all the patient records.
In this retrospective work, the study period was dated mostly after the COVID-19 pandemic, to avoid biases in assessing incident diagnoses.
The Padua register consists of a network including neurological and geriatric services (Neurology Unit AOPD and CRIC), involved in the care of cognitive disorders, covering all cases of dementia in the reference geographical area of Padua province. They provide care and promote awareness of dementia and actively

collaborate with general practitioners. In Italy, every citizen has free access to health care through the National Health System.

Each patient fulfilled clinical and imaging diagnosis, according to current clinical criteria. (26) Only patients with YOD, namely dementia diagnosed ≤ 65 years old, were considered.

Moreover, we considered FTLD subtypes, such as behavioral variant FTD (YO-bvFTD), primary progressive aphasia (YO-PPA), progressive supranuclear palsy (YO-PSP), corticobasal syndrome (YO-CBS), and frontotemporal dementia–amyotrophic lateral sclerosis (YO-FTD-ALS). With regard to PPA subtypes, we considered both non-fluent variant PPA (nfvPPA) and semantic variant PPA (svPPA) belonging to the FTLD spectrum.

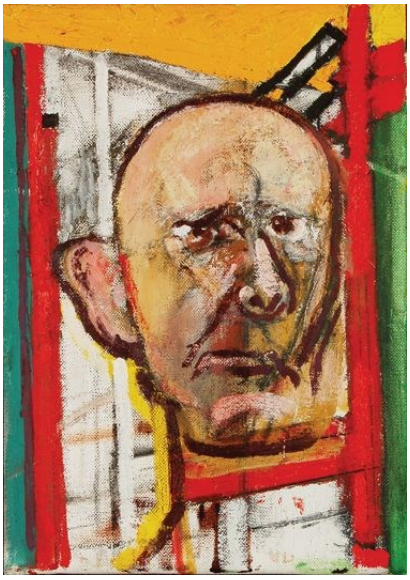
The present study involved a two-step process: the suspected cases were first referred by general practitioners to CDCD, based on symptom onset. The CDCD staff are made up of neurologists or geriatricians with extensive experience in the field of dementia and primarily involved in the diagnosis and treatment of neurodegenerative dementing disorders.

Each referred patient with suspected YOD was then evaluated by the research team carefully recording demographic characteristics, family history and clinical features.

According to the standardized protocol of the Italian National Health System, during the first visit, dementia experts performed general, cognitive, and behavioral examinations. Eligible patients underwent a standardized neuropsychological and behavioral evaluation as well as brain magnetic resonance imaging (MRI). To further confirm clinical diagnosis, in selected cases, cerebrospinal fluid (CSF) analysis (tau, phospho-tau and amyloid beta42), functional imaging scan (positron emission tomography [PET] amyloid scan or brain fluorodeoxyglucose [FDG] PET scan or single-photon emission computed tomography dopamine transporter scan), or genetic screening for monogenic neurodegenerative dementias, were carried out.

A detailed clinical history was carefully recorded. We considered age at disease onset and time from onset to diagnosis. The age at onset was defined as the age at which the first symptoms consistent with YOD were observed by the partner or caregiver. Family history was also computed. The neuropsychological assessment

included tests tapping global cognitive functions, specific cognitive domains, and behavioral disturbances.



X: 1998, Utermohlen's self-portrait.

RESULTS

First retrospective study (2018-2019): pre-consensus guidelines

This chapter shows the results of the first analysis about retrospective patients from Padova.

From 2018 to 2019, a total of 235 patients were collected: 70 non-diagnostic follow-up patients, 108 patients with clinical diagnosis without biomarkers and 57 diagnostic patients with biomarkers.

As for sociodemographic variables, patients with biomarkers-based diagnosis are younger and more frequently males (table 2).

	Total sample N=235	**ND N=70**	**DNB N=108**	**DB N=57**	**Comparison[a]** ANOVA or χ^2
Age (T1)[b]	74.16 ± 10.64	73.41 ± 11.29	77.58 ± 9.07	68.81 ± 10.27	F(2,226) = 14.224, ***p* < 0.001**
Gender – Female (T1)	129 (54.9)	40 (57.1)	66 (61.1)	23 (40.4)	$\chi^2(3) = 6.698$, ***p* = 0.035**
MMSE[c] (T1)	22.48 ± 5.63	23.26 ± 5.08	21.89 ± 5.93	23.24 ± 5.33	F(2,153) = 1.126, *p* = 0.327

2: Demographic variables of patients recruited in the retrospective study.
ND: non-diagnostic follow-up patients, DNB: patients with clinical diagnosis without biomarker, DB: patients with biomarkers-based diagnosis.
Notes: a: ANOVA for continuous variables or Chi-Square for categorical variables. b: For Age, in years: ND (N = 68), DNB (N = 104), DB (N = 57). c: For MMSE score (questionnaire, n/30): ND (N = 35), DNB (N = 88), DB (N =33).

The group of patients with clinical diagnosis performed almost all neuropsychological assessments and brain MRI (90% cases, table 3).

About the frequencies of exams and tests, for non-diagnostics patients no data were collected, except for NPSY assessments, MRI and blood tests (very high percentages).

About patients with biomarkers-based diagnosis, a part the neurophysiological evaluation and the MRI, first level of investigation, the most frequent investigations were CSF analysis and FDG-PET.

A bias for the number of PET-MRI may be represented by the fact that in Padova PET (63.1% in DB patients, table 3) and MRI (73.7% in DB patients, table 3) are often carried out as an associated technique in a single nuclear medical exam.

Exams	Performed DNB N=108	Available DB N=57	Performed DB N=57
None	-	21 (36.8%)	-
Blood exams	98 (90.7%)	15 (26.3%)	30 (52.6%)
EEG	-	4 (7.0%)	6 (10.5%)
NPSY assessment	106 (98.1%)	19 (33.3%)	36 (63.1%)
MRI	98 (90.7%)	15 (26.3%)	42 (73.7%)
CT	-	9 (15.8%)	11 (19.3%)
TAU-pet	-	0 (0)	0 (0)
AMY-pet	-	0 (0)	4 (7.0%)
FDG-pet	-	5 (8.8%)	36 (63.1%)
DaT-SPECT	-	2 (3.5%)	10 (17.5%)
CSF	-	0 (0%)	32 (56.1%)

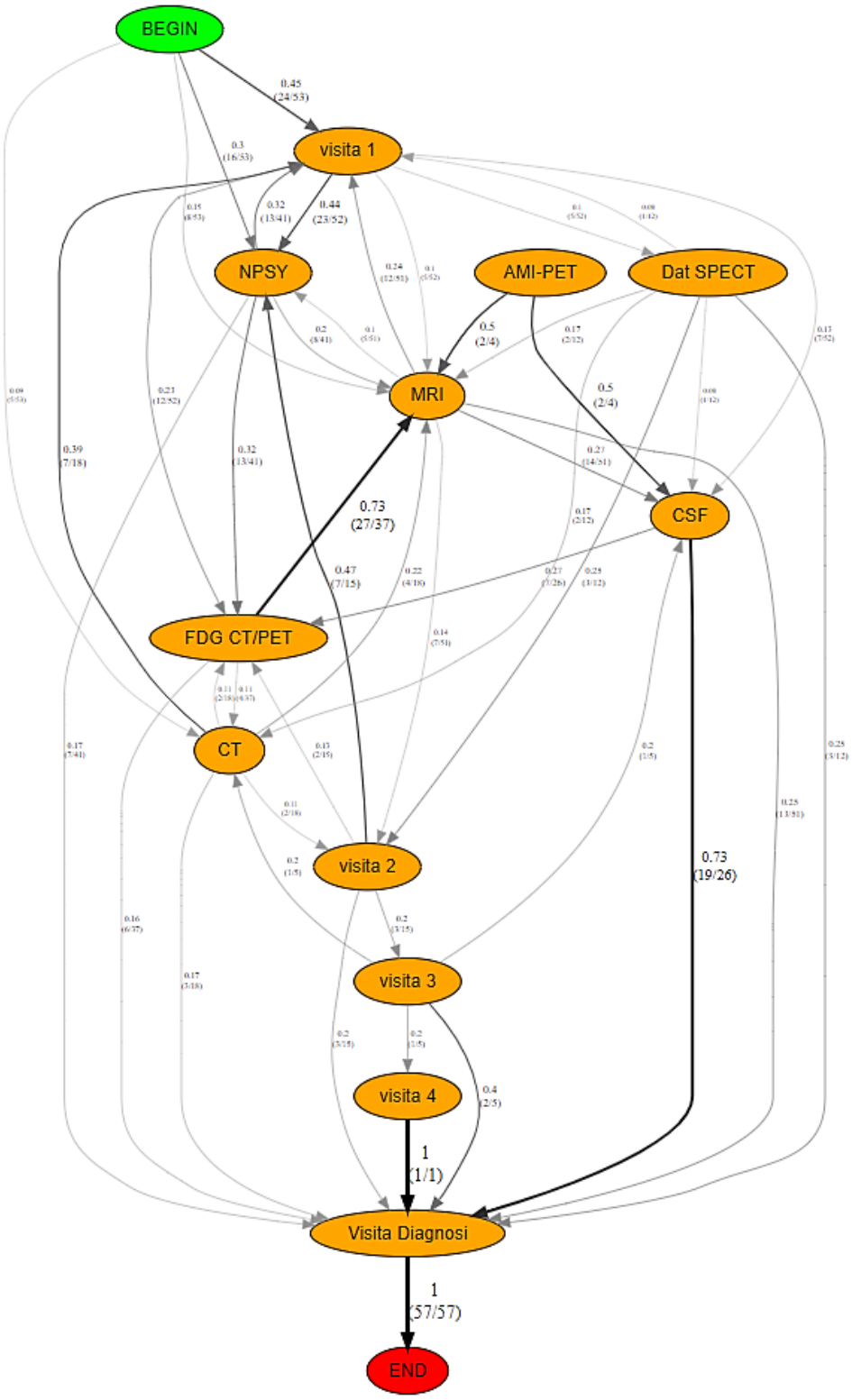
3: Frequency of diagnostic investigation in patients with clinical and biological diagnosis.

We therefore used an analysis based on FOMM, which stands for First Order Markov Model. A Markov model is a stochastic model that describes a sequence of possible events (states) in which the probability of each event depends on a subset of previous events. Markov models have orders, which represent the number of previous states considered in determining the probability of the next state. We therefore tried to use the FOMM to identify the most frequent diagnostic path (based on tests' date of execution, therefore in the order in which they were performed).

For the retrospective data from Padova this analysis did not identify a "most frequent path" and this is due to the great heterogeneity of the paths. This can be seen immediately from the graph; after the first visit we have a strong heterogeneity of the tests between the first and the second visit, without a precise order.

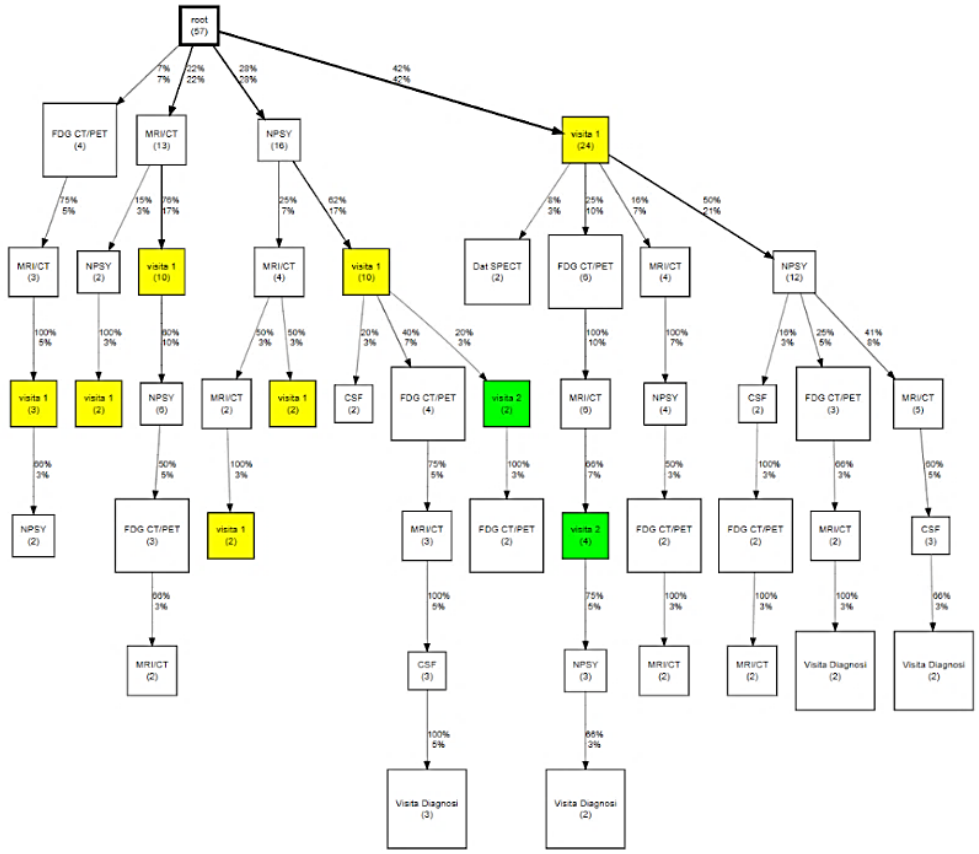
This heterogeneity in the paths of each patient emerges also using the graph created by the CareFlow Miner function.

Through CFM analyses, the most frequent path has the sequence: NPSY, visit 1, FDG PET, MRI, CSF and diagnostic visit. This is because it has the highest number (3) in the diagnostic visit box. Compared to the others we can say that the various patients are very spread out in their paths, remembering that the threshold number is 3.



XI: FOMM (First Order Markov Model) representation of Padova retrospective patients' diagnostic path.

To explain the concept of threshold we can say that just the paths followed by at least 3 people appear on the graph.

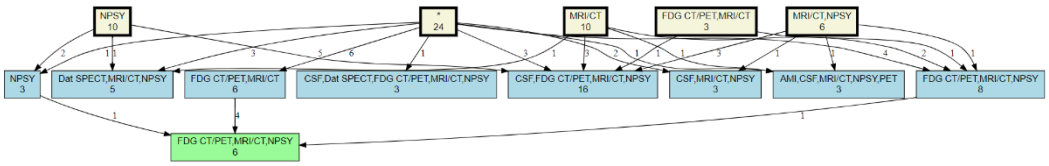


XII: CFM (Care Flow Mining) representation of Padova retrospective patients' diagnostic path.

For the last graph (XIII, cumulative exam profile) we are no longer based on times/dates (like the previous two), but only on the frequency of tests carried out.

Those who receive the diagnosis on the second visit have mainly done the tests in the blue square with number 16, while those who go beyond those have mainly done the tests in the green square.

In conclusion, this part of the analysis shows that the most used biomarkers for retrospective patients were PET-FDG and CSF. With the comparison with prospective patients we will outline the most followed diagnostic procedure and carry out a pre- and post-guideline comparison.



XIII: CF (Cumulative Frequencies) representation of Padova retrospective patients' diagnostic path.

Second prospective study (2023): post-consensus guidelines

In the prospective study, 32 patients are recruited by now. Characteristics of this group patients and the comparison with the patients group in the retrospective study are detailed in Table 4.

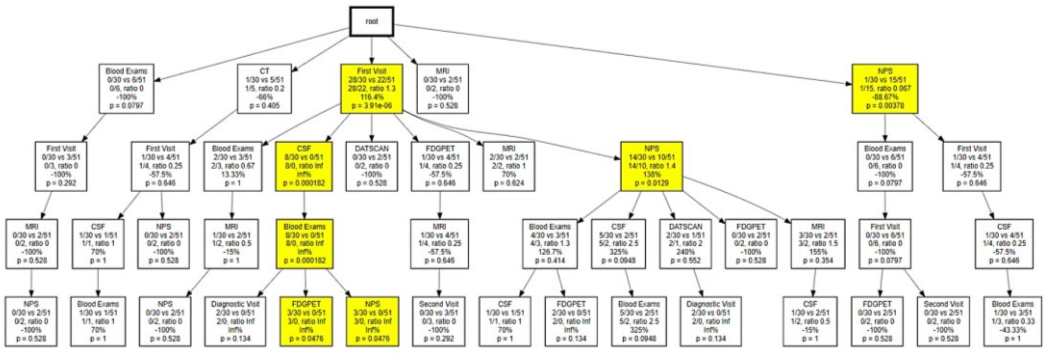
Variable	Retrospective cohort (N=57)	Prospective cohort (N=32)	p
	M±SD or N (%)	M±SD or N(%)	t-test or χ^2
Age (years)	68.81±10.27	67.22±6.97	t(87)=0.779, p = 0.438
Gender – female	23 (40.3)	17 (53.1)	$\chi^2(1)$=1.352, p = 0.245
Gender – male	34 (59.7)	15 (46.9)	
M/F rate	1.48	1.07	
MMSE (questionnaire, n/30)	23.24±5.33*	22.52±4.25**	t(54)=0.540, p = 0.592

* N=33; ** N=23

4: Comparison of demographic factors between Padova's retrospective and prospective patients.

From the following anamnestic data, a reduction in the average age and MMSE is observed in prospective patients. The percentage of female patients appears decreased, and the one of men increased. None of these values have a significant p value difference.

Through CFM analyses, the most significative path from the comparison between retrospective and prospective patients has the sequence: visit 1, CSF, blood exams, FDG-PET. This is because it has the highest number in the diagnostic visit box. Compared to the others we can say that the various paths are very spread out, and the following frame is just a part of the complex and branched total representation of the comparison.



XIV: CFM representation of comparison between Padova's retrospective and prospective patients' diagnostic path.

Focusing on the tests included in the diagnostic work-up and on the significant p-values, CT, NPSY and EEG were performed more frequently in the retrospective cohort. About biomarkers, PET-FDG and DaT Scan were performed more in retrospective cohort, instead CSF analysis was performed less in the same cohort (table 5).

Exam	Retrospective cohort (N=57)	Prospective cohort (N=32)	p
	N (%)	N (%)	χ^2
MRI	45 (78.9)	21 (65.6)	$\chi^2(1)=1.898$, $p = 0.168$
CT	18 (31.6)	2 (6.3)	$\chi^2(1)=7.547$, $\mathbf{p = 0.006}$
Blood exams	44 (77.2)	25 (78.1)	$\chi^2(1)=0.010$, $p = 0.919$
NPSY	53 (93.0)	23 (71.9)	$\chi^2(1)=7.320$, $\mathbf{p = 0.007}$
FDG-PET	40 (70.2)	19 (59.4)	$\chi^2(1)=1.070$, $p = 0.301$
AMY-PET	4 (7.0)	5 (15.6)	$\chi^2(1)=1.670$, $p = 0.196$
CSF analysis	32 (56.1)	21 (65.6)	$\chi^2(1)=0.765$, $p = 0.382$
DAT-SPECT	12 (21.0)	4 (12.5)	$\chi^2(1)=1.017$, $p = 0.313$
EEG	7 (12.3)	0 (0)	$\chi^2(1)=4.265$, $\mathbf{p = 0.039}$

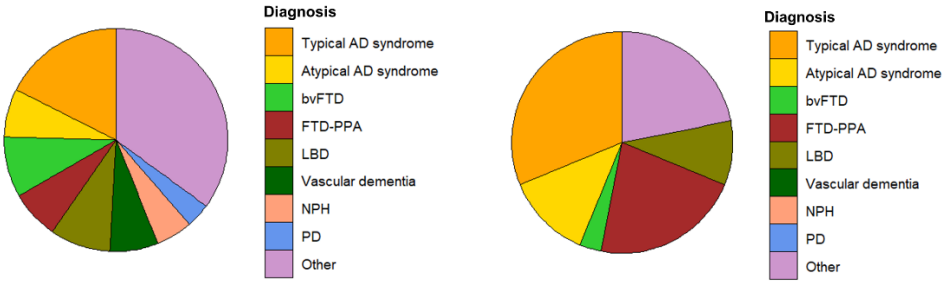
5: Comparison in exams between Padova's retrospective and prospective patients.

Considering the comparison of diagnoses between retrospective and prospective patients, the data with a significant p value claim that in the prospective cohort more diagnoses of FTLD (primary progressive aphasia) were made (table 6).

Diagnosis	Retrospective cohort (N=57)	Prospective cohort (N=32)	p
	N (%)	N (%)	χ^2
AD typical	10 (17.5)	10 (31.3)	$\chi^2(1)=2.210$, $p = 0.137$
AD atypical	4 (7.0)	4 (12.5)	$\chi^2(1)=0.753$, $p = 0.385$
FTLD – behavioral	5 (8.8)	1 (3.1)	$\chi^2(1)=1.039$, $p = 0308$
FTLD – APP	4 (7.0)	7 (21.9)	$\chi^2(1)=4.175$, $\mathbf{p = 0.041}$
LBD	5 (8.8)	3 (9.4)	$\chi^2(1)=0.001$, $p = 0.924$
VAD	4 (7.0)	0 (0)	$\chi^2(1)=0.633$, $p = 0.426$
Hydrocephalus	3 (5.3)	0 (0)	$\chi^2(1)=0.245$, $p = 0.620$
PD	2 (3.5)	0 (0)	$\chi^2(1)=0.015$, $p = 0.903$
Other	20 (35.1)	7 (21.9)	$\chi^2(1)=1.693$, $p = 0.193$

6: Comparison in diagnoses between Padova's retrospective and prospective patients.

From this comparison, the most frequent diagnosis in retrospective patients was typical AD. A large percentage belongs to the "others" category. This could be because on the platform this category included psychiatric diagnoses and sMCI. In the prospective patients analyzed so far, the most numerous categories remain, as for the retrospective patients, typical AD and "others".



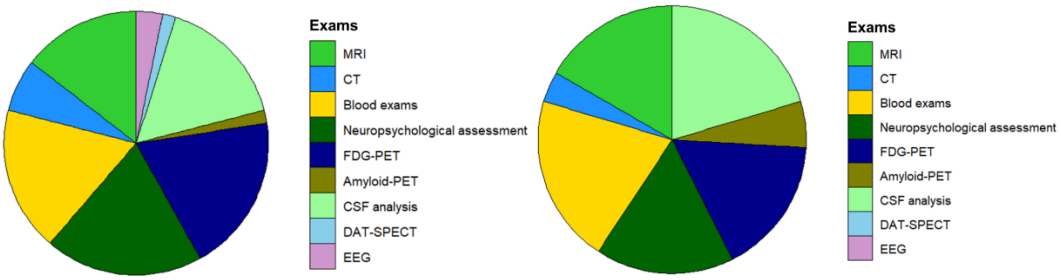
XV: Graphic comparison in diagnoses between Padova's retrospective (on the left) and prospective patients (on the right).

The diagnoses were divided into 4 groups (AD, FTLD, LBD, others) to classify the relative exams. Starting from table 7, there are data about AD patients.

Exam	Retrospective cohort (N=14)	Prospective cohort (N=14)	p
	N (%)	N (%)	χ^2
MRI	9 (64.3)	9 (64.3)	$\chi^2(1)=0$, $p = 1$
CT	4 (28.6)	2 (14.3)	$\chi^2(1)=0.848$, $p = 0.357$
Blood exams	11 (78.6)	11 (78.6)	$\chi^2(1)=0$, $p = 1$
NPSY	12 (85.7)	9 (64.3)	$\chi^2(1)=1.714$, $p = 0.190$
FDG-PET	12 (85.7)	9 (64.3)	$\chi^2(1)=1.714$, $p = 0.190$
AMY-PET	1 (7.1)	3 (21.4)	$\chi^2(1)=1.167$, $p = 0.280$
CSF analysis	10 (71.4)	11 (78.6)	$\chi^2(1)=0.190$, $p = 0.662$
DAT-SPECT	1 (7.1)	0 (0)	$\chi^2(1)=0.005$, $p = 0.997$
EEG	2 (14.3)	0 (0)	$\chi^2(1)=0.373$, $p = 0.541$

7: Exams for Padova's AD patients.

For the diagnosis of AD (typical and atypical), in retrospective patients the most frequently performed tests were neuropsychological evaluation and PET-FDG.



XVI: Graphic comparison in exams between Padova's retrospective (on the left) and prospective (on the right) AD patients.

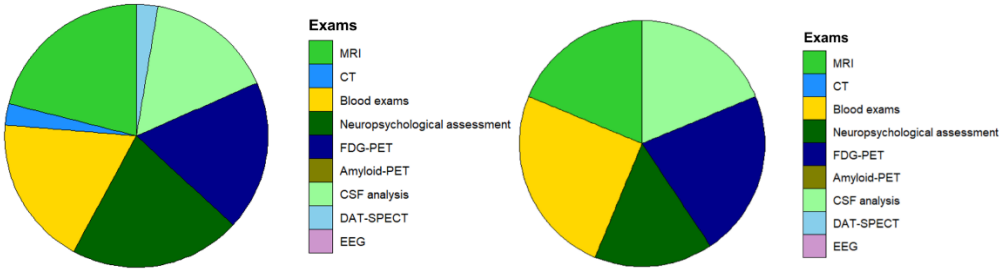
For prospective AD patients, the most commonly performed tests were blood exams and CSF analysis. None of the p values were significant in the comparison about exams for retrospective and prospective patients.

In table 8, there are data about FTLD patients. FTLD includes both the behavioral variant and primary progressive aphasia.

Exam	Retrospective cohort (N=9)	Prospective cohort (N=8)	p
	N (%)	N (%)	χ^2
MRI	8 (88.9)	6 (75.0)	$\chi^2(1)=0.562$, $p = 0.453$
CT	1 (11.1)	0 (0)	$\chi^2(1)=0.255$, $p = 0.787$
Blood exams	7 (77.8)	8 (100.0)	$\chi^2(1)=0.443$, $p = 0.527$
NPSY	8 (88.9)	5 (62.5)	$\chi^2(1)=1.639$, $p = 0.200$
FDG-PET	7 (77.8)	7 (87.5)	$\chi^2(1)=0.275$, $p = 0.599$
AMY-PET	0 (0)	0 (0)	$\chi2(1)=0$, p = 1
CSF analysis	6 (66.7)	6 (75.0)	$\chi^2(1)=0.142$, $p = 0.707$
DAT-SPECT	1 (11.1)	0 (0)	$\chi^2(1)=0.255$, p = 0.787
EEG	0 (14.3)	0 (0)	$\chi^2(1)=0$, $p = 1$

8: Exams in Padova's FTLD patients.

No significant p values were found in the comparison about exams for retrospective and prospective patients. The most used biomarker, both for retrospective and prospective patients, appears to be FDG-PET.



XVII: Graphic comparison in exams between Padova's retrospective (on the left) and prospective (on the right) FTLD patients.

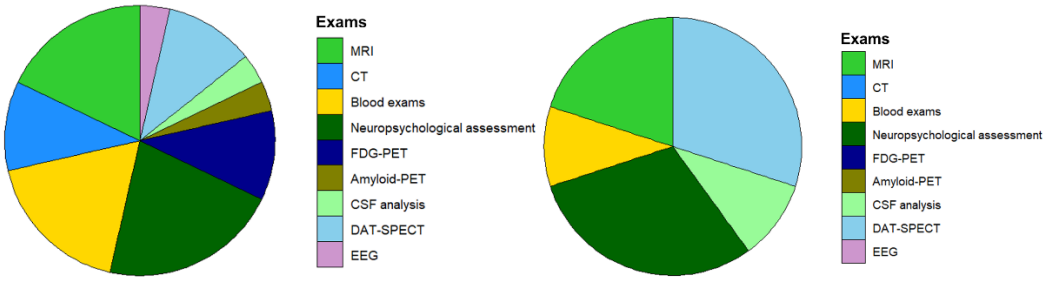
In table 9, there are data about LBD patients, with relative exams. This LBD category technically includes Lewy Body Disease and Parkinson's Disease.

Exam	Retrospective cohort (N=7)	Prospective cohort (N=3)
	N (%)	N (%)
MRI	5 (71.4)	2 (66.7)
CT	3 (42.9)	0 (0)
Blood exams	5 (71.4)	1 (33.3)
NPSY	6 (85.7)	3 (100.0)
FDG-PET	3 (42.9)	0 (0)
AMY-PET	1 (14.3)	0 (0)
CSF analysis	1 (14.3)	1 (33.3)
DAT-SPECT	3 (42.9)	3 (100.0)
EEG	1 (14.3)	0 (0)

9: Exams for Padova's LBD patients.

Statistical significance was not calculated because in this case the sample size was too low.

The most used biomarkers for these retrospective patients were PET-FDG and DAT-SPECT. The most frequent biomarker for these prospective patients was DAT-SPECT.



XVIII: Graphic comparison in exams between Padova's retrospective (on the left) and prospective (on the right) LBD patients.

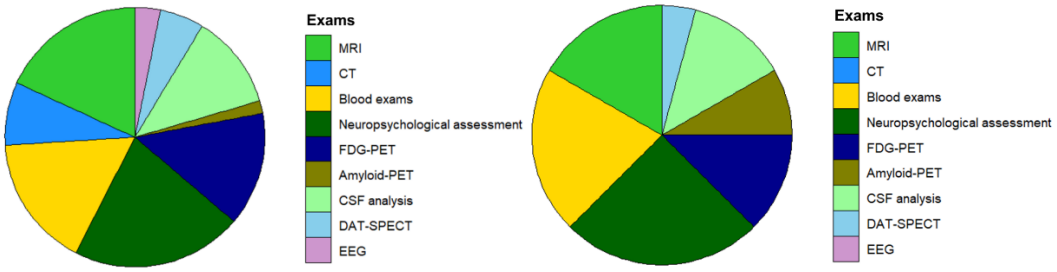
For the "others" category (table 10), note that patients were mainly diagnosed with SCD and psychiatric disorder.

Exam	Retrospective cohort (N=27)	Prospective cohort (N=7)	p
	N (%)	N (%)	χ^2
MRI	23 (85.2)	4 (57.1)	$\chi^2(1)=2.674$, p = 0.102

CT	10 (37.0)	0 (0)	$\chi^2(1)=1.315$, p = 0.251
Blood exams	21 (77.8)	5 (71.4)	$\chi^2(1)=0.124$, p = 0.724
NPSY	27 (100.0)	6 (85.7)	$\chi^2(1)=1.124$, p = 0.289
FDG-PET	18 (66.7)	3 (42.9)	$\chi^2(1)=1.334$, p = 0.248
AMY-PET	2 (7.4)	2 (28.6)	$\chi^2(1)=2.399$, p = 0.121
CSF analysis	15 (55.6)	3 (42.9)	$\chi^2(1)=0.360$, p = 0.549
DAT-SPECT	7 (25.9)	1 (14.3)	$\chi^2(1)=0.419$, p = 0.518
EEG	4 (14.8)	0 (0)	$\chi^2(1)=0.001$, p = 0.972

10: Exams for Padova's "others" patients.

The p values do not indicate significance. The tests performed most frequently, both for retrospective and prospective patients, were neuropsychological evaluation, MRI and blood tests.



XIX: Graphic comparison in exams between Padova's retrospective (on the left) and prospective (on the right) "others" patients.

Young onset dementia: epidemiological study

Seen the results of the ongoing analysis of the VALICO project, it was consistent and coherent to study also the cases of young onset dementia in Padova's cohorts of the years 2020, 2021 and 2022.

This work can be divided into two sub-studies.

In the first study, the epidemiology of YOD patients arriving for their first visit in 2022 was analyzed, with clinical, demographic and diagnostic characteristics. Patients were included among those referring to the two mayor CDCD based at the University-Hospital of Padova: neurology clinic and CRIC centre.

In the second study, the epidemiology of the 2022 incidences was compared with the ones of the years 2020 and 2021, considering both patients arriving for a first visit and follow-up visits.

Starting from the first study, residents in Padua in 2022, aged between 20 and 65, were 517.266, and in Italy 35,367,994. (59)

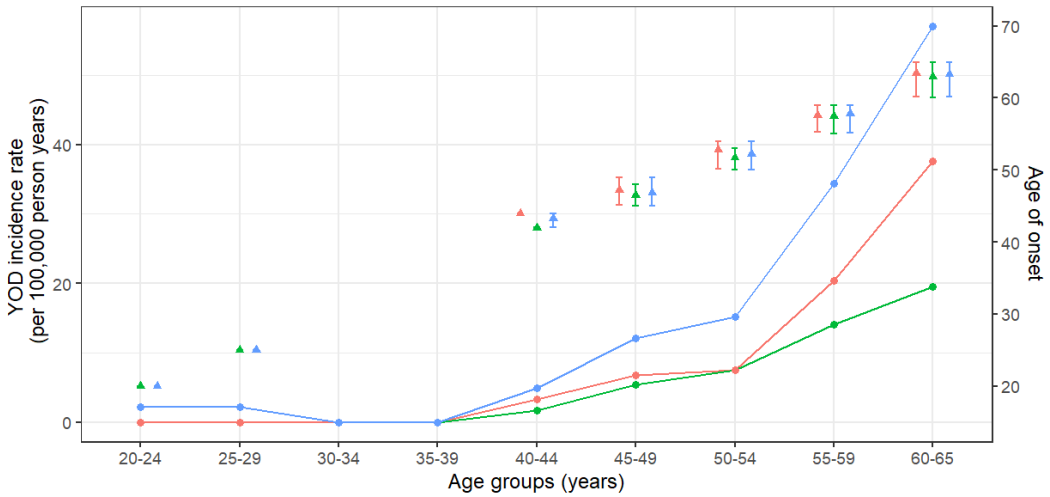
In 2022, in Padova, total AOPD and CRIC patients with young onset dementia, aged between 20 and 65 years, were 204, 97 of which arrived at the clinic for the first time in 2022.

The incidence rate of YOD was 17.25 (95% CI, 13.99–21.04) per 100,000 PY, while the age–sex standardized incidence rate was 16.93 (95% CI, 13.72-20.65) per 100,000 PY.

This incidence would yield an estimated 5987 (95% CI, 4852–7303) of YOD new cases in the whole Italian population, ignoring mortality (table 11).

Age at diagnosis (years)	Gender	Cases	Incidence	95% CI
20-24	M	1	2.22	0.06-12.35
20-24	F	0	0	0-8.18
20-24	Total	1	2.22	0.06-12.35
25-29	M	1	2.17	0.05-12.09
25-29	F	0	0	0-8.00
25-29	Total	1	2.17	0.05-12.09
30-34	M	0	0	0-9.21
30-34	F	0	0	0-9.21
30-34	Total	0	0	0-9.21
35-39	M	0	0	0-7.08
35-39	F	0	0	0-7.08
35-39	Total	0	0	0-7.08
40-44	M	1	1.65	0.04-9.17
40-44	F	2	3.29	0.40-11.89
40-44	Total	3	4.94	1.02-14.40
45-49	M	4	5.38	1.46-13.77
45-49	F	5	6.72	2.18-15.69
45-49	Total	9	12.10	5.53-22.98
50-54	M	6	7.56	2.77-16.46
50-54	F	6	7.56	2.77-16.46
50-54	Total	12	15.13	7.82-26.43
55-59	M	11	14.01	6.99-25.07
55-59	F	16	20.38	11.64-33.09
55-59	Total	27	34.39	22.66-50.04
60-65	M	15	19.46	10.89-32.09
60-65	F	29	37.62	25.19-54.03
60-65	Total	44	57.08	41.47-76.62
Total M		39	6.93	4.93-9.48
Total F		58	10.31	7.83-13.33
Total		97	17.25	13.99-21.04

11. Incidence rates of young-onset dementia by 5-year age groups (per 100,000 person years), considering total AOPD and CRIC patients.



XX: YOD age at onset and incidence by age groups and sex, considering AOPD and CRIC patients. Red = female, green = male, blue = total.

In the following table 12, we can see the mean values with standard deviation of each anamnestic parameter. A group of 72.2% of these patients has generic comorbidities and a group of 40% has psychiatric comorbidities. Few MMSE value were not available: therefore, we converted the MoCA score in their MMSE equivalent using the norms for Italian population. (60) When not administrable, MMSE were excluded from the analyses.

N = 97

Variable	Mean ± SD or N (%)
Age (n = 97)	57.58 ± 8.20
Gender – Female (n = 97)	58 (59.8)
Education (years) (n = 87)	11.55 ± 4.26
Age at symptoms onset (n = 87)	55.41 ± 7.79
Age at disease diagnosis (n = 87)	57.17 ± 7.84
MMSE at disease diagnosis (n = 92)	22.97 ± 8.28
Psychiatric comorbidity – yes (**n = 80**)	32 (40.0)
Other comorbidities – yes (n = 90)	65 (72.2)
Time to disease diagnosis (months) (n = 84)	4.25 ± 4.48
Living alone – yes **(n = 79)**	6 (7.6)
Retired – yes (n = 83)	35 (42.2)
Retired due to cognitive impairment (n = 84)	12 (14.3)
Caregiver gender – female (**n = 20**)	11 (55.0)

12. Demographic and clinical features of YOD total patients (AOPD and CRIC) and demographical features of caregivers.

From table 13, the most frequent diagnoses were AD (22.1%) and FTD (13.7%), while the most frequent exams were PET-FDG and CSF.

N=97

Exams	**yes**	**no**
	N (%)	N (%)
CSF	28 (28.9)	69 (71.1)
FDG-PET	37 (38.1)	60 (61.9)
AMY-PET	8 (8.2)	89 (79.6)
Genetic study	23 (23.7)	74 (76.3)
Genetic counseling	2 (2.1)	95 (97.9)
Speech therapy counseling	18 (18.6)	79 (81.4)
Hospitalization	25 (25.8)	72 (74.2)
Apoe	38 (39.2)	59 (60.8)

Diagnoses*	**Number** N (%)
LBD	1 (1.1)
AD	21 (22.1)
FTD	13 (13.7)
MCI	30 (31.6)
Other primary dementias	9 (9.5)
Secondary dementias	1 (1.1)
Other	20 (21.1)
	*N=95

13: Statistical representation of exams and diagnoses of Padova's YOD AOPD and CRIC new patients, in 2022.

In regression models (table 14), none of the anamnestic factors were significantly associated with time until diagnosis ($p > 0.05$), considering time to disease diagnosis as dependent variable.

Dependent variable: time to disease diagnosis (N = 79)

Predictor variable	**B**	**S.E.**	**β**	***p***
Age	-0.043	0.084	-0.069	0.611
Gender	-0.263	1.071	-0.029	0.807
Education	0.082	0.140	0.073	0.557
MMSE	0.038	0.079	0.059	0.631
Age at symptoms onset	-0.046	0.278	-0.081	0.869
Age at disease diagnosis	0.166	0.277	0.294	0.551
Comorbidities	1.003	1.172	0.101	0.395
Diagnosis – AD	3.774	1.808	0.259	0.130
Diagnosis – FTLD	3.380	2.086	0.250	0.110
Diagnosis – MCI	0.642	1.623	0.068	0.694

14. Univariable linear regression analyses (time to disease diagnosis as dependent variable) across AOPD and CRIC patients (in bold the significant variables).

Continuing with the second study, in 2020, the most frequently performed exam for the study of young onset dementia was CSF, and secondly PET-FDG. Considering the graph of cumulative frequencies (XXV, appendix) about tests, at the top there

was hospitalization in DH, for the carrying out of CSF and FDG-PET. The average age was 57.47 y.o.

In the 2020 YOD patients cohort, the most frequent diagnosis was FTD (table 17, appendix). The “Others” category includes especially psychiatric cases.

In the 2021 YOD patient cohort, the most frequent diagnosis was AD (table 18, appendix).

The most frequently performed exam for the study of young onset dementia was CSF, and secondly genetic study. Considering the graph of cumulative frequencies about tests (XXVII, appendix), at the top there was a series of genetic exams, CSF and FDG-PET. The average age was 59.76 y.o.

In the 2022 YOD patient cohort, the most frequent diagnosis was AD (table 19, appendix).

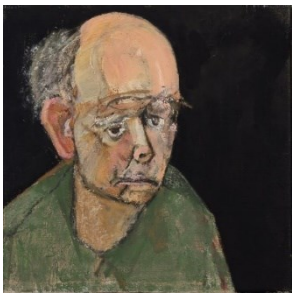
The most frequently performed exam for the study of young onset dementia was FDG-PET, and secondly CSF. Considering the graph of cumulative frequencies about tests (XXIX, appendix), at the top there was a series of genetic exam, CSF and FDG-PET.

By making a comparison (table 15) between the tests carried out for YOD in 2020, 2021, 2022, we obtained a significant increase in frequencies for CSF, PET-FDG, genetic analyses and genetic counseling.

Variable	**2020**	**2021**	**2022**	**X(DoF), *p*-value**
CSF				
Y	36	50	51	$\chi(2) = 9.413$, **0.009**
N	59	32	56	
FDG-PET				
Y	34	48	56	$\chi(2) = 10.080$, **0.006**
N	61	34	51	
AMY-PET				
Y	9	17	20	$\chi(2) = 4.948$, 0.084
N	86	65	86	
Genetic exam				
Y	15	38	39	$\chi(2) = 20.047$, **< 0.001**
N	80	44	68	
Genetic counseling				
Y	5	16	13	$\chi(2) = 8.484$, **0.014**
N	90	66	94	
Speech therapy counseling				
Y	7	9	10	$\chi(2) = 0.739$, 0.691
N	88	72	97	
Hospitalization				
Y	24	21	25	$\chi(2) = 0.155$, 0.925
N	71	61	82	
Apoe				

Y	0	2	4	$\chi(2) = 3.460, 0.177$
N	95	80	103	

15: Comparison of exams of the three cohorts (2020, 2021, 2022).



XXI: 1997, Utermohlen's self-portrait.

DISCUSSIONS

This work is part of an ongoing project (the VALICO study), that has been created to overcome the problem of a harmonized and structured diagnostic pathway for neurocognitive disorders. A consensus biomarker-based diagnostic algorithm has been defined, guiding clinicians of Italian memory clinics to a rational and harmonized use of the most consolidated aetiological biomarkers for the aetiological diagnosis of neurocognitive disorders. Expert decisions are consistent with current clinical guidelines and with the most up-to-date research diagnostic criteria and scientific advancements; following the European guidance for guideline definition, the patient's perspective is included and is promoted as a principal component in the diagnostic procedure.

To our knowledge, the statistical analysis using the process mining is new in the field of neurodegenerative diseases and may have a role in helping the development of future evidence-to-decision-based guidelines. The algorithm includes the most mature biomarkers for the aetiological diagnosis of neurocognitive disorders. These examinations should be prescribed with the awareness of this limitation; their assessment and reporting should be performed in expert centres or by adequately trained personnel, based on the most advanced procedures and taking care of proper communication with patients and caregivers.

Biological diagnosis in the field of dementia represents an ever-increasing resource. Keeping updated with progress in the field is essential. (61)

The need of biological diagnosis: when and how

Given these premises, research priorities for such progress include the formal assessment of the relative and combined incremental diagnostic value for the most consolidated biomarkers specifically computed for the DLB, FTLD and AD diagnostic branches and overcoming the most frequent methodological faults. The clinical diagnosis was relegated to patients with an average age of 77 years.

For both retrospective and prospective cohorts, AD remains the most frequent biological diagnosis. Within the AD diagnostic branch, the panelists gave priority to CSF over amyloid-PET for prospective patients, based on the lower costs and larger array of information (table 7). Recalling Boccardi et Al. recommendations, negative MRI requires FDG-PET to look for evidence of this early neuronal

damage. With positive MRI or FDG-PET, amyloid and tau in cerebrospinal fluid (CSF) are the first choice examination to investigate etiology up to age 75.

For FTLD diagnostic path, the main biomarker was still confirmed to be PET-FDG (table 8). This is coherent with Boccardi et Al. recommendations, that claim the differential frontal or temporoparietal hypometabolic patterns in FDG-PET help the differential diagnosis with AD in most cases (34) (36).

Dopamine transporter SPECT has a well-established role for the differential diagnosis between DLB and AD. However, in suspected DLB with clear parkinsonism, DaT-SPECT has limited added value and cannot exclude other neurodegenerative parkinsonian syndromes presenting with cognitive impairment (table 9). The request for biomarker assay as well as the interpretation of findings should finally take into account patients with mixed pathology (amyloidosis, vascularity).

The present consensus did not specifically address mixed forms but recognizes them as a source of uncertainty in individual patients. Finally, genetic analyses that may be required by the patients should be performed only based on the presence of precise indicators, first of all an age <65 years old. Considering our 2022 YOCD cohort, genetic exams were performed with a frequency of 23.7% and ApoE with a frequency of 39.2%.

The problem of young-onset dementia

YOD patients have unique needs compared to those with late-onset dementia, but the impact of YOD is still under-researched. In the present register-based study, we estimated the incidence rates of neurodegenerative YOD. Incidence rates increased with age, with the peak in the 60 to 65 age group.

Compared to previous studies, the present work has covered the Padova county population for estimating the incidence of YOD. It considered the revised criteria for AD, FTLD, and DLB and took into consideration structural and functional brain imaging as well as amyloid markers in the diagnostic work-up, including the overall spectrum of FTLD phenotypes.

Diagnoses were confirmed by dementia specialists. This was principally based on the existing organization and structure of the Italian National Health System, under which all suspected cases of YOD are referred to the CCDD, providing certain numbers of new diagnoses. (62)

The incidence rate of YOD was 17.25 (95% CI, 13.99–21.04) per 100,000 PY. The most frequent diagnoses were AD (22.1%) and FTD (13.7%), while the most frequent exams were PET-FDG and CSF. In regression models, none of the anamnestic factors was significantly associated with time-lapse until diagnosis ($p > 0.05$, table 14). These results are consistent with those of the first outcome of this study. Biomarkers, especially genetic exams, appear to be a great resource for the study of YOCD, whose epidemiological study for biological diagnosis appears to be important.

A relevant new finding of this study was that these data underline the alarm that young onset dementia can represent. This is the first epidemiological study about YOD in the province of Padova and it could be a starting point for new initiatives of local institutions, as well as clinicians. Statistical significance does not always correspond to clinical significance.

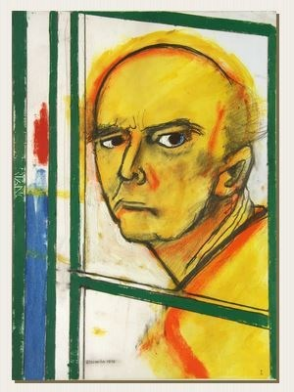
There are several limitations and strengths of the study. Collecting incidence data is challenging but enables us to make the best estimate of the new burden of a disease per year in a specific population and to characterize the phenotype spectrum. However, we acknowledge that population-based registers require several years of activity to ensure that early biases are solved.

One possible limitation of our study is the potential under ascertainment due to lack of referral by other neurologists, geriatricians, and psychiatrists to the multidisciplinary register.

Another limitation is possible misdiagnosis or changes in doctors' modus operandi and retirements. However, the comprehensive clinical evaluation, imaging and biomarker assessment, although implementable, along with diagnostic confirmation at follow-up, makes this unlikely.

Collaborative work among multinational registries, studying different populations and ethnicities, should be the next step to improve our understanding of YOD. This will allow methodological approaches to be adopted in terms of inclusion/exclusion criteria and reference populations, to strengthen YOD incidence rate results on larger population-based registries, to clearly define eventually geographical diversities of YOD subtypes, and to implement knowledge of anamnestic bases of YOD. Despite these limitations, the results of the present study highlight the need to promote appropriate public health service policies and to design effective

diagnostic algorithms for YOD cases. More awareness on YOD is needed in primary care.



XXII: 1996, Utermohlen's self-portrait.

CONCLUSIONS

Neurology's favorite word is "deficit", denoting an impairment or inability of neurological function. Such disorders, and their depiction and study, indeed a discipline that can be called "neurology of identity", deal with the neural foundations of the self, the age-old problems of mind and brain. (63)

Research is important, and dementia will be the main field of neurology in the near future. In the past decades, it was time to collect and study biomarkers, but now it's time to use them to act and reach new frontiers of discovery.

XXIII: 1967, Utermohlen's self-portrait.

BIBLIOGRAPHY

1. American Psychiatric Association. Manuale diagnostico e statistico dei disturbi mentali – Quinta edizione. DSM-5. . Tr.it. Raffaello Cortina, Milano, 2015.; 2013.

2. Corrado Angelini, Leontino Battistin. Neurologia Clinica. Esculapio; 2022.

3. Pawlowski M, Meuth S, Duning T. Cerebrospinal Fluid Biomarkers in Alzheimer's Disease—From Brain Starch to Bench and Bedside. Diagnostics. 2017 Jul 13; 7(3): 42.

4. Frisoni GB, Altomare D, Thal DR, Ribaldi F, van der Kant R, Ossenkoppele R, et al. The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. Nat Rev Neurosci. 2022 Jan 23; 23(1): 53–66.

5. Spalletta G, Caltagirone C, Padovani A, Sorbi S, Attar M, Colombo D, et al. Cognitive and Affective Changes in Mild to Moderate Alzheimer's Disease Patients Undergoing Switch of Cholinesterase Inhibitors: A 6-Month Observational Study. PLoS One. 2014 Feb 19.

6. Chinnery PF. Precision mitochondrial medicine. Cambridge Prisms: Precision Medicine. 2023; 1.

7. Ashleigh T, Swerdlow RH, Beal MF. The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis. Alzheimer's and Dementia. 2023 Jan 1;19(1): 333–42.

8. Walsh S, Merrick R, Milne R, Brayne C. Aducanumab for Alzheimer's disease? Vol. 374, The BMJ. BMJ Publishing Group; 2021.

9. Swerdlow RH, Hui D, Chalise P, Sharma P, Wang X, Andrews SJ, et al. Exploratory analysis of mtDNA haplogroups in two Alzheimer's longitudinal cohorts. Alzheimer's & Dementia. 2020 Aug 16;16(8): 1164–72.

10. Swerdlow RH, Koppel S, Weidling I, Hayley C, Ji Y, Wilkins HM. Mitochondria, Cybrids, Aging, and Alzheimer's Disease. In 2017. p. 259–302.

11. Califf RM. Biomarker definitions and their applications. Exp Biol Med. 2018 Feb 6; 243(3): 213–21.

12. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010 Nov; 5(6): 463–6.

13. Matteo Grittani. Il grande sorpasso: le malattie neurologiche colpiscono più delle cardiache. La Repubblica; 2024.

14. Kraus VB, Burnett B, Coindreau J, Cottrell S, Eyre D, Gendreau M, et al. Application of biomarkers in the development of drugs intended for the

treatment of osteoarthritis. Osteoarthritis Cartilage. 2011 May; 19(5): 515–42.

15. Tondo G, De Marchi F. From Biomarkers to Precision Medicine in Neurodegenerative Diseases: Where Are We? J Clin Med. 2022 Aug 3; 11(15): 4515.

16. Cagnin A, Kassiou M, Meikle SR, Banati RB. Positron Emission Tomography Imaging of Neuroinflammation. Neurotherapeutics. 2007 Jul; 4(3): 443–52.

17. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, et al. Carotid Intima-Media Thickness Progression as Surrogate Marker for Cardiovascular Risk. Circulation. 2020 Aug 18; 142(7): 621–42.

18. Van der Ende EL, Meeter LH, Poos JM, Panman JL, Jiskoot LC, Dopper EGP, et al. Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. Lancet Neurol. 2019 Dec; 18(12): 1103–11.

19. Sellami L, Rucheton B, Ben Younes I, Camuzat A, Saracino D, Rinaldi D, et al. Plasma progranulin levels for frontotemporal dementia in clinical practice: a 10-year French experience. Neurobiol Aging. 2020 Jul.

20. Lu T, Aron L, Zullo J, Pan Y, Kim H, Chen Y, et al. REST and stress resistance in aging and Alzheimer's disease. Nature. 2014 Mar 27; 507(7493): 448–54.

21. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceedings of the National Academy of Sciences. 1993 Mar; 90(5): 1977–81.

22. Pasinetti GM. Use of cDNA microarray in the search for molecular markers involved in the onset of Alzheimer's disease dementia. J Neurosci Res. 2001 Sep 15; 65(6): 471–6.

23. Nordberg A, Rinne JO, Kadir A, Långström B. The use of PET in Alzheimer disease. Nat Rev Neurol. 2010 Feb; 6(2): 78–87.

24. Khachaturian ZS. Calcium Hypothesis of Alzheimer's disease and brain aging: A framework for integrating new evidence into a comprehensive theory of pathogenesis. Alzheimer's & Dementia. 2017 Feb 3; 13(2): 178.

25. Chételat G. How to use neuroimaging biomarkers in the diagnosis framework of neurodegenerative diseases? Rev Neurol (Paris). 2022 May; 178(5): 490–7.

26. Boccardi M, Nicolosi V, Festari C, Bianchetti A, Cappa S, Chiasserini D, et al. Italian consensus recommendations for a biomarker-based aetiological

diagnosis in mild cognitive impairment patients. Eur J Neurol. 2020 Mar 18; 27(3): 475–83.

27. Boccardi M, Nicolosi V, Festari C, Bianchetti A, Cappa S, Chiasserini D, et al. Italian consensus recommendations for a biomarker-based aetiological diagnosis in mild cognitive impairment patients. Eur J Neurol. 2020 Mar 1; 27(3): 475–83.

28. Impiego delle tecniche di imaging nelle demenze. Sistema nazionale per le linee guida, Istituto Superiore di Sanità. 2013.

29. Conti S BSLMMMCM. Montreal Cognitive Assessment (MoCA)-Italian version: regression based norms and equivalent scores.

30. Novi G, Canosa A, Nobili F, Bongianni M, Zanusso G, Balestrino M, et al. Longitudinal brain magnetic resonance imaging and real-time quaking induced conversion analysis in presymptomatic Creutzfeldt–Jakob disease. Eur J Neurol. 2018 Dec 7; 25(12).

31. Jutten RJ PCLS et al. Detecting functional decline from normal aging to dementia: development and validation of a short version of the Amsterdam IADL Questionnaire.

32. Tiraboschi P CAGU et al. (123)I-FP-CIT SPECT and 123I-MIBG in differentiating dementia with Lewy bodies from other dementias: a comparative study.

33. McKeith IG BBDD et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium.

34. Nobili F AJBF et al. EANM-EAN recommendations for the use of brain 18F-fluo rodeoxyglucose positron emission tomography (FDG PET) in neurodegenerative cognitive impairment and dementia: Delphi consensus.

35. Walker Z GFOS et al. Clinical utility of FDG PET in Parkinson's disease and atypical parkinsonism associated with dementia.

36. Arbizu J FCAD et al. Clinical utility of FDG-PET for the clinical diagnosis in MCI.

37. Nestor PJ, Altomare D, Festari C, Drzezga A, Rivolta J, Walker Z, et al. Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia. Eur J Nucl Med Mol Imaging. 2018 Jul 7; 45(9): 1509–25.

38. Guedj E, Varrone A, Boellaard R, Albert NL, Barthel H, van Berckel B, et al. EANM procedure guidelines for brain PET imaging using [18F]FDG, version 3. Eur J Nucl Med Mol Imaging. 2022 Jan 9; 49(2): 632–51.

39. Engelborghs S, Niemantsverdriet E, Struyfs H, Blennow K, Brouns R, Comabella M, et al. Consensus guidelines for lumbar puncture in patients with neurological diseases. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2017 Jan 18; 8(1): 111–26.

40. Meyer PT, Frings L, Rücker G, Hellwig S. ^{18} F-FDG PET in Parkinsonism: Differential Diagnosis and Evaluation of Cognitive Impairment. Journal of Nuclear Medicine. 2017 Dec; 58(12): 1888–98.

41. Frisoni GB, Festari C, Massa F, Cotta Ramusino M, Orini S, Aarsland D, et al. European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders. Lancet Neurol. 2024 Mar; 23(3): 302–12.

42. Munoz-Gama J, Martin N, Fernandez-Llatas C, Johnson OA, Sepúlveda M, Helm E, et al. Process mining for healthcare: Characteristics and challenges. J Biomed Inform. 2022 Mar 1; 127.

43. Giorgio J, Landau SM, Jagust WJ, Tino P, Kourtzi Z. Modelling prognostic trajectories of cognitive decline due to Alzheimer's disease. Neuroimage Clin. 2020 Jan 1; 26.

44. Chen K, Abtahi F, Carrero JJ, Fernandez-Llatas C, Seoane F. Process mining and data mining applications in the domain of chronic diseases: A systematic review. Vol. 144, Artificial Intelligence in Medicine. Elsevier B.V.; 2023.

45. Cuendet MA, Gatta R, Wicky A, Gerard CL, Dalla-Vale M, Tavazzi E, et al. A differential process mining analysis of COVID-19 management for cancer patients. Front Oncol. 2022 Dec 7; 12.

46. Dagliati A, Tibollo V, Cogni G, Chiovato L, Bellazzi R, Sacchi L. Careflow Mining Techniques to Explore Type 2 Diabetes Evolution. J Diabetes Sci Technol. 2018 Mar 1; 12(2): 251–9.

47. Borroni B, Libri I, Rota M, Binetti G, Benussi L, Ghidoni R, et al. Incidence of young-onset dementia in Italy: The Brescia register study. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring. 2024 Jan 1; 16(1).

48. Filippi M, Cecchetti G, Cagnin A, Marra C, Nobili F, Parnetti L, et al. Redefinition of dementia care in Italy in the era of amyloid-lowering agents for the treatment of Alzheimer's disease: an expert opinion and practical guideline. J Neurol. 2023 Jun 9; 270(6): 3159–70.

49. Progress in Mind, G. B. Frisoni. Alzheimer's Disease: ethics of early diagnosis and practicalities of prevention. 2016.

50. Il Sole 24 ORE. Nasce il nuovo Intergruppo parlamentare per le neuroscienze e l'Alzheimer. 18 maggio 2023.

51. Agostino Gemelli Policlinic Foundation, AIMA, IRCCS-INRCA, Istituto Superiore di Sanità. Interceptor Project.

52. Benussi A, Cantoni V, Grassi M, Brechet L, Michel CM, Datta A, et al. Increasing Brain Gamma Activity Improves Episodic Memory and

Restores Cholinergic Dysfunction in Alzheimer's Disease. Ann Neurol. 2022 Aug 6; 92(2): 322–34.

53. Rosenberg A, Mangialasche F, Ngandu T, Solomon A, Kivipelto M. MULTIDOMAIN INTERVENTIONS TO PREVENT COGNITIVE IMPAIRMENT, ALZHEIMER'S DISEASE, AND DEMENTIA: FROM FINGER TO WORLD-WIDE FINGERS. J Prev Alzheimers Dis. 2019; 1–8.

54. Giordano Bruno. Ars memoriae. 1582.

55. Lucia Benini. 'SELF PORTRAITS' (1967-2000) DI WILLIAM UTERMOHLEN. S.I.M.G.

56. Chris Boïcos Fine Arts in Paris France, Jennifer Norback Fine Arts in Chicago USA, GV Art in London UK. William Utermohlen : A Persistence of Memory - Loyola University Museum of Art, Chicago. 2016.

57. Kusuma GP, Kurniati AP, Rojas E, Mcinerney CD, Gale CP, Johnson OA. Process mining of disease trajectories: A literature review. In: Public Health and Informatics: Proceedings of MIE 2021. IOS Press; 2021. p. 457–61.

58. Teije A ten, Popow C (Christian), Holmes J (John H), Sacchi L. Artificial intelligence in medicine : 16th Conference on Artificial Intelligence in Medicine, AIME 2017, Vienna, Austria, June 21-24, 2017, proceedings.

59. www.demo.istat.it.

60. Aiello EN, Pasotti F, Appollonio I, Bolognini N. Equating Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores: conversion norms from a healthy Italian population sample. Aging Clin Exp Res. 2022 Jul 19; 34(7): 1721–4.

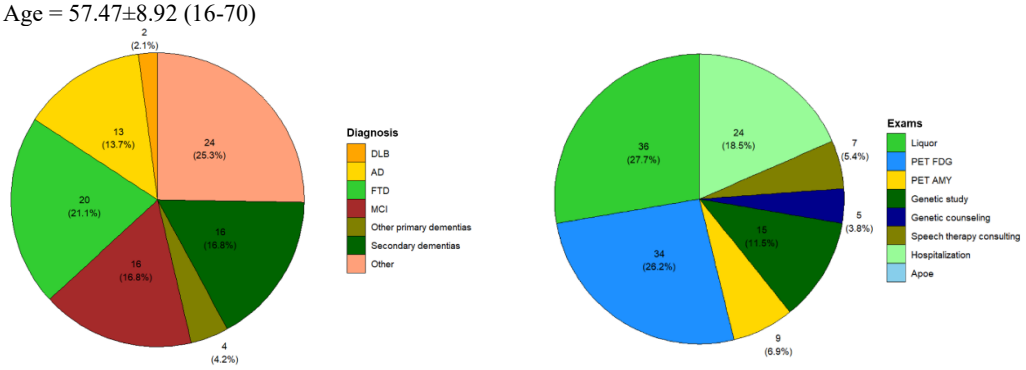
61. Borroni B, Libri I, Rota M, Binetti G, Benussi L, Ghidoni R, Cotelli MS, Fostinelli S, Guerini F, Boffelli S, Magni E, Pengo M, Gennuso M, Bianchi M, Cossu B, Palomba V, Crucitti A, Bianchetti A, Logroscino G, Padovani A. Incidence of young-onset dementia in Italy: The Brescia register study. Alzheimers Dement (Amst). 2024 Feb 29.

62. Chiari, A., Tondelli, M., Galli, C. *et al.* How long does it take to diagnose young-onset dementia? A comparison with late-onset dementia. *Neurol Sci* 43, 4729–4734, 2022.

63. Oliver Sacks, The Man Who Mistook His Wife for a Hat: And Other Clinical Tales, 1985.

APPENDIX

N=95
Age = 57.47±8.92 (16-70)



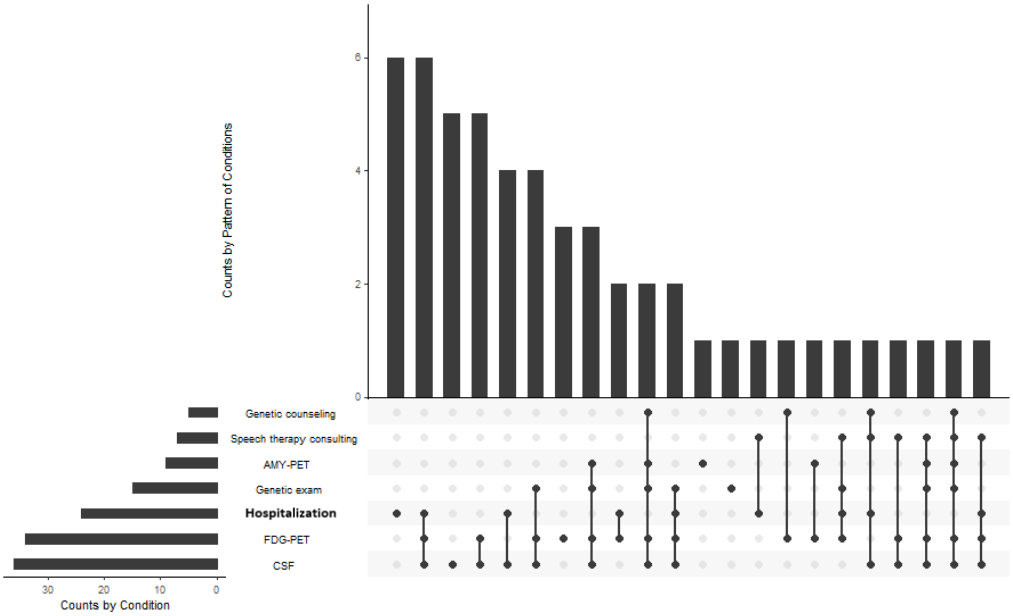
XXIV: Graphic representation of diagnoses and exams of Padova's YOD patients, in 2020.

Exams	yes	no
	N (%)	N (%)
CSF	36 (37.9)	59 (62.1)
FDG-PET	34 (35.8)	61 (64.2)
AMY-PET	9 (9.5)	86 (90.5)
Genetic study	15 (15.8)	80 (84.2)
Genetic counseling	5 (5.3)	90 (94.7)
Speech therapy counseling	7 (7.4)	88 (92.6)
Hospitalization	24 (25.3)	71 (74.7)
Apoe	0 (0)	95 (100)

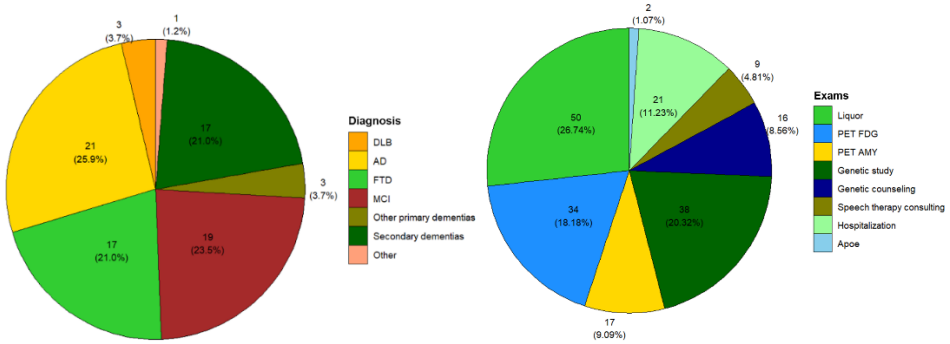
16: Analysis of exams of Padova's YOD patients, in 2020.

Diagnoses	Number
	N (%)
LBD	2 (2.1)
AD	13 (13.7)
FTD	20 (21.1)
MCI	16 (16.8)
Other primary dementias	4 (4.2)
Secondary dementias	16 (16.8)
Other	24 (25.3)

17: Analysis of diagnoses of Padova's YOD patients, in 2020.



XXV: Cumulative frequencies representation of diagnostic exams for YOD in 2020.



XXVI: Graphic representation of diagnoses and exams of Padova's YOD patients, in 2021.

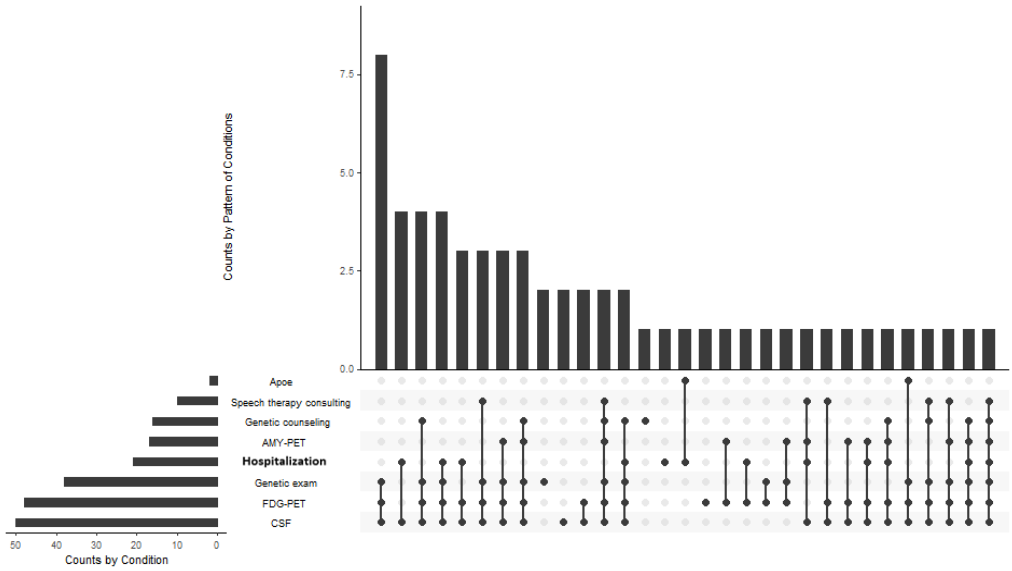
N=82
Age = 59.76±7.03 (36-77)

Exams	**yes** N (%)	**no** N (%)
CSF	50 (61.0)	32 (39.0)
FDG-PET	34 (41.5)	48 (58.5)
AMY-PET	17 (20.7)	65 (79.3)
Genetic study	38 (46.3)	44 (53.7)
Genetic counselling	16 (19.5)	66 (80.5)
Speech therapy counseling*	9 (11.0)	72 (87.8)
Hospitalization	21 (25.6)	61 (74.4)
Apoe	2 (2.4)	80 (97.6)

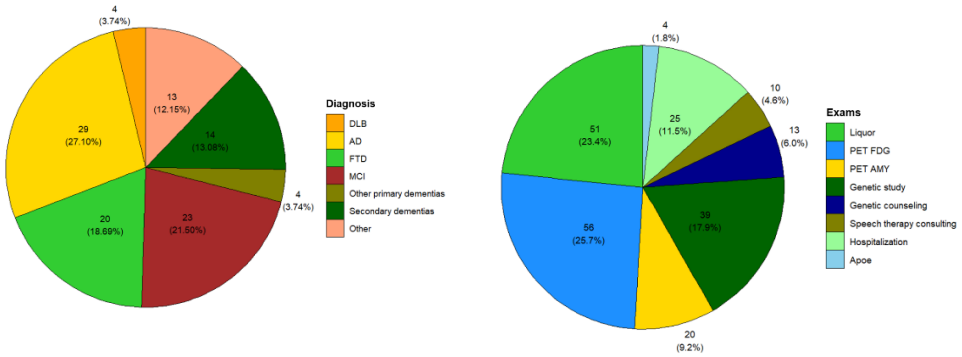
Diagnoses*	**Number** N (%)
LBD	3 (3.7)
AD	21 (25.6)
FTD	17 (20.7)
MCI	19 (23.2)
Other primary dementias	3 (3.7)
Secondary dementias	17 (20.7)
Other	1 (1.2)

* N = 1 missing.

18: Analysis of diagnoses and exams of Padova's YOD patients, in 2021.



XXVII: Cumulative frequencies representation of diagnostic exams for YOD in 2021.



XXVIII: Graphic representation of diagnoses and exams of Padova's YOD patients, in 2022.

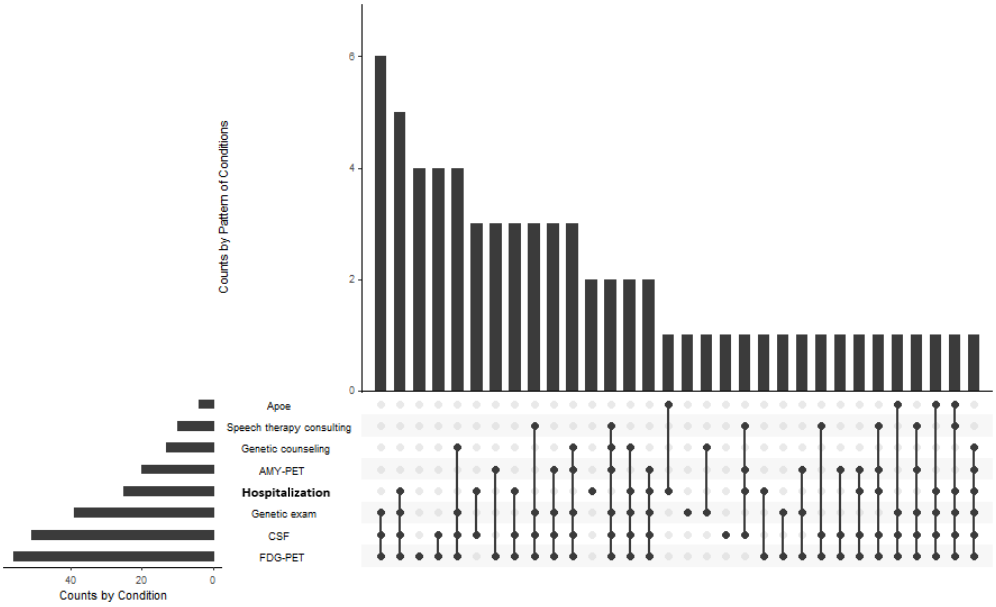
N=107
Age = 59.74±7.55 (25-69)

Exams	**yes** N (%)	**no** N (%)
CSF*	51 (47.2)	56 (51.9)
FDG-PET*	56 (51.9)	51 (47.2)
AMY-PET**	20 (18.5)	86 (79.6)
Genetic study*	39 (36.1)	68 (63.0)
Genetic counseling*	13 (12.0)	94 (87.0)
Speech therapy counseling*	10 (9.3)	97 (89.8)
Hospitalization*	25 (23.1)	82 (75.9)
Apoe*	4 (3.7)	103 (95.4)

* N = 1 missing; ** N = 2 missing.

Diagnoses*	Number N (%)
LBD	4 (3.7)
AD	29 (26.9)
FTD	20 (18.5)
MCI	23 (21.3)
Other primary dementias	4 (3.7)
Secondary dementias	14 (13.0)
Other	13 (12.0)

19: Statistical representation of diagnoses and exams of Padova's YOD patients, in 2022.



XXIX: Cumulative frequencies representation of diagnostic exams for YOD in 2022.