XII Convegno

IL CONTRIBUTO DEI CENTRI PER I DISTURBI COGNITIVI
E LE DEMENZE NELLA GESTIONE INTEGRATA
DEI PAZIENTI

15 – 16 novembre 2018

Lo studio "Interceptor"

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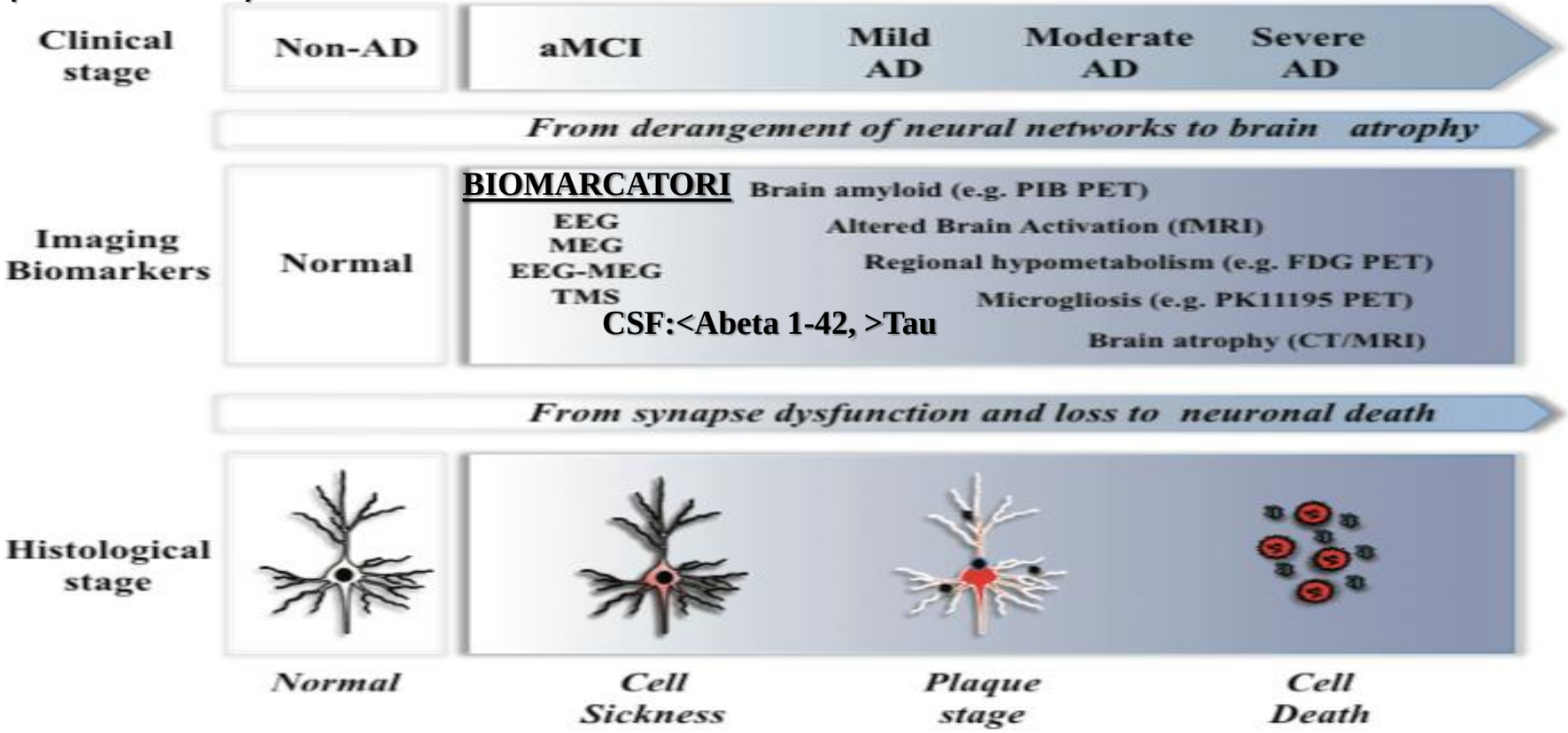
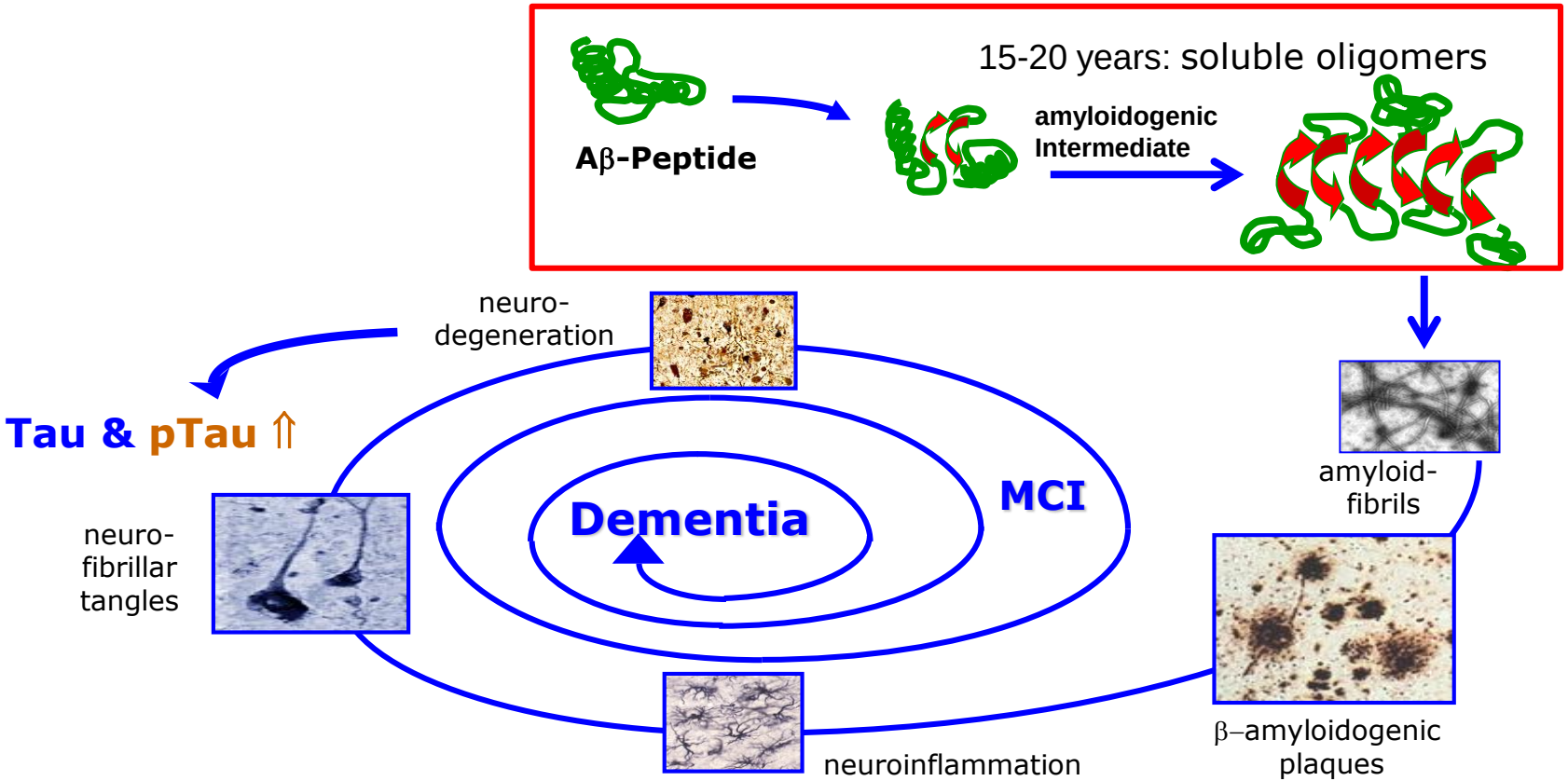
Il **disturbo cognitivo** esordisce tardivamente, molti anni dopo l'inizio del processo degenerativo, la lunghezza di questo intervallo viene determinata da:

- fattori genetici (es. ApoE-ϵ4)
- età
- stile di vita (dieta, esercizio fisico)
- riserva cerebrale e cognitiva: livello di scolarizzazione, complessità delle interazioni sociali, comorbidità (es. diabete mellito, dislipidem vasculopatia cerebrale etc.)



Alzheimer‘s disease hypothesis



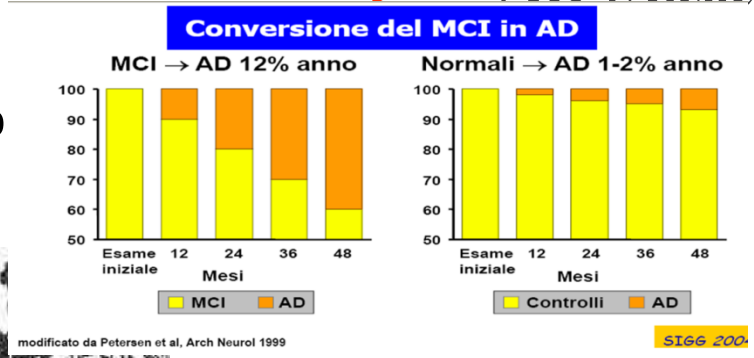
Modified from: Jens Wiltfang, Göttingen

La grande sfida!

MCI (mild cognitive impairment)

Persone con lieve ma oggettivo declino cognitivo con elevato rischio di progredire verso

AD (Alzheimer's disease)



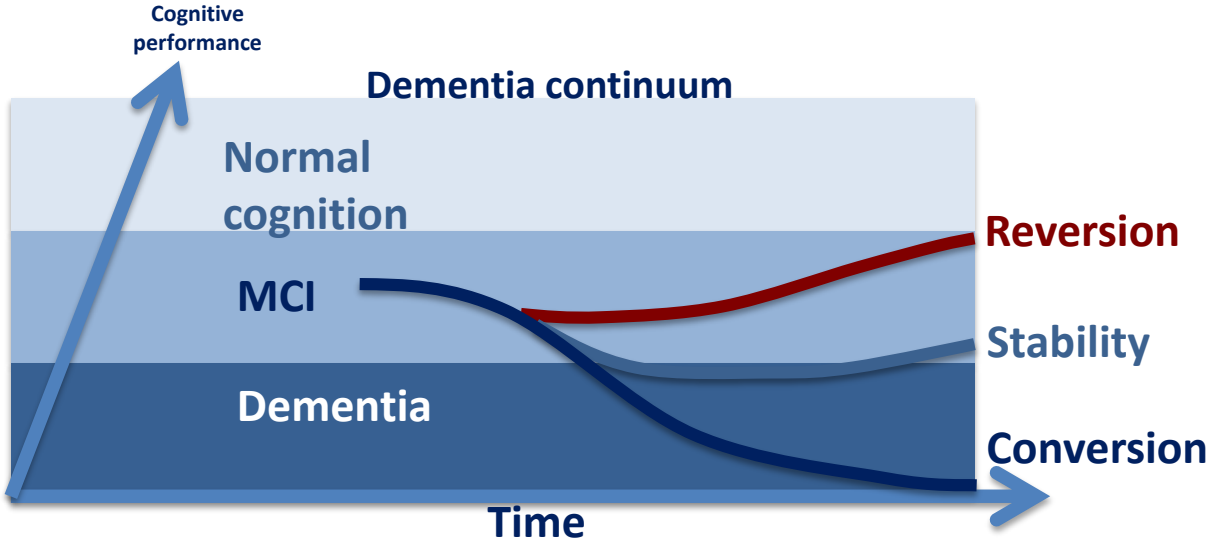
?

Età	% di conversione Anziani ad AD	% di conversione MCI ad AD
65 - 69	0,17 %	da 6% ad 38 %
85 - 89	3,86 %	

7-800.000 in Italia di cui il 50% prodromici di demenza

An AD diagnosis is often made late in the disease continuum

- **A more timely and accurate dementia diagnosis may reduce the impact of misdiagnosis**
- **A timely and accurate diagnosis provides access to a pathway of care and enables patients and their families to plan for the future**
- **Early diagnosis and treatment of patients with AD can improve the efficacy of the presently available drugs and of lifestyle changes leading to a better QoL, a longer patient's autonomy and reduced direct and indirect costs**



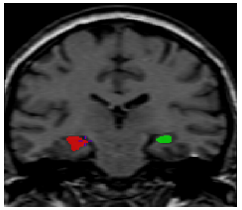
REVERSIONE ALLA NORMALITÀ DEL MILD COGNITIVE IMPAIRMENT: REVISIONE SISTEMATICA DELLA LETTERATURA E METANALISI. *Canevelli Marco, Grande Giulia, Lacorte Eleonora, Mariani Claudio, Bruno Giuseppe, Vanacore Nicola*

Alzheimer‘s disease: current diagnosis

Clinical standard

neuropsychological test

- ▶ diagnosis of **late stages** of disease
- ▶ **low diagnostic accuracy**

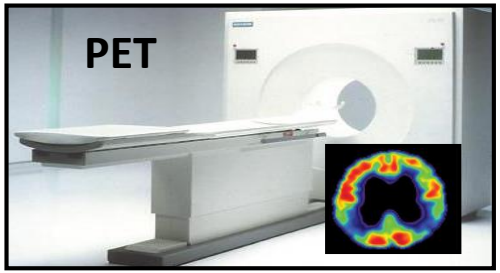


- ▶ **hippocampal volumetry**

neurochemical biomarkers
(e.g. ELISA)

- ▶ **only for CSF**

Additional tests



- ▶ **sensitive and specific**
- ▶ **expensive techniques** (5000 $)
- ▶ **visualisation of amyloid-plaques**
- ▶ diagnosis of **very early stages**?

Electroencephalography for ‘brain connectivity’

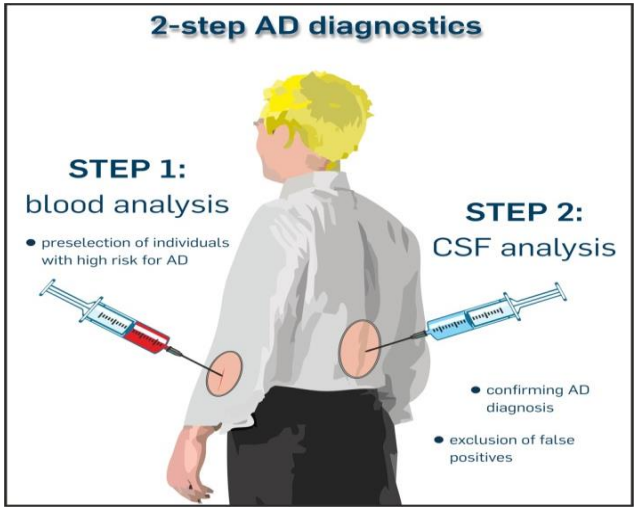
- **unmet medical need for early stage diagnosis**
- **urgent need for a non-invasive blood-test**

Biomarkers

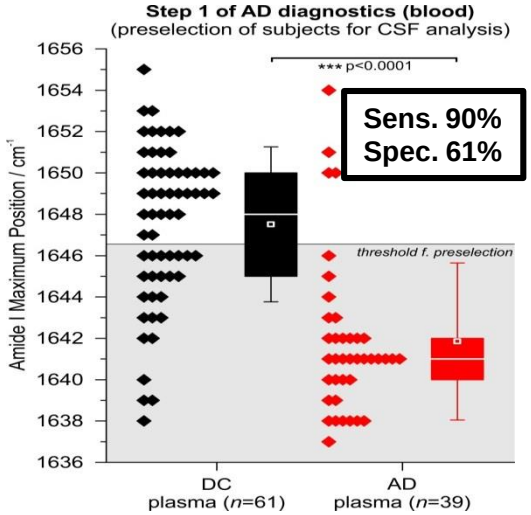
Parte della “caratterizzazione” fenotipica di malattia:

- Modificazioni strutturali del cervello “visibili” alla RMN
- Modificazioni molecolari “visibili” con la PET
- Modificazioni molecolari “visibili” nel LCR
- Connettività EEG alterata
- Fattori di rischio geneticamente determinati
- Altri…

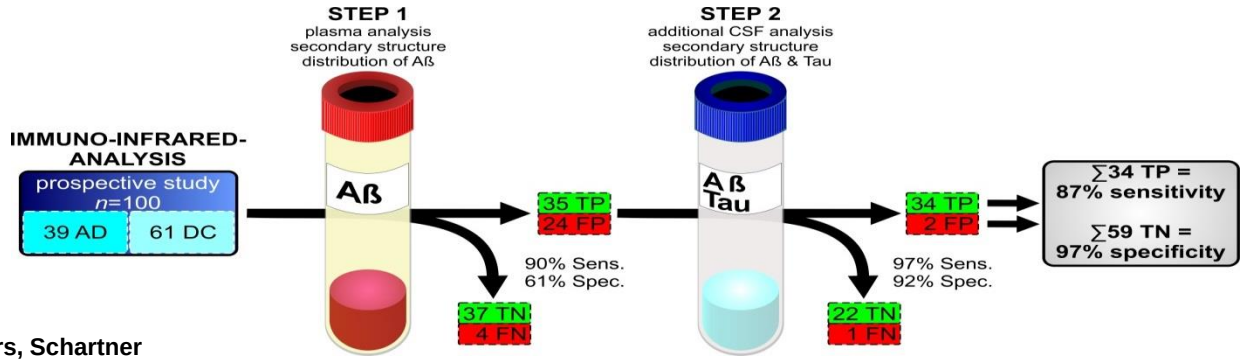
2-step Alzheimer‘s disease diagnostics: sensitivity 87% specificity 97%



- Step 1



- Step 2



Patent EP16199792, Nov 2016, Gerwert, Nabers, Schartner

TABLE 1. Clinical Data of the 2 Groups of Amnesic Mild Cognitive Impairment

	Stable		Converted	
	Mean	SE	Mean	SE
Educational level	10.15	0.71	10.02	0.70
RAVLT immediate recall	26.95	1.19	24.50	0.99
RAVLT delayed recall	3.87	0.49	2.32	0.34
RAVLT recognition correct	10.34	0.53	9.06	0.72
RAVLT recognition false	4.97	0.97	4.31	1.00
RAVLT recognition accuracy	0.85	0.02	0.81	0.03
Constructional praxis	9.26	0.36	8.59	0.41
Constructional praxis landmarks	66.26	0.75	64.85	1.03
MFTC accuracy	0.96	0.01	0.90	0.02
MFTC false alarms	0.43	0.18	1.55	0.65
MFTC time	95.96	5.04	96.52	9.29
Raven Matrices '47	24.53	0.99	25.13	2.84
Phonological verbal fluency	30.57	1.94	25.09	1.38
Categorical verbal fluency	10.96	0.83	10.52	0.65
Stroop SF interference time	33.71	3.93	55.52	9.19
Stroop SF Interference errors	1.89	0.58	5.19	1.56
Corsi forward	4.69	0.26	3.71	0.39
Corsi backward	3.50	0.29	3.60	0.24
Clock-drawing	3.13	0.44	2.43	0.53
Prose memory	3.63	1.08	1.43	0.57
Span forward	5.23	0.30	5.22	0.32
Span backward	4.00	0.41	3.17	0.40

MFTC = Multiple Features Target Cancellation; RAVLT = Rey

Sustainable Method for Alzheimer Dementia Prediction in Mild Cognitive Impairment: Electroencephalographic Connectivity and Graph Theory Combined with Apolipoprotein E

Dr Fabrizio Vecchio, PhD,[1] Dr Francesca Miraglia, PhD,[1,2] Dr Francesco Iberite,[1] Dr Giordano Lacidogna,[3] Dr Valeria Guglielmi,[3] Dr Camillo Marra,[2,3] Dr Patrizio Pasqualetti,[4] Dr Francesco Danilo Tiziano,[5] and Prof Paolo Maria Rossini[2,6]

Objective: Mild cognitive impairment (MCI) is a condition intermediate between physiological brain aging and dementia. Amnesic-MCI (aMCI) subjects progress to dementia (typically to Alzheimer-Dementia = AD) at an annual rate which is 20 times higher than that of cognitively intact elderly. The present study aims to investigate whether EEG network Small World properties (SW) combined with Apo-E genotyping, could reliably discriminate aMCI subjects who will convert to AD after approximately a year.
Methods: 145 aMCI subjects were divided into two sub-groups and, according to the clinical follow-up, were classified as Converted to AD (C-MCI, 71) or Stable (S-MCI, 74).
Results: Results showed significant differences in SW in delta, alpha1, alpha2, beta2, gamma bands, with C-MCI in the baseline similar to AD. Receiver Operating Characteristic(ROC) curve, based on a first-order polynomial regression of SW, showed 57% sensitivity, 66% specificity and 61% accuracy(area under the curve: AUC=0.64). In 97 out of 145 MCI, Apo-E allele testing was also available. Combining this genetic risk factor with Small Word EEG, results showed: 96.7% sensitivity, 86% specificity and 91.7% accuracy(AUC=0.97). Moreover, using only the Small World values in these 97 subjects, the ROC showed an AUC of 0.63; the resulting classifier presented 50% sensitivity, 69% specificity and 59.6% accuracy. When different types of EEG analysis (power density spectrum) were tested, the accuracy levels were lower (68.86%).
Interpretation: Concluding, this innovative EEG analysis, in combination with a genetic test (both low-cost and widely available), could evaluate on an individual basis with great precision the risk of MCI progression. This evaluation could then be used to screen large populations and quickly identify aMCI in a prodromal stage of dementia.

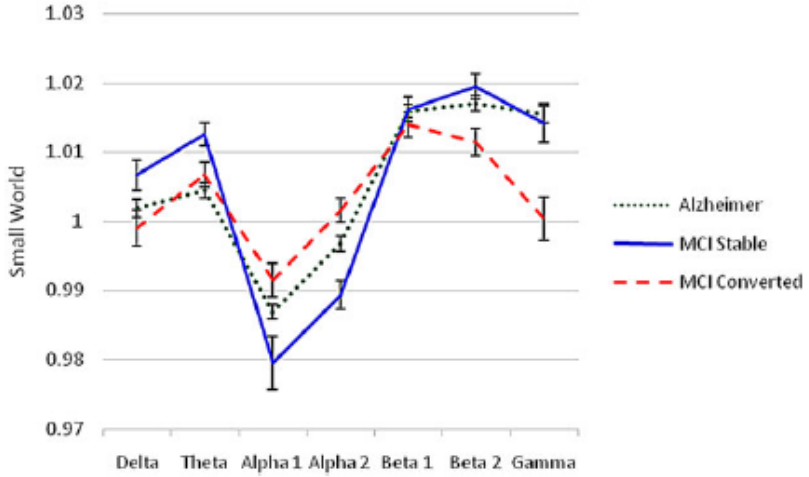


FIGURE 1: Small world characteristics across electroencephalographic frequency bands in stable and converted amnesic mild cognitive impairment (MCI) subjects with respect to Alzheimer dementia patients.

showed an AUC of 0.64 (indicating moderate classification accuracy). The resulting classifier showed 57% sensitivity, 66% specificity, and 61% accuracy for the classification of the aMCI state as a prodromal indicator of AD. This result was obtained when all subjects were included.

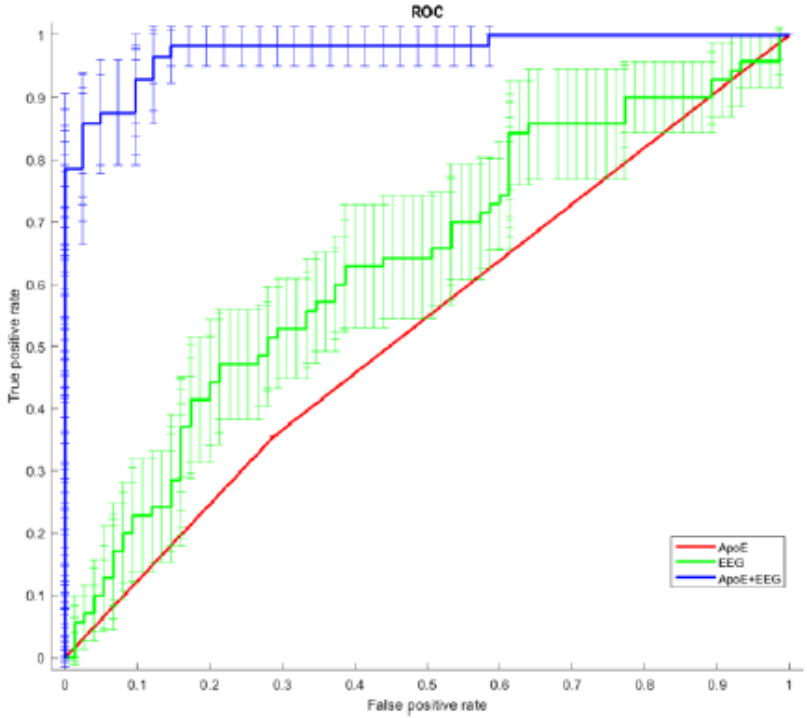
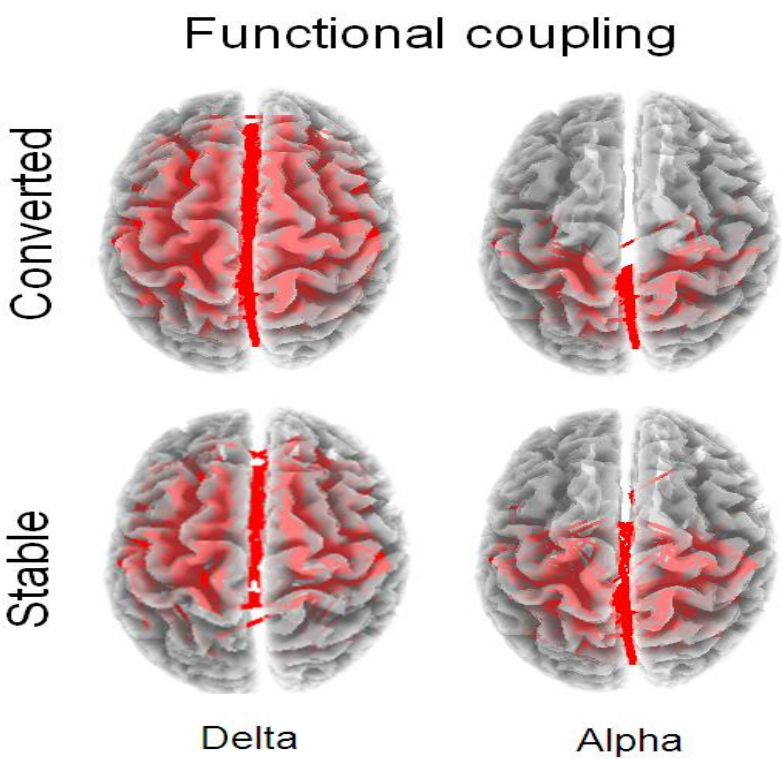
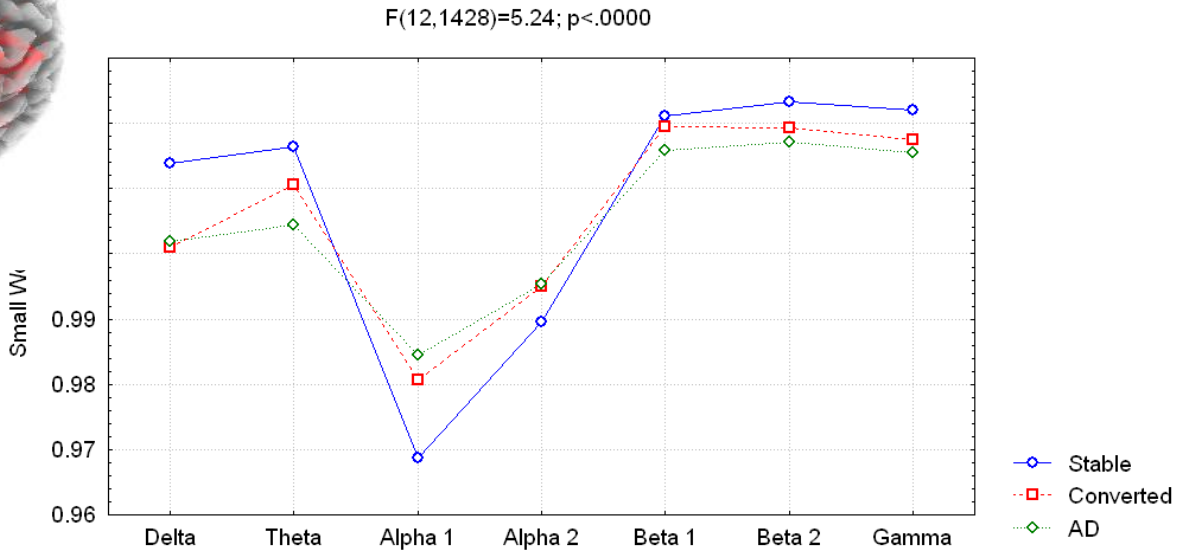


FIGURE 3: Average receiver operating characteristic (ROC) curves and their confidence intervals, illustrating the classification of the stable and converted amnesic mild cognitive impairment individuals based on the apolipoprotein E (ApoE; red line, 97 patients), small world (green line, 145 patients), and ApoE + electroencephalographic (EEG; blue



145 aMCI according to clinical follow-up, classified as Converted to AD (C-MCI, 71) or Stable (S-MCI, 74). Significant differences in SW organization in delta, alpha1, alpha2, beta2 and gamma bands, with C-MCI organization in baseline similar to that in AD. Receiver Operating Characteristic (ROC) curves, based on first-order polynomial regression of SW. In 97 MCI, ApoE alleles testing was also available. By adding this genetic risk factor, 96.7% sensitivity, 86% specificity and 91.7% accuracy (AUC=0.97) were obtained.



Aspirational AD Biomarkers through Assay Commercialization: "Soup to Nuts"

Aspirational markers:
- PD assays
- Enrichment
- Surrogate

Biomarker Discovery & Development (analytically validated)

Clinical Hypothesis

Identify biomarkers that could be clinically meaningful

Third Party Shared Data Platform

Develop Standards for Select Markers

CDISC

Expansive Clinical Trial Adoption of Novel Biomarkers
- *Company A*
- *Company B*
- *Company C*

Regulatory Qualification of Biomarker

Prototype Assay Development

Commercialization of Assay

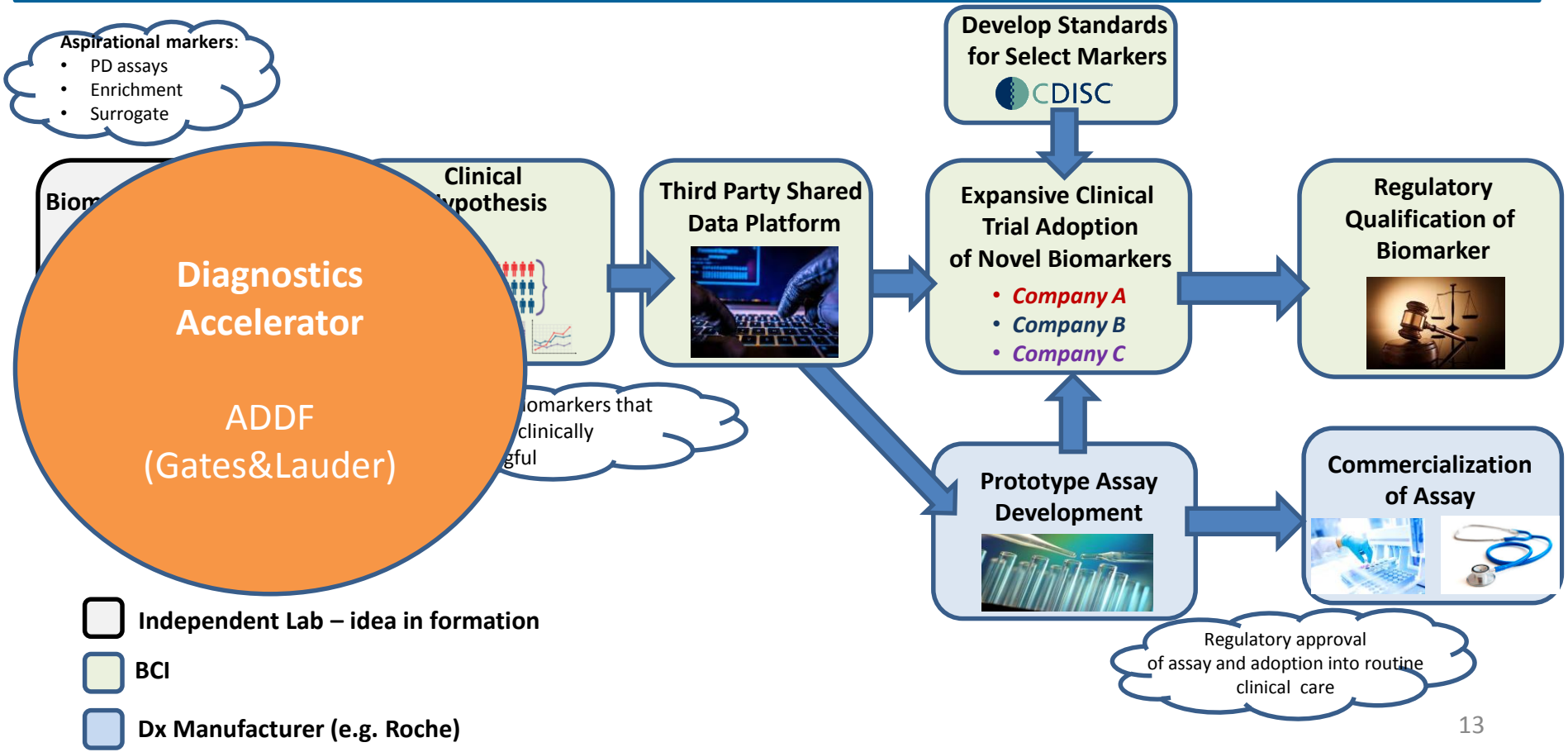
Regulatory approval of assay and adoption into routine clinical care

Independent Lab – idea in formation

BCI

Dx Manufacturer (e.g. Roche)

Aspirational AD Biomarkers through Assay Commercialization: "Soup to Nuts"



Aspirational AD Biomarkers through Assay Commercialization: "Soup to Nuts"

Aspirational markers:
- PD assays
- Enrichment
- Surrogate

Diagnostics Accelerator

ADDF
(Gates&Lauder)

AD Data Coalition

Develop Standards
Select Markers
CDISC

Clinical
ypothesis

Third Par
Data Pla

nsive Clinical
rial Adoption
of Novel Biomarkers
- *Company A*
- *Company B*
- *Company C*

Regulatory
Qualification of
Biomarker

omarkers that
clinically
gful

Prototype Assay
Development

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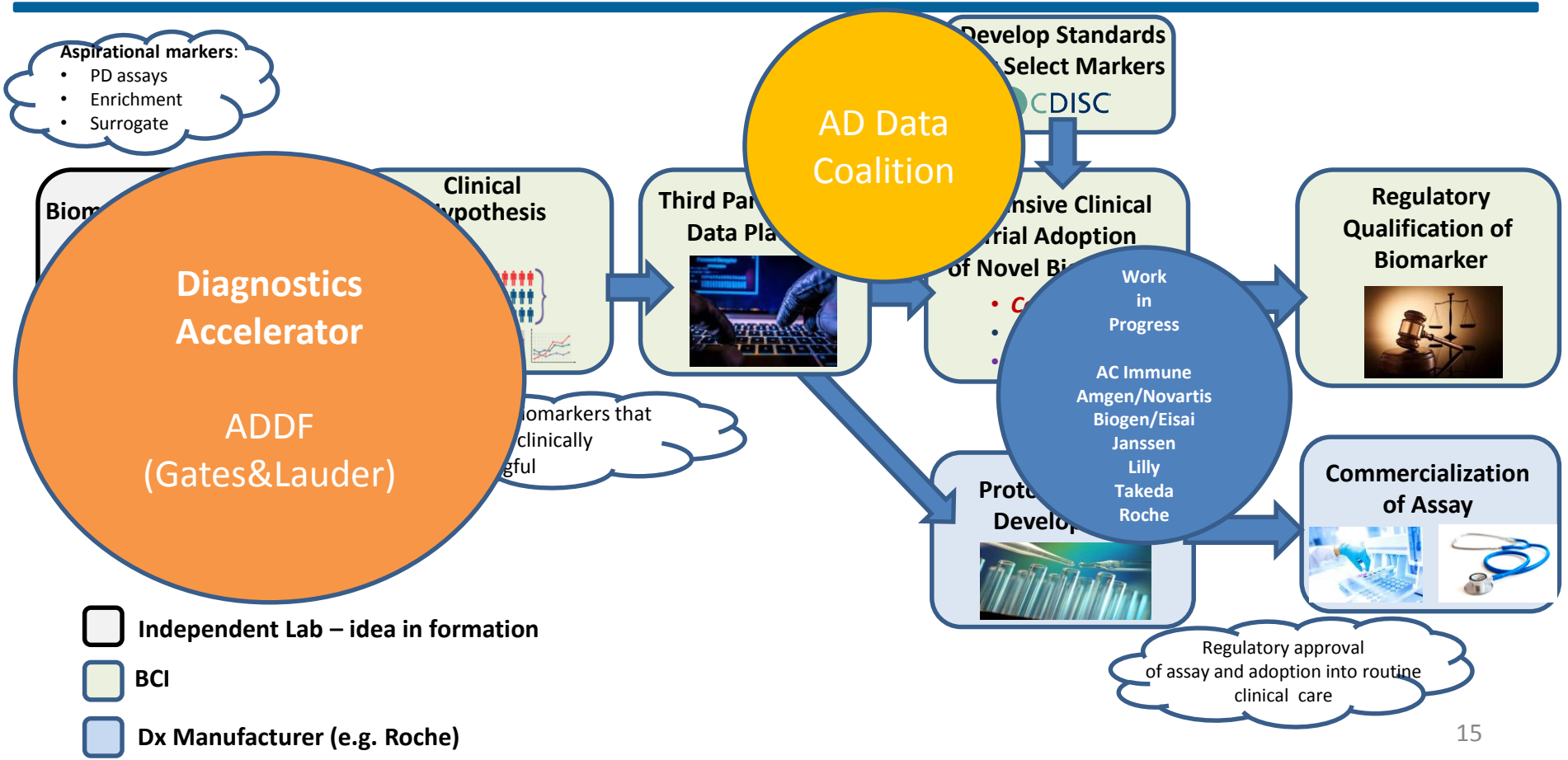
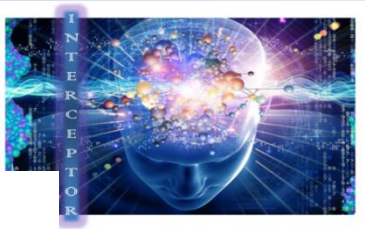
Aspirational AD Biomarkers through Assay Commercialization: "Soup to Nuts"





Terapie farmacologiche sperimentali
Farmaci "disease modifying"

- Per *'disease modifying'* si definisce un farmaco in grado di modificare la storia naturale della malattia ritardando o arrestando il processo patogenetico
- L'efficacia della terapia è limitata alle fasi precoci della malattia (MCI-AD lieve)

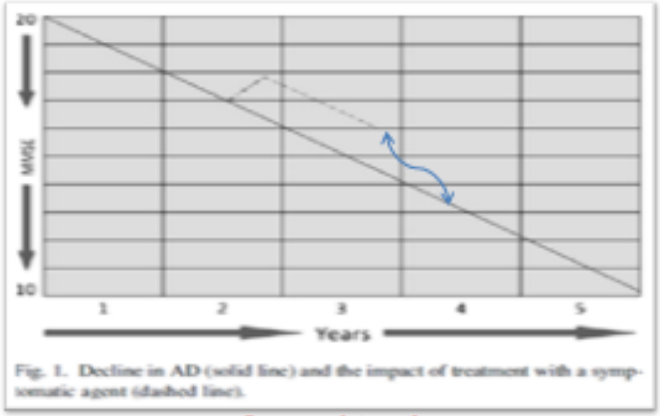


Fig. 1. Decline in AD (solid line) and the impact of treatment with a symptomatic agent (dashed line).

Farmaco sintomatico

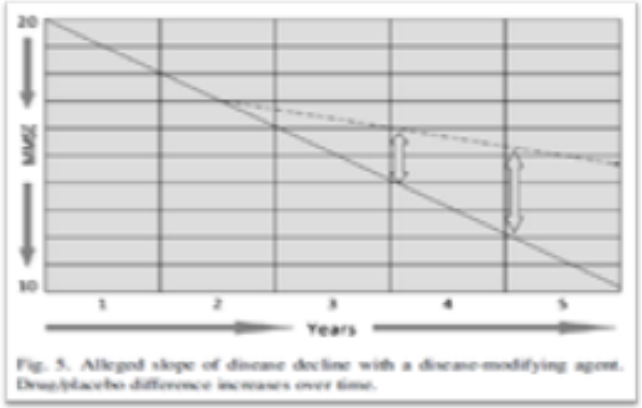


Fig. 5. Alleged slope of disease decline with a disease-modifying agent. Drug/placebo difference increases over time.

Farmaco *'disease modifying'*

(Cummings et al. 2012)

Strategic project promoted
by Italian Medicines Agency (AIFA)

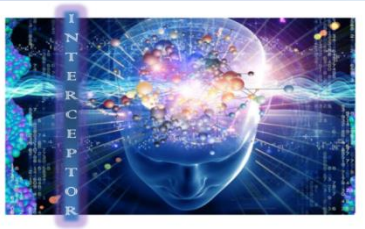
INTERCEPTOR PROJECT

ON THE EARLY DIAGNOSIS OF THE PRODROMAL STAGE OF ALZHEIMER DISEASE. THE PROGRESSION FROM MILD COGNITIVE IMPAIRMENT (MCI) TO DEMENTIA: THE ROLE OF BIOMARKERS IN THE EARLY INTERCEPTION OF PATIENTS TO WHOM PROVIDE FUTURE DISEASE-MODIFYING DRUGS

Best combination of Biomarkers

High accuracy (specificity/sensibility), non-invasive,
Higly available on the territory, financially sustainable

AIFA
AGENZIA ITALIANA DEL FARMACO
Tutela Ricerca e Sviluppo per la Salute



8 nov 2016
14 nov 2016
23 mar 2017
2 mag 2017
22 mag 2017
10 lug 2017
8 set 2017
20 set 2017
26 set 2017
20 dic 2017
19 gen 2018
8 feb 2018
22 mag 2018
29 mag 2018

30 LUG 2018 !

TAVOLO DI LAVORO

Presieduto da D.G. AIFA

S. CAPPA, IRCCS Fatebenefratelli-Brescia, Università di Pavia

L. PROVINCIALI, Università Ancona, Società Italiana Neurologia

F. LATTANZIO, IRCCS I.N.R.C.A. Ancona

P. M. ROSSINI, Neurologia, (IRCCS)-Fondazione Policlinico Gemelli -Università Cattolica Sacro Cuore, Roma

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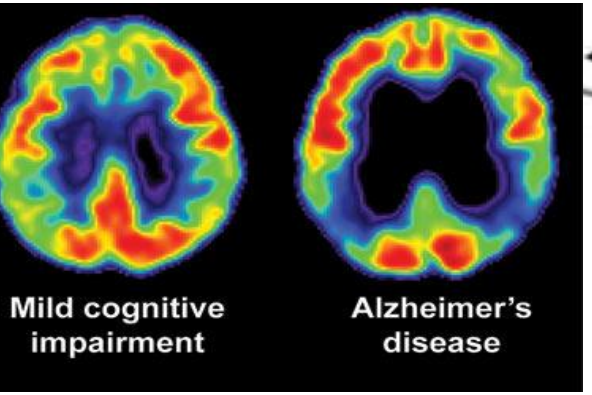
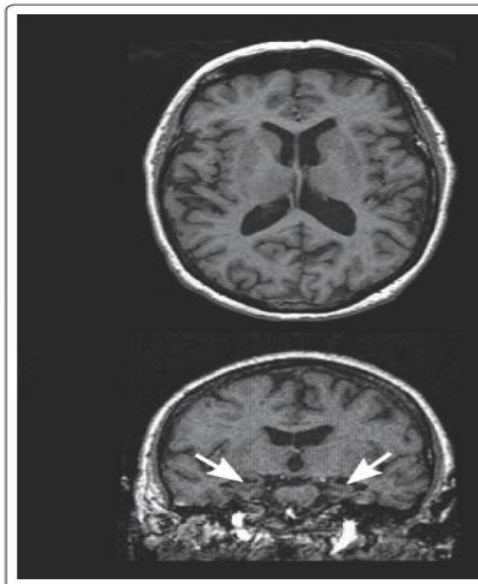
N. VANACORE, P. POPOLI Istituto Superiore di Sanità

R. SCHIAVO, C. SANTINI, V. MANTUA, F.GALEOTTI,

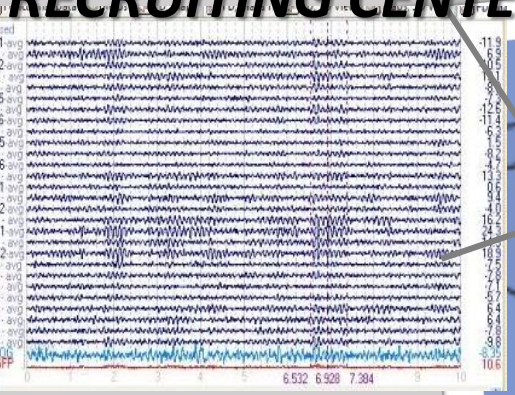
P. FOGGI, G. TAFURI, S. MONTILLA- AIFA,





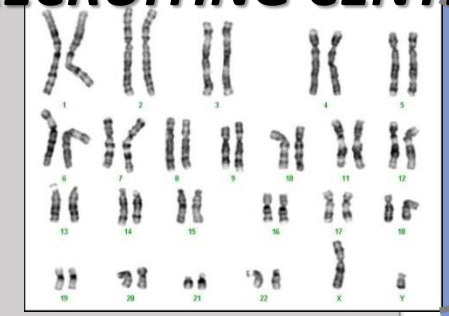
Cloud service

RECRUITING CENTER

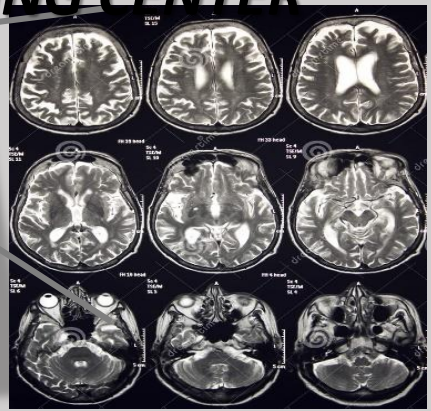


EXPERT CENTER

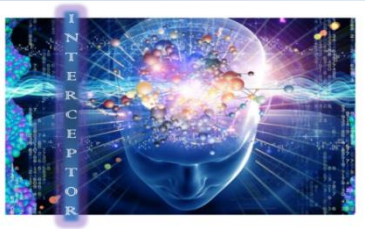
RECRUITING CENTER



RECRUITING CENTER



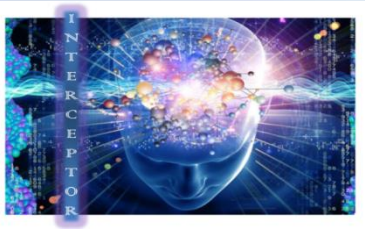
Cloud service



The primary aim of INTERCEPTOR is to identify a biomarker or a set of biomarkers able to predict with greatest accuracy, highest risks/costs ratio, lowest invasiveness and best availability on the territorial level, the conversion of diagnosis of MCI to dementia in a 3 years follow-up period.

This in order to initiate as soon as possible all those initiatives to contrast disease progression.

The secondary aim is to define an optimal organizational model, both in terms of transferability in clinical practice of diagnostic path defined of the primary objective and the sustainability of costs, to identify patients able to prescription of antidementia drug that now are in the course of experimentation by RCTs.



- Lo studio avrà una durata complessiva di 54 mesi. Sei mesi saranno impiegati per predisporre la rete organizzativa ed operativa, 6 mesi per il reclutamento dei pazienti e la raccolta dei bio-marcatori, 3 anni di follow-up clinico e 6 mesi nel corso dei quali verranno analizzati i risultati di tutti i marcatori e preparata la relazione finale. La Frequenza del follow-up neuropsicologico e clinico sarà di ogni 6 mesi In tal modo verranno effettuate 7 valutazioni dal T0 (reclutamento) al T6 (42 mesi).
- Tutti i farmaci assunti al momento della diagnosi di MCI -a meno di urgenze successive al reclutamento da fronteggiare- sono ammissibili senza cambiamenti nel corso dello studio a meno che essi interferiscano a giudizio del Medico Reclutante con processi attentivo-cognitivi al punto da rendere i tests neuropsicologici non affidabili. Entro 60 giorni dal T0 (reclutamento sulla base della batteria dei TNP e dell'acquisizione del 'consenso informato') si dovranno eseguire i marcatori individuato nello studio.

PRIMARY & SECONDARY ENDPOINTS: percentage of MCI to AD conversion during a 3.5 years follow-up. Best combination of biomarkers able to predict conversion with the the highest accuracy low or no invasiveness and best financial sustainability. Biorepository for biomarkers.

Longitudinal, Multicentric, Coort study

500 MCI subjects (aMCI 75% na-MCI 25%) from 20 recruiting centers on the Italian territory.

Total project duration 54 months. From the day of recruitment (T0) during 60 days acquisition of of the following ‘standard’ biomarkers:

Neuropsycological tests (MMSE e DRF – FCSRT)

MRI with hyppocampal volumetry

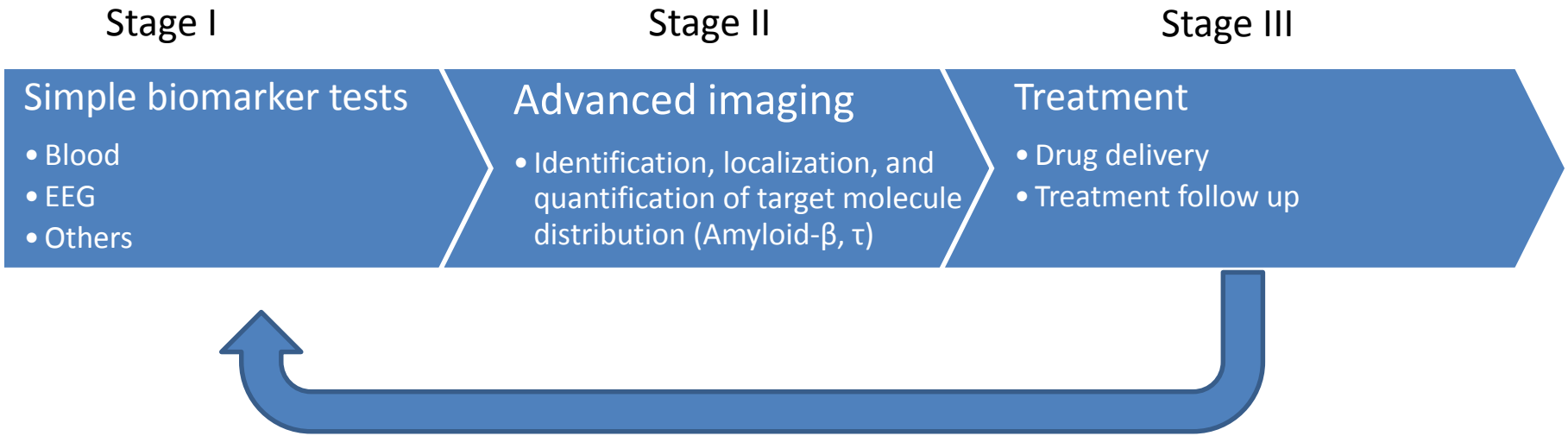
PET-FDG

CSF for Beta/Tau metabolites

ApoE

EEG x brain connectivity via graph theory

Curing AD: prevention (combination) therapies based on early diagnosis



LA PROPOSTA ITALIANA

Su queste basi una stima prudente ci dice che OGGI sono presente in Italia tra I 700 e gli 800.000 casi di MCI di cui il 60% circa diventerà AD nei prossimi 3-5 anni.

Gli AD in Italia sono OGGI oltre 750.000 con una sopravvivenza media di circa 10 anni che si va progressivamente allungando.

PROPOSTA DI ALGORITMO ORGANIZZATIVO:

SCREENING POPOLAZIONE M.C.I.

1° liv (ApoE, EEG, etc)→ NEG. → follow-up TNP

→POS. -→ 2° liv. (CSF, Vol. Ipp.)→NEG follow-up TNP

→POS 3° liv. PET+Amyvid→ NEG follow-up TNP

→ POS AChEI-Mem+Riab.Cogn.

Fattori genetici

Dosaggi CSF (<Abeta 1-42, > Tau

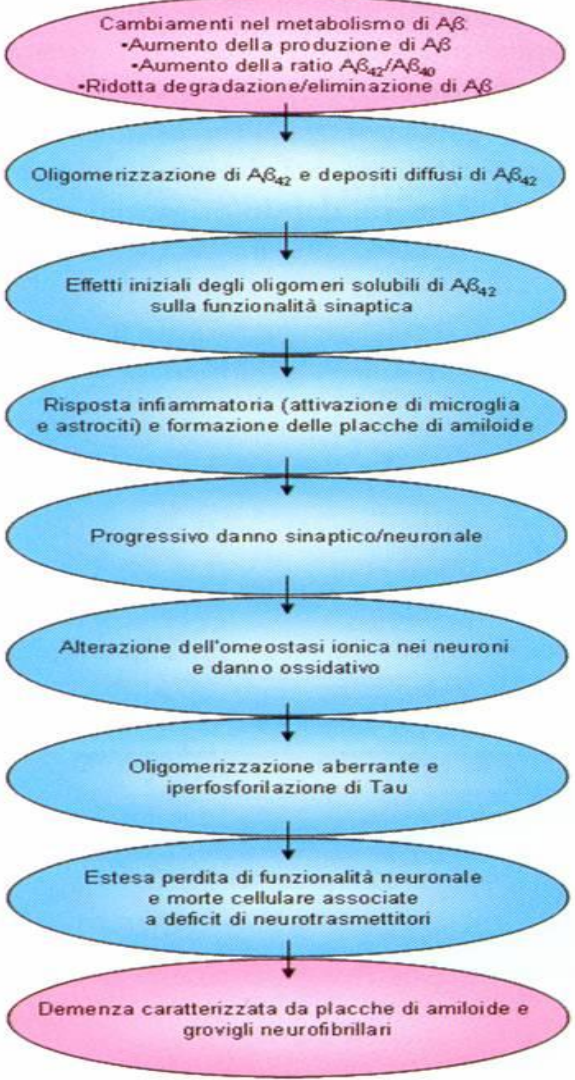
EEG/MEG ----------→

Etc.

PET+radioligandi x Abeta------→

Volumatria Ippocampale,

Spessore grigia, DTI etc.--------→



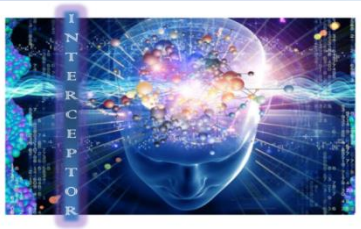
←----15-10 aa prima

←---10-5 aa prima

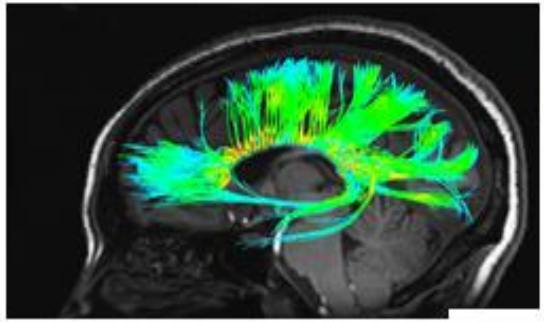
←---3-5 aa prima

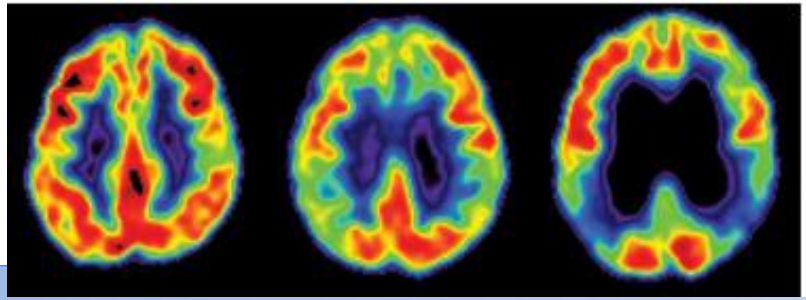
AIFA
AGENZIA ITALIANA DEL FARMACO
Tutela Ricerca e Sviluppo per la Salute

Grazie al Prof. Mario Melazzini ed a tutti i Collaboratori dell'AIFA e del Min. Salute



GRAZIE PER L' ATTENZIONE





Converted