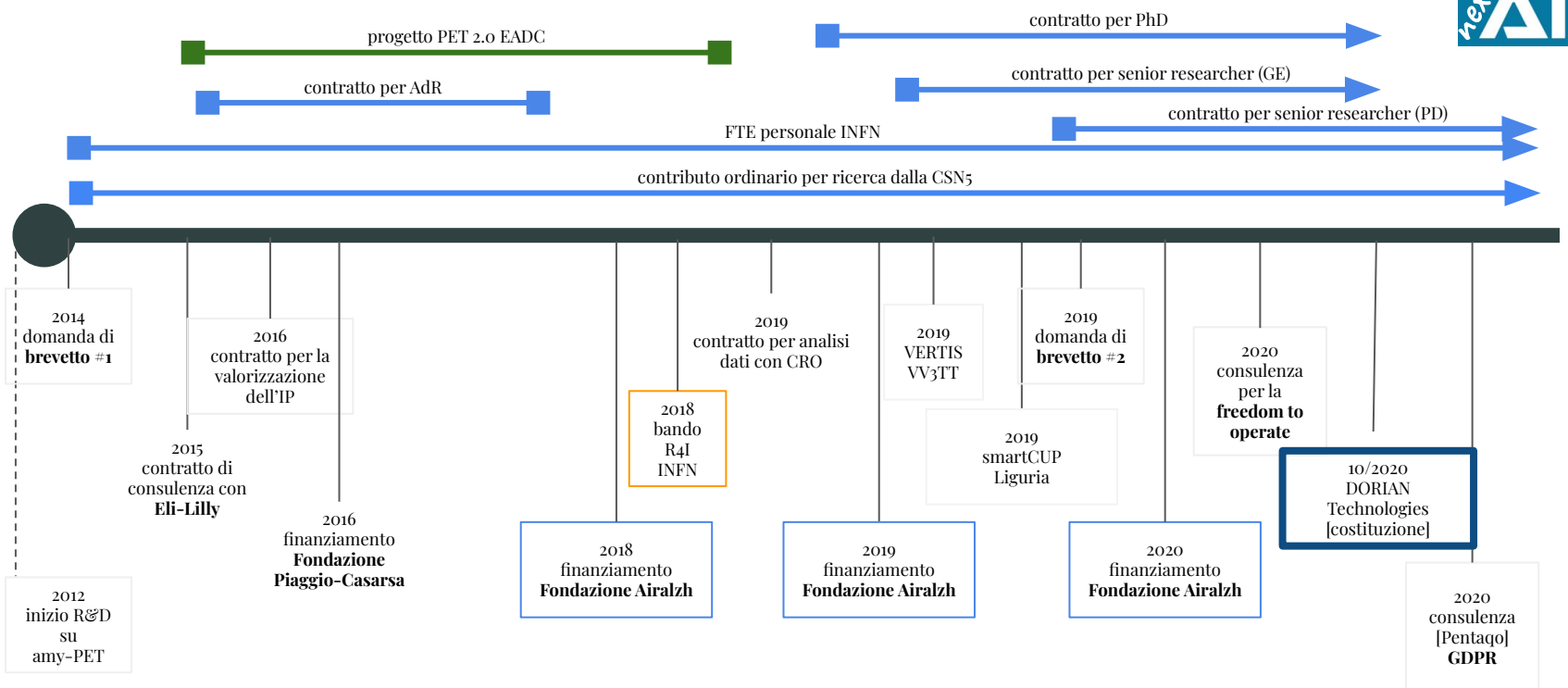
next AIM: the spin-off experience

A. Chincarini

for the INFN Genova group:

Francesco Sensi
Enrico Peira
Ruben Gianeri
Luca Rei
Mirko Corosu
Nicola Alchera
Paolo Bosco

it takes more than an idea …



the importance of R&D

[NM papers only, 2015 - 2021]

methods

A 3D deep learning model to predict the diagnosis of dementia with Lewy bodies, Alzheimer's disease, and mild cognitive impairment using brain 18F-FDG PET - (2022) European Journal of Nuclear Medicine and Molecular Imaging

Probing the Role of a Regional Quantitative Assessment of Amyloid PET- (2021) Journal of Alzheimer's disease

A kinetics-based approach to amyloid PET semi-quantification - (2020) European Journal of Nuclear Medicine and Molecular Imaging

Striatal dopamine transporter SPECT quantification: head-to-head comparison between two three-dimensional automatic tools - (2020) EJNMMI Research

Metabolic patterns across core features in dementia with lewy bodies - (2019) Annals of Neurology

Head-to-Head Comparison among Semi-Quantification Tools of Brain FDG-PET to Aid the Diagnosis of Prodromal Alzheimer's Disease - (2019) Journal of Alzheimer's Disease

18F–FDG PET diagnostic and prognostic patterns do not overlap in Alzheimer's disease (AD) patients at the mild cognitive impairment (MCI) stage - (2017) European Journal of Nuclear Medicine and Molecular Imaging

Early identification of MCI converting to AD: a FDG PET study - (2017) European Journal of Nuclear Medicine and Molecular Imaging

Progressive disintegration of brain networking from normal aging to Alzheimer disease: Analysis of independent components of 18F-FDG PET data - (2017) Journal of Nuclear Medicine

Predicting the transition from normal aging to Alzheimer's disease: A statistical mechanistic evaluation of FDG-PET data - (2016) NeuroImage

Standardized Uptake Value Ratio-Independent Evaluation of Brain Amyloidosis - (2016) Journal of Alzheimer's Disease

Volume of interest-based [18F]fluorodeoxyglucose PET discriminates MCI converting to Alzheimer's disease from healthy controls. A European Alzheimer's Disease Consortium (EADC) study - (2015) NeuroImage: Clinical

clinical validation

Amyloid PET in the diagnostic workup of neurodegenerative disease - (2021) Clinical and Translational Imaging

Validation of FDG-PET datasets of normal controls for the extraction of SPM-based brain metabolism maps - (2021) European Journal of Nuclear Medicine and Molecular Imaging

Added value of semiquantitative analysis of brain FDG-PET for the differentiation between MCI-Lewy bodies and MCI due to Alzheimer's disease - (2021) European Journal of Nuclear Medicine and Molecular Imaging, .

Emerging topics and practical aspects for an appropriate use of amyloid PET in the current Italian context - (2019) Quarterly Journal of Nuclear Medicine and Molecular Imaging

Semi-quantification and grading of amyloid PET: A project of the European Alzheimer's Disease Consortium (EADC) - (2019) NeuroImage: Clinical

The role of molecular imaging in the frame of the revised dementia with Lewy body criteria - (2019) Clinical and Translational Imaging

The impact of automated hippocampal volumetry on diagnostic confidence in patients with suspected Alzheimer's disease: A European Alzheimer's Disease Consortium study - (2017) Alzheimer's and Dementia

clinical applications

Associations among education, age, and the dementia with Lewy bodies (DLB) metabolic pattern: A European-DLB consortium project - (2021) Alzheimer's and Dementia

The fate of patients with REM sleep behavior disorder and mild cognitive impairment - (2021) Sleep Medicine

Dopaminergic imaging and clinical predictors for phenoconversion of REM sleep behaviour disorder - (2021) Brain

Metabolic Correlates of Dopaminergic Loss in Dementia with Lewy Bodies - (2020) Movement Disorders

Presynaptic dopaminergic neuroimaging in REM sleep behavior disorder: A systematic review and meta-analysis - (2018) Sleep Medicine Reviews

Metabolic correlates of reserve and resilience in MCI due to Alzheimer's Disease - (2018) Alzheimer's Research and Therapy

DORIAN TECHNOLOGIES

your key to better data analysis

www.dorian-tech.com

DORIAN Technologies s.r.l. is an innovative startup based in Genova that unlocks the potential of quantitative imaging and AI to optimize diagnosis, prognosis and longitudinal monitoring of patients, targeting Alzheimer's, Parkinson's, and other neurological diseases

Longstanding data analysis, modeling and IT experience.

Abiliting expertises

20+ years of strong medical background in NM and Neurology.

Prof. Guerra
NM phys
MENTOR

Prof. Nobili
Neurologist
MENTOR

Dr. Bosco
Physics PhD
CEO

Dr. Chincarini
Physics PhD
CSO

Dr. Peira
Physics PhD
DEVELOPER

Dr. Sensi
Physics PhD
CTO

Dr. Fabrizi
Legal
Counsel

Dr. Gianeri
Physics
DEVELOPER

Dr. Gozzi
GDPR
Specialist

Dr. Corosu
Physics
IT SPEC

Dr. Sestini
NM phys
ADVISOR

Prof. Cecchin
NM phys
ADVISOR

Dorian Team
Advisors & Mentors

PROBLEM

Current approaches to diagnosis in neurological Nuclear Medicine diagnosis **lack reliable quantification** and understanding of the most recent advances.

a) clinical data contains more information than what meets the eye

but more importantly...

b) the real gap is the transition from a qualitative to a quantitative practice

SOLUTION

To provide the Nuclear Medicine community seamless access to state-of-the-art data analysis & to deliver **easily interpretable results** to improve **diagnostic impact**, reliability and clinical confidence.

The impact of Quantification in Nuclear Medicine Imaging

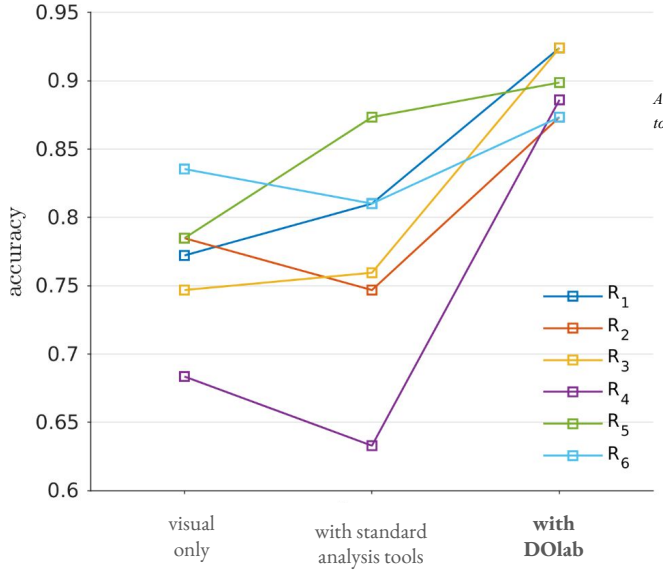
Our solutions can

improve inter-rater agreement

minimize diagnostic errors

enhance clinician's confidence

provide a timely response to the patient

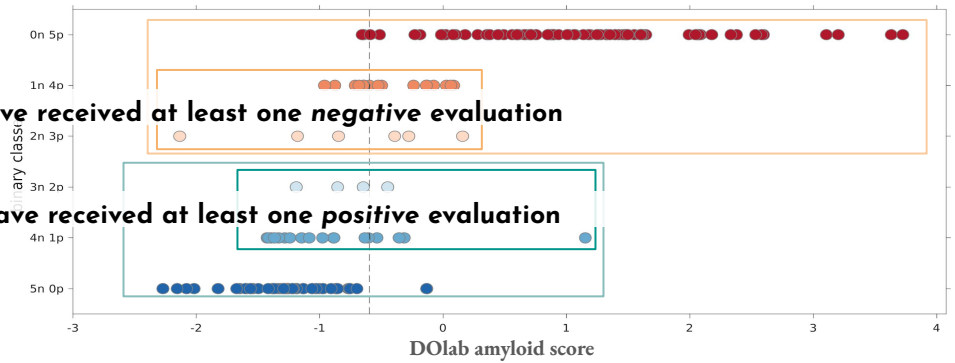


Accuracy of FDG-PET at the individual level in MCI-LB versus MCI-AD: a stepwise approach from visual to semi-quantitative analysis, EJNMMI (2021)

75% → 90% accuracy increase w.r.t. follow-up clinical end point

evaluation accuracy significantly improved with the DOlab-assisted reading
(DLB vs. AD odds-ratio map)

Semi-quantification and grading of amyloid PET: a project of the European Alzheimer's Disease Consortium, NEUROIMAGE CLINICAL (2019)



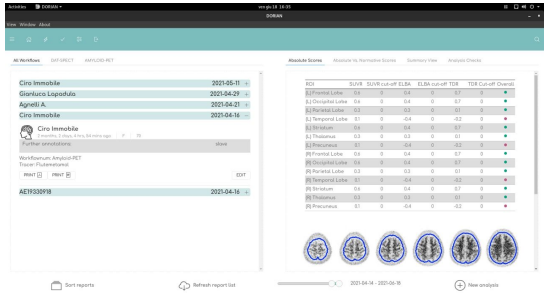
21% **of all *positive* scans have received at least one *negative* evaluation**

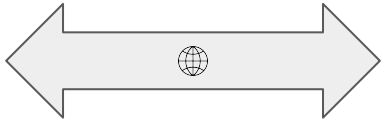
31% **of all *negative* scans have received at least one *positive* evaluation**

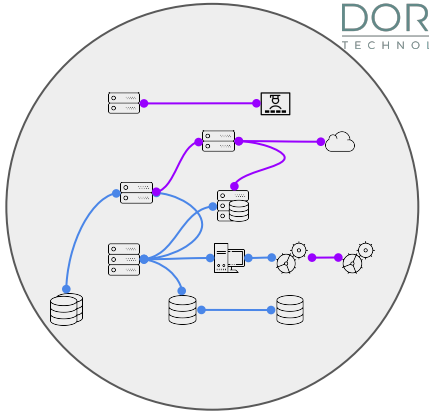
OUR SOLUTION

DOlab

DORIAN TECHNOLOGIES







key features

customer-oriented interface

lean, app-style client

remote assistance 24/7

easily interpretable results

platform independent

easily deployed on hospital PC:
no administrative privileges required
no dedicated workstation required

versatile backend

scalable cloud-based servers
remotely upgradable

safe for your data

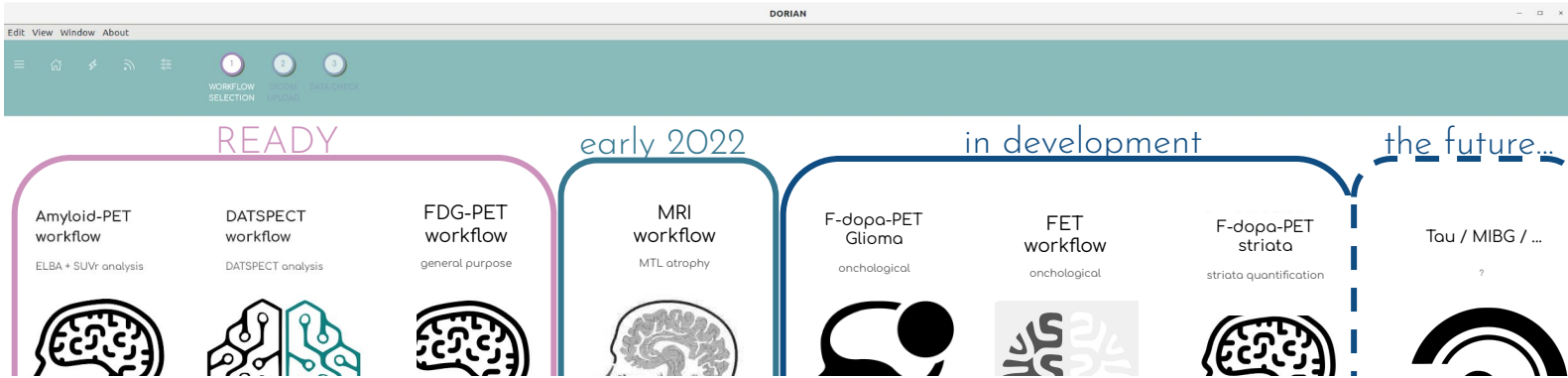
PENTAQO SECURITY FOR VALUE GDPR compliant
two-factors authentication

AL

evolving NMI

DOlab

is more than an analysis software



- **Extensible, modular framework** built on a secure platform to suit all NM needs
  - perform concurrent analyses without installing dedicated software
- Tailored workflows on **PET** & **SPECT**
  - customize reports, atlases
- **AI**, where it counts
  - Keep trustworthy, explainable algorithms for the analyses while boosting pre-processing, QC and error handling with AI
- **Automatically deploy**
  - new pipelines, methods and features to your clients

COMPUTING MODEL

GDPR-compliant data model

Scalable computing

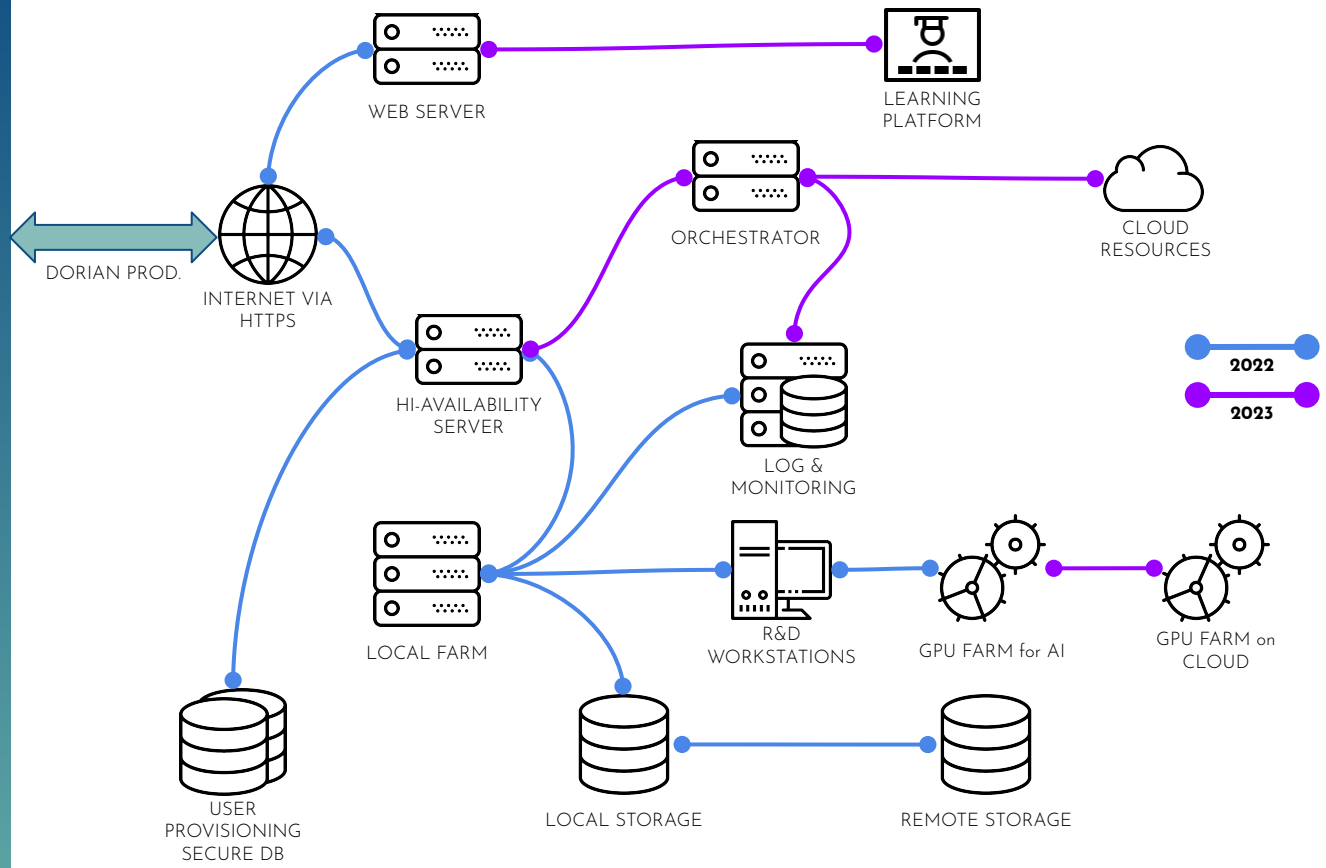
Docker-based implementation

Cloud-ready

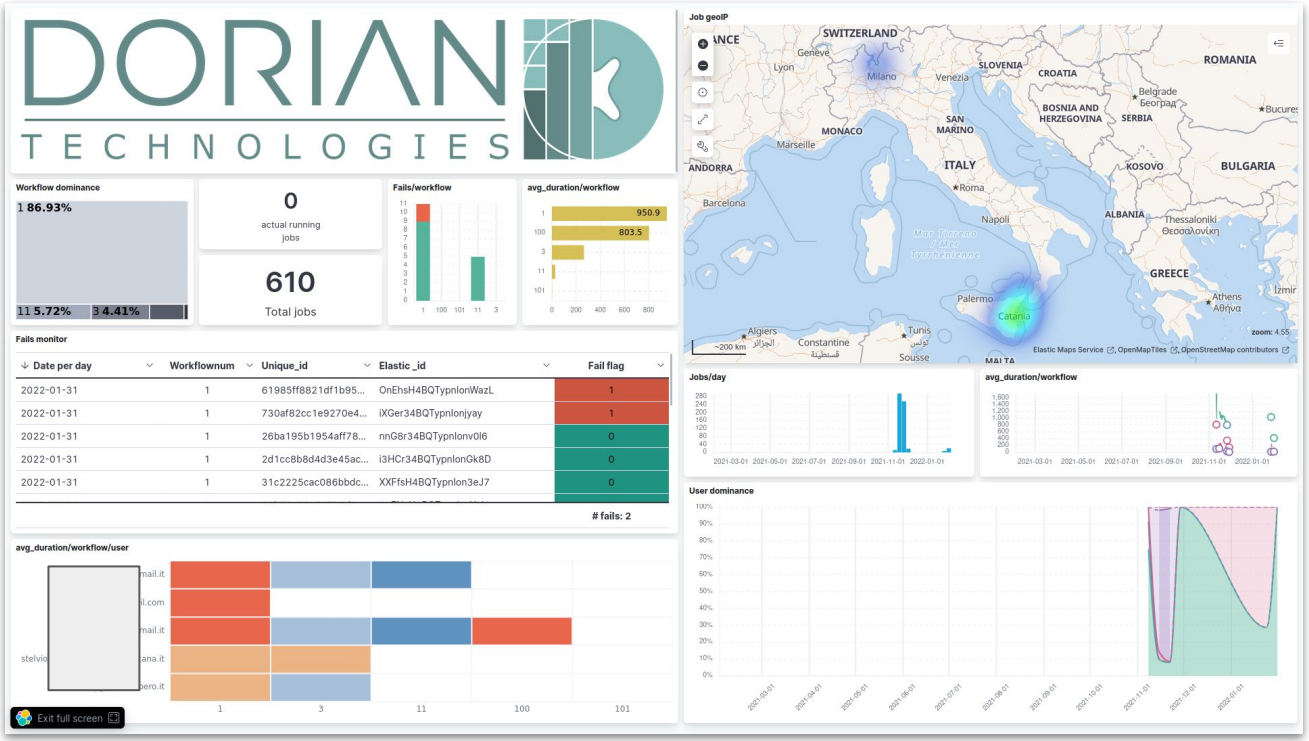
Secure & Manageable

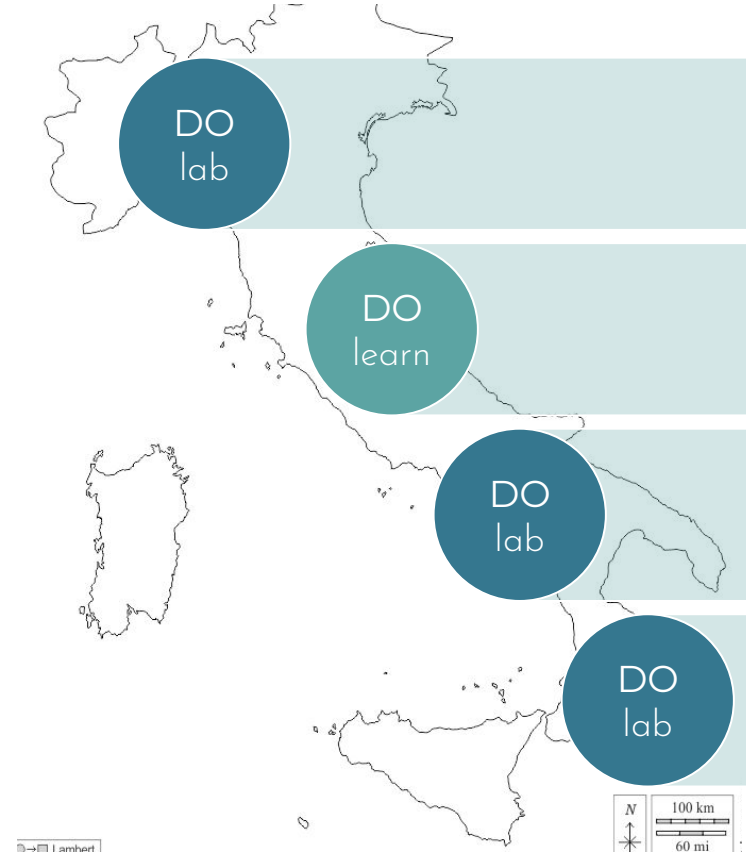
Virtualized components

Dedicated development farm for AI



Business analytics platform





2021-2022
clinical testing in 5 Italian centers:
Genoa, Milan, Prato, Bergamo, Padua

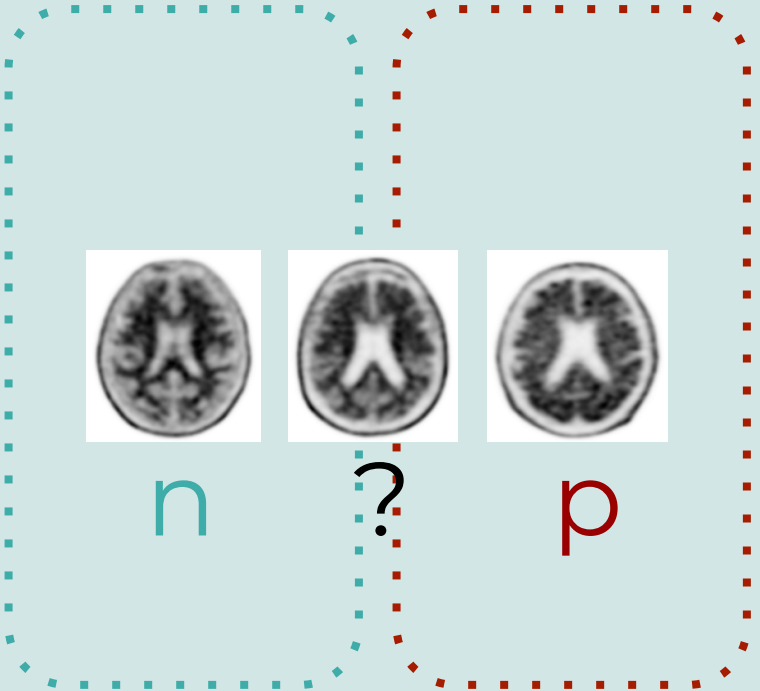
10/2021
Training session at the
National School of Nuclear Medicine (AIMN)

09/2022
First release installation in AIMN-Neurology centers
15 Hospitals Nationwide

12/2022
First release installation in all AIMN centers
40 Hospitals Nationwide

amyloid-PET

what changed after FDA approval of aducanumab [aduhelm™]

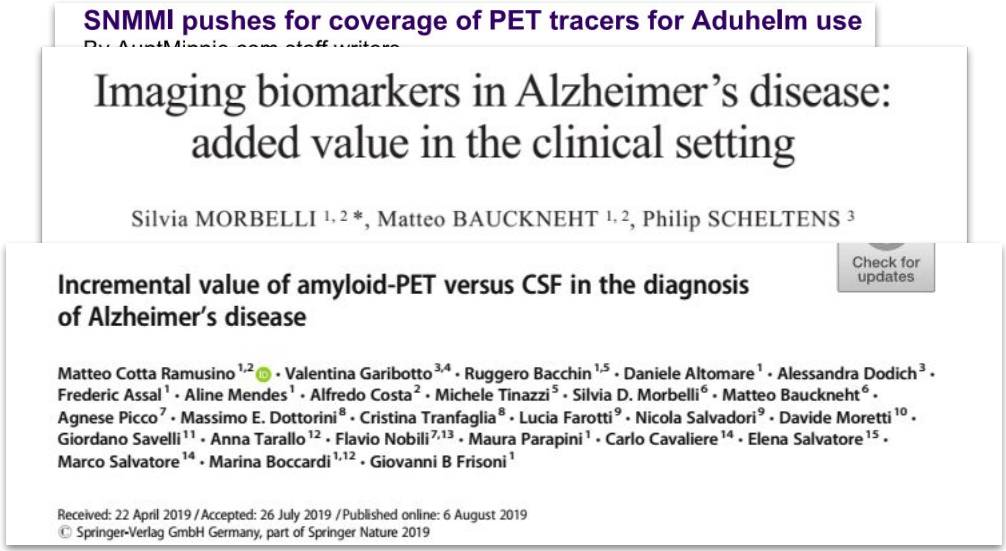


The need for quantification to define inclusion/exclusion criteria has been mentioned by:

- **Alzheimer's Association**
  - *"… additionally, patients will need* ***to have confirmed amyloid presence in their brain*** *which will require a lumbar puncture or brain scan prior to initiating treatment. Regular MRI scans may be appropriate, in order to monitor potential side effects."*
- **EADC**
  - *"what decision the European regulatory authority will make here, including type of approval pathways, indications relating to disease stage, patient's ages,* ***types of requirements for amyloid positivity****, treatment duration and monitoring"*
- **EANM-Neuroimaging group**
  - *"Imaging has been extensively used in therapeutic trials of amyloid-targeting agents as inclusion criterion/sample enrichment tool … The first line evaluation will presumably be the dosage of amyloid …* ***A more accurate and quantitative measure*** *could allow increasing statistical power and reducing sample size, with major economical advantages. "*

In the post-aducanumab era, there will likely be more complex measures to complement the evaluation, possibly combining multi-domain information with amyloid-PET (i.e. FDG, MRI, tau-PET …) and using pattern-based analyses.

amyloid-PET



SNMMI pushes for coverage of PET tracers for Aduhelm use

By AuntMinnie.com staff writers

Imaging biomarkers in Alzheimer's disease: added value in the clinical setting

Silvia MORBELLI [1, 2] *, Matteo BAUCKNEHT [1, 2], Philip SCHELTENS [3]

Check for updates

Incremental value of amyloid-PET versus CSF in the diagnosis of Alzheimer's disease

Matteo Cotta Ramusino [1,2] · Valentina Garibotto [3,4] · Ruggero Bacchin [1,5] · Daniele Altomare [1] · Alessandra Dodich [3] · Frederic Assal [1] · Aline Mendes [1] · Alfredo Costa [2] · Michele Tinazzi [5] · Silvia D. Morbelli [6] · Matteo Bauckneht [6] · Agnese Picco [7] · Massimo E. Dottorini [8] · Cristina Tranfaglia [8] · Lucia Farotti [9] · Nicola Salvadori [9] · Davide Moretti [10] · Giordano Savelli [11] · Anna Tarallo [12] · Flavio Nobili [7,13] · Maura Parapini [1] · Carlo Cavaliere [14] · Elena Salvatore [15] · Marco Salvatore [14] · Marina Boccardi [1,12] · Giovanni B Frisoni [1]

Received: 22 April 2019 / Accepted: 26 July 2019 / Published online: 6 August 2019

We can exploit the impact of amyloid tracers

Not just as support to patient management but also as

1. Amyloid-PET imaging as **eligibility criterion** and anticipating the associated needs
2. Evaluating amyloid PET changes as **surrogate outcomes** in clinical trials.

~ 30 - 35% of new patients won't be eligible for CSF

DOlab approach

Rank
odds ratio
5
Comprehensive evaluation vs. the normative dataset using Bayesian analysis

Regional values vs normative dataset
case review
4
User-selectable atlas, MRI / CT to improve ROI registration, EU-wide multicentric normative dataset

TDr
kinetics
3
Chincarini A. , et al. " A kinetics-based approach to amyloid PET semi-quantification" Eur J Nucl Med Mol Imaging 2020 Aug;47(9)

Cortical-cerebellar SUVr
uptake
1
Klunk, W. E., "The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET". Alzheimer's & Dementia, 11

ELBA
radiomics
2
Chincarini, A, et al. "Standardized Uptake Value Ratio-Independent Evaluation of Brain Amyloidosis". J Alzheimers Dis. 2018

Validated over several dataset: ADNI, EADC, AIMN, ... & vs. the SLOPE index*

*Cecchin D. "A new integrated dual time-point amyloid PET/MRI data analysis method." Eur J Nucl Med Mol Imaging. 2017 Nov;44(12)

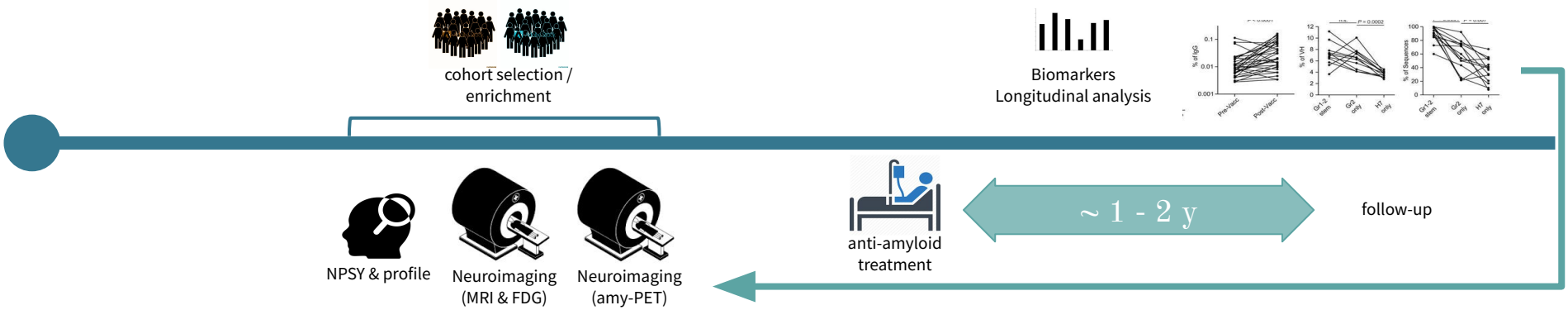
3-methods
SBR / Segmentation / Radiomics (shape)

+

regional striata quantification (3 ROIs)

- **DAT-SPECT & Striascan** workflow is the first to be deployed online.
- We have validated the system on 1000+ cases with multiple, independent visual evaluation.
- Publication on the validation assessment is being prepared

- Financial support from CURIUM pharma & IRCCS-SM to sustain the development of DAT quantification in 2022



1. **pharma trials**
   a. inclusion/exclusion criteria, endpoints, population enrichment, smaller sample size / shorter trial time
2. **therapy eligibility criteria**
   a. reimbursement, legal controversies
3. **therapy efficacy** (follow-up)
   a. dosage, adverse effects, pattern response

"Assessment of disease-modifying effect in a slowly progressive process such as neurodegeneration is difficult to target solely on the basis of cognitive measures."

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J Alzheimers Dis. 2021;80(1):383-396. doi: 10.3233/JAD-201156.

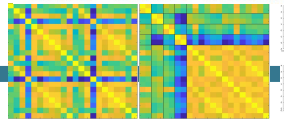
Probing the Role of a Regional Quantitative Assessment of Amyloid PET

Enrico Peira [1 2], Matteo Grazzini [2], Matteo Bauckneht [3 4], Francesco Sensi [1], Paolo Bosco [5], Dario Arnaldi [2 6], Silvia Morbelli [3 4], Andrea Chincarini [1], Matteo Pardini [2 6], Flavio Nobili [2 6]

Phenotyping

Neuroimaging
(MRI & FDG)

Neuroimaging
(amy-PET)

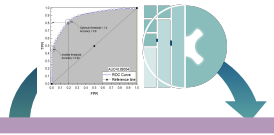


Biomarkers pattern evaluation

cohort pattern studies with clinics & outcome

personalized treatment

Precision Medicine



Peripheral marker validation

general population

Asymptomatic at risk

blood screening
1-level

Neuroimaging
(amy-PET, FDG-PET, Tau-PET)
2-level

OUR PRODUCTS

Quantification solutions for nuclear medicine

DOlab - Client-server diagnostic app

Hospitals, Clinical Centers, Medical Associations

DOstat - B2B statistical / AI service

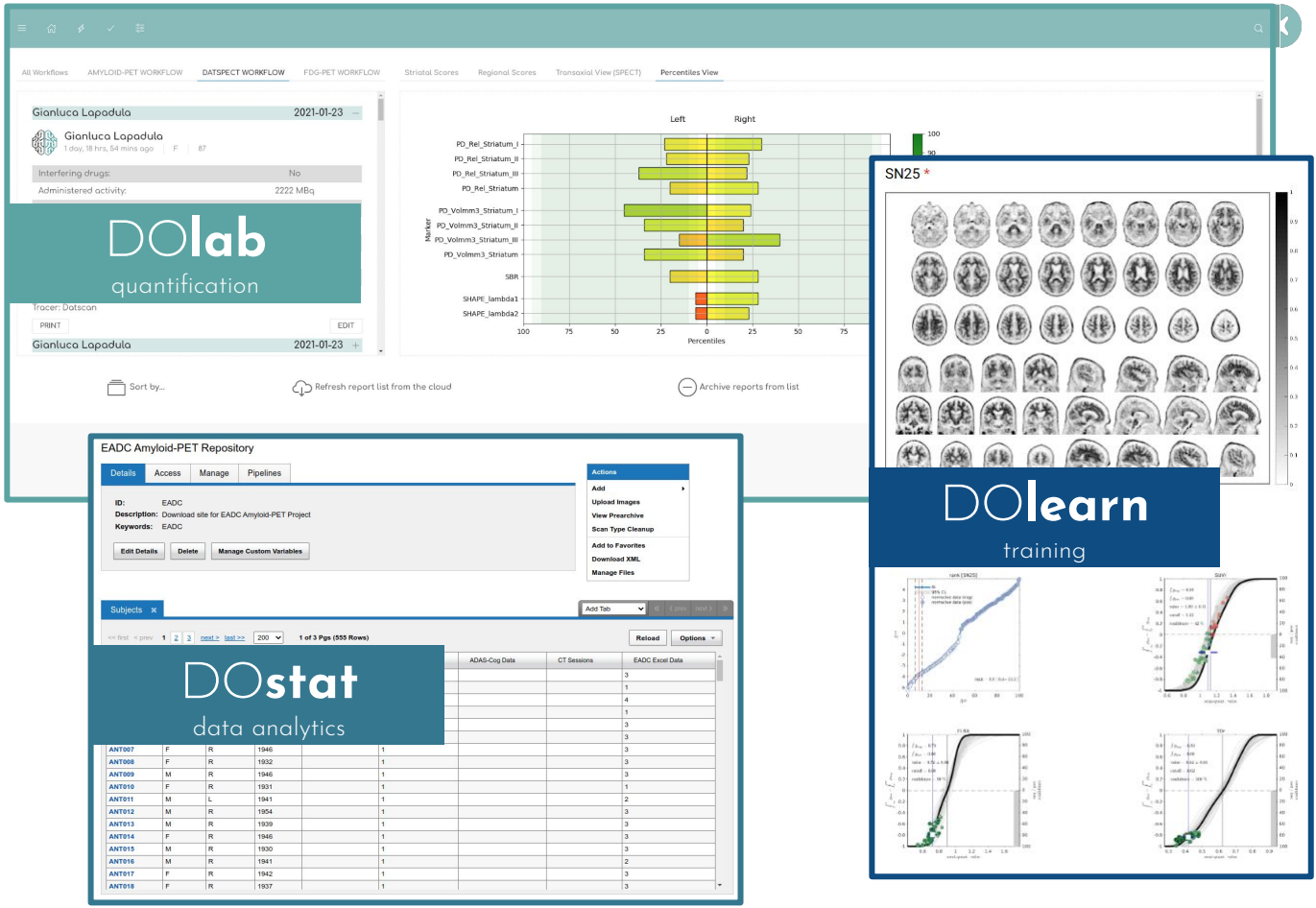
Pharma, Research Institution, Medical Associations, NHS

DOlearn - e-Learning platform

Medical Associations, single NM physician, Pharma, NHS

DAT-SPECT, amyloid-PET*, FDG-PET, MRI, fdopa-PET, tau-PET..

*2 patents



Data analytics

The business model of DORIAN Tech. can leverage the increasing volume of data acquired with a enhanced research-based agreements to enrich its cases database.

DOlab
NM-friendly app for quantification and diagnosis

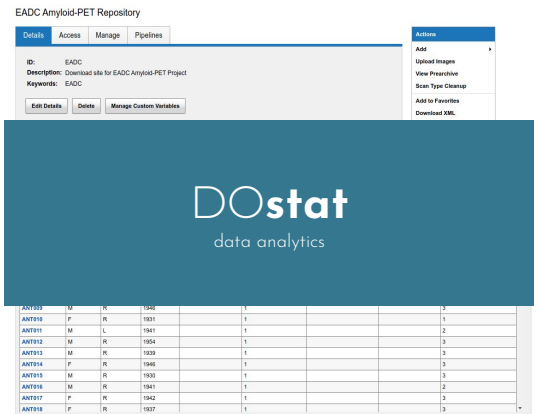
single NM / Hospitals
Medical Associations
Pharma
Research

DOstat
anonymized images & clinical data DB + on-demand, customized analysis

Medical Associations
Pharma
NH systems

Pharma

tailored analytics
normative cohorts
subgroup clustering
trials quant. interface
cohort-specific avatars



NH systems

advanced statistics
batch analyses
unified research DB

Precision medicine

AI-driven studies
covariates associations
rare cases identification

what about the link to next-AIM?

- we are currently structuring DORIAN Tech. to become a solid company
  - CE marking, FDA marking, strong partnerships and marketing strategies, consolidate current products
- development of new analysis pipelines: DTech has a standing research agreement with INFN

new analyses **must** have specific requirements:

1. have a sound, explainable method:
   a. complex AI models are ok for marketing & statistical assessment but is not ethical on the single patient [yet]
   b. trustworthiness & reliability outweigh performance
   c. has been published both as methodological and as clinical application
2. have a direct impact [= added value] on the clinical workflow (diagnosis, prognosis, …)
3. is validated on a naturalistic & multicentric dataset (national, EU or larger)

DORIAN
TECHNOLOGIES

Thank you

Questions?

info@dorian-tech.com

WP5: Exploitation of results and communication

WP conveners: M.E. Fantacci (PI),
C. Talamonti (FI), A. Chincarini (GE)

Technology Transfer
This WP is also devoted to the exploitation of research results in publications and knowledge transfer processes in connection with the INFN spin-off DORIAN Technologies and the INFN Technology Transfer.

Collaboration with associations and consortia
Collaboration with associations and consortia will be promoted, in particular with AIFM, EANM, will be enforced thanks to the collaborations started in the previous project (AIM).
Moreover, the collaboration with clinicians involved in the WP3 will be strengthened.

Dissemination
An Editorial Board involving at least a representative of each INFN group will be defined with the aim to promote the dissemination of the results through the participation in conferences and publications on relevant Journals for the community of Medical Physicists.
Workshop will be also organized in collaboration with associations and consortia.

Milestones:

- 31/12/2022 Workshop organization «AI methods and organization in Medical Physics»
- 31/12/2023 Workshop organization «The right of explanation»
- 31/12/2024 Submission of at least 1 scientific pubblication per use case

WP5: Exploitation of results and communication

WP conveners: M.E. Fantacci (PI),
C. Talamonti (FI), A. Chincarini (GE)

Publications:

- Open access policy
- Technical papers
- Clinical validation papers

Conferences:

- List of those already known: most interesting and/or with better indexed proceedings
- Young people (on behalf at least SIF, INFN preprints)
- Financing of poster presentations

Dissemination:

- Web site
- Bright (general video/pptx/poster for all?)
- Local activities

WP5: Exploitation of results and communication

WP conveners: M.E. Fantacci (PI),
C. Talamonti (FI), A. Chincarini (GE)

Collaboration with associations and consortia:

- **AIFM**
  - WEBINAR (Scientific commeette C. Talamonti, A. Retico) 4talks (to be defined
  - To be discussed : Common project

- **EANM**
  - To be discussed