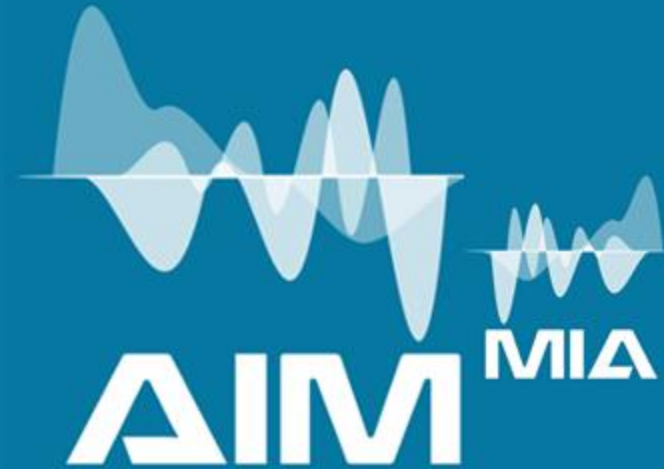


Artificial Intelligence in Medicine: focus on **Multi-Input Analysis**

Alessandra Retico
INFN
Sezione di Pisa



Kick-off meeting, February 13, 2025

Outline

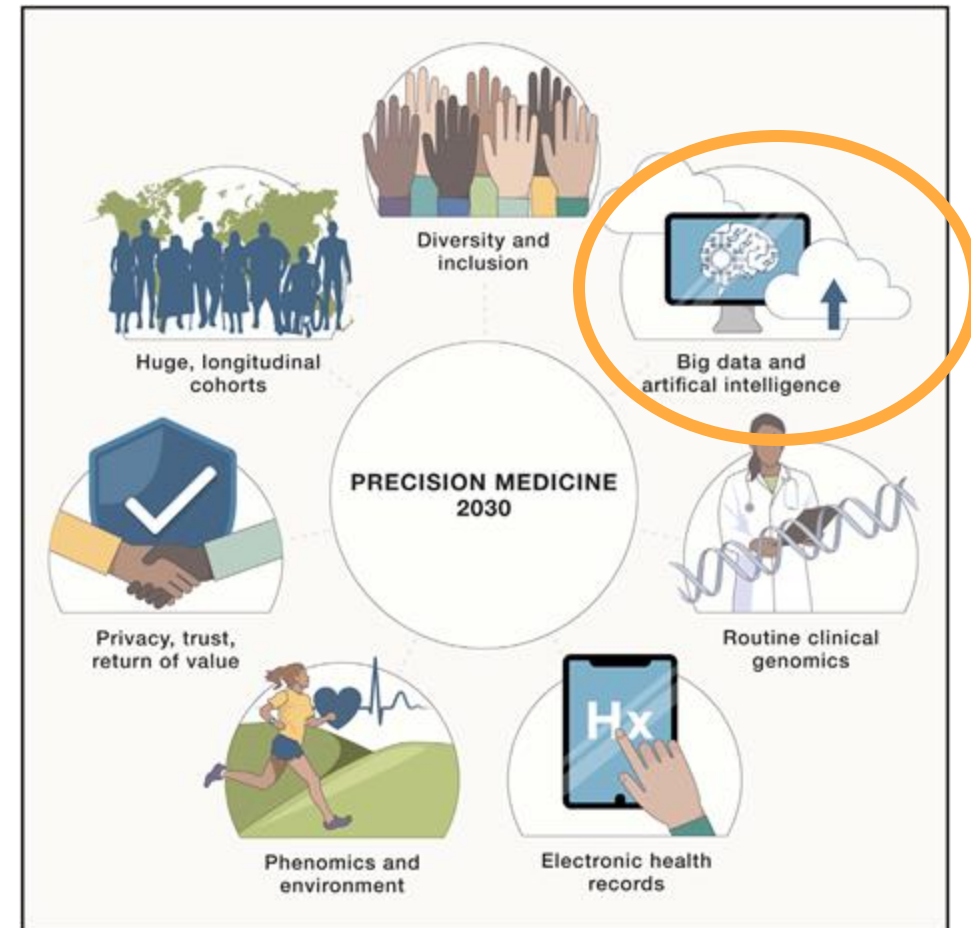
- **Research context**
- State of art
- The AIM_MIA project
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 - Methods
 - Implementation
 - Connections
 - Expected impact
- People & Budget

A. Retico - Artificial Intelligence in Medicine: focus on Multi-Input Analysis

Artificial Intelligence in Medicine

- **Artificial Intelligence (AI)** is already *pervasive* in many domains of our daily life including the Healthcare sector.
- **AI** is expected to make an important contribution to achieving the goal of **precision medicine**.
- **Precision medicine** promises improved health by accounting for individual variability in genes, environment, and lifestyle.
- **Big data collections** and **advanced analytics approaches** (including AI-based methods) are needed to fully exploit the potential of the large amount of digital information available today for each patient.

[Denny and Collins, Precision medicine in 2030—seven ways to transform healthcare. Cell 2021;184:1415–9. [https://doi.org/10.1016/j.cell.2021.01.015.](https://doi.org/10.1016/j.cell.2021.01.015)]



Outline

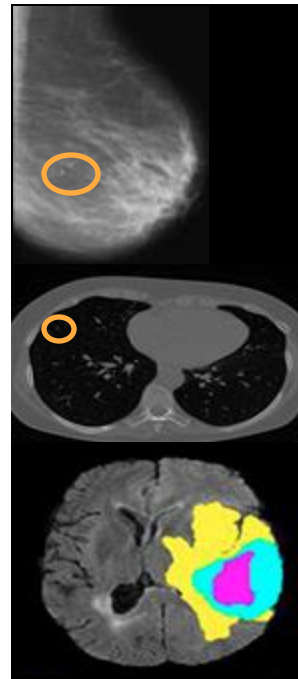
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3

State of art, limitations and open issues



Since the 80s the scientific community has been developing AI-based systems to support clinicians (**Decision Support Systems, DSS**), especially in the field of diagnostic imaging, to facilitate the clinical workflows in radiological screening programs.

DSS are meant to support clinicians and not to replace them.

Several DSS are already available to clinicians as **CE-marked products**

<https://radiology.healthregister.com/>

Nonetheless, most of them:

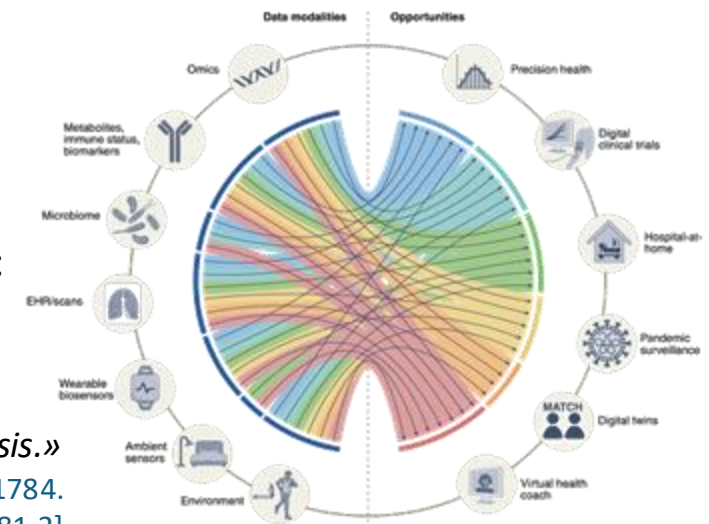
- **lack in-depth validation** on large and independent data samples
- **need to move from *narrow scopes*** (lesion identification/segmentation) **to more clinically meaningful endpoints**

To make AI-tools predict relevant endpoints (e.g. need for treatment, patient's survival, relapses after treatment) the **complementary information** encoded in omics data, electronic health records, imaging data should be exploited.

AI methods to **mine multi-input data** should be developed.

«... we are far better at collating and storing data, than we are at data analysis.»

[Acosta et al (2022). Multimodal biomedical AI. *Nature Medicine*, 28(9), 1773–1784. <https://doi.org/10.1038/s41591-022-01981-2>]





State of art, limitations and open issues

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A. Retico - Artificial Intelligence in Medicine: focus on Multi-Input Analysis

Despite its relevance, how to effectively fuse the multi-modal medical data has received relatively little attention.

Current literature highlights the need for effective multi-input algorithms for medical data [Huang et al, 2020; Acosta et Al, 2022; Lipkova et al, 2022; Pei et al, 2023]

However, **practical implementations** are limited.

Data availability is crucial

- UK Biobank (since 2006), >500k participants, 30y of follow up;
- US “Million Veteran Program”;
- US “All of Us Research Program” enrolled 400k diverse participants (target 1M participants)

Prediction of Pulmonary Embolism from CT and Electronic Medical Record (EMR)

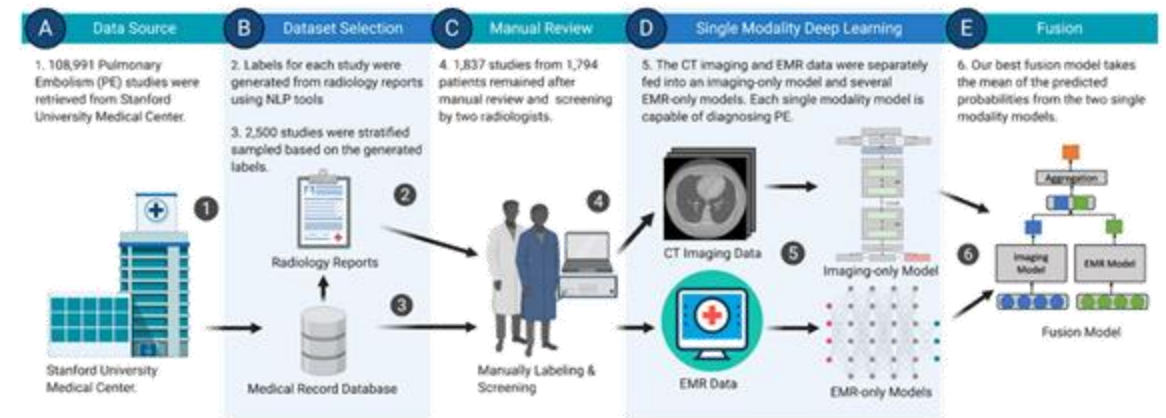


Figure 1. Overview of the workflow for this study. We extracted a total of 108,991 studies from Stanford University Medical Center (A) and sampled a subset (B) for manual review (C). 1837 studies remained after screening by two radiologists and were used to train and evaluate our models. Single modality models were created (D) both as baselines for comparisons as well as components for the fusion models (E).

Performance (AUC):

- CT alone: 79.1%
- EMR alone: 91.1%
- Late fusion: **94.7%**

Huang, S.C. et al (2020). Multimodal fusion with deep neural networks for leveraging CT imaging and electronic health record: a case-study in pulmonary embolism detection. *Scientific Reports*, 10(1), 1–9. <https://doi.org/10.1038/s41598-020-78888-w>

Large Language Models (LLMs)

LLMs, like **ChatGPT**, which rely on Transformer architecture, can analyze images and are suitable to be fine-tuned to medical images and multi-input data analysis problems.

Tian, D. et al. (2024). The role of large language models in medical image processing: a narrative review. *Quantitative Imaging in Medicine and Surgery*, 14(1), 1108–1121. <https://doi.org/10.21037/qims-23-892>

Table 5 Comparison of current functions of LLMs in the biomedical field

Current LLMs	ClinicalBERT	BioBERT	ChatGPT	BioMedLM	GeneGPT
Use of clinical notes	✓	✓	✓	✓	✓
Biomedical text mining	N/A	✓	✓	✓	✓
Biomedical Q&A	N/A	N/A	✓	✓	✓
Multimodal integration	×	×	✓	N/A	✓
Interactivity	×	×	✓	✓	✓
Domain-specific	✓	✓	×	✓	✓

✓, have the function; ×, do not have the function. LLMs, large language models; GPT, Generative Pre-trained Transformer; BERT, Bidirectional Encoder Representations from Transformers; Q&A, Questions and Answers; N/A, not applicable.

Previous projects @ INFN on this topic



Outline

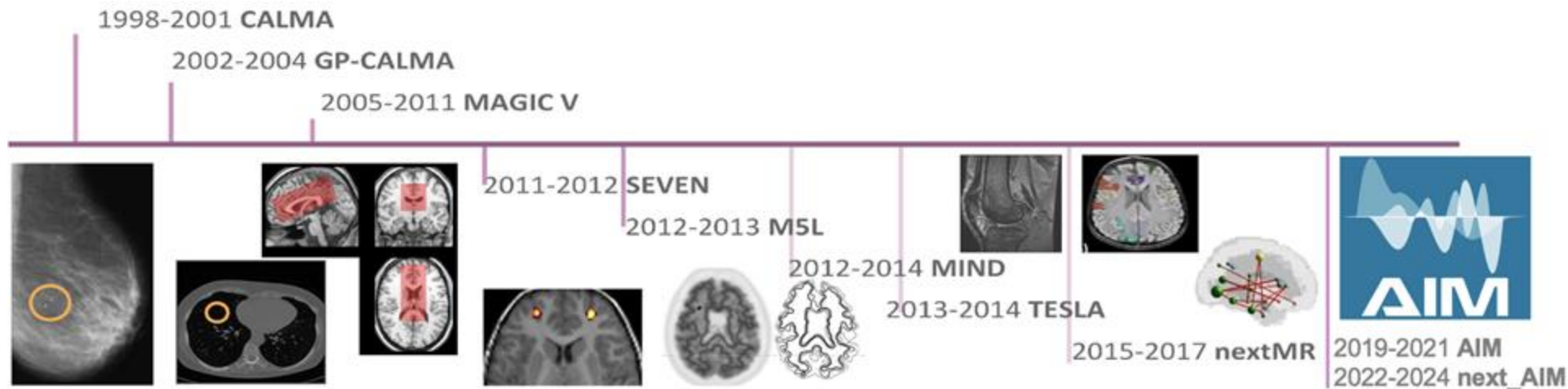
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INFN CSN5 funded projects



INFN CNTT related activities

- CNTT R4I → INFN Spin-off **DORIAN** (<https://www.dorian-tech.com/>), A. Chincarini (GE)
- CNTT R4I project **Deeplook** (A deep learning computed diagnosis support for digital breast tomosynthesis), G. Mettivier (NA)



Previous projects @ INFN on this topic

Artificial Intelligence to become the next revolution in **medical diagnostics** and **therapy**.

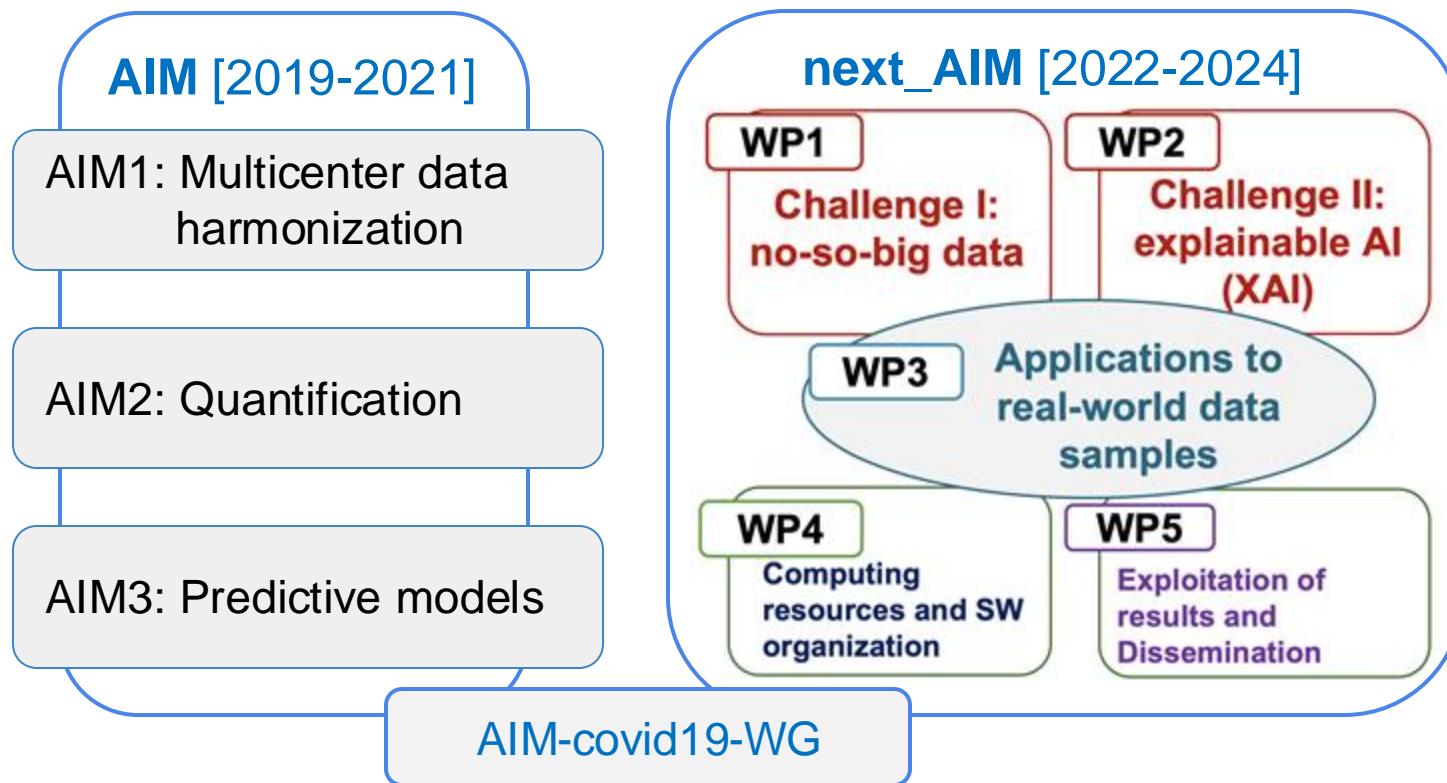
➔ New image processing and data analysis strategies (including radiomics ML and DL), need to be developed and extensively validated.



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Resp. Naz.: A. Retico

- 13 Research Units:
- Bari (S. Tangaro)
 - Bologna (D. Remondini)
 - Cagliari (P. Oliva)
 - Catania (M. Marrale)
 - Ferrara (G. Paternò)
 - Firenze (C. Talamonti)
 - Genova (A. Chincarini)
 - Lab. Naz. Sud (G. Russo)
 - Milano (C. Lenardi)
 - Napoli (G. Mettivier)
 - Pavia (A. Lascialfari)
 - Padova (A. Zucchetta)
 - Pisa (M.E. Fantacci)

Researchers from INFN divisions and University Departments collaborate closely with Clinicians and Medical Physicists of many Italian hospitals and IRCCS, and with international consortia sharing data

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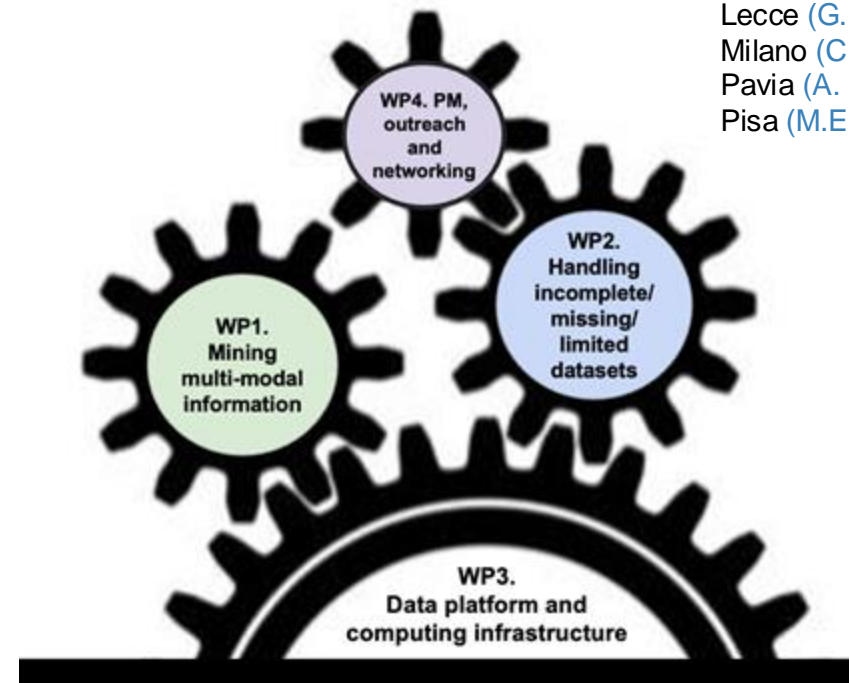
A. Retico - Artificial Intelligence in Medicine: focus on Multi-Input Analysis

Artificial Intelligence in Medicine: focus on Multi-Input Analysis (AIM_MIA)

General goal: *to take a step forward in the development and validation of AI-based tools for medical data analysis*

Objectives

1. Mining multi-modal information
2. Handling incomplete/missing/limited datasets
3. Development of a dedicated data and computing platform



Resp. Naz.: A. Retico

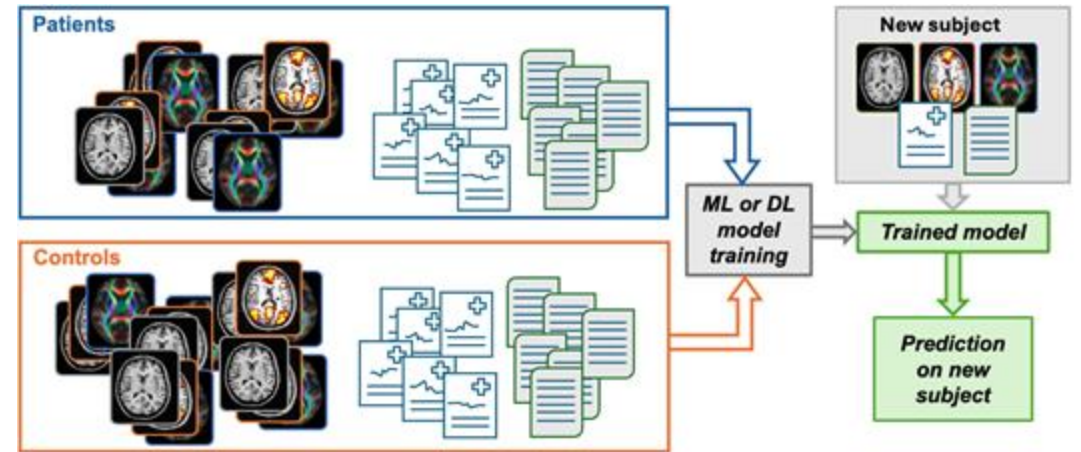
12 Research Units:

- Bari (S. Tangaro)
- Bologna (D. Remondini)
- Cagliari (P. Oliva)
- Catania (M. Marrale)
- Ferrara (G. Di Domenico)
- Firenze (C. Talamonti)
- Genova (A. Chincarini)
- Lab. Naz. Sud (G. Russo)
- Lecce (G. De Nunzio)
- Milano (C. Lenardi)
- Pavia (A. Lascialfari)
- Pisa (M.E. Fantacci)

Methods: multi-input analysis (WP1)

- Data from different sources (image modalities, text and clinical scales, omics data) should be combined

→ **Multimodal Fusion**



Outline

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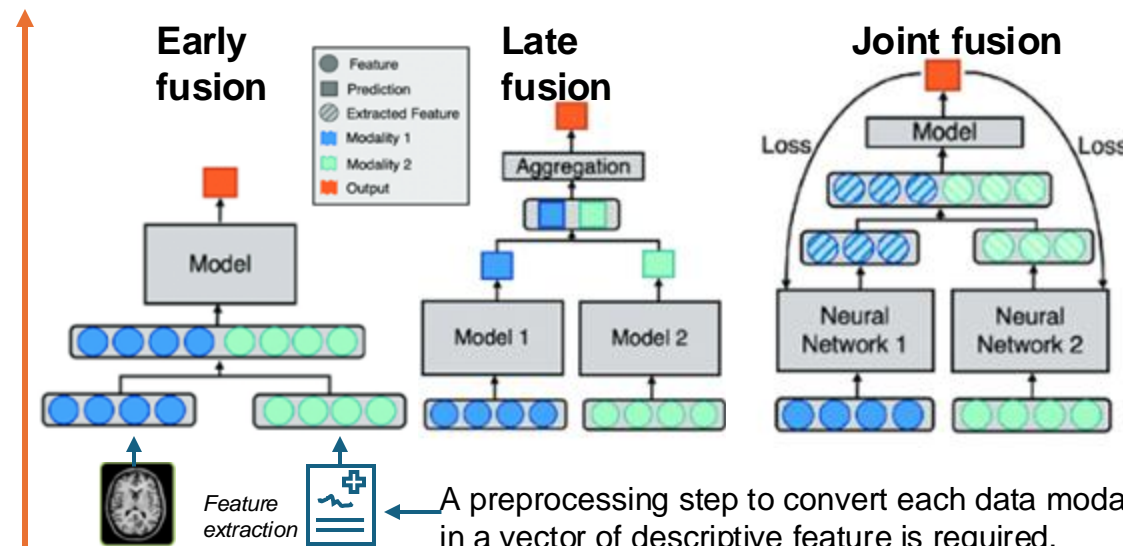
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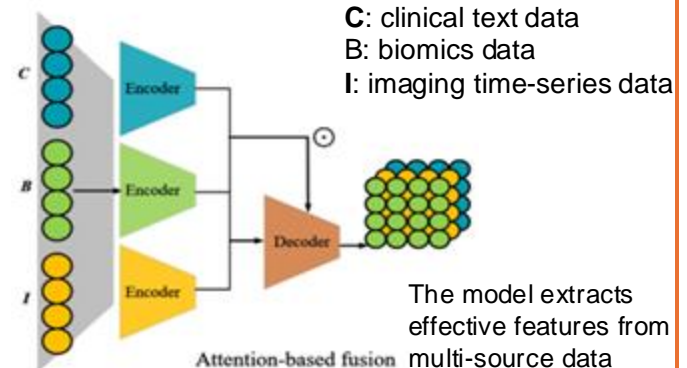
Feature-based approach

Model architectures for different fusion strategies:



Advanced DL methods

Based on the attention mechanism of the Transformers, the attention-based fusion approach enable to weight the image features according to the information encoded in the clinical text



Methods: multi-input analysis (WP1)

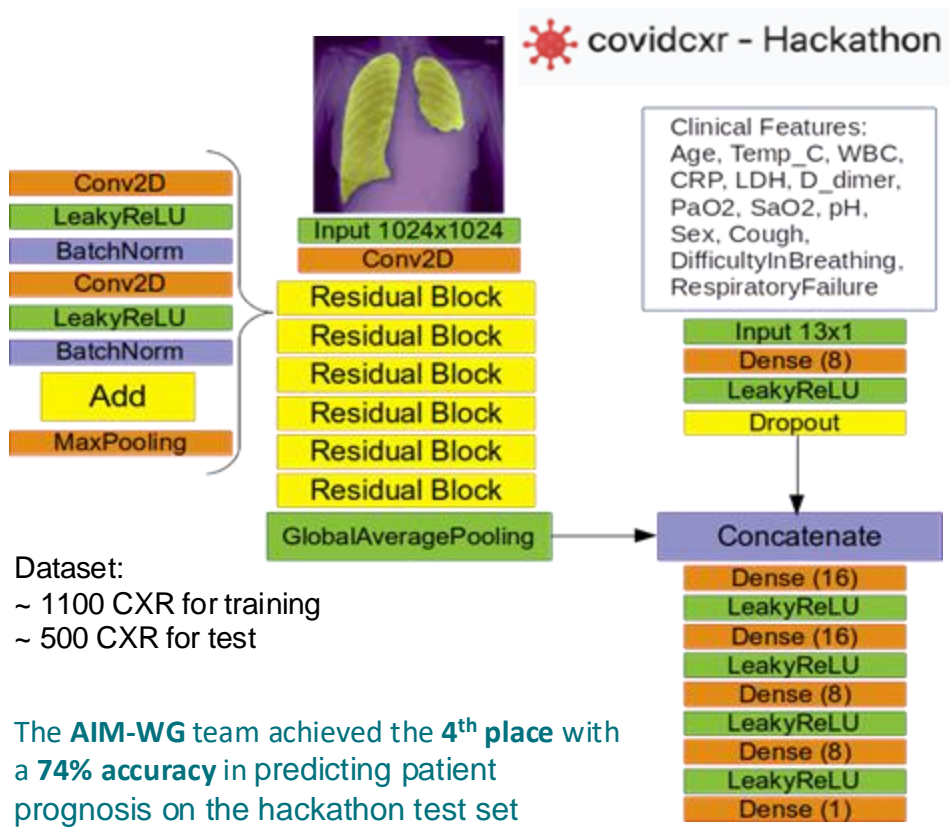
Previous results of the collaboration on this topic

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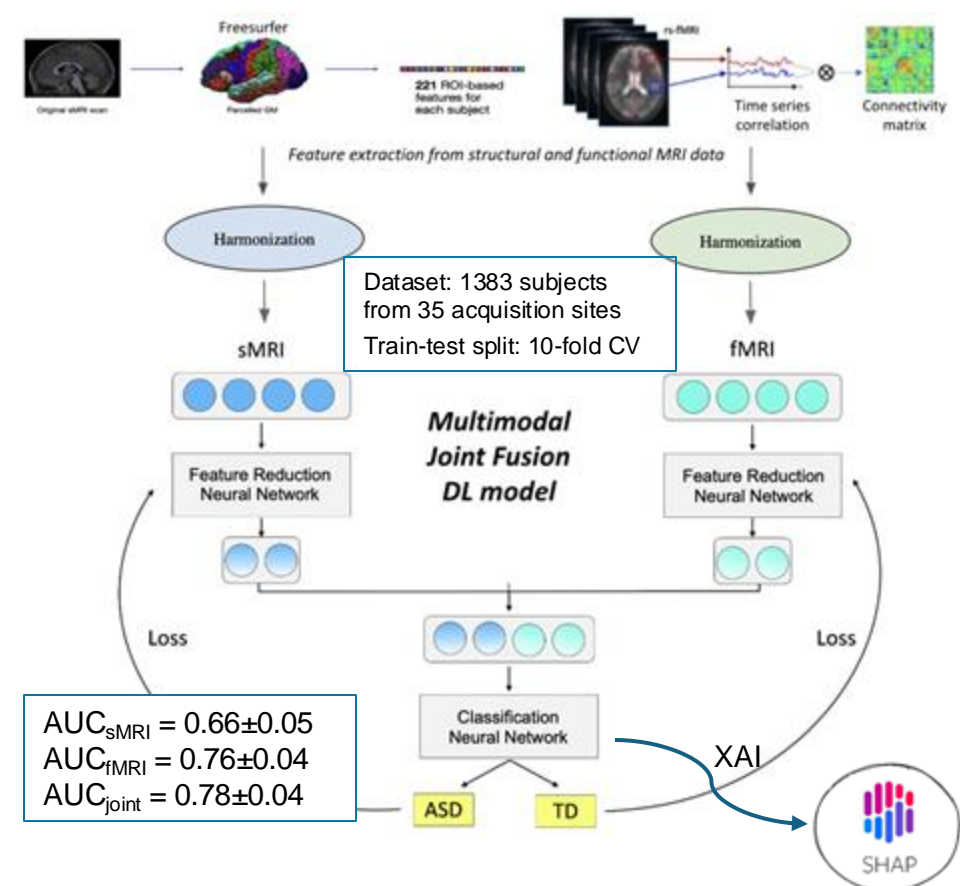
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RX images + clinical data



Lizzi F, Brero F, Fantacci ME, Lascialfari A, Paternò G, Postuma I, Oliva P, Scapicchio C, Retico A (2024). A multi-input deep learning model to classify COVID-19 pneumonia severity from imaging and clinical data. IWBBIO, 1–12.

Structural MRI + functional MRI data



Saponaro S, Lizzi F, Serra G, Mainas F, Oliva P, Giuliano A, Calderoni S, Retico A. (2024). Deep learning based joint fusion approach to exploit anatomical and functional brain information in autism spectrum disorders. Brain Informatics, 11(1), 2. <https://doi.org/10.1186/s40708-023-00217-4>

Methods: handling incomplete/unbalanced/limited datasets (WP2)

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incomplete

A high proportion of missing data may affect multimodal data collections.

Simply excluding patients with missing data:

- reduces the dataset dimensionality
- may lead to a selection bias

→ **Data imputation** techniques infer missing values from the existing part of the data.

unbalanced

It happens very often that one class of subjects is under-represented with respect to the other one(s)

→ **Data resampling** techniques (over-sampling and under-sampling); **balancing data** in training: stratified k-fold CV, adjusting the cost function (e.g. setting different weights for different classes); **reformulate the problem** as an anomaly detection one

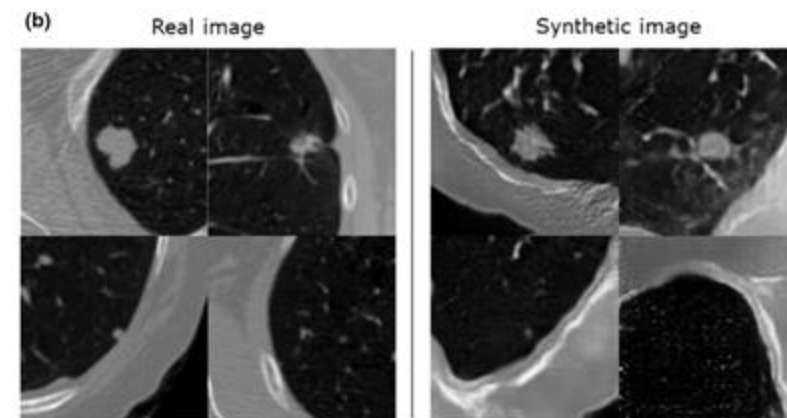
limited

Collecting large annotated datasets still represents a major challenge in medical data analysis

→ Traditional **data augmentation** techniques and **synthetic data generation**

FILE_ID	AGE	FIG	DR GROUP	L Mean Thickness	T Mean Thickness	L Cortex Vol	R Cortex Vol
Caltech_0051457	22.9	107	1	2.58	2.57	321132	317005
Caltech_0051458	39.2	93	1	2.85	NaN	266419	266456
Caltech_0051459	23.8	106	1	2.71	2.73	307157	310540
Caltech_0051461	37.7	99	1	2.59	2.61	263933	269417
Caltech_0051464	20.9	101	1	2.76	2.78	381573	394085
Caltech_0051472	17.5	125	1	NaN	2.77	345432	345834
Caltech_0051474	20.9	100	1	NaN	2.63	298059	309524
CMU_a_0050654	24	95	1	2.68	2.71	287015	287915
CMU_a_0050669	27	109	-1	2.72	2.72	330374	330325
CMU_a_0050660	25	NaN	-1	2.74	2.74	279281	284870
CMU_a_0050663	21	101	-1	2.63	2.67	292910	296389
CMU_a_0050664	21	109	-1	2.58	2.58	262753	261800
CMU_a_0050665	33	109	-1	2.55	2.57	327432	327280
CMU_a_0050666	31	107	-1	2.59	2.56	315076	311584
CMU_a_0050668	25	NaN	-1	2.65	2.65	NaN	250974
CMU_b_0050643	21	123	1	2.65	2.66	257398	NaN
CMU_b_0050645	20	124	1	2.58	2.59	264307	260833
CMU_b_0050651	39	116	1	2.47	2.45	306868	306173
KKI_0050814	8.46	108	-1	2.79	2.81	351159	355034
KKI_0050815	10.6	105	1	2.46	2.62	NaN	219226
KKI_0050816	9.73	119	-1	2.61	2.69	271211	275917
KKI_0050817	9.97	NaN	-1	2.61	2.60	298531	299597
KKI_0050818	11.8	98	-1	2.67	2.69	277684	286714
KKI_0050819	9.71	101	-1	2.61	2.62	296599	295511
KKI_0050821	11.2	114	-1	2.75	2.75	288554	288993
KKI_0050822	12.4	88	-1	2.74	2.72	287403	289102
KKI_0050823	11.4	120	1	2.86	2.83	314385	310731

data imputation
→



[Chlap P et al, A review of medical image data augmentation techniques for deep learning applications. *Journal of Medical Imaging and Radiation Oncology*, 65(5), 545–563 (2021)]

Methods: handling incomplete/unbalanced/limited datasets (WP2)

A selection of the proposed activities...

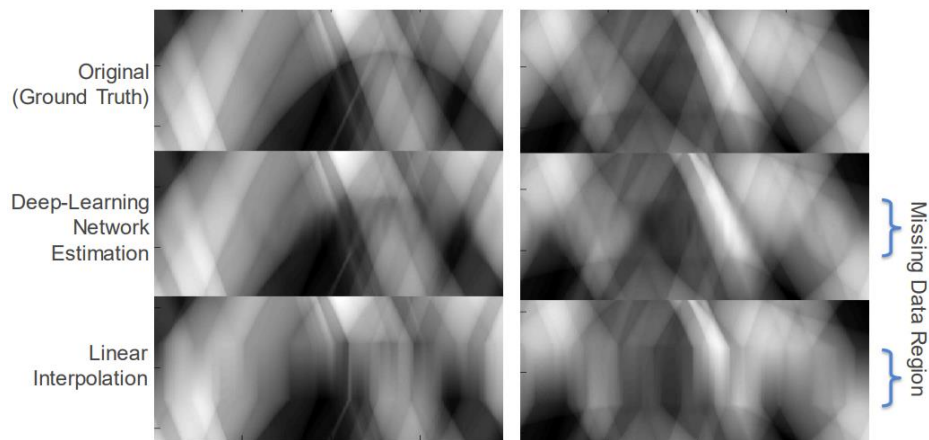
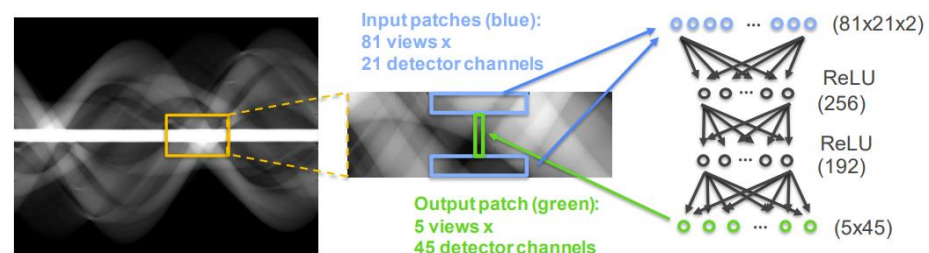
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Sinogram inpainting

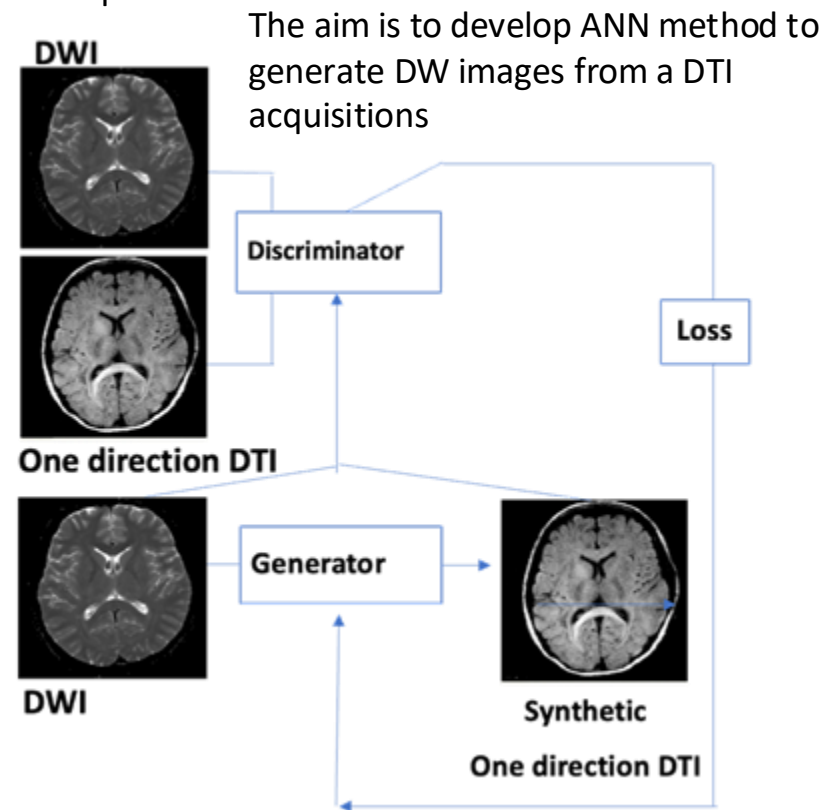
The aim is to develop deep learning methods for inpainting sinograms affected by metallic implant problems.



Metal-Artifact Reduction Using Deep-Learning Based Sinogram Completion: Initial Results, Bernhard E. H. Claus, Yannan Jin, Lars A. Gjestebj, Ge Wang, Bruno De Man, Fully3D-2017

Generation of highly-resolved diffusion MR images (DWI) with ANN

DWI with multiple b-values and high number of gradient directions allow a unique insight into human brain microstructure. However, extremely long acquisition time are required.



Methods: data platform (WP3)

The FAIR Guiding Principles for scientific data management

Scientific data should be: Findable, Accessible, Interoperable, and Reusable

[Wilkinson, M., Dumontier, M., Aalbersberg, I. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 3, 160018 (2016). <https://doi.org/10.1038/sdata.2016.18>]

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→ Development of a dedicated data platform for medical data management

It will be based on an open-source imaging IT platform developed by Washington University for neuroimaging data analysis: XNAT
Thanks to its **extensibility**, XNAT can be used to support a wide range of imaging-based projects.



Extensible Neuroimaging Archive Toolkit <https://www.xnat.org/>



Full DICOM Integration and Anonymization:
Get image data in, and keep PHI out.



Secure Access & Permission Control:
You decide who does what with your data.



Integrated Search & Reporting: Report on your image and clinical data together.



Pipeline Processing: Use the power of high-performance computing on your data.



Modular Extensibility: Expand the capabilities of your XNAT to meet your needs.



Developer Community: Benefit from an active and engaged set of XNAT power users.

XNAT's overall security infrastructure is well-suited to clinical research, particularly in adhering to strict patient data privacy regulations. The INFN DPO will be involved.

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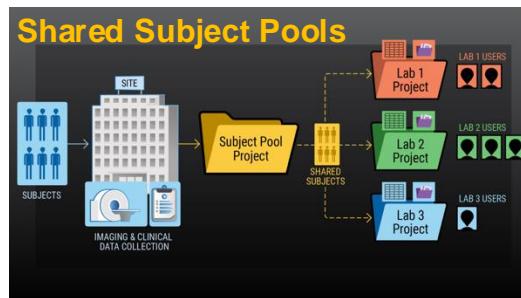
Methods: data platform (WP3)

Preliminary work @ INFN-PI

First implementation of a platform prototype to collect, store and analyze CT images and data of phantoms



Planned collaboration with AIFM



Subject	Phantom_name	Scanner	CTDIvol	ReconstructionAlgorithm	IterativePercentage	PixelSpacing	SliceThickness	ConvolutionKernel
CAT_fc18_2_aidrSTD	Catphan	TOSHIBA	2	AIDR3D	40	0.428	1	FC18
CAT_lung_2_asir10	Catphan	GE	2	ASIR	10	0.406	1.25	LUNG
RAD_lung_4_FBP	Radiomik	TOSHIBA	4	FBP	0	0.781	1	LUNG
RAD_lung_7_asir10	Radiomik	GE	7	ASIR	10	0.703	1.25	LUNG

Subject Details: RAD_lung_4_FBP

Details | Projects

Accession # XNAT_S00003
 Date Added 2024-03-25 16:30:49 (camilla)
 Birth year --
 Gender --
 Handedness --
 Group radiomik Phantom

Searchable fields to make specific queries and retrieve subsets of data

Custom Variable Sets

Parameters used to reconstruct the image

ReconstructionAlgorithm	FBP
IterativePercentage	0
PixelSpacing	0.781
SliceThickness	1
ConvolutionKernel	LUNG

Parameters used for the acquisition

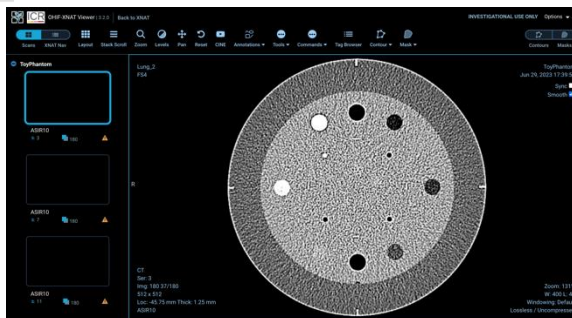
Scanner	TOSHIBA
CTDIvol	4
kVp	120

Details on the phantom models

Phantom_name	Radiomik
--------------	----------

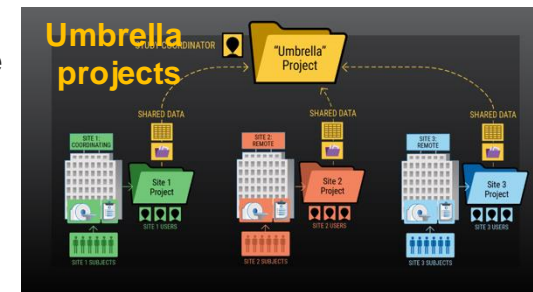
Experiments

Date	Experiment	Project	Label
2023-10-31	CT_Session	Toy Platform Phantom	999999-003

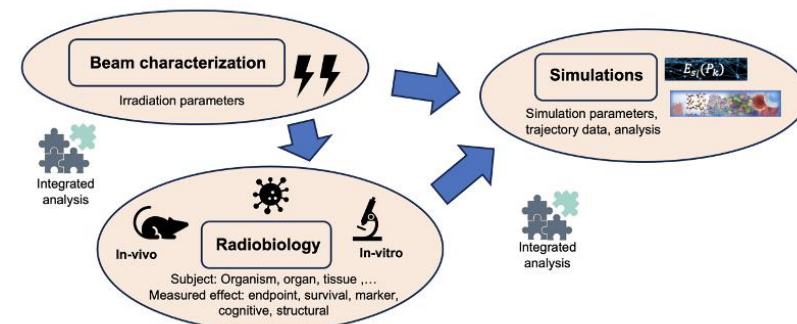


CT images of phantoms in the DICOM standard format

Design of a platform prototype to collect, store and analyze the heterogeneous data acquired in the PNRR ECS THE project



THE Tuscany Health Ecosystem



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Methods: datasets to be shared

Only public data will be stored in the XNAT platform

Dataset ID	Target pathology/condition/task	Approximate sample size	Data types	link
ABIDE	Autism Spectrum Disorders (ASD)	> 2000 subjects including subjects with ASD and controls	demographic, clinical, sMRI, fMRI	https://fcon_1000.projects.nitrc.org/indi/abide/
ADNI	Alzheimers' disease	>3000 participants	clinical, biochemical.sMRI, fMRI, DWI, PET	https://adni.loni.usc.edu/
AIBL	Alzheimers' disease	>3000 participant	clinical, biochemical, sMRI, fMRI, DWI, PET	https://aibl.org.au/
GBM	De novo glioblastoma	630 subjects with many missing data	demographic, clinical, genetic, sMRI, DWI	https://www.cancerimagingarchive.net/collection/upenn-gbm/
Lung-PET-CT-Dx	Lung cancer	355 participants, 436 studies, 1295 series	PET CT	https://www.cancerimagingarchive.net/collection/lung-pet-ct-dx/
MMIST ccRCC	Kidney cancer	618 Patients	clinical CT, MRI, WSI, Genomics	https://multi-modal-ist.github.io/datasets/ccRCC/
CPTAC-PDA	Pancreatic Ductal Adenocarcinoma	168 patients	US CT, MR, PET, histopathological images, clinical info	https://www.cancerimagingarchive.net/collection/cptac-pda/
CT-MAR	Metal artifact reduction in CT reconstruction	14000 cases (1773 head + 12227 body) for training 1000 cases for testing	set of CT image pairs and sinogram pairs generated from NIH DeepLesion dataset	https://www.aapm.org/GrandChallenge/CT-MAR/
BLUES	Covid-19 pneumonia: COVID Bluepoint Lung Ultrasound	63 patients (33 COVID-positive and 30 COVID-negative) 362 videos corresponding to 31,746 frames	patient characteristics, lung ultrasound (US) videos, symptoms, comorbidities, blood test data, vital parameters, and the PCR test result testing for COVID-19	https://github.com/NinaWie/COVID-BLUES
SARCOMA	Soft-tissue sarcoma	51 patients	RTSTRUCT, CT, MR (T1-weighted, T2-weighted with fat-suppression) , PT	https://www.cancerimagingarchive.net/collection/soft-tissue-sarcoma/

Implementation

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Gantt

- WP1 Mining multi-modal information**
- T1.1 Feature-based approach to multi-input analysis
 - T1.2 Integration of multi-parametric and multi-modal imaging data
 - T1.3 AI solutions for heterogeneous data analysis
- WP2 Handling incomplete/missing/limited datasets**
- T2.1 Traditional approaches for data curation and augmentation
 - T2.2 Medical Image Data Generation
 - T2.3 Data inpainting with CNN
- WP3 Data platform and computing infrastructure**
- T3.1 Definition of requirements and user roles
 - T3.2 Realization and maintenance of the data platform prototype
 - T3.3 Integration of data processing pipelines and output storing
 - T3.4 SW organization and repository
 - T3.5 Data collection
- WP4 Project management, outreach and collaborations with external parties**
- T4.1 Project management and networking
 - T4.2 Collaboration with AIFM and medical associations
 - T4.3 Outreach

Sedi coinvolte													timeline			
BA	BO	CA	CT	FE	FI	GE	LE	LNS	MI	PI	PV	2025	2026	2027		
						○								M1.1	M1.2	M1.3
x	x	○			x	x	x	x			x					
	x				○	x	x	x			x					
			○		x	x	x	x	x	x	x					
		○												M2.1	M2.2	M2.3
		x					○		x							
	○			x	x						x					
		x	x	○												
										○			M3.1	M3.2	M3.3	
x										○	x					
x	x	x				x				○	x					
		x				○				x						
	x					x				x	○					
	○	x								x						
												○		M4.1	M4.2	M4.3
x	x	x	x	x	x	x	x	x	x	○	x					
x	x	x	x	x	○	○	x	x	x	x	x					
x	x	x	x	x	x	x	x	x	x	○	x					

Legend:

- WP coordination
- Task coordination
- x Task participation

Outline

- Research context
- State of art
- The AIM_MIA project
 - Objectives
 - Methods
 - **Implementation**
 - Connections
 - Expected impact
- People & Budget

A. Retico - Artificial Intelligence in Medicine: focus on Multi-Input Analysis

Implementation: Milestones

Deadline		Milestone	Description
31/12/2025	M1.1		Development of a DL-based analysis pipeline for feature extracted from multiple sources and release to the SW repository
31/12/2025	M2.1		Implementation and release to the SW repository of traditional data augmentation and data imputation techniques.
31/03/2025	M3.1a		Initialization of the shared SW repository and release of guidelines for contributors
31/12/2025	M3.1b		Release of an internal note reporting the guidelines to set up the data platform (definition of the requirements, user roles, allowed data types)
31/03/2025	M4.1		Kick-off meeting organization and release of a plan of collaboration with external parties
31/12/26	M1.2		Definition of a generalizable AI-based pipeline that integrated multiparametric or multimodal images
31/12/26	M2.2		Inpainting of metal artifact corrupted sinograms with NN
31/12/26	M3.2		Instantiation of a XNAT platform prototype and integration of data sets
30/06/26	M4.2		Identification of joint research or dissemination activities to promote the networking among researchers from different Institutions and associations
31/12/27	M1.3		Definition of an AI-based pipeline that integrates images and features extracted from heterogeneous data
31/12/27	M2.3		GAN generation of medical images
31/12/27	M3.3		Integration of data processing pipelines and output storing
31/12/27	M4.3		Organization of a workshop to discuss the results of the project with stakeholders

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Connections with external entities and other projects

- Collaboration with Italian Association of Medical Physicists (AIFM)
 - A **5-year research framework agreement** has been renewed in January 2024 between INFN and the Italian Association of Medical Physicists (AIFM). This agreement foresees the collaboration between the parties for the synergistic realization of common research objectives in the healthcare field.
 - Roles of INFN and associated researchers in AIFM boards and initiatives:
 - **A. Retico, M.E. Fantacci, M. Marrale** and **C. Lenardi** are members of the Research Committee of AIFM
 - **C. Talamonti** coordinates the AI working group of AIFM
 - **A. Lascialfari** is the chair of the Research Committee of AIFM
 - **C. Lenardi** is in the Executive Board of AIFM
 - Example of joint activities
 - Organization of **joint webinars INFN-AIFM** on research topics related to the use of AI in the medical field:
 - e.g. in 2024 <https://fisicamedica.it/formazione/agenda-eventi-formativi/come-affrontare-insieme-le-sfide-dellia/>
 - Participation of AIFM medical Physicists to INFN projects
 - Joint organization of workshop, training opportunities and dissemination events (e.g. Bright-Nights)
 - <https://fisicamedica.it/formazione/agenda-eventi-formativi/workshop-aifm-infn-oltre-la-diagnosi-e-la-terapia-la-ricerca-che-rivoluziona-la-clinica/>
- Collaboration with other associations
 - **A. Chincarini** is a member of the
 - Executive Board of European Alzheimer’s Disease Consortium (**EADC**, <https://eadc.online/>)
 - Neurological Study Committee of the Italian Association of Nuclear Medicine (**AIMN**, <https://aimn.it/>)
 - **C. Testa** is a member of the Executive Board of the Italian Chapter of the International Society of Magnetic Resonance in Medicine (**AIRMM**, <https://www.ismrm.it/it/airmm/>)
 - ...



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Expected impact

- The AIM_MIA project is expected to deliver:
 - **robust and effective analysis pipelines** to make predictions about the health status of individuals, by extracting and combining via **multi-input AI-based tools** the complementary and heterogeneous information provided by different data sources (e.g. images, diagnostic tests, phenotypic and genetic data);
 - many **scientific publications** on peer-reviewed journals on this topic;
 - a **data platform prototype** able to collect and share samples according to FAIR principles and GDPR compliant.
- The acquired **knowledge** in the field will be shared within the scientific community, after evaluating its potential for transferability and exploitability together with INFN CNTT
- The **data platform prototype** will serve as a fundamental reusable/repurposing resource for several additional research studies in the field
- The **network** of INFN researchers, technologists and associated personnel interested in AI developments for medical applications will be consolidated and further expanded

