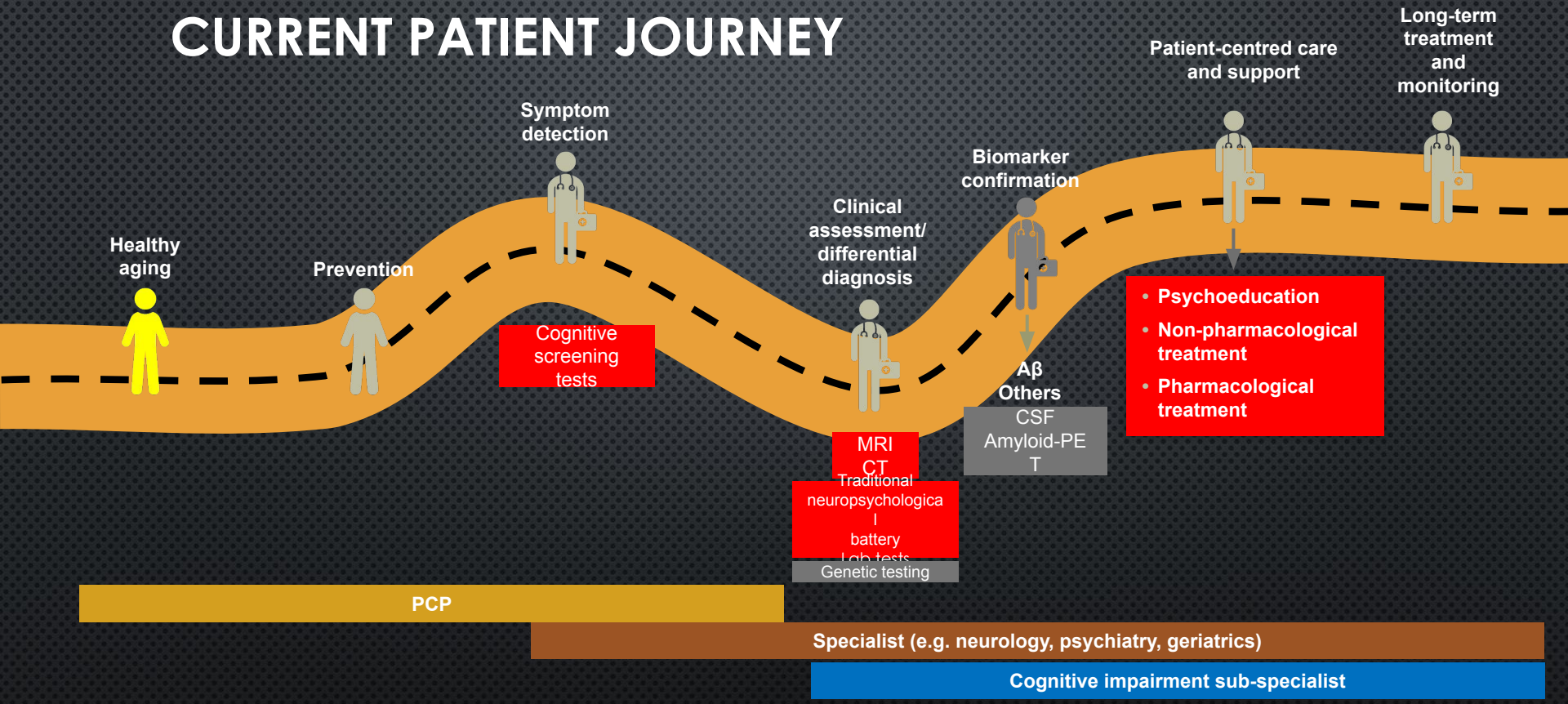
MANAGEMENT OF ANTI-AMYLOID MONOCLONAL ANTIBODIES IN ITALY: IS THE SYSTEM READY?

ALESSANDRO PADOVANI

ON BEHALF OF THE ITALIAN EXPÈRT PANEL ON ALZHEMER DISEASE

CURRENT PATIENT JOURNEY



Ab, amyloid beta; CSF, cerebrospinal fluid; CT, computerised tomography; MRI, magnetic resonance imaging; NMDA-R, N-methyl-D-aspartate receptor; PCP, primary care physician; PET, positron emission tomography

1. Hlavka JP, et al. *Rand Health Q*. 2019;8(3):2; 2. Fowler NR, et al. *J Am Geriatr Soc*. 2012;60(6):1037–1043; 3. Wong-Lin K, et al. *BMC Med*. 2020;18(1):398; 4. Budelier MM, et al. *J Appl Lab Med*. 2020; 5(1): 194–208; 5. Hampel H, et al. *Nat Rev Neurol*. 2018;14:639–652; 6. Cummings J, et al. *Alzheimers Dement* (NY). 2021;7:e12179; 7. Parsons C, et al. *BMC Palliat Care*. 2019;18(1):6; 8. Hampel, H, et al. *Nat Rev Neurol*. 2018;14(11):639–652; 9. Kourtis LC, et al. *NPJ Digit Med*. 2019:2:9; 10. Au R, et al. *Adv Geriatr Med Res*. 2019;1:e190003; 11. Mattke S, et al. Implications of Alzheimer's treatment for organization and payment of medical practices in the United States; Available at: https://cesr.usc.edu/sites/default/files/Implications%20of%20Alzheimer%27s%20Treatment%20for%20Organization%20and%20Payment%20of%20Medical%20Practices%20in%20the%20United%20States%20%282020%29.pdf. Accessed 17 June 2021

THE ARRIVAL OF ANTI-AMYLOID DRUGS: OPPORTUNITIES AND LIMITATIONS

A THERAPEUTIC REVOLUTION BETWEEN BENEFITS AND RISKS

- **New therapeutic phase:** Monoclonal antibodies pave the way for potentially disease-modifying treatments, intervening in the biology of the disease.
  Demonstrated but limited efficacy: In clinical trials: −27% cognitive decline with lecanemab and −35% with donanemab in selected patients, especially in the MCI phase.
  Relevant clinical risks: Frequent ARIAs, especially in ApoE ε4 carriers, require serial monitoring with MRI and expert centers.
  Conditional value: Limited benefits to early patients; significant organisational and economic impact on the SSN.

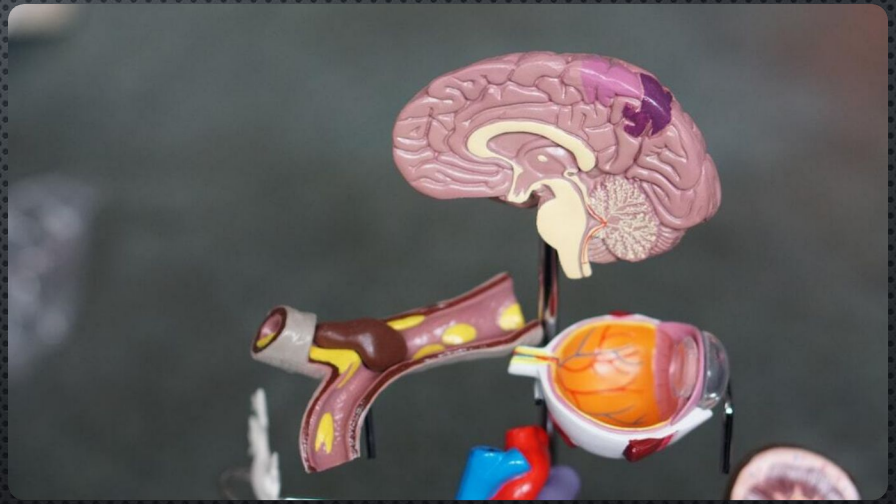
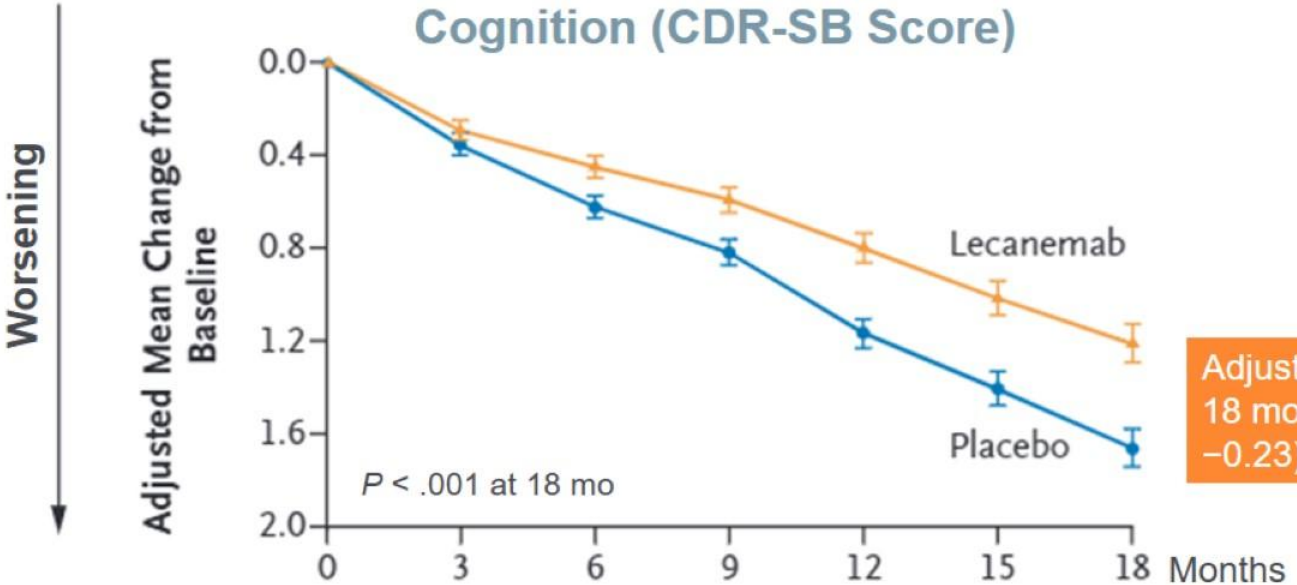


Photo by Robina Weermeijer on Unsplash

CLARITY: Phase 3 Trial of Lecanemab vs Placebo
Efficacy

Amyloid-positive patients, 50 to 90 y, with MCI due to AD or mild AD dementia (N = 1795)



Adjusted mean difference at 18 mo: **−0.45** (95% CI: −0.67, −0.23); *P* < .001)

No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

van Dyck CH, et al. N Engl J Med. 2022;388:9-21.

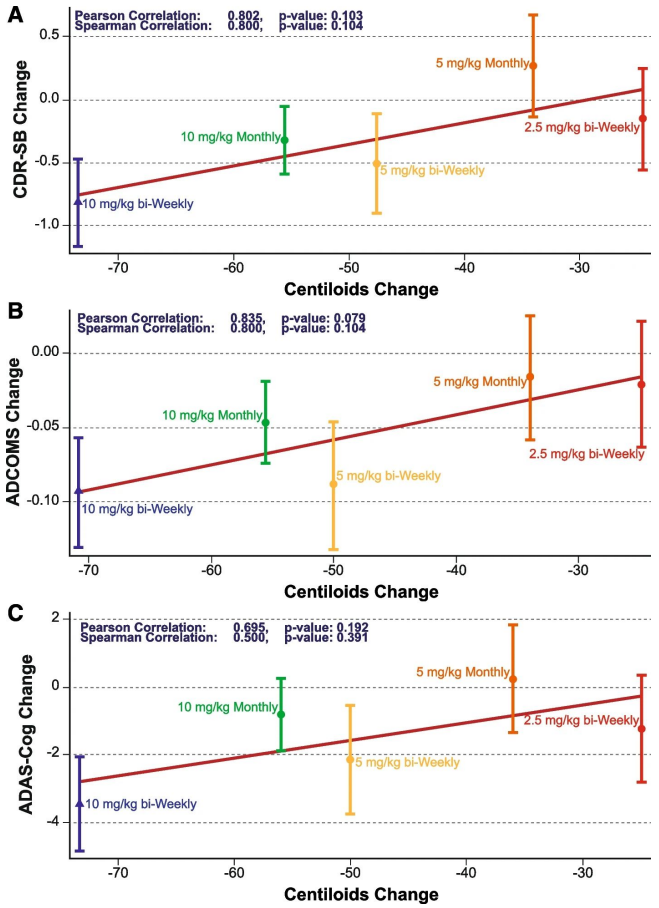
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

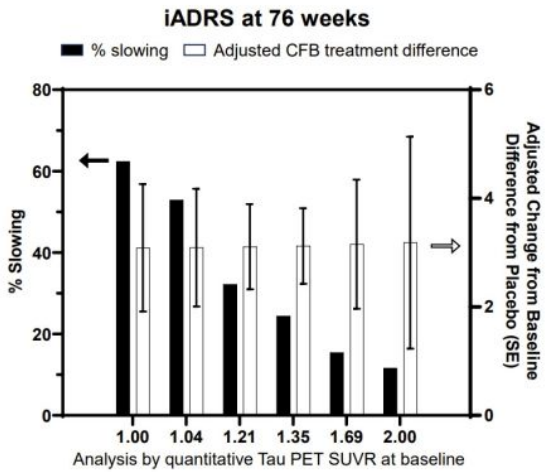
Lecanemab in Early Alzheimer's Disease

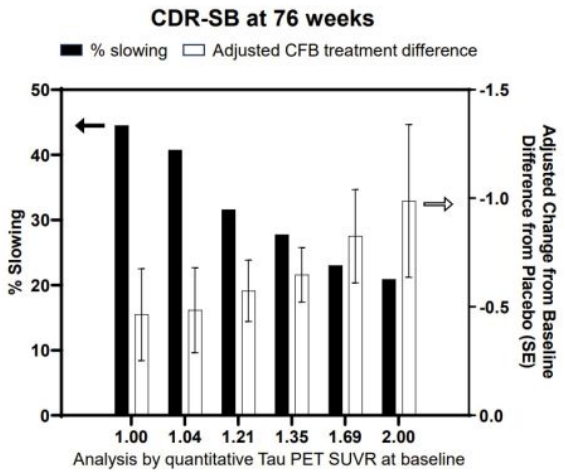
Christopher H. van Dyck, M.D., Chad J. Swanson, Ph.D., Paul Aisen, M.D., Randall J. Bateman, M.D., Christopher Chen, B.M., B.Ch., Michelle Gee, Ph.D., Michio Kanekiyo, M.S., David Li, Ph.D., Larisa Reyderman, Ph.D., Sharon Cohen, M.D., Lutz Froelich, M.D., Ph.D., Sadao Katayama, M.D., Marwan Sabbagh, M.D., Bruno Vellas, M.D., David Watson, Psy.D., Shobha Dhadda, Ph.D., Michael Irizarry, M.D., Lynn D. Kramer, M.D., and Takeshi Iwatsubo, M.D.

Is there a clear relationship between drug dosage and amyloid clearance?
The case of Lecanemab



Fewer Tangles, Better Results.



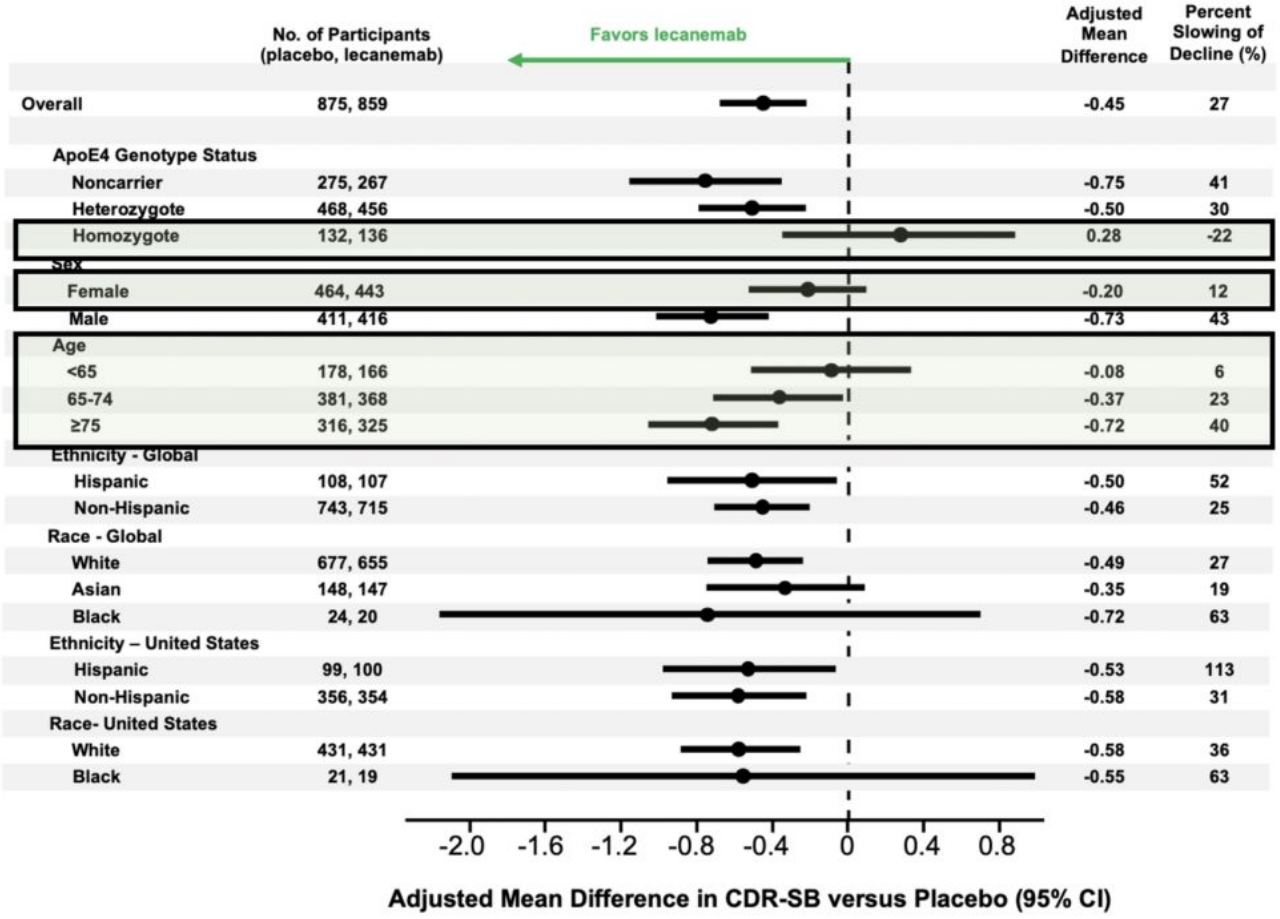


Modeling based on these data predicted that for people with a tau SUVR of 1, cognitive decline would slow by 60 percent on the iADRS and 45 percent on the CDR-SB.

At an SUVR of 2, by contrast, those numbers would be as low as 10 and 20 percent (see image above). This compares with measured values of 35 and 36 percent in the intermediate-tau trial population.

Modeling based on donanemab Phase 3 data predicts that people with the lowest tau PET SUVRs (x axis) will maintain their cognitive abilities the best (black bars). [Courtesy of Eli Lilly.]

Subgroup Analyses: CDR-SB



DMT targets might vary across Alzheimer stages?

COMMENTARY

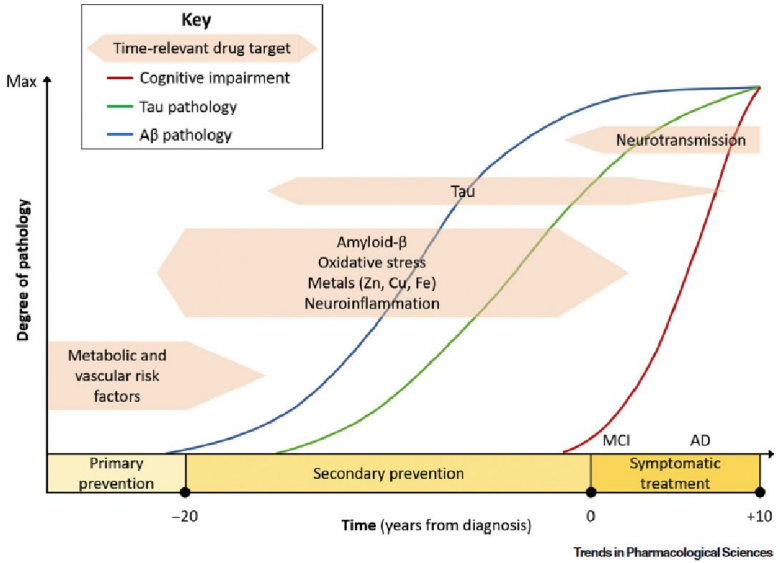
ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

Reisa A. Sperling,[1*] Clifford R. Jack Jr.,[2] Paul S. Aisen[3]

Alzheimer's disease (AD) is the only leading cause of death for which no disease-modifying therapy is currently available. Recent disappointing trial results at the dementia stage of AD have raised multiple questions about our current approaches to the development of disease-modifying agents. Converging evidence suggests that the pathophysiological process of AD begins many years before the onset of dementia. So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?

www.ScienceTranslationalMedicine.org 30 November 2011 Vol 3 Issue 111 111cm33



EUROPEAN REGULATORY FRAMEWORK AND IMPLICATIONS FOR ITALY

Rigour, appropriateness and organisational challenges

EMA 2025 Decisions
Lecanemab authorised at EU level for early Alzheimer's disease; donanemab approved after re-examination.

Strict conditions of use
Use limited to patients with early diagnosis and biomarker-based confirmation; intensive monitoring with MRI and ApoE genetic testing.

Italian challenge
Need for up-to-date national registries, accredited prescribing centers (CDCD level 3), and PDTAs to ensure equity and sustainability.

La selezione dei pazienti

- Un punto critico per determinare l'effetto è la selezione dei pazienti per la DMT: questo è saldamente stabilito nel contesto degli studi clinici randomizzati (RCT) ma non è chiaro come funzioni in uno scenario reale di cura clinica per i disturbi cognitivi.
- I centri per la cura dell'AD sono estremamente eterogenei per riferimento, organizzazione, capacità tecnica e competenza degli specialisti coinvolti nell'assistenza clinica;
- La definizione del setting clinico è quindi fondamentale.

Target population in the real world

- Diversi studi hanno affrontato la questione di quale percentuale di pazienti con AD lieve sarebbe disponibile per la DMT. Questo è stato fatto in Italia in centri per la cura clinica della demenza denominati CDCD [5, 6], in Irlanda in un servizio cognitivo specializzato su base geriatrica [7] e negli Stati Uniti con richieste di servizi medici [8] e in uno studio basato sulla popolazione a Rochester (MN) [9].
  Quando sono stati applicati i criteri di inclusione ed esclusione dell'RCT DMT, tutti gli studi hanno mostrato che il numero di candidati per la DMT è in media <10% dei soggetti inizialmente reclutati in ciascun contesto per il trattamento con DMT.
- L'unica eccezione è stata lo studio irlandese [7], in un contesto con competenze neurologiche e geriatriche, con una percentuale maggiore di soggetti (27%).

5.Togher Z, Dolphin H, Russell C, Ryan M, Kennelly SP, O'Dowd S. Potential eligibility for Aducanumab therapy in an Irish specialist cognitive service-Utilising cerebrospinal fluid biomarkers and appropriate use criteria. Int J Geriatr Psychiatry. 2022;37(8). doi. 10.1002/gps.5789 [DOI] [PMC free article] [PubMed] [Google Scholar] 6.Padovani A, Caratozzolo S, Rozzini L, Pilotto A, Benussi A, Tedeschi G. Real-world eligibility for aducanumab depends on clinical setting and patients' journey. J Am Geriatr Soc. 2022;70(2):626-628. doi. 10.1111/jgs.17530 [DOI] [PMC free article] [PubMed] [Google Scholar] 7.Canevelli M, Rossi PD, Astrone P, Consorti E, Vanacore N, Cesari M. Real world eligibility for aducanumab. J Am Geriatr Soc. 2021;69(10):2995-2998. doi. 10.1111/jgs.17390 [DOI] [PubMed] [Google Scholar] 8.Anderson TS, Ayanian JZ, Souza J, Landon BE. Representativeness of participants eligible to be enrolled in clinical trials of aducanumab for Alzheimer disease compared with Medicare beneficiaries with Alzheimer disease and mild cognitive impairment. JAMA. 2021;326(16):1627-1629. doi. 10.1001/jama.2021.15286 [DOI] [PMC free article] [PubMed] [Google Scholar] 9.St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ III, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. Mayo Clin Proc. 2012;87(2):151-160. doi. 10.1016/j.mayocp.2011.11.009 [DOI] [PMC free article] [PubMed] [Google Scholar]

THE ITALIAN CONTEXT

The process of implementation in the real world

- The translation of therapies into real-world clinical practice requires **a precise redefinition of diagnostic and care pathways, the establishment of standardized monitoring protocols, and robust organisational frameworks** to ensure equity of access and patient safety
- The Italian context presents specific challenges**. The current national dementia guidelines, published before the approval by EMA of anti-amyloid monoclonal antibodies**, recommend biomarker-supported diagnosis only in individuals with dementia and provide a strong negative recommendation for their use in mild cognitive impairment (MCI)
- **the Italian healthcare system is undergoing reorganization under the Ministerial Decree** 77/2022 (DM77), which defines new standards for community-based care. DM77 establishes "community homes" as multidisciplinary hubs for chronic disease management, and strengthens the integration between primary care and specialist services

THE CHALLENGE OF ALZHEIMER'S IN ITALY

EPIDEMIOLOGY, SOCIO-ECONOMIC IMPACT AND URGENCY OF INNOVATION

- **Growing epidemiology:** In Italy it is estimated that over 1 million people suffer from dementia, of which about 60% from Alzheimer's; Demographic aging will lead to a doubling of cases by 2050.
  Socio-economic impact: The total annual cost of dementia in Italy exceeds 15 billion euros, of which more than 70% is borned by families in terms of informal care.
  Complex care challenge: The disease requires multidimensional care, involving early diagnosis, pharmacological and non-pharmacological treatments, caregiver support and integrated territorial services.

Photo by Diz Play on Unsplash

COMPARISON TABLE: AUR COMMONALITIES VS ITALIAN DISTINCTIONS

Common Across AURs	Distinct in Italian EPA Proposal
Amyloid PET or CSF required for diagnosis	Explicit **GP role** in early detection and referral
Baseline MRI mandatory for ARIA risk assessment	Mandatory involvement of **multidisciplinary teams** including ethics boards
Eligibility focused on early-stage Alzheimer's (MCI/mild)	Centralized PDTA integration across regions and levels of care
Infusion sites must be prepared for ARIA response	**Ethical frameworks** and caregiver-informed consent emphasized
APOE genotyping increasingly recommended	Nationally coordinated **data collection** and **equity enforcement**
Initial monitoring involves structured MRI timeline	**Transregional adaptation** within a national care framework

THE CHALLENGES IN THE ITALIAN SYSTEM

HTA AND SUSTAINABILITY SCENARIOS

International experiences and challenges for Italy

- **International experiences**: USA, UK, France and Germany have adopted differentiated approaches for access and reimbursement, with HTA models and national registries.
  Challenge for Italy: Need to build an interoperable national registry, accredited prescribers and innovative reimbursement models.
  Complex balance: The introduction of anti-amyloid drugs requires balancing innovation, equity of access, and economic sustainability.

CHALLENGE FOR ITALY: REGISTERS AND REIMBURSEMENT MODELS

GOVERNANCE TOOLS FOR EQUITABLE AND SUSTAINABLE ACCESS

- **Interoperable national registry:** Essential for collecting real-world data on efficacy and safety, ensuring transparency and continuous monitoring.
  Accredited Prescribing Centers: Key role of Level 3 CDCDs, equipped with multidisciplinary teams and advanced diagnostic capabilities.
  Innovative reimbursement models: Tools such as payment by results can balance equity of access and sustainability of the SSN.

BALANCING INNOVATION, EQUITY AND SUSTAINABILITY

Necessary condition for the adoption of anti-amyloid drugs

- **Therapeutic innovation**: New anti-amyloid therapies usher in a paradigm shift, offering unprecedented opportunities for early-stage patients.
  Equity of access: It is necessary to ensure territorial uniformity, avoiding that only some regions or centers can offer drugs.
  Economic sustainability: The high cost and monitoring requirements pose a risk to the financial stability of the SSN.
  Integrated governance: Only a careful balance between these elements will be able to translate innovation into value for the health system.

THE ROLE OF CDCD

THE CDCD NETWORK AND MINISTERIAL DECREE 77

Hospital-community integration for innovative drugs

Role of CDCDs
Centers for Cognitive Disorders and Dementia as fundamental nodes for diagnosis, management and follow-up.

Integration with DM 77
The new structure of territorial assistance enhances the CDCDs and strengthens their function in the proximity model.

Prescribing centers
For anti-amyloid drugs, only level 3 CDCDs, equipped with multidisciplinary expertise and advanced technologies, will be able to prescribe and monitor.

HUB-AND-SPOKE JOURNEY AND SPECIALIST ROLES

An integrated organizational model for the management of Alzheimer's

- **Referral hub**: Highly specialized centers (CDCD level 3) with multidisciplinary skills, advanced diagnostics and complication management capabilities.
- **Territorial spokes**: GPs, neurologists and geriatricians in the area guarantee early interception, triage and follow-up, in connection with the hubs.
- **Integrated network:** The structured collaboration between hub and spoke ensures equity of access, appropriateness and continuity of care.

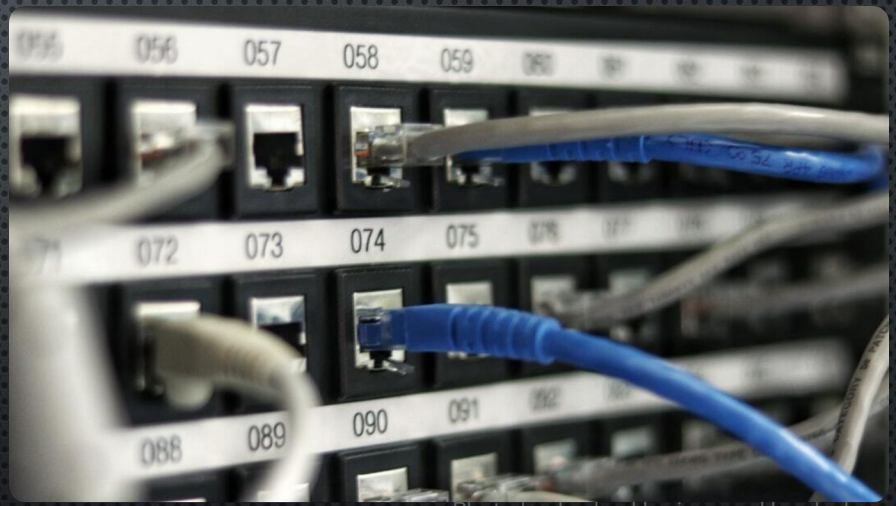
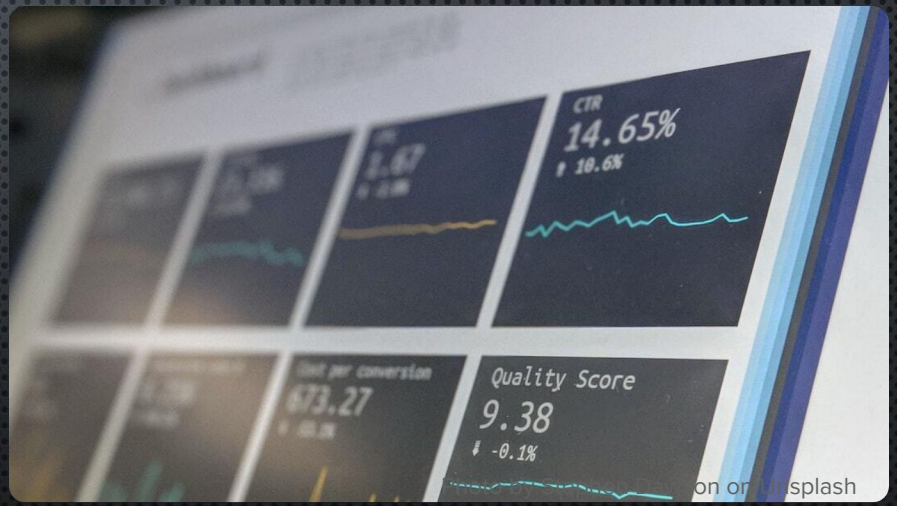


Photo by Jordan Harrison on Unsplash

KPIs for timeliness, appropriateness and fairness

Measuring the effectiveness of the organizational model

- **Timeliness:** Indicators of average time from the onset of symptoms to diagnosis and from the start of the path to therapy.
  Appropriateness: Percentage of treated patients who meet the clinical and biomarker-based criteria defined by the guidelines.
  Equity: Geographical distribution and even access to prescribing centers and innovative treatments.
  Measurable outcomes: Use of PROMs and PREMs to assess the real impact on patients and caregivers.



THE ROLE OF CAREGIVERS IN THE THERAPEUTIC PATH

A PILLAR OF THE CARE SYSTEM

- **Essential support**: In Italy, more than 80% of assistance to people with Alzheimer's is guaranteed by family caregivers.
  Complex needs: High emotional, psychological, and economic burden, often with a risk of burnout and social isolation.
  Enhancement of the role: We need psychological support programs, training and dedicated economic support.
  Outcome indicators: PROMs and PREMs include the caregivers' point of view, which is essential for measuring the real impact of care.

Photo by Bruno Aguirre on Unsplash

DIGITAL INNOVATION AND REAL-WORLD DATA

New technologies to support the management of Alzheimer's disease

- **Interoperable National Registry:** Digital tool to collect real-world data on the efficacy and safety of anti-amyloid drugs.
  Telemedicine and remote monitoring: Digital tools, sensors and apps enable home follow-up and reduce the pressure on specialist centres.
  Artificial intelligence: AI and machine learning support early diagnosis, patient stratification, and outcome prediction.
  Dynamic HTA models: The use of real-world data allows for up-to-date cost-effectiveness assessments and outcome-based reimbursement systems.

Photo by National Cancer Institute on Unsplash

RESEARCH AND FUTURE PROSPECTS

Towards new frontiers in the fight against Alzheimer's

Pragmatic trials

Necessary to evaluate the efficacy of innovative drugs in real-world contexts and on heterogeneous populations.

Emerging biomarkers

Plasma tests (p-tau217, NfL, GFAP) represent a potential game-changer for screening and early diagnosis.

Multimodal approach

Combination of pharmacological, digital therapies and prevention interventions to maximize the benefits.

Italy's role

Our country has the opportunity to strengthen its contribution to international clinical research.

CONCLUSIONS AND RECOMMENDATIONS

IS ITALY READY FOR ANTI-AMYLOID DRUGS?

NOT YET BUT

Historic opportunity

New therapies offer a paradigm shift, but only if integrated into an organized and resilient system.

Enabling conditions

Prevention, updated PDTAs, enhancement of caregivers and digital innovation are essential pillars.

Open criticalities

Territorial inhomogeneity, need for registries, qualified prescribing centers and intensive monitoring.

Integrated vision

Strong national governance to ensure equity, appropriateness and sustainability of the NHS.