

Ministero dell'Università e della Ricerca
Direzione generale della ricerca

Call as to the funding of research initiatives for technologies and innovative trajectories in the health and care sectors

National Plan for NRRP Complementary Investments - Law Decree May 6, 2021, n. 59, converted and modified as to Law n. 101/2021 Research initiatives for technologies and innovative trajectories in the health and care sectors

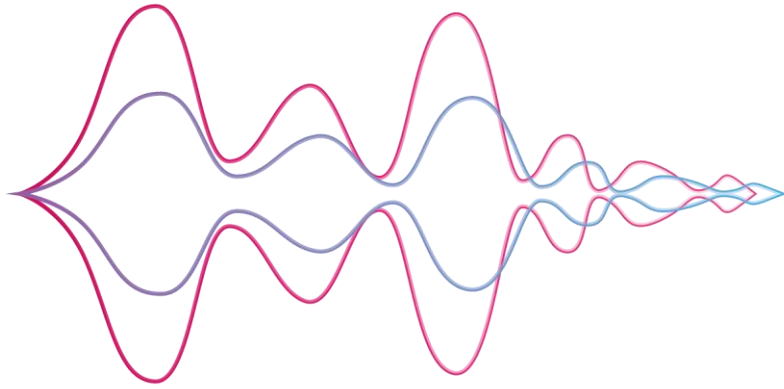
Annex 1 – “Initiative” proposal
(Article 10, paragraph 3 letter a, and Article 12 of the Call)

(This attachment must be completed and digitally signed by the Legal Representative - or its delegate according to an entrusted delegate authority - of the proposing entity)

NB: The drafting of the project proposal must respect limits indicated for each paragraph with the following characters: Times New Roman font, font size 11, single line spacing.

NAME OF THE “INITIATIVE”: ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)

Each Proposal is evaluated according to the criteria set out in Article 12 of the Call.



Anthem

AdvaNced Technologies for Human-centEred Medicine



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ANTHEM Participants

Short Name	Name	Spoke	Affiliate	Hub
UNIMIB	Università degli Studi di Milano-Bicocca	✓	✓	✓
UNIBG	Università degli Studi di Bergamo	✓	✓	✓
UNICT	Università degli Studi di Catania	✓		✓
POLIMI	Politecnico di Milano	✓	✓	✓
HUNIMED	Humanitas University		✓	✓
UNICAL	Università della Calabria		✓	✓
UNICAMP	Università degli Studi della Campania Luigi Vanvitelli		✓	✓
UNIME	Università degli Studi di Messina		✓	✓
UNISALENTO	Università degli Studi del Salento		✓	✓
INFN	Istituto Nazionale di Fisica Nucleare		✓	✓
ASST BGEST	Azienda Socio Sanitaria Territoriale Bergamo Est		✓	
ASST MONZA	Azienda Socio Sanitaria Territoriale di Monza		✓	
ASST PG23	Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII		✓	
CANNIZZARO	Azienda Ospedaliera Cannizzaro Catania		✓	
AST MI	Agenzia di Tutela della Salute Milano		✓	
BIOGEM	Biogem Scarl		✓	✗
FERB	Fondazione Europea Ricerca Biomedica Onlus		✓	
IOM	Istituto Oncologico del Mediterraneo		✓	
NEGRI	Istituto di Ricerche Farmacologiche Mario Negri		✓	✓
ABM	Ab Medica Spa		✓	
ART	Artemide Spa		✓	
CHIESI	Chiesi Farmaceutici Spa		✓	✓
DIA	Diapath Spa		✓	



List of Acronyms

AB	Advisory Board	ML	Machine Learning
AI	Artificial Intelligence	MS	Milestone
ASST	Territorial Socio-Sanitary Company	M€	Million(s) Euro
ATS	Health Protection Agency	MSCA	Marie Skłodowska-Curie Actions
BGL	Blood Glucose Level	MUR	Ministry of University and Research
BNCT	Boron Neutron Capture Therapy	NCD	Non-Communicable Disease
CCM	Chronic Care Model	NDA	Non-Disclosure Agreement
COPD	Chronic Obstructive Pulmonary Disease	NHS	National Health System
D	Deliverable	NPC	National Plan for Chronicity
DL	Deep Learning	NRRP	National Recovery and Resilience Plan
DMP	Data Management Plan	PD	Parkinson's Disease
ED	Emergency Department	PM/y	Person-Month/year
EHR	Electronic Health Record	PoC	Point of Care
ERC	European Research Council	QoL	Quality of Life
FNA	Fine Needle Aspiration	R&D	Research and Development
GBM	Glioblastoma	R&I	Research and Innovation
GD	Gaucher Disease	RRI	Responsible Research and Innovation
GDP	Gross Domestic Product	SW	Software
GDPR	General Data Protection Regulation	T1D	Type 1 Diabete
ICT	Information and Communications Technology	TRL	Technology Readiness Level
IP(R)	Intellectual Property (Rights)	TT	Technology Transfer
KIP	Key Impact Pathway	VR	Virtual Reality
KPI	Key Performance Indicator	WHO	World Health Organization
M	Month	yo	years old

A. TARGETS AND SCIENTIFIC QUALITY

A.1 Characteristics, objectives, relevance and motivations underlying the activities program

Characteristics and objectives. ANTHEM (AdvaNced Technologies for Human-centrEd Medicine) is a multidisciplinary project aimed to cover the existing gap in healthcare of frail and chronic patients within **specific target territories and high-incidence and therapy-orphan pathology-defined communities**. ANTHEM will develop innovative **sensors, digital-based advanced diagnostic, monitoring and therapeutics** systems integrated with the latest methodologies in the field of Artificial Intelligence (AI, including *Data Mining*) to improve territorial medicine approach for Non-Communicable Diseases (NCD) and rehabilitation.

ANTHEM adopts a patient-centred approach: the patient's specific health needs, the characteristics of living environments and the desired outcomes are the key elements in determining care and/or treatment pathways and, most importantly, in **health care processes reengineering**. Project objectives will be pursued by developing activities in four main areas:

1. **Smart Monitoring:** development of new sensors and technologies to monitor patients, frail populations and environments (i.e. home, Point of Care, PoC, mobile units) that include continuous real-time data collection and integration.
2. **Prevention and Diagnosis:** development of new technologies and AI-methodologies aimed at improving early diagnosis, implementing digital pathology and allowing their scalability at pathology and/or territorial level.
3. **Personalised Medical Treatments:** development of advanced treatments for orphan cancers, chronic conditions dedicated to specific target populations and territories.
4. **Technological Enhancement and Transferability:** development of methodologies for heterogeneous health data management, protection, interoperability and for data integration with existing or developing information technology platforms.

The project activities are organised in four *Spokes* (Figure 1) dedicated to innovative technologies targeting selected diseases and territorial communities (see pag. 9 and section B1 for details) and will have a direct impact on: a) reinforcement of health data interoperability, b) development of digital tools and diagnostic/monitoring devices adaptable to different territorial contexts and reference populations, c) development of innovative NCD therapeutic strategies for target populations. The Spokes include a variety of Pilots at different Technology Readiness Levels (TRLs):

- **Spoke 1.** Data and technology driven diagnosis and therapies;
- **Spoke 2.** Connecting patients and therapists through adaptive environments and intelligent sensors to enhance proximity medicine;
- **Spoke 3.** Risk factors monitoring, diagnostic tools and therapies in chronic diseases;
- **Spoke 4.** Preclinical and clinical breakthrough theranostic and treatments for cancer.

The four main objectives of this project are realised by a project team consisting of 23 partners located throughout the country: 8 public and 1 private universities; 1 national public research centre; 5 public healthcare institutions, among which 4 public hospitals and 1 health agency; 4 private research & healthcare institutes and 4 private companies.

The partners will act through an institution legally recognized and formally operating under Italian law, named: "Fondazione ANTHEM". With the aim of pursuing strategic goals and determining working policies for the entire project, the governance of the project will include four **Scientific Expert Committees** consisting of experts from the four spokes, as follows: 1) Data expert committee; 2) AI expert committee; 3) NCD expert committee; 4) Health system expert committee. To foster project activities and synergies between the research team and third parties, the project will include three external **Advisory Boards** composed of representatives of 1) the involved Regional Healthcare Institutions; 2) the beneficiaries of the project (i.e. local communities, patients' associations) and of 3) the relevant industrial associations. The **Ethics Committee** will provide independent guidance.

The research teams will design and conduct their research activities, where possible, **directly in operational environment conditions** (e.g., living labs, PoC, hospitals, patients' home).

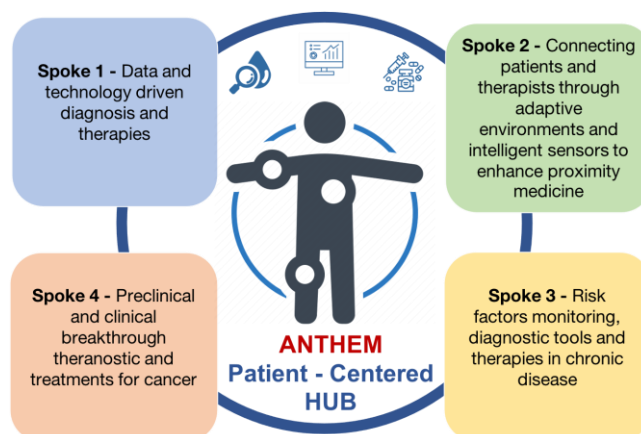


Figure 1. ANTHEM Spoke structure.



To ensure rapid translation into a real social benefit, all the planned initiatives (*Pilots*) will be developed allowing their immediate connection with existing/developing health data management and communication infrastructures. The *IT&Digital Health Unit* of the Regione Lombardia already granted its willingness to host tests and to collaborate for the optimization of our findings in Lombardia. This collaboration will foster best practices, scalability and validation also in other reference communities (see below for further details).

Responsible Research and Innovation (RRI) strategies and tools and translational actions will be adopted to share and exploit data and stakeholders from previous research programs, and to overcome traditional disciplinary boundaries. ANTHEM will also develop thematic working groups and guidelines to support the Technology Transfer (TT) of innovations and to share data and information with institutional entities (e.g. hospitals, treatment centres, technology clusters, government bodies such as the Ministry of Health).

ANTHEM adheres to the European Data Space¹ regulation, standards and good practices to: a) ensure and improve digital access to healthcare data; b) improve the efficacy of medical devices and sensors assisted by AI; c) provide an efficient set-up of healthcare data taking advantage of selected end-users and territories.

To ensure long-term sustainability of the project activities and goals, **multidisciplinary joint training courses at the doctoral level** will be planned to train future scientists in the field of digital medicine (see section C for further details). In addition, to guarantee a high impact on the population, the health care system, and consequently on the economy, additional training activities will be planned: i) professional training for territorial and hospital healthcare staff, and ii) training activities to make patients more aware of, and thus bringing them closer to, the advanced technologies that will be developed within the project.

Relevance and motivations underlying the activities program. Frail and chronic populations represent a large plethora of patients that need continuous intervention of healthcare systems and caregivers. Italy is the second country globally for longevity, with a related increase of NCD². The *World Health Organization (WHO)* estimated that NCD such as cancer, degenerative, cardiovascular, pulmonary diseases are responsible for 71% of the total deaths worldwide³: cardiovascular diseases account for most deaths (17,9 million annually), followed by cancers (9,3 million), respiratory diseases (4,1 million), and diabetes (1,5 million).

The Italian *National Plan of Chronicity (NPC)* indicates that the most representative pathologies or co-morbidities in the chronic and frail population are represented by cardiovascular diseases as a whole (32,8%), followed by chronic respiratory diseases (24,5%), diabetes (20,3%) and tumours (12,7%)⁴.

Frail and chronic patients are a challenge for the health system at the level of organisation, process efficiency, quality and effectiveness of care, and healthcare economy. The efficiency of medical assistance at national level displays peaks of excellence and disparities due to the geographical structure of the country, variations in population density, connectivity services, lack of qualified personnel and local socio-economic conditions.

Three directions can be taken to reduce the gap between peaks of excellence and disparities: i) **remote monitoring**: development of an efficient diagnosis and monitoring system for patient and environment suitable for different territorial structures and homes (modular and scalable), also direct on co-morbidities to prevent complications thus reducing the pressure on ‘hospital hubs’ and reducing the geographical gap, ii) **detection of early signs**: implementation of monitoring systems for chronic patients so as to identify early signs of worsening of the health conditions thus reducing the intervention time due to geographical issues; and iii) **personalisation**: introduction of innovative treatments for the frail population calibrated on the characteristics of the patient (socio-economic status, autonomy, family support) and of the residency territory.

The idea that telemedicine can improve the quality of health care for patients in remote areas and reduce health care costs is not new⁵. The first experiments in telemedicine certainly coincide with the beginning of telecommunication technologies. For example, during the Civil War in the late 1800s, the telegraph was used to request medical supplies for the wounded soldiers. In the 1930s, radio was used to monitor remote areas in Alaska and Australia. Other pioneering examples include those carried out by NASA scientists who developed sophisticated astronaut medical telemetry systems. The arrival of television as a means of communication expanded the application areas and the spread of telemedicine even further. In 1964 an interactive video link was established to connect the Nebraska Psychiatric Institute in Omaha with Norfolk State Hospital, which was 112 miles away. Again, in 1967, an early telemedicine system was established to link a Boston airport medical station to the Massachusetts General Hospital.

¹ https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en

² Petrelli et al. Chronic Care Model in Italy: a narrative review of the literature. *Prim Health Care Res Dev*. 2021

³ <https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases>

⁴ https://www.salute.gov.it/imgs/C_17_pubblicazioni_2584_allegato.pdf

⁵ Zundel, K. M. (1996). Telemedicine: history, applications, and impact on librarianship. *Bulletin of the Medical Library Association*, 84(1), 71.



These early experiments certainly confirmed that remote diagnosis was technologically possible and that it might be worth investing in this direction to increase the use of telemedicine. Since then, several successful telemedicine experiments have been conducted. In 1992, some telemedicine trials of rural communities in Texas demonstrated the effectiveness of the approach, despite the fact that technologies at that time were not so mature⁶.

In Italy, in 2012 the Higher Health Council approved the national guidelines on telemedicine, which later became the subject of the State-Regions and autonomous regions and provinces Agreement in 2014⁷. In 2019, the Ministry of Health launched a survey of regional telemedicine experiences from which a varied and heterogeneous context emerges. For example, the TELPASS platform, telemedicine and specialist teleconsultation for paediatric palliative care, was activated in January 2019 and implemented with the contribution of the National Research Council⁸. As an example in one of our target communities, in Puglia region, COREHealth, a Regional Telemedicine Operations Center for Chronic Care and Clinical Networks, was launched in 2021⁹. This is a regional telemedicine central, at patients' home: they are accompanied to a self-management of their chronic disease and avoid hospitalizations and visits to clinics. Other examples of telemedicine in Italy are reported here¹⁰. The integration of AI technologies with telemedicine systems has been widely discussed as a possibility to further increase the effectiveness of telemedicine systems. AI can be used to interpret images, videos, physiological signals, and even to predict events¹¹.

There are now well-established demonstrations that telemedicine is an indispensable tool for making the health care system more efficient. In fact, there is a national initiative within the NRRP for the design, implementation and management of the National Telemedicine Platform.¹² To ensure coordinated, harmonious and consistent development of telemedicine within the National Health Service, an agreement was also signed in 2020 with the autonomous regions and provinces to update the national guidelines already approved in 2014¹³. The National Telemedicine Platform initiative includes three groups of services, literally: 1) core services: which includes the essential components for service delivery to patients and health personnel; 2) local complementary service: auxiliary application component that complements the service model of the context in which it is integrated; and 3) innovative experimental service: application component that aims to enrich the local minimal and complementary services with innovative features enabled by new technological paradigms.

Recently, advances have been made in this direction. Organisational guidelines of the digital model for the implementation of home care have been approved by the Italian government¹⁴. This is considered as a first milestone in the realisation of the objective M6C1 (Neighborhood networks, facilities and telemedicine for community health care) of the Italian NRRP¹⁵.

The motivation of this project is **technological**, because it is necessary both to develop new systems of diagnosis, monitoring and treatment and to adapt them to the context of territorial medicine and to the areas of intervention; **scientific**, because it is necessary to understand and analyse remote-collected parameters and data to make diagnoses and treatments as efficient as in a hospital context; **educational**, as both the medical and nursing community and the citizens must change their approach to the treatment of diseases.

At a **geographical** and **demographic** level, the reason behind ANTHEM project comes from territorial analysis which has shown that the 50,9% of the Italian population resides in areas defined as “mountainous”, and may experience difficulties in reaching highly specialised hospitals closer to large urban centres. Italy has also densely populated areas with a high number of daily accesses to emergency services. It is thus **necessary to intervene with proximity medicine**, especially for the diagnostic and assistance in chronic and frail patients, to reduce the pressure on hospitals. At a **socio-economic** level, Italy has obvious difficulties in equipping all the local structures with adequate technologies and personnel, so it is necessary to develop modular environments with a good level of automation and thus requiring less specialised operators.

⁶ Preston, J., Brown, F. W., & Hartley, B. (1992). Using telemedicine to improve health care in distant areas. *Psychiatric Services*, 43(1), 25-32.

⁷ <https://www.salute.gov.it/portale/ehealth/dettaglioContenutiEHealth.jsp?lingua=italiano&id=5525&area=eHealth&menu=telemedicina>

⁸ Telemedicina e intelligenza artificiale - Quotidiano Sanità <https://www.quotidianosanita.it/allegato3026980>

⁹ <https://www.regione.puglia.it/web/salute-sport-e-buona-vita/-/arriva-corehealth-la-prima-centrale-operativa-regionale-di-telemedicina>

¹⁰ <https://www.salute.gov.it/portale/ehealth/dettaglioContenutiEHealth.jsp?lingua=italiano&id=5524&area=eHealth&menu=telemedicina>

¹¹ <https://www.agenas.gov.it/component/k2/il-connubio-tra-telemedicina-e-intelligenza-artificiale-per-un-salto-di-qualit%C3%A0-nelle-cure>

¹² <https://www.agenas.gov.it/comunicazione/primo-piano/2061-agenas-pubblica-1%E2%80%99avviso-per-la-piattaforma-nazionale-di-telemedicina>

¹³ <https://www.statoregioni.it/media/3221/p-3-csr-rep-n-215-17dic2020.pdf>

¹⁴ <https://www.agenas.gov.it/comunicazione/primo-piano/2092-linee-guida-organizzative-il-modello-digitale-per-1%E2%80%99attuazione-dell%E2%80%99assistenza-domiciliare>

¹⁵ <https://www.agenas.gov.it/pnrr/missione-6-salute>



Incompliance with the **National Guidelines on Telemedicine**¹⁶, it is thus fundamental to strengthen home health services by: a) maximising the opportunities offered by new technologies, such as telemedicine, home automation, digitization; b) integrating home health care with social interventions. Telemedicine services contribute to address the main challenges of the National Health Systems (NHS) by: a) helping to reduce the current geographical and territorial gaps in health terms by harmonising standards of treatment by technology; b) ensuring a better "care experience" for patients; c) improving the efficiency of regional health systems through the promotion of home care and remote monitoring protocols.

To ensure a close link between technological innovation and local demand, the project considers **territorial communities** that are representative of the country diversity and that display specific criticalities and needs:

1. **Mountain communities** (Val Seriana, Val Brembana): the two valleys have different characteristics by type of patients and needs but share territorial characteristics and the presence of difficult access to hospitals (at least 30 minutes to reach the emergency services by road). These communities are representative of several Italian mountain and rural areas with critical territorial connections.
2. **Metropolitan and district communities** (Milano, Monza and Brianza, Napoli, Taranto, Bari, Lecce): selected for the high population density, the variety of patients and the high density of hospitals together with the modest presence of proximity structures capable of reducing pressure on hospitals. These communities will be used as benchmarks through regional data.
3. **Island community** (Sicilia): Sicilia represents a good example of a Mediterranean island, geographically isolated and with an autonomous healthcare structure that is characterised by peaks of technological excellence, but also by areas with very low levels of territorial healthcare.

The participating Regions have been selected for the differences between health systems in terms of organisation, technology and inhomogeneous diagnostic and therapeutic efficiency and therefore constitute a good representation of the country.

In terms of pathology, according to the NPC, ANTHEM will consider the following chronic diseases: **cancers** selected on the basis of limited availability of treatments or in presence of clinically-relevant diagnostic challenges (i.e. Glioblastoma GBM, melanoma, lung and thyroid cancers); **degenerative diseases** (i.e. neurodegenerative diseases), **cardiovascular** and **pulmonary** diseases (i.e. fibrotic, atherosclerotic diseases), and **diabetes** selected on the basis of their social impact and high incidence.

A.2 Description of research activities and methodology to be used for the implementation of the activities program

AI has been employed in many healthcare applications¹⁷. For instance, Machine Learning is used to analyse big data, in data mining applications, to discover and reveal hidden patterns in health records, images and physiological signals, thus helping health workers to improve disease outcomes. Decision support systems are used to cross-correlate all the health data of the patients to help clinicians to make decisions about diagnosis, care, and treatments of patients¹⁸. Finally, the use of deep learning for medical imaging processing has been proved to be effective in many diagnostics applications and the COVID pandemic represented an extraordinary boost for bringing deep neural network from laboratory research to clinical application.

AI can support and complement healthcare professionals in improving the quality of patients' management in several ways. AI can be used to *augment human* intelligence and so it provides tools to be integrated in daily clinical practice. *Intelligent infrastructures*, made of web of computation, data, and physical entities, can be used to make human environments more supportive, interesting, and safe.

Artificial Intelligence (AI) in ANTHEM development

AI has a key role in the realisation of ANTHEM objectives. For a long time, the role of AI in medicine has been related to the idea of realising the "Imitative AI"^{19,20}, i.e. the realisation of an expert system with human-level intelligence. In other words, the realisation of an artificial clinician capable of learning from the experience and capable of accurately diagnosing and treating diseases. Consider, for example, the early attempts of IBM's Watson

¹⁶ https://www.agenas.gov.it/images/monitor/2021/46/art_agenas_18_appendice.pdf

¹⁷ Rajpurkar, P., Chen, E., Banerjee, O., & Topol, E. J. (2022). AI in health and medicine. *Nature Medicine*, 28(1), 31-38.

¹⁸ <https://www.ibm.com/topics/artificial-intelligence-medicine>

¹⁹ <https://www.britannica.com/technology/MYCIN>

²⁰ Jordan, M. I. (2019). Artificial intelligence—the revolution hasn't happened yet. (<https://hdsr.mitpress.mit.edu/pub/wot7mkc1/release/10>)



system which integrates machine learning and natural language processing methodologies for cancer treatment and diagnosis.

In contrast, we believe that the role of the clinician, and of the health workers, is still central to patient care and treatment and it can not be replaced by an intelligent machine or an expert system. Instead, we believe that recent advances in the field of AI and especially in the fields of Data Mining, Knowledge Discovery, Computer Vision, Signal Processing, and Intelligent Sensing make it possible to imagine a different role for AI in healthcare.

What is rather new in our **vision** is the fact that we do not want only to use AI as a support or complement to the work of healthcare professionals, but we want to design complete systems that integrates AI, monitoring, sensors and biomedical technology in a tailor-made and personalised experience of diagnosis, care and treatment of the chronic and frail patients.

In fact, we will refer to specific territorial or pathology-driven communities, and thanks to a multidisciplinary team composed of clinical physicians, medical researchers, engineers and researchers in the field of AI we will redesign the processes of care, diagnosis and treatment of these patients by keeping the patients themselves at the centre of the design. The approach is not top-down, i.e., prompted by the needs of the clinician, nor is it bottom-up, i.e., prompted by the technologist, but rather it is a hybrid approach that takes from both directions and more importantly it keeps the needs of the **patient at the centre**.

Our ambitions are supported by changes that are taking place in healthcare from the perspective of data and communication technologies. Digital transformation is revolutionising healthcare both from the point of view of data digitization and process efficiency. Data digitization means not only making medical records electronic but also making digital systems interoperable resulting in large repositories of healthcare data available to healthcare professionals but more importantly to data mining algorithms and artificial intelligence methodologies which are able to generate knowledge about the patient that is immediately useful and usable by the clinicians in their daily activities. In addition to the digital revolution is the revolution of network-connected devices, the so-called Internet of Things (IoT) now also known as the Internet of Everything (IoE), which predicts 30 billion computing devices connected to the Internet by 2025. Of these devices about one-third will be wearable devices which are typically employed in medical applications²¹.

To this aim, we will also consider open questions and key challenges for the future of AI in medicine. Key challenges are mainly related to the data collection, data quality, data annotation and data storage, as well as to accountability and fairness.

In addition, AI can also provide a solution to the management and proper interpretation of other healthcare-related unsettled issues tackled by the ANTHEM project, related to digital pathology, large-scale genomic screenings, advanced radiation therapies and correlative imaging. Moreover, the innovative treatments for orphan cancer will develop guidelines for the proper collection and use of data, allowing the treatment of future patients to benefit from the AI-based interpretation set by ANTHEM.

The collection of data may be, in certain applications, very difficult since the cost of the devices used for the acquisition is expensive. The quality of the data is not always guaranteed since the acquisition process is sometimes noisy and most importantly, to enable AI applications, data should be annotated. Physician-level annotation is not always of good quality and it is a very time consuming and costly process. Moreover, big data requires it to be stored and accessed, so suitable technology should be employed to guarantee that data is safely stored.

Accountability of AI-based systems is relevant to reach a very high level of technology-readiness level. AI-based healthcare systems require validation studies that show the effectiveness, efficiency and generalisation of

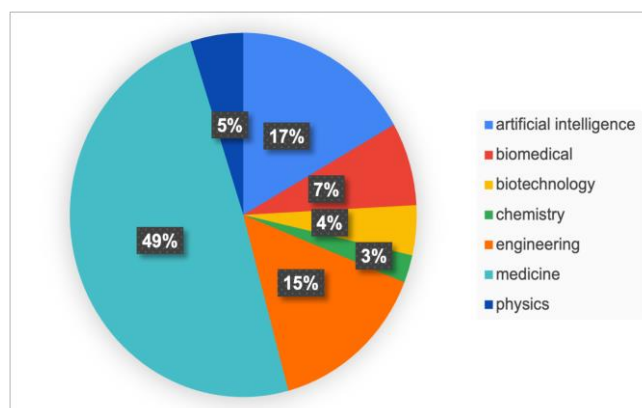


Figure 2. skills involved in Anthem project

²¹ <https://iot-analytics.com/state-of-the-iot-2020-12-billion-iot-connections-surpassing-non-iot-for-the-first-time/>



such systems across clinical settings and reference communities. Another challenge to take into account is the one regarding the fairness of the AI-based healthcare systems. Healthcare data should be managed in a fair way so that bad actors should not take advantage of medical datasets.

AI team in the ANTHEM project

For the realisation of project ambitions, we have formed a multidisciplinary team of more than 200 researchers and specialists that cover areas as diverse as medicine, biology, bio-engineering, artificial intelligence, management engineering, control engineering, mathematics, physics, etc. In particular the following chart shows the distribution of skills within the project.

As the project is in the healthcare sector the prevalent skill is in the field of medicine (about 50%), while the second skill is artificial intelligence (about 17%), followed by engineering skills (about 15%). The remaining 20% is divided into biomedical, biotechnology, physics and chemistry skills (Figure 2).

The AI team is made of valuable researchers with different specialisations such as machine and deep learning, medical imaging, signal and image processing, intelligent sensing, natural language processing, causal networks, and many others. Several members of the team are listed as world's top 2% researchers in "Artificial Intelligence" according to the Science-wide author databases of standardised citation indicators²².

Our team counts several members of the European Laboratory for Learning and Intelligent System (ELLIS²³) which is a pan-European AI network of excellence which focuses on fundamental science, technical innovation and societal impact. Mentioning the ELLIS website: "*founded in 2018, ELLIS builds upon **machine learning** as the driver for modern AI and aims to secure Europe's sovereignty in this competitive field by creating a multi-centric AI research laboratory.*" It "*wants to ensure that the highest level of AI research is performed in the open societies of Europe and follows a three-pillar strategy to achieve that*". The ELLIS society has three units in Italy and one in Milan whose founding members include the University of Milan-Bicocca and the Milan Polytechnic.

One of the aims of the ANTHEM project is to increase synergies with the ELLIS society especially in the creation of a network of excellence for the training activities at doctoral and postgraduate level.

Our project **vision** considers AI as a key element in the implementation of our activities. For this reason, we design for each spoke a pilot (Pilot 1.1, Pilot 2.0, Pilot 3.0 and Pilot 4.0) devoted to the AI-based activities so that it will serve as support for all the intra spokes activities. Moreover, to better guarantee that our vision about the role AI is pursued in the right manner, the project's governing board includes an AI expert committee that is cross-spoke and consists of both people from the team and two people from leading scientific societies in the field of AI, e.g., ELLIS.

Contribution of ANTHEM participants in clinical translation

The second chart (Figure 3) shows the distribution within the team of clinicians, researchers and technicians. Overall, more than half of the team is made of pure researchers, while about 14% is made of pure clinicians. About 28% of the team members are researchers working in hospitals and so they are also clinicians. Combining both pure clinicians and researchers/clinicians we came up with a percentage of 42% of clinicians that ensures the achievement of two important goals: 1) a detailed definition of use cases, and 2) the testing and validation in relevant and operational environments. In this respect, the choice of a Proposal coordinator with extensive clinical experience was cautiously pondered and deliberate, with the ultimate goal of maintaining an overall view of the progress and direction of the project and assuring that ANTHEM will remain "patient centred". The importance of clinics in translational research is indeed widely recognized, both at the institutional level and in scientific literature. Just to mention a few examples, the Horizon Europe "Cluster Health" includes a Destination targeted to:

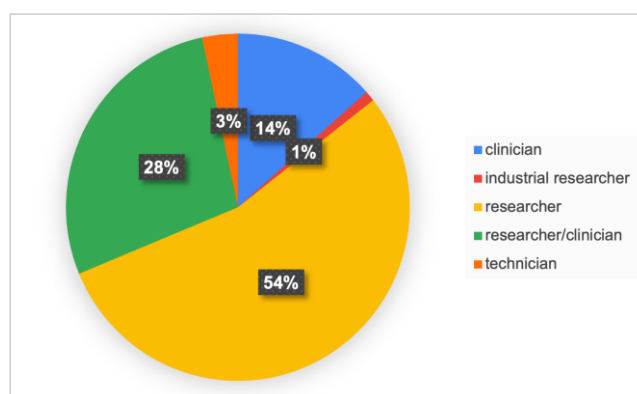


Figure 3. distribution within the team of clinicians, researchers and technicians

"Tackling diseases and reducing disease burden: Health care providers are able to better tackle and manage diseases (infectious diseases, including poverty-related and neglected diseases, non-communicable and rare

²² For more information visit here: <https://elsevier.digitalcommonsdata.com/datasets/btchxktzyw/3>

²³ <https://ellis.eu/>



diseases) and reduce the disease burden on patients effectively thanks to better understanding and treatment of diseases, more effective and innovative health technologies, better ability and preparedness to manage epidemic outbreaks and improved patient safety²⁴”.

Contributions to scientific debate on the matter state that:

“Even with a strong biological hypothesis, translation into the clinic remains a major bottleneck. Careful consideration of how to implement this must occur early, and requires a critical mass of integrated investigators and the infrastructure to maximize the likelihood of success. Modern drug development requires expertise in molecular and cellular biology, molecular pathology and medical oncology and input from medicinal chemists, structural biologists, pharmacokinetic-pharmacodynamic modellers and biomarker teams. A critical aspect of this is reiterative cycles of interrogation between the laboratory and the clinic and back to the laboratory. These reiterative studies should be designed as early as possible in clinical trial development to allow the acquisition of samples such as tumour tissue to investigate, for example, mechanisms of drug resistance (primary and acquired). This would allow the development of further hypotheses for evaluation in future clinical trials such as studies to reverse drug resistance²⁵”.

“The uncomfortable truth is that scientists and clinicians have been unable to convert basic biology advances into therapies or resolve why these conversion attempts so often don't succeed. Together, these failures are hampering clinical research at a time when it should be expanding. Enter translational research. The concept has been pushed hard over the past decade by funders as a way to bridge the gap between the laboratory and the clinic. New money has been found to foster high-risk, high-reward research, develop the necessary tools and methodologies, fill knowledge gaps, and change academic culture to foster collaboration. The term translational was well-chosen. Those who work at the bench and the bedside speak in separate tongues: scientists of hypotheses and mechanisms; clinicians of populations and effects. Two communities divided by uncommon language²⁶”.

Synergies with stakeholders

synergies with industries to undertake translational medicine at industrial level during and after the project end are expected to be consolidated provided the variety of expression of interest in project results that the proposal has received by commercial companies active in technological and health sectors (focus of the project) already in this submission phase but also from patient, medician associations and communities, italian Regions and one consortium. This expressed interest, provides a good insight also on sustainability opportunities after project funding but also demonstrates the interest in the project of patients, medicians and Regional Systems. These are early insights that corroborate the feasibility of the implementation of a quadruple helix model during and after the project (virtuous synergy between academy, industry, government and civil society. Entities that endorse the project are:

- **Industries** - Siemens s.p.a, Rottapharm Biotech s.r.l, Italfarmaco s.p.a, Tensive S.r.l., STMicroelectronics, Huawei Technologies Italia s.r.l., Emotiva s.r.l.; Zeiss S.p.A
- **Patient, physicians associations and communities:** Aircam, Comunità Val Seriana, Un Respiro di Speranza, Aimac;
- **Regional Bodies:** Lombardia, Puglia, Campania and Calabria Region;

Research plan

The main scope of the project is to cover the existing gap in healthcare of **frail and chronic patients** within specific target territories and high-incidence, and orphan pathology-defined communities. As discussed above, according to the *World Health Organization (WHO)*, noncommunicable diseases kill 41 million people each year, equivalent to 74% of all deaths globally²⁷. It is globally recognized that possible directions of intervention to reduce the impact of NCD on our society²⁸ are: 1) produce scientific evidence on NCDs, risk factors, and interventions; improve NCD surveillance, monitoring and evaluation systems; strengthen public health infrastructure and workforce.

²⁴ European Commission, 2021. https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2021-2022/wp-4-health_horizon-2021-2022_en.pdf

²⁵ De Bono and Ashworth. Translating cancer research into targeted therapeutics. *Nature* 467 (2010). <https://www.nature.com/articles/nature0933>

²⁶ Hope in Translation. *Nature* 467 (2010). <https://www.nature.com/articles/467499a>

²⁷ <https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases>

²⁸ <https://www.cdc.gov/globalhealth/healthprotection/ncd/about.html>



The Anthem project planned research activities to address these directions of intervention. The project consists of 4 Spokes that cover main areas of intervention for the **care, monitoring, prevention, early diagnosis and treatment** of chronic diseases, and are targeted to specific communities: territorial and/or pathology-driven. Spoke 1 is mainly focused on clinical decision support, personalised medicine solutions and diagnostic **process re-engineering**. It mostly leverages health records data to improve the responsiveness of acute **care systems** to the patients' needs and to improve **diagnoses and therapies of selected orphan-pathologies**. It also leverages images to improve the early detection and diagnosis of selected pathologies, such as cancers. Spoke 2 is mostly focused on **remote monitoring** and new technologies to improve remote monitoring. It leverages signals acquired by **custom, off-the-shelf and prototype** sensors with the aim of monitoring **environments and people** of given **communities**. Spoke 3 is mostly focused on the **monitoring of living environments** and the **detection of risk factors** of NCD with high incidence such as **chronic heart and lung diseases**. It leverages mainly signals acquired with **off-the-shelf medical devices**. Spoke 4 mainly deals with **innovative therapeutic solutions** to specific tumours that cannot be treated with conventional approaches. It leverages mainly **cutting edge devices**, such as , for diagnosis and therapies of tumours, and it also leverages multi-omics data and AI to develop **precision medicine** for the treatment of cancers.

~~The project consists of 4 Spokes that cover 4 main areas of intervention for the care, monitoring, prevention, early diagnosis and treatment of chronic diseases; these areas are: data analysis and mining; optimization and enhancement of the efficiency of healthcare processes; tele-monitoring and new diagnostic and therapeutic technologies.~~

Each Spoke includes one or more university partners, private partners and one or more reference community, identified through partnerships with hospitals and local health authorities. Each Spoke consists of different pilot projects that pursue well-defined subgoals and with **different TRLs** so as to guarantee a **continuous transfer and flow of results** to application scenarios from earliest stages and along the entire duration of the project. For Pilots

consisting of multiple activities, the TRLs indicated in the tables below refer to the whole range covered, not to the expected TRL increase of individual activities: these Pilots are explicitly indicated. Each pilot has its own deliverables and milestones (Tables B.13-B.41), and it targets a reference community having a territorial, pathological or mixed nature (see B.1). The 28 Pilots are clustered in four categories as shown in Figure 4 and are the principal directions of intervention. All pilots have inter and intra spoke connections with other pilots to ensure that the pilot activities are carried out in cooperation and/or complementarity with other pilots. This is designed to ensure that research activities are carried out in a way that is consistent with the overall **vision** of the project both in terms of the role of AI and the directions of intervention to reduce the impact of NCDs on our society.

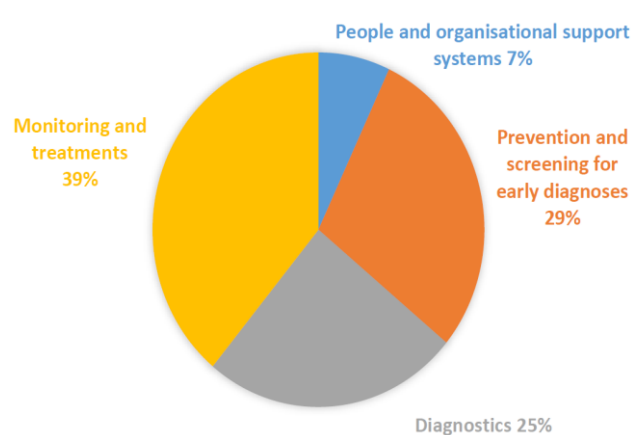


Figure 4. Pilot distribution by category.

Spoke 1 - Data and technology driven diagnoses and therapies			
Leveraging data, software and hardware technologies for clinical decision support, personalised medicine solutions and diagnostic process re-engineering.			
Leader	UNIBG	Affiliates	UNIMIB, UNIME, UNICAMP, ASST BGEST, ASST MONZA ASST PG23, DIA, FERB, NEGRI

Pilot 1.1: Leveraging data for clinical decision support system and data management (UNIBG, UNIMIB, NEGRI). Design and development of Artificial Intelligence (AI), machine learning (ML) and deep learning (DL) models for patient-specific decision making and personalised medicine (Territorial/Pathology) TRL 3→5
Pilot 1.2: Digital Triage at the emergency room (UNIBG, ASST BGEST, FERB). Design and development of an innovative digital triage solution for improving the responsiveness of acute care systems to the patients' needs with a particular attention to socially frail patients (Territorial). TRL 4→7
Pilot 1.3: AI based Artificial Pancreas for children (UNIBG, ASST PG23). Design a personalised patient-centred real-time blood glucose (BGL) control algorithm for Artificial Pancreas exploiting the patient's personal data to understand and learn the specific BGL dynamics by the means of data mining and AI modelling. Unannounced meals detectors and their amount estimation should be integrated to the control loop, together with specific patients-

tailored hyper-/hypo-glycemia alarms (Pathology). TRL 4→8
Pilot 1.4: Timely genomic diagnosis for children with rare diseases toward precision medicines (UNIBG, ASST PG23, NEGRI). Development of new AI based tools to support the clinicians in activating the genomic diagnostic process of rare diseases. A new digital genomic infrastructure will allow the collaboration between partners and clinical teams and the sharing of available datasets (Pathology). TRL 2→6
Pilot 1.5: Mass spectrometry for tissue biopsy investigation (UNIMIB). Use of the 4-dimensional SpatialOMix Mass Spectrometry imaging approach to investigate cytologic and tissue specimens for the precise diagnosis of several high-incidence diseases (e.g. thyroid lesions) through their “molecular signature”. AI tools will be exploited to identify markers in the cytological or bioptic tissue section (Pathology). TRL 3→7
Pilot 1.6: Improved multi-source image-based diagnostic for early cancer detection (UNICAMP, UNIMIB, ASST MONZA). Design of an “Intelligent” Territorial Screening of high-incidence cancers integrated by telemedicine and multisource diagnostic images improved by 3D rendering and enhancement, surgical endoscopic fluorescence images, clinical, pathological and “omics” data, powered by AI analysis. Improving cancer prevention by designing, optimising and commissioning a demo of TOF-PET insert for MRI powered by AI (Pathology). TRL 2→8*
Pilot 1.7: Genetic insights in neurodegenerative disease (UNIME, ASST MONZA). Identification of the reasons for Parkinson’s Disease (PD) high risk in patients with Gaucher disease (GD) and their family using genomic approaches and exploiting the underlying pathways in pre-clinical models by imaging and molecular analysis (Pathology). TRL 3→4
Pilot 1.8: MicroCT-based 3D digital histology (UNIBG, UNIMIB, DIA, ASST MONZA, ASST PG23). Development of a new 3D digital diagnostic methodology (virtual histology) using X-ray micro-CT imaging analysis of tumour specimens for allowing a unique visualisation of the tissue’s microstructures and their segmentation to follow up the details over entire volumes without destroying the samples as in conventional histology workup (here used as validation benchmark) (Pathology). TRL 6→8

Spoke 2 - Connecting patients and therapists through adaptive environments and intelligent sensors to enhance proximity medicine

Innovative sensors, devices and digital tools to early evaluate and treat environmental, lifestyle factors and pathological phenomena in frail and chronic populations.			
Leader	UNIMIB	Affiliates	UNIBG, UNICAL, ASST PG23, ART, ATS MI, ASST BGEST, FERB, ASST MONZA

Pilot 2.0: Leveraging sensor data for smart environments and intelligent monitoring (UNIMIB, UNIBG, UNICAL). Design and development of Artificial Intelligence (AI), machine learning (ML) and deep learning (DL) models for intelligent monitoring of patients and living environments. (Territorial/Pathology)
Pilot 2.1 Remote physical therapy and sensorized environments (UNIBG, UNIMIB, ASST PG23). Development of innovative solutions for rehabilitation using medical sensors, VR and smart assistive devices that will be developed and employed. Automatic generation of medical information by using raw sensor data and AI modules ad-hoc developed for each specific use case involved in the project. (Pathology). TRL 3→6
Pilot 2.2 Epidemiological study of cardiovascular diseases in a mountain area (UNIBG, UNIMIB, ASST PG23, ATS MI). Development of e-technologies for long-term control of cardiovascular risk factors and investigation of the link between those risk factors and future incidence of cardiovascular diseases (Pathology). TRL 5→7
Pilot 2.3 Smart wearable and portable sensors to monitor human healthiness and pathological states (UNIMIB, UNIBG, ATS MI). Development of cutting-edge technologies, devices and solutions to accelerate the adoption of proximity medicine, focusing on diagnosis, monitoring and treatment of chronic and frail patients. Integration of patients’ motion/interactions and biological outputs. Innovative wearable, transdermal, implantable, and portable sensors will be developed and integrated with modular web-based platforms to elaborate data for each specific application (Territorial). TRL 2→8 *
Pilot 2.4 Wide spectrum light and devices to sanitise surfaces and air (UNIMIB, ART, ASST MONZA). Development of devices and tools based on wide spectrum light for air flow sanitation and surface disinfection. The systematic assessment of the sanitation and disinfection capabilities of the different techniques and an online monitoring platform will be designed, built and tested in operative environments (Territorial). TRL 5→9

Pilot 2.5 Development of nanosensors for the detection of pathogens and biohazards (UNIMIB). Development of proximity care advanced nanosensors for the detection of pathogens and biohazards to monitor patients and their living environment (i.e. home, PoC, medical centres). A baseline analysis of the macro- and micro-environments will be performed to define biological and physico-chemical variables associated with increased health risk and to monitor skin microbiota perturbations with an integrated approach. Nanosensors and related data for the detection of pathogens and biohazards with other detectable risks will be developed and assessed based on the analyses of human body fluids and skin physico-chemical parameters (**Territorial**). TRL 3→6

Pilot 2.6 Remote monitoring of groups and community (UNICAL, UNIMIB). Development of an effective controlling system exploiting consumer technologies for monitoring patients along the entire pathology life cycle and before extensive use of hospital facilities. The system will be designed and updated by adding specific functionalities for remote monitoring and controlling of both ill and healthy people. The system will be used to monitor residents of remote locations with logistics problems to access healthcare facilities (**Territorial**). TRL 5→8

Pilot 2.7 Wearable devices for remote monitoring of Parkinson's disease and frail patients (UNIBG, ASST BGEST, FERB, ASST MONZA) Development of remote-monitoring system for Parkinson's and frail patients including sensors for daily quantification of neurological motor symptoms and data management system for healthcare professionals to early detect and timely respond to neurological health threats (**Pathology**). TRL 3→7

Spoke 3 - Risk factors monitoring, diagnostic tools and therapies in chronic disease

Design and development of innovative solutions for the assessment of chronic patients, the evaluation of the impact of environmental factors and lifestyle on health and identification of risk factors.

Leader	POLIMI	Affiliates	HUNIMED, UNISALENTO, CHIESI, ABM
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Pilot 3.0: Leveraging sensor data for disease progression monitoring and treatment (POLIMI, HUNIMED, UNISALENTO). Design and development of Artificial Intelligence (AI), machine learning (ML) and deep learning (DL) models for monitoring of disease progression and development of new tools for intelligent treatment of chronic diseases. (Territorial/Pathology)

Pilot 3.1 New technologies for air quality and lifestyle assessment (POLIMI, HUNIMED, UNISALENTO, ABM). Development of a wearable system for improving the scalability of conventional environmental air monitoring systems; development of a wearable device for the collection of vital signs; development of AI algorithms to detect signs of NCD and predict their progression based also on collected vital signs; definition of risk prediction mapping for cardiovascular and respiratory diseases produced on the basis of data collected from wearable devices, and/or retrospective data on a given territory (**Territorial**). TRL 2 → 5

Pilot 3.2 Environmental determinants of health (POLIMI, HUNIMED, UNISALENTO). Development of lung- and gut-on-chip models and of tools for air pollutants monitoring and identification of microplastics in food using advanced analytical techniques; analysis of the components of atmospheric particulate in the modulation of airway and intestinal microbiota, and host cell response using *in vitro* models (**Territorial**). TRL 3 → 5

Pilot 3.3 Innovation of diagnostic approaches in chronic heart and lung diseases (POLIMI, HUNIMED, UNISALENTO, ABM). Implementation of innovative imaging systems for diagnosis, follow-up, prediction of disease progression and response to treatment of cardio-pulmonary NCD; image-based quantification of cardiovascular biomechanics to support early diagnosis, patient selection and stratification; definition of AI models able to increase the quality of diagnostic imaging and manage lung cancer screening and early diagnosis; development of PoC diagnostic tools based on exhaled breath biomarkers analysis by electronic noses, a multi-parametric wearable system, and portable optical systems for tissue composition and blood parameters monitoring (**Pathology**). TRL 2 → 4

Pilot 3.4 Innovation of therapeutic approaches in chronic heart and lung diseases (POLIMI, HUNIMED, UNISALENTO, CHIESI). Implementation of AI based monitoring and assistance in critically-ill patients affected by NCD; development of: i) new tools for intelligent mechanical ventilation and for the analysis of critical care data; ii) new imaging modalities and *in silico* platforms for the evaluation of new drugs; iii) augmented and extended reality tools for therapy planning and treatment (**Pathology**). TRL 4 →7

Spoke 4 - Preclinical and clinical breakthrough theranostic and treatments for cancer

Innovative therapeutic solution, with the potential to be a response for those tumours that cannot be treated with conventional approaches. Innovation in methods of preclinical and clinical research. In particular, the pilots dedicated to these innovations (4.4 and 4.9) will take advantage of new developments in the drug delivery methodologies pursued by other pilots.

Leader	UNICT	Affiliates	POLIMI, HUNIMED, UNICAL, UNIME, UNISALENTO, UNICAMP, INFN, CANNIZZARO, BIOGEM, IOM
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<p>Pilot 4.0: Leveraging biology, multi-omics and imaging data for innovative disease theranostic and treatments for cancer (UNICT, POLIMI, HUNIMED, UNICAL, UNIME, UNISALENTO, UNICAMP, INFN). Design and development of Artificial Intelligence (AI), machine learning (ML) and deep learning (DL) models for innovative disease theranostic and treatments for cancer (Pathology)</p>			
<p>Pilot 4.1 Multifunctional materials for advanced theranostics (POLIMI, HUNIMED, UNISALENTO). Development of multifunctional nanocarriers for theranostic applications and for personalised medicine, to improve targeting ability and to increase drug efficacy. Development of nanoparticles loaded with radionuclides to implement theranostics approaches based on radio compounds (Pathology). TRL 2→4</p>			
<p>Pilot 4.2 Optical microsensors (POLIMI, HUNIMED, UNISALENTO). Development of Optical microsensors for sensing cell metabolism and cell-cell interactions in tumour models (Pathology). TRL 6→8</p>			
<p>Pilot 4.3 Multi-modal correlative microscopy platform (POLIMI, HUNIMED, UNISALENTO). Development of a multi-modal correlative microscopy platform for <i>in vitro</i>, <i>in vivo</i> and <i>ex vivo</i> biological imaging. The imaging workflow will enable an extremely wide resolution range, spanning from the single molecule scale to clinical imaging in the small animal model (Pathology). TRL 6→8</p>			
<p>Pilot 4.4: FLASH therapy effect on glioblastoma (GBM) (UNICT, INFN, CANNIZZARO, IOM, BIOGEM). Achievement of a biological response to FLASH and ULTRA-FLASH therapies of tumour and healthy tissues by: 1) 2D and 3D <i>in vitro</i> tumour and healthy cells response to therapy; 2) <i>in vivo</i> tumour and healthy tissues response to therapy, in a murine and zebrafish GBM model; 3) development of complementary therapies to improve the efficacy of treatment and quality of patient's life (Pathology). TRL 3→5</p>			
<p>Pilot 4.5 Sonoporation and drug delivery for GBM and melanoma treatment (UNICT, UNIME, INFN, IOM, CANNIZZARO, BIOGEM). Development of a sonoporation-based systems to improve drug delivery through: 1) synthesis of sonoporation-inducible liposomes; 2) <i>in vitro</i> tests on healthy, GBM and melanoma cell lines of ultrasound-inducible liposomes and combination with radiotherapy; 3) evaluation of sonoporation-inducible liposomes and radiotherapy combination in murine and zebrafish model of GBM and melanoma; 4) <i>ex vivo</i> samples analysis for conventional pathological, metabolomic, transcriptomic analyses and gene expression profile (Pathology). TRL 2→4</p>			
<p>Pilot 4.6 Innovative nanoparticles for drug delivery (UNICAL, BIOGEM). Implementation of an innovative multiple solution developed for the treatment of cancer characterised from high expectations in terms of increase of therapeutic efficacy and reduction of toxicity if compared to the traditional treatments (Pathology). TRL 2→4</p>			
<p>Pilot 4.7 Development of a perfusion-based bioreactor platform (UNICAL, IOM). Development of a perfusion-based bioreactor platform to successfully maintain 3D and freshly excised tissues obtained from Triple Negative Breast Cancer patients. This platform will allow the study of the response of cancer cells in close contact with tumour microenvironment in different controlled conditions by using an integrated approach of data from genomics, proteomics and metabolomics (Pathology). TRL 6→8</p>			
<p>Pilot 4.8. AI Based Systems Biology Approaches in Cancer Multi-Omics Data Analysis (UNICAL). Design of a platform for precision medicine able to suggest personalised treatments through the following steps: 1) database design and multi-omics data acquisition; 2) design and development of AI models for the prediction of the multi-omics risk score; 3) explainable AI (XAI) analysis to evaluate the predictive power of the omics parameters on the prognosis of the patients; 4) design of a risk score based on the XAI analysis (Pathology). TRL 1→3</p>			
<p>Pilot 4.9 Realisation of a boron neutron capture therapy (BNCT) facility in Caserta (UNICAMP, INFN). Realisation of a BNCT facility in Caserta, using technology, informatics and nuclear physics methods already available at INFN completed by the biological and clinical expertise of UNICAMP. UNICAMP will be responsible for constructing the bunker and its services while INFN will realise the high-technology part. Installation and commissioning will be a common activity. Research teams will address the necessary steps to integrate the technology and the preclinical studies to enlarge the knowledge on the interaction of a mixed radiation field with biological tissue. To this end, a set of preclinical radiobiological evaluations will be carried out by UNICAMP using existing neutron facilities while INFN will complete and install the necessary technology to produce the neutron beam. Targets will be GBM, but also head&neck, gastrointestinal, genito-urinary and gynaecological tumours based on the natural sensitivity to the radiotherapy (Pathology). TRL 4→8</p>			

*In these Pilots multiple activities with different start/end TRLs are foreseen. The whole range covered is indicated, not the expected TRL advancement of individual activities.



In Figure 5 we show a graphical representation of all the interconnections among pilots. For each spoke, AI-based activities are connected with most of the intra-spoke pilots (coloured connections), and most importantly, AI-based activities are all interconnected with each other (red dashed line). Given a spoke, activities of each pilot are connected with activities of other spokes (black connections).

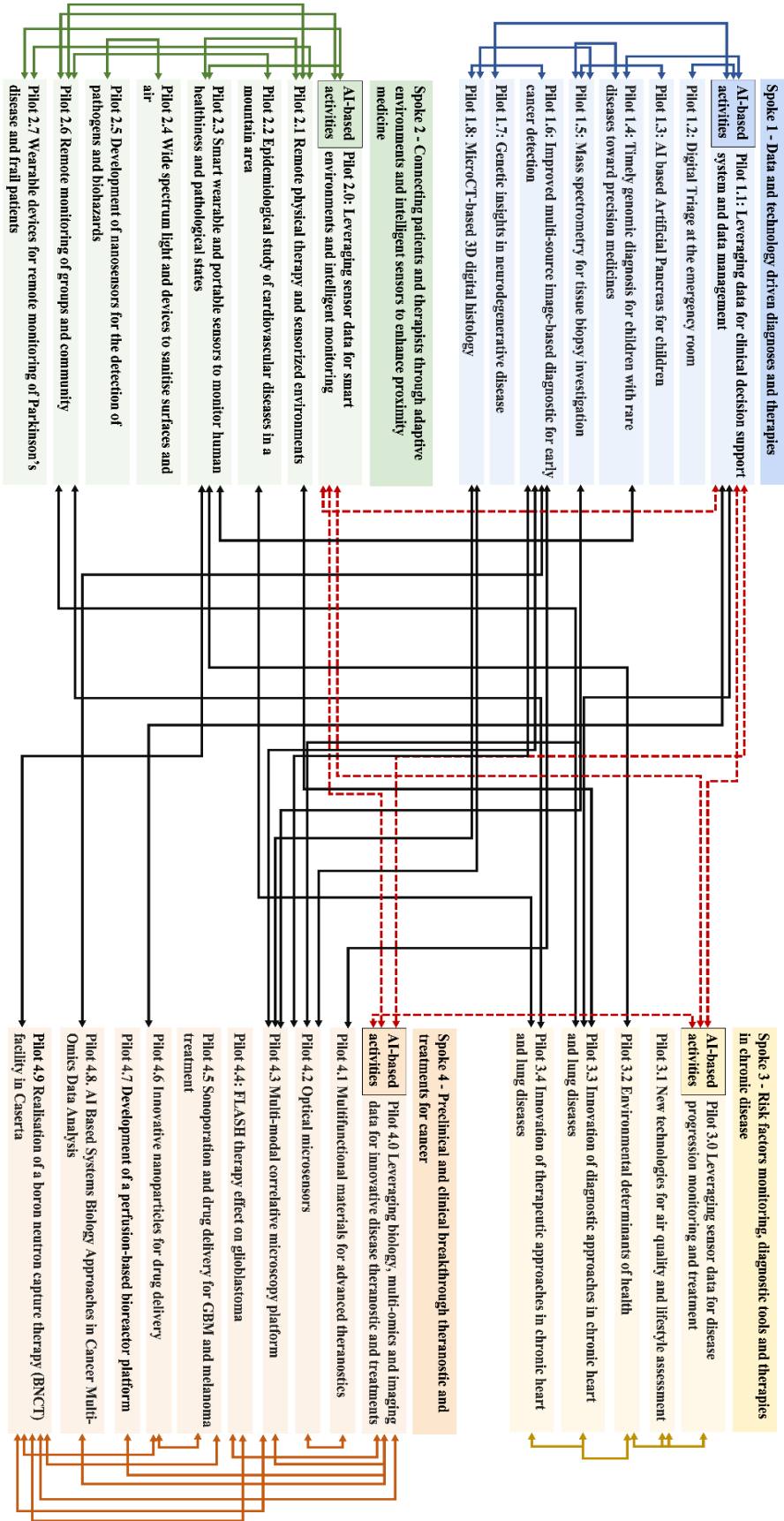


Figure 5. graphical representation of all the interconnections among pilots.

References

In the table below are collected a selection of publications of Pilots participants, the table aims at demonstrating the existence of an appropriate expertise (at academic level) that will guarantee the achievement of the project targets.

References: Spoke 1 - Data and technology driven diagnoses and therapies

Pilot 1.1: Leveraging data for clinical decision support system and data management (UNIBG, UNIMIB, NEGRI).

1. Automatic Segmentation of Kidneys using Deep Learning for Total Kidney Volume Quantification in Autosomal Dominant Polycystic Kidney Disease. Sharma K, Rupprecht C, Caroli A, Aparicio MC, Remuzzi A, Baust M, Navab N. *Sci Rep.* 2017 May 17;7(1):2049. doi: 10.1038/s41598-017-01779-0.
2. The use of AVF.SIM system for the surgical planning of arteriovenous fistulae in routine clinical practice. Bozzetto M, Poloni S, Caroli A, Curtò D, D'Haeninck A, Vanommeslaeghe F, Gjorgjievski N, Remuzzi A. *J Vasc Access.* 2022 Jan 6;11297298211062695. doi: 10.1177/11297298211062695.
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3. Switching to the Minimed™ 780G system achieves clinical targets for CGM in adults with type 1 diabetes regardless of previous insulin strategy and baseline glucose control. Lepore G, Rossini A, Bellante R, Corsi A, Scaranna C, Dodesini AR, Trevisan R. *Acta Diabetol.* 2022 Jul 20.
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Pilot 4.6 Innovative nanoparticles for drug delivery (UNICAL, BIOGEM).

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<p>Pilot 4.9 Realisation of a boron neutron capture therapy (BNCT) facility in Caserta (UNICAMP, INFN).</p> <ol style="list-style-type: none"> 1. Microdosimetry of an accelerator based thermal neutron field for Boron Neutron Capture Therapy. Selva A., Bellana L., Bianchi A., Giustiniani A., Colautti P., Fagotti E., Pisenta A., Conte V. <i>Applied Radiation and Isotopes</i>. 182, 2022, 110144. 2. The Hallmarks of Glioblastoma: Heterogeneity, Intercellular Crosstalk and Molecular Signature of Invasiveness and Progression. Torrisi F, Alberghina C, D'Aprile, Pavone AM, Longhitano L, Giallongo S, Tibullo D, Di Rosa M, Zappalà A, Cammarata FP, Russo G, Ippolito M, Cuttone G, Giovanni Li Volti G, Vicario N, Parenti R. <i>Biomedicine</i>, 2022, 30;10(4):806. 3. Novel Approach to Design and Evaluate BNCT Neutron Beams Combining Physical, Radiobiological, and Dosimetric Figures of Merit, Biology, 2021. 4. Multimodal evaluation of ¹⁹F-BPA internalization in pancreatic cancer cells for boron capture and proton therapy potential applications, Physica Medica 94, 2022.

A.3 Participants' description

The ANTHEM partnership integrates a network of excellence in academic research with the expertise and capacity of public healthcare representatives (hospitals and a territorial agency), the outstanding experience of private research institutes in the health field, and the development and technology capabilities of the industrial sector. For each participating organisation, the elements of excellence are detailed below, including: significant expertise and relevant previous projects and activities, associated to the ability to manage them; important results and technologies developed; existing educational programmes, notably at the doctoral level, in which the PhD students to be recruited will be enrolled; previous and ongoing national and international collaborations and networks. Moreover, for

universities and for the research centres the scientific excellence is stressed, also through facilities and laboratories, high-impact publications, patents and bibliometric indicators; for organisations of the healthcare system, information on medical infrastructures and expertise on clinical trials is provided; for private research institutes and companies key infrastructures are highlighted, as well as patents and granted technologies especially in the case of companies. Specific equipment already owned by the participants and which will be used in the framework of the project are described in Section B.4.

It is of paramount importance to stress that the participants have already conducted common projects, activities and programmes in the past: the ANTHEM partnership builds on an already consolidated network of successful experiences. Figure 6 represents the network of already existing collaborations within ANTHEM, which are detailed in the dedicated section of each partner's table.

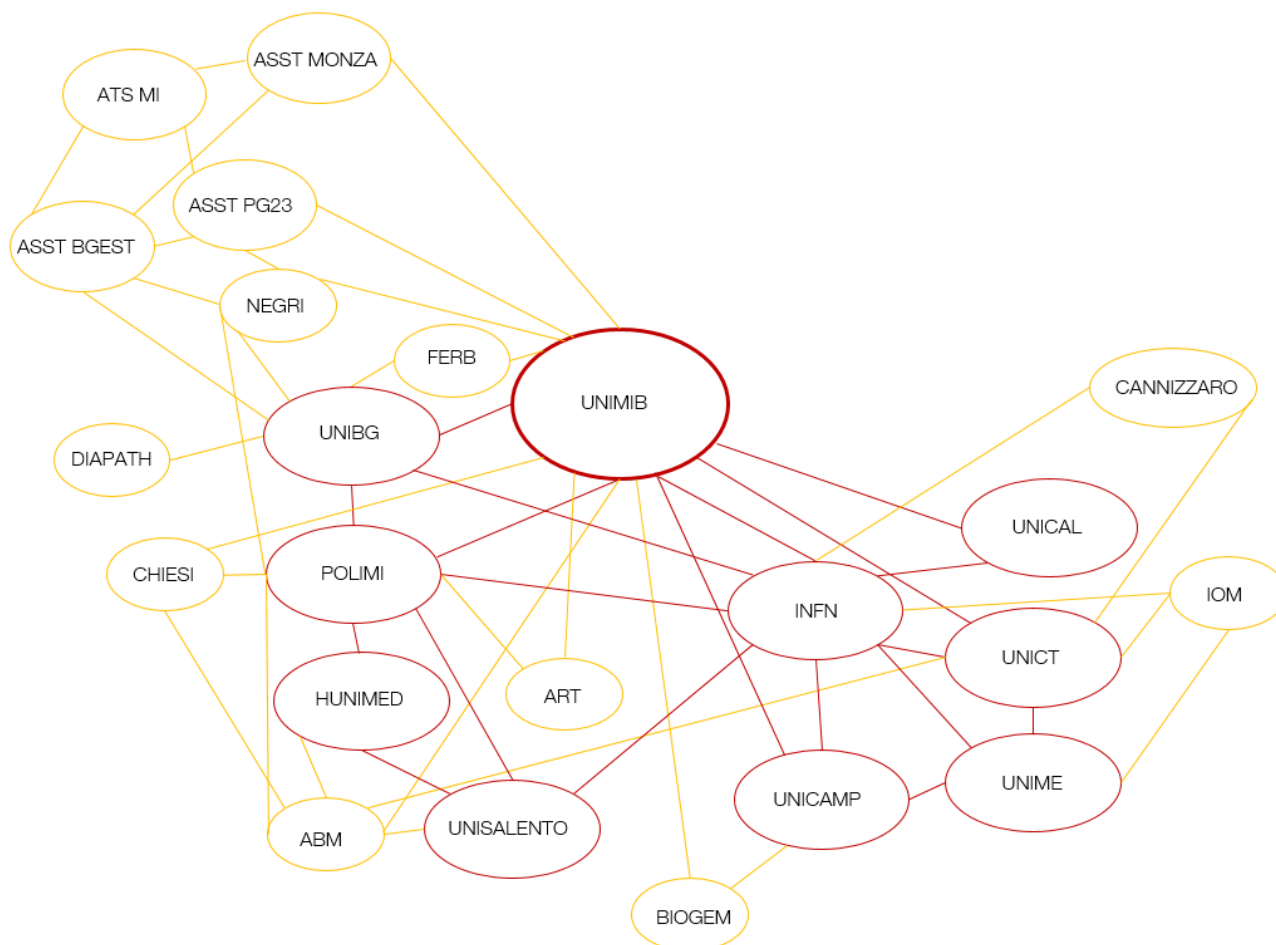


Figure 6: network of already existing main collaborations within ANTHEM

University of Milano-Bicocca (UNIMIB)

UNIMIB includes fourteen Departments, in the fields of Medicine and Surgery, Informatics, Physics, Biotechnology, Material Sciences, Educational Sciences, Economics, Business Administration and Management, Law, Mathematics, Psychology and Sociology. **Interdepartmental platforms and facilities.** Microscopy Platform, *in vivo* Imaging Platform, Mass Spectrometry and *-omics* technologies platform, Plasma Prometeo, Biotechnium, Unidata Center, Eurocold Lab. Centres of Excellence and Consortia have been created to cope with the needs of large multidisciplinary research activities and are managed according to guidelines that guarantee high scientific standards. UNIMIB has heavily invested in technologies to enhance and strengthen learning effectiveness. A Multimedial and e-Learning Centre has been constituted with the aim of developing a wide range of e-learning tools. UNIMIB also provides several research facilities to support advanced research, like super calculation and High-Performance Computing MARCONI, through an agreement with CINECA consortium (provider of the service). **Technology Transfer.** UNIMIB has 84 active patents in the areas of ICT&Web, Materials&Manufacturing, Life Science&Biotech, Agrifood, Energy&Environment, (of a total of 146 registered patents since its foundation) and 17 operating Spin Off companies. Research contracts: 168 in 2019, 132 in 2020, 142 in 2021.

Single participating groups
School of Medicine and Surgery, Dept. of Biotechnology and Biosciences, Dept. of Informatics, System and Communication, Dept. of Physics, Dept. of Materials Science, Dept. of Economics, Management and Statistics, Dept. of Statistics and Quantitative Methods.
Leading scientific activity in the last 10 years
Eight Departments were nominated as “Department of Excellence” in 2017 by the Italian Ministry of Research (MUR), including <i>PRECISION Medicine Approach: bringing biomarker research to clinic</i> , Dept of Medicine and Surgery; <i>CHRONICAL multifactorial disorders explored by NOVEL integrated Strategies</i> , Dept of Biotechnology and Biosciences; <i>ENERGIA elettrica e vettori energetici da fonti rinnovabili</i> , Dept of Material Science. In 2022, 11 Departments have been evaluated as eligible for the “Departments of excellence” grants.
Selected high impact Publications of UNIMIB over the last 5 years
<ul style="list-style-type: none"> • Perego, J., et al. Highly luminescent scintillating hetero-ligand MOF nanocrystals with engineered Stokes shift for photonic applications. (2022) Nature Communications, 13 (1), 3504. • Vellano, C.P., et al. Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy (2022) Nature, 606 (7915), 797-803. • Colombo, N., et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer (2021) New England Journal of Medicine, 385 (20), 1856-1867. • Pirastu, N., et al. Genetic analyses identify widespread sex-differential participation bias (2021) Nature Genetics, 53 (5), 663-671. • Rajewsky, N., et al. LifeTime and improving European healthcare through cell-based interceptive medicine. (2020) Nature, 587 (7834), 377-386. • Abbafati, C., et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study (2020) The Lancet, 396 (10258), 1204-1222. • Bouzin, M., et al. Photo-activated raster scanning thermal imaging at sub-diffraction resolution (2019) Nature Communications, 10 (1), 5523. • Vian, E., et al. Spectroscopic identification of r-process nucleosynthesis in a double neutron-star merger. (2017) Nature, 551 (7678), 67-70. • Böhm, M., et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials (2017) The Lancet, 389 (10085), 2226-2237. • Chan, L.N., et al. Metabolic gatekeeper function of B-lymphoid transcription factors (2017) Nature, 542 (7642), 479-483
Ability to manage and implement excellent projects
UNIMIB has been granted and managed 102 projects under Horizon 2020 and more than 500 national and 60 regional projects over the last 10 years. Selected projects:
<ul style="list-style-type: none"> • TWIST project (Training With Stakeholders – applying EU drug and addiction research). 2.012.000 € • EU-VIORMED -European Study on Risk Factors for Violence in Mental Disorder and Forensic Care: a multicentre project. 2.012.000 € • H2020-ITN-2019-DoSSIER: Domain Specific Systems for Information Extraction and Retrieval 904,185 € • H2020-NMBP-15-2017-GA-760986. iNanoBIT. Integration of Nano- and Biotechnology for beta-cell and islet Transplantation. 6.999.997 € • H2020-FET-GA-964481. IN2SIGHT: An in vivo bioengineered chip as a smart intravital multiphoton imaging Window for new validation protocols of biomaterials. 3.438.959 €. • MUR-IVASCOMAR. Identificazione, validazione e sviluppo commerciale di nuovi biomarcatori diagnostici e prognostici per malattie complessi 770.400 € • Multi-center Translational Trial of Remote Ischemic Conditioning in Acute Ischemic Stroke (TRICS). A collaborative study from the Italian Stroke Organisation (ISO) Basic Science Network. 331.661 € • VESPA study: Vortioxetine in the Elderly vs. SSRIs: a Pragmatic Assessment 627.000 € • Regione Lombardia FES-POR-ImmunHUB: Sviluppo di nuove molecole di seconda generazione per immunoterapia oncologica 624.577 € • UNICA4EU - Towards an UNIQUE approach for artificial intelligence data-driven solutions to fight Childhood cAnceR FOR EUROPE 1.733.668 €.
National and international collaborations
UNIMIB is institutional partner in the ESFRI Research Infrastructures, being part in and collaborating with a total

of 9 ESFRI RIs (BBMRI-ERIC, Elixir, IBISBA, ISBE, MIRRI, EuroBioImaging-ERIC for the Health & Food ESFRI area; LifeWatch-ERIC for the Environment area; CESSDA-ERIC for the Social & Cultural Innovation area; ESS-ERIC for Physical sciences & Engineering). The University also relies on several international agreements in all its disciplines and a solid visiting professor's programme. UNIMIB is a partner of ECRIN - The European Clinical Research Infrastructure Network. ItaCRIN, the national network, provides various support services (pharmacovigilance, monitoring and data management). Multiple Academic and Industrial Collaboration in clinical, diagnostic and therapeutic fields are indicated in the attached CVs.

UNIMIB also has ongoing collaborations with ANTHEM partners, e.g. with UNICAL on the STAR facility, a powerful X-Ray source of novel conception presently under construction, with UNIBG in the University4Innovation Foundation, with POLIMI on the Innovation Ecosystem MUSA (funded under Mission 4 of the NRPP), as well as common programmes with ASST MONZA.

Collaborations with other partners of ANTHEM

UNIMIB - UNIBG: Clinical decision support system and data management. Deep learning for signal and biomedical image processing. Causal models for statistical inference. Natural Language Processing for data mining and extraction. Bioartificial pancreas. Wearable devices for remote monitoring of chronic and frail patients. Joint Graduate Training Program - School of Medicine and Surgery (SMS)

UNIMIB - POLIMI: Digital Health and Therapeutic adherence. Technological platforms for the study and improvement of workers' safety and wellbeing (MUSA - (National Recovery and Resilience Plan (PNRR) Project). Amperometric sensors, L-NESS (Epitaxial nanostructures on Silicon and Spintronics) (<https://lness.como.polimi.it/index.php>). 3D devices and microfluidic platforms.

UNIMIB - HUNIMED: Medical devices with antibacterials and antiadhesive properties. Virgilio Program - Training Program in biomedical research for students of medicine and surgery.

UNIMIB - UNICAL - INFN: X-Ray Star Facility

UNIMIB-INFN: Agreement for the activation of the PhD programme in Physics; agreement for the management of the cryogenics laboratory; 3D Digital Pathology

UNIMIB- UNICAL-UNICT: Innovative technology for minimally invasive sampling (FISR 2019-04543)

UNIMIB - NEGRI: Neurological disorders diagnosis and therapy. Theranostic nanoformulation for neurological disorders (i.e. EU NAD Large Project).

UNIMIB-UNIBG-DIA: 1) Investigation with X-ray microCT about the thermofluids dynamical processes in a histologic sample; 2) Mathematical and numerical modelling of biological systems.

UNIMIB - CHIESI: proteomic characterization for lung chronic pathologies diagnosis.

UNIMIB - ASST MONZA: Joint Training and Specialization Courses in Medicine and Surgery. Joint Translational Research in chronic and frail diseases (i.e. excellence centres and multi on neurological diseases, endocrine diseases, cancer diseases)

UNIMIB - ASST BGEST: 3D Digital Pathology

UNIMIB - ATS MI: ATS is involved in the Residency Program in Biostatistic and Medical Epidemiology

UNIMIB - ABM: various projects funded by Lombardia Region on tele-rehabilitation, including Ability, ReAbility and SideraB.

UNIMIB-UNICT: PON Ricerca e Innovazione 2014-2020, Asse II - Progetti Tematici, Azione 2 - Cluster Tecnologici: Avviso D.D. 1735 del 13 luglio 2017 per la presentazione di progetti di ricerca industriale e di sviluppo sperimentale nelle 12 Aree di specializzazione individuate dal PNR 2015-2020.

UNIMIB - ART: innovative sterilisation methodologies and antibacterial method

UNIMIB - ASST MONZA: Grant Fondazione Cariplo 2021 "Networking, ricerca e formazione sulla sindrome post COVID" (Networking, research and training on post COVID syndrome), funded project: "The Post-Covid-19 Syndrome: network building and innovative management to address a new public health emergency"

UNIMIB - FERB - : Framework Collaboration for activities in the disability motor, cognitive and behavioral sector.

Educational activities including the activation of research doctorates

MSc and BSc Courses: UNIMIB has active MSc and BSc courses strongly related to the ANTHEM project aims, including a newly established course in Artificial Intelligence for Science and Technology, Medicine and Surgery, Material Science, Physics, Chemistry, Biotechnology and Biological Science.

PhD programs: Multidisciplinary PhD programs includes PhD in Medical Area (Translational Medicine – DIMET, Neuroscience, Public Health), Computer Science, Material Science and Nanotechnology, Physics and Astronomy, Converging Technologies for Biomolecular Systems (TeCSBI), Chemical, Geological and Environmental Sciences, Economics, Statistics and Data Science, National PhD in Artificial Intelligence, National PhD in Robotics and Intelligent Machines and National PhD in Blockchain and Distributed Ledger Technology.

Transversal skills courses and initiatives: Students and early-stage researcher at UNIMIB take advantage of

programs and courses devoted to the development of transversal skills i.e iBicocca (program on innovation, management and entrepreneurship); Bbtween (program on soft skills); Grant writing courses (Starting a Grant proposal: from idea to practice (GPIP); GSS - Grant Starter School); Jemib (Junior enterprises UNIMIB). The PhD school offers mandatory courses on open data and open science, ethics in research, IPR management.

International bibliometric indicators and qualification of the Proposal coordinator

Proposal coordinator: Guido Cavaletti. SCOPUS ID: 7004360275, ORCID ID: 0000-0003-4128-2406.

372 Papers (PubMed). 6 Book Chapters. H index 66 (Scopus) - Citations 14.960 (Scopus)

The Proposal coordinator's outstanding experience in the clinical field is deemed essential for the successful translation of technological solutions for health in real-world scenarios. In addition, the Proposal coordinator led and participated in several research activities focused on technology for health, including:

- NanoCosPha: Technological update of research laboratories to favour academic/industrial collaboration (PI, funded by Regione Lombardia, 2 M€)
- Radiation-enhanced metal-based chemotherapy in the treatment of solid tumors (PI, funded by AIRC, 280 k€)
- Research contract for the assessment of the efficacy and tolerability of nanoformulated silica-based carriers for cancer treatment (PI, Nanosilical, 400 k€)
- ImmunHub: Private/public research program aimed at improving cancer treatment using nanocarrier (Team leader, funded by Regione Lombardia, 1,2 M€)
- NEDD: Development of new drugs through an in-silico approach (Team leader, funded by Regione Lombardia, 2,5 M€)
- Successful application for several radiation-based projects on highly-competitive basis at the European Synchrotron Radiation Facility (ESRF) as PI and Team leader
- Delta-2-Tubulin As A Biomarker And Therapeutic Target For Peripheral Neuropathy (Patent, WO2019108835A1)
- Methods And Materials For Treating Neurotoxicity (Patent, WO2021067697A1)

Guido Cavaletti serves as member of the Scientific Advisory Board for ESRF (for the selection of radiation-based and award of ID17 beamtime on highly-competitive basis), Algo Therapeutics (concerning the development of new topical formulations for improved drug delivery) and Voluntis (for the development of new applications by empowering patients and their care team with personalised, algorithms-based digital therapeutics). Finally, Guido Cavaletti is Vice-Rector of Research at UNIMIB since 2019.

UNIMIB qualification: 55 UNIMIB researchers (among them the proposal coordinator) are listed among the World Top 2% 2021, produced by Stanford University.

At the last National Assessment of the Research Quality (VQR), 62,6% of the publication in the Medical area, 81% in the Physics and Informatics area, and 91% in the Chemistry and Material Sciences area were ranked as "excellent with high impact (A)" or "excellent (B)".

University of Bergamo (UNIBG)

Established in 1968, the UNIBG currently has about 24.000 enrolled students, about 450 professors and faculty members, and about another 450 research staff members. The administration staff involves about 300 persons. The research activity is carried on by 8 Departments, with a School of Economics and a School of Engineering. UNIBG has a complete and large training offer, involving 17 Bachelor's degree courses and 25 Master's degree programs, with 10 Masters taught in English. UNIBG and UNIMIB offer a joint Master's degree course in Medicine and Surgery in partnership with the Medical School of the University of Surrey. The educational offer is complemented by a Doctoral School with 7 PhD programs involving about 230 students. Moreover, UNIBG has more than 240 student exchange agreements in more than 50 nations with about 700 incoming/outgoing students every year and about 1.700 students are enrolled from abroad, confirming the international vocation of UNIBG. The international educational offer is completed by 8 double-degree programs. The training offer also includes 17 postgraduate Master's programs specifically designed for professional workers continuous training. In the last 10 years, UNIBG participated in 32 PRIN projects (National Relevant Projects), 26 international research projects (12 under H2020) and coordinated 5 large international research initiatives.

Technology transfer. UNIBG strongly contributes to the cultural, social and economic progress of the territory, with an effective TT Office and 7 Competence Centres which provide services and support to companies that want to innovate their businesses. One of these, the "Human factors and Technology in Healthcare (HTH)" is devoted to technology transfer in healthcare. The main goal is to support companies and public institutions in the territory for the realisation of projects with a high content of technology and also organisational innovation. Every

year UNIBG establishes about 40 new projects in cooperation with private companies in many different areas of research. UNIBG has 39 patents, 12 spin-off companies (created by students, professors and researchers) and has promoted 32 start-up companies. Promoting entrepreneurial culture is an important mission of UNIBG: to stimulate the generation of innovative ideas and support aspiring entrepreneurs, curricular and extra-curricular training courses are periodically organised also in collaboration with associations and local authorities, such as the Health Contamination Lab (HC.Lab) created to stimulate new business ideas in healthcare industry through an entrepreneurial training program. UNIBG and UNIMIB are co-founder of the “Foundation University for Innovation (U4I)” with the goal of promoting the transfer of science and technology research into market-bound initiatives. UNIBG has recently started an international technology transfer roadmap. The first step is the China-Italy Technology Transfer Centre (CITTC), a “platform” to boost cooperation and coordination of research centres, universities, public bodies and industry to promote bilateral technology transfer and the China-Italy joint Lab on Advanced Manufacturing (CILAM), established in 2017 with Tsinghua University.

Single participating groups

Biomedical Engineering, Computer Engineering, Data Science and Control System Engineering, Management Engineering, Social Sciences, Thermal Physics

Leading scientific activity in the last 10 years

UNIBG has promoted a number of research and project proposals in public-private partnership in many areas (Medical Imaging, Decision Support Systems for diagnostic, 3D Modelling and Simulation, Virtual and Augmented Reality, Sensors, Medical Devices and Artificial Organs, Telemedicine and Medical Software, Bioinformatics) creating solid partnerships with primary medical research institutions in Italy (Istituto Mario Negri, Humanitas and many others) and abroad (Centro Hospitalar de Trás os Montes e Alto Douro, University of Toronto and many others) and developing joint clinical research with the local hospitals (ASST PG23, ASST BGEST, FERB). The creation of the new SLIM (Smart Living in Manufacturing) laboratory, specifically designed to finalise research and technology transfer activities realising demonstrators and pilot studies for the development and application in industry of technologies to monitor and enhance the health status and wellness of industry workers. The laboratory also contains a smart environment to test assistive technologies for the disabled and people with movement limitations. In addition, an X-ray microCT facility has been active for over 10 years, specifically developed for scans in radiolucent biological materials and various collaborations have used this technique for medical analysis. This laboratory is part of a framework agreement for scientific collaborations with the Italian national ELETTRA synchrotron in Trieste.

Ability to manage and implement excellent projects

In the last 10 years, UNIBG has been involved as a leader or participant in more than 150 initiatives at the regional, national and international level. UNIBG has experience as coordinator of large research projects (>10 M€) both at national and international level and has developed the ability to manage coordination with various actors, cooperating effectively and efficiently to jointly achieve specific objectives. In addition, the university has developed different management and innovation skills by participating personally in national and/or European projects both as part of the partnership and as a coordinator. Recent research programs in the application of technology and engineering in healthcare are:

Regional: SMARTLIVING - alarm systems for newborns health monitoring; MIRATO - targeted support for patients discharged after hospitalisation for coronavirus infection and comorbidity; TELECOVID - telemedicine platform for Sars-coV2 infected patients; QuAMeSS- Quality Assurance of medical software systems. **National:** SMART AGING - data-driven service design for the prolongation of active life and the improvement of the well-being and prevention in the elderly population; BODY-SCAN - integrated solutions for virtual prototyping and ICT techniques for the acquisition and modelling of the human body and movement analysis. I4BIO-I4BIO2-I4BIO3 - medical imaging 3D reconstruction systems for Computational Fluid Dynamics. **International:** MIDAS - Motion-Intention-Driven Adaptive Stimulator for stroke rehabilitation; PREPACARE(XR) - Digital twins for healthcare training by combining e-resources and cross-border practices.

National and international collaborations

Main collaborations on technology in healthcare:

- TU-Berlin, Fachgebiet Regelungssysteme, DE, in the rehabilitation engineering area
- University of Stuttgart, DE, X-ray microCT research projects in biological porous media and multiphase fluids
- CONICET - Universidad Nacional del Litoral, AR, in artificial pancreas research
- Universidad Nacional de Colombia, Facultad de Minas, CO in artificial pancreas research
- University of Toronto, CA, Computational fluid dynamics of cerebral aneurisms

- Eindhoven Technical University, NL, Theoretical models of vascular access hemodynamics.
- Centro Hospitalar de Trás os Montes e Alto Douro, Vila Real, PT, XR for medical training
- Braude College of Engineering, Karmiel, IL, AI, CAD, Digital Human Modelling, XR
- UAS Technikum Wien, AT, XR for medical training
- Lapland University of Applied Sciences, FI, XR for medical training
- Mediclinics, IT, for the development of telemedicine systems
- ST-microelectronics, IT, in the research area of wearable sensors

Collaborations with ANTHEM participants

In addition to stable agreements both with ASST PG23 and ASST BGEST for the development of research and educational activities, research collaborations have been carried on with ANTHEM partners, e.g.:

- FERB, ASST BGEST: Concept study of the MyTravelCare platform, a support to foreign travellers in Italy.
- ASST BGEST: Telemedicine technologies and process management.
- DIA, UNIMIB: 1) Investigation with X-ray microCT about the thermofluids dynamical processes in a histologic sample; 2) Mathematical and numerical modelling of biological systems.
- NEGRI: Modelling and computational fluid dynamics, AI-based Medical imaging
- ASST PG23: 1) Artificial intelligence algorithms for the development of critical care evaluation of AKI; 2) Development of a no-SQL database for the management of genetic data and effective diagnosis of rare diseases; 3) Data-driven design of MPC controller for artificial pancreas; 4) XR for tele-rehabilitation.

UNIBG - UNIMIB: Clinical decision support system and data management. Deep learning for signal and biomedical image processing. Causal models for statistical inference. Natural Language Processing for data mining and extraction. Bioartificial pancreas. Wearable devices for remote monitoring of chronic and frail patients. Joint Graduate Training Program - School of Medicine and Surgery (SMS), University 4 Innovation (U4I) - Foundation focussed on technology Transfer Activities

UNIBG - UNICAL: 3D Digital Histology

UNIBG - POLIMI: Imaging and diagnostic for chronic diseases (lung). 3D in vitro advanced systems to mimic organs and tissues. Biomechanical characterization of arteriovenous fistulas.

UNIBG - HUNIMED: Wearable devices for remote monitoring of chronic and frail patients.

UNIBG - NEGRI: Clinical decision support system and data management. AI-based tools for genomic diagnosis for precision medicine. AI-based medical imaging analysis. Computational Fluid Dynamics for vessel stress modeling

UNIBG - FERB: Digital health e data analytics. Digital triage. Wearable devices for remote monitoring of chronic and frail patients

UNIBG - ASST PG23: Clinical decision support system and data management. AI-based artificial Pancreas and endocrinological therapies. AI-based tools for genomic diagnosis for precision medicine. Remote physical therapy and telemedicine

UNIBG - ASST BGEST: AI-based tools for genomic diagnosis for precision medicine. AI-based tools for genomic diagnosis for precision medicine. 3D Digital Histology. GBM Diagnosis. Digital health e data analytics. Digital triage. Remote physical therapy and telemedicine Wearable devices for remote monitoring of chronic and frail patients

UNIBG - INFN: 3D Digital Histology, Agreement for the Italian participation in the GASP: General AntiParticle Spectrometer

UNIBG - DIA: 3D Digital Histology

Educational activities including the activation of research doctorates

Relevant activities include: BSc in Engineering of the technologies for healthcare; MSc in Engineering and Management for Health, taught in English; Summer School in Applied Health Econometrics and Health Policy; PhD projects at UNIBG in collaboration with NEGRI on development of medical imaging techniques for effective and rapid diagnosis and in modelling of kidney circulation and vein stresses; Professional Master in Management of Hospitals and in Coordination and organisation of hospital and local services.

International bibliometric indicators

For lead researchers participating in ANTHEM, H-index/number of publications/number of citations are reported (source: Scopus): Paolo Cazzaniga (20/88/1.191); Matteo Kalchschmidt (22/48/1.582); Antonio Ferramosca (17/81/1.101); Fabio Previdi (18/146/1.231); Andrea Remuzzi (58/226/13.403); Caterina Rizzi (17/122/996); Maurizio Santini (13/30/595).

University of Catania (UNICT)

Founded in 1434, UNICT is the oldest university in Sicilia. Currently it counts more than 42.000 students, 1.034 professors, 216 researchers and 1.125 administrative staff. UNICT educational system is run and overseen by 17 Departments, a Medical School and 2 other educational units, respectively located in the city of Ragusa - as far as Modern Languages are concerned - and in Syracuse for the School of Architecture. Another special unit is the Scuola Superiore di Catania, a higher education centre based on excellence that was founded in 1998 for the selection and the recognition of the brightest young minds, offering a variety of studies including analysis, research and experimentation. The Scuola has its own laboratories and invests in industrial research in collaboration with many firms of the "Etna Valley". It offers innovative courses at the highest level: pre-undergraduate additional teaching, Masters, Advanced Post-graduate and Ph.D. courses. UNICT governance is made up of a Rector, an academic senate, a board of directors and auditors, an evaluation body and a director general as an integral part of its own decision-making policies. The Central Administration is made up of 12 Administrative Divisions, each of them deals with a particular sphere of activity and is internally split into various organisational units (sectors, services, offices) in charge of particular tasks. The Research Division is organised to provide professors and researchers with the necessary support to carry out their scientific activities. It is made up of several specific units which offer administrative, organisational and managerial assistance throughout the life cycle of research projects. It works closely also with all other administrative offices involved in the management of the research projects both at central and departmental level. The University of Catania carries out its research activities both in departments and in research centres. Departments promote, coordinate and manage the research activities and they are in charge of relations with external institutions, favouring the transfer of knowledge. Research centres are set up to manage scientific initiatives for which the cooperation of professors coming from several departments is required. Noteworthy are the Services Centre for Research and Innovation in Bio and Nanotechnology and Centre for Advanced Preclinical *in vivo* Research. The Centres were set up with the ambitious mission of using high-end scientific equipment of great complexity, providing a highly qualified interdisciplinary service available to the departments of the University of Catania and Italian public and private bodies, promoting Bio- and Nanotechnological research as well as advanced *in vivo* imaging activities developed at the University. The Centres have various advanced platforms oriented for synergistic research. They are equipped with specialised technical staff and have administrative autonomy.

Technology Transfer. The UNICT TT Office aims to create new initiatives for supporting applied research and patenting with the goal of promoting entrepreneurship and innovation within UNICT as well as with the involvement of both large and SME. A non-exhaustive list of the main actions of the Office includes:

- The institution of vouchers to financially support research groups proposing patents or, in any case, the protection of intellectual property for innovative technologies.
- The development of innovative educational programs aimed to promote the knowledge of IP, patents, academic entrepreneurship between PhD students and young researchers. Academic, graduate & student entrepreneurship programs will also be set up to encourage the genesis of innovative, possibly multi-disciplinary, start-up and spin-off;
- A strong scouting action in the Departments and Research Centres to identify the most innovative and promising technologies to progress from low (2-3) to a high TRL (6-7) that allows at least the POC ;
- A continuous networking between all the subjects involved in applied research to enhance the excellence already present and to stimulate new ones also through the development of patents co-developed with large companies as well as with SMEs;
- Set up dedicated spaces for co-working, incubation and acceleration within UniCT and its Departments, physical spaces to synthesise technology transfer, patenting and new entrepreneurship for valorization and exploitation of the results of scientific research, also with the involvement of students.

Single participating groups

The 16 researchers involved are active in the Dept. of Biomedical and Biotechnological Sciences, Dept. of Drug and Health Science, Dept. of General Surgery and Medical-Surgical Specialties, Dept. of Medical, Surgical Sciences and Advanced Technologies, Dept. of Physics and Astronomy, and in the Medical School.

Leading scientific activity in the last 10 years

Selected publications:

- Longhitano al. Lactate modulates microglia polarization via IGF1R expression and remodels tumor microenvironment in GBM. **Cancer Immunol Immunother** 2022.
- Longhitano et al. Lactate Induces the Expressions of MCT1 and HCAR1 to Promote Tumor Growth and Progression in Glioblastoma. **Front Oncol.** 2022; 12:871798.

- Cinotti et al. The integration of dermoscopy and reflectance confocal microscopy improves the diagnosis of lentigo maligna. **J Eur Acad Dermatol Venereol**. 2019;33(10): e372-e374.
- Castello et al. A robust and versatile platform for image scanning microscopy enabling super-resolution FLIM. **Nat Methods**. 2019;16(2):175-178.
- Vai et al. Proton Radiation Therapy for Nasopharyngeal Cancer Patients: Dosimetric and NTCP Evaluation Supporting Clinical Decision. **Cancers** (Basel). 2022;14(5):1109.
- Tirrò et al. A Custom DNA-Based NGS Panel for the Molecular Characterization of Patients With Diffuse Gliomas: Diagnostic and Therapeutic Applications. **Front Oncol**. 2022; 12:861078.
- Giallongo et al. CXCL12/CXCR4 axis supports mitochondrial trafficking in tumor myeloma microenvironment. **Oncogenesis**. 2022;11(1):6.
- Camiolo et al. Iron regulates myeloma cell/macrophage interaction and drives resistance to bortezomib. **Redox Biol**. 2020; 36:101611.
- Giallongo et al. TLR4 signaling drives mesenchymal stromal cells commitment to promote tumor microenvironment transformation in multiple myeloma [published correction appears in Cell Death Dis. 2019 Oct 28;10(11):820]. **Cell Death Dis**. 2019;10(10):704.
- Castruccio Castracani et al. Heme Oxygenase-1 and Carbon Monoxide Regulate Growth and Progression in Glioblastoma Cells. **Mol Neurobiol**. 2020;57(5):2436-2446.

Ability to manage and implement excellent projects

UNICT has a long experience of participation, both as coordinator and partner, to international, European and Italian projects since the end of 90's. UNICT is involved in many projects funded by Horizon 2020, Horizon Europe and other Italian and European research and training programs in all scientific fields (e.g. ERA-NET actions, INTERREG programmes, LIFE+, ITALIA-MALTA projects, ENI ITALIE-TUNISIE, ERASMUS+, etc.). In the last 5 years, about 300 projects have been funded, with a total financial contribution of almost 47 M€. In addition, UNICT, INFN and CANNIZZARO are already realising a preclinical facility for ultra-flash proton therapy thanks to the BCT program funded by the Sicilia region. This facility will be upgraded for electron ultra-Flash preclinical studies in the framework of this proposal.

National and international collaborations

UNICT pays great attention to research and a remarkable part of its resources is allocated, every year, to fund research projects in all scientific fields according to merit. It also supports scientific activity of young researchers in all departments by providing, each year, about 200 research grants to young fellows. UNICT is strongly committed to implement EU policies for the development of scientific careers and, in particular, the principles of the European Charter of Researchers and the Code of conduct for recruitment. To this end, its Research Division hosts one of the 18 Italian Mobility Centres participating in the EURAXESS network, created by the European Commission to support international mobility and careers' development of researchers. UNICT has also an intensive collaboration with research organisations and enterprises of the territory, which led to the implementation of many joint projects and activities. Great attention is paid to the exploitation of research results through the management of its patents and the creation of spin-offs.

Collaborations with ANTHEM Partners

UNICT - UNIMIB - UNICAL: Innovative technology for minimally invasive sampling (FISR 2019-04543)
 UNICT - UNIMIB: PON Ricerca e Innovazione 2014-2020, Asse II - Progetti Tematici, Azione 2 - Cluster Tecnologici: Avviso D.D. 1735 del 13 luglio 2017 per la presentazione di progetti di ricerca industriale e di sviluppo sperimentale nelle 12 Aree di specializzazione individuate dal PNR 2015-2020.
 UNICT-UNISALENTO: PON Ricerca e Innovazione 2014-2020, Asse II - Progetti Tematici, Azione 2 - Cluster Tecnologici: Avviso D.D. 1735 del 13 luglio 2017 per la presentazione di progetti di ricerca industriale e di sviluppo sperimentale nelle 12 Aree di specializzazione individuate dal PNR 2015-2020. Integrated approach to tackle the interplay among adaptation, stressful conditions and antimicrobial resistance of challenging pathogens (PRIN 2017)
 UNICT - UNICAMP: project PRIN 2020 (2020LM8WNW_004) "Metabolic aspects of vascular disease: relevance for atherosclerosis development and identification of new therapeutic targets and companion biomarkers"
 UNICT - IOM - INFN: Drug Delivery for cancer. Research platform on cancer research. Joint training program for postgraduate students. "Dioncgen: diagnostica innovativa", finanziato dal programma PO FESR Sicilia 2014/2020, e del progetto "Drug Delivery, veicoli per una innovazione sostenibile" finanziato dal MIUR su fondi PON – Ricerca e Competitività 2007-2013
 UNICT- IOM-UNIME: Drug delivery and therapies. Research platform on oncological research. "Drug Delivery, veicoli per un'innovazione sostenibile" funded by the Ministry of Education, University and Research on the



programme PON – Ricerca e Competitività 2007-2013
 UNICT-INFN-UNICAMP: Project PRIN2017 “PBCT Proton Boron Capture Therapy” (2017XKWWK9)
 UNICT-CANNIZZARO: Preclinical research
 UNICT-INFN-CANNIZZARO: BCT (Breast Cancer Therapy) funded by Sicilia Region
 UNICT-INFN: Agreement for the activation of the PhD programme in Physics
 UNICT-INFN-UNIME: Memorandum of Understanding for Collaboration in the Construction, Maintenance and Operation of the ALICE Detector
 UNICT-UNIME: SAMOTHRACE foundation; Network TT of Complementary National Plan of Health Ministry.
 UNICT-POLIMI: Network on sociological italian departments (CIDAS)
 UNICT-ABM: The two partners were involved in the joint project SMART HEALTH
 UNICT-IOM: Joint training program for postgraduate students
 UNICT-BIOGEM R&S activities on biomarkers identifications and development of new diagnostic methods (Project “Identificazione di biomarcatori e sviluppo metodi diagnostici e terapeutici nel campo dell’oncologia e della biologia vascolare”, funded by MIUR PON – Ricerca e Competitività 2007-2013)

Educational activities including the activation of research doctorates

MSc and BSc Courses: UNICT has active MSc and BSc courses strongly related to the ANTHEM project aims, including a new established course in preclinical imaging and nutraceuticals in oncological research. **PhD programs:** Multidisciplinary PhD programs includes PhD in Medical Area (Translational Medicine, Neuroscience, Biotechnology)

International bibliometric indicators

For lead researchers participating in ANTHEM, H-index/number of publications/number of citations are reported: Francesco Di Raimondo (60/404/16.950); Giovanni Li Volti (47/299/7.155); Gaetano Magro (35/299/5.045); Giuseppe Micali (43/486/6.597); Giuseppe A. Palumbo (33/155/3.909); Rosario Caltabiano (33/236/3.651).

Polytechnic University of Milano (POLIMI)

POLIMI is a scientific-technological university, which trains engineers, architects and industrial designers. Founded in 1863, POLIMI is one of the most outstanding universities in the world, ranked in QS World University Ranking 2022 (June 2021) 1st in Italy and 142nd in the world. POLIMI has always focused on the quality and innovation of its teaching and research, developing a fruitful relationship with the business and productive world by means of experimental research and technological transfer. Education is at bachelor, master’s, and PhD level. Currently more than 1.400 professors and researchers work at Polimi and 47.000 students (of which 7.000 foreign students) study in 7 different campuses.

POLIMI is committed to achieving excellence in research. The path towards excellence is developed along the following actions: support advanced and fundamental research activities; develop strategic partnerships with academia and industry around the world to make significant contributions to society; develop new interdisciplinary research lines to tackle societal challenges; embed scientific developments and research results into university education. The 12 Departments are responsible for the implementation of the mission in their scientific domains: through them, the University plans to enhance its impact on society by favouring sustainable and responsible scientific and technological innovation capable of contributing to post-Covid-19 progress.

Strategic research is carried out in the fields of energy, transport, planning, management, design, mathematics and natural and applied sciences, ICT, built environment, cultural heritage, with more than 280 research facilities including 6 Large Infrastructures: the Wind Tunnel (unique in the world for configuration and features), the Materials Testing Laboratory, PoliFAB (the University’s Research infrastructure for micro and nano production), PoliFactory, the makerspace of the Politecnico di Milano where new design processes are developed, the Dynamic Driving Simulator Lab, a new generation medium-sized simulator and the LABORA (a physical and virtual modelling laboratory).

Single participating groups

The Dept. of Electronics, Information and Bioengineering participates with 10 researchers; other Departments involved are Dept. of Chemistry Materials and Chemical Engineering; Dept. of Mathematics; Dept. of Physics.

Leading scientific activity in the last 10 years

- Moccia et al. Blood vessel segmentation algorithms — Review of methods, datasets and evaluation metrics (2018) **Computer Methods and Programs in Biomedicine**, 158, 71-91.
- Protti et al. Lung stress and strain during mechanical ventilation: Any difference between statics and dynamics? (2013) **Critical Care Medicine**, 41 (4), 1046-1055.

- Cimolin and Galli. Summary measures for clinical gait analysis: A literature review (2014) **Gait and Posture**, 39 (4), 1005-1010.
- Votta et al. Toward patient-specific simulations of cardiac valves: State-of-the-art and future directions (2013) **Journal of Biomechanics**, 46 (2), 217-228.
- Laveneziana et al. ERS statement on respiratory muscle testing at rest and during exercise (2019) **European Respiratory Journal**, 53 (6), art. no. 1801214.
- Richter et al. First clinical application of a prompt gamma based in vivo proton range verification system (2016) **Radiotherapy and Oncology**, 118 (2), pp. 232-237.
- Demontiset al. Human pathophysiological adaptations to the space environment (2017) **Frontiers in Physiology**, 8 (AUG), art. no. 547.
- King et al. Technical standards for respiratory oscillometry. (2020) **European Respiratory Journal**, 55 (2), art. no. 1900753.
- Pavesi et al. A 3D microfluidic model for preclinical evaluation of TCR-engineered T cells against solid tumors (2017) **JCI Insight**, 2 (12), art. no. e89762.
- Aliverti, A. Wearable technology: Role in respiratory health and disease (2017) **Breathe**, 13 (2), e27-e36.
- Lomauro and Aliverti. Sex differences in respiratory function (2018) **Breathe**, 14 (2), pp. 131-140.
- Landry et al. Investigating CT to CBCT image registration for head and neck proton therapy as a tool for daily dose recalculation (2015) **Medical Physics**, 42 (3), art. no. 4908223.
- Frederix et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine (2019) **European Journal of Preventive Cardiology**, 26 (11), 1166-1177. Paganelli, et al. MRI-guidance for motion management in external beam radiotherapy: Current status and future challenges (2018) **Physics in Medicine and Biology**, 63 (22), art. no. 22TR03.

Ability to manage and implement excellent projects

POLIMI annually attracts about 140 M€ through research contracts and external funding. These self-financing activities account for a large part of its total budget. The University is the 1st in Italy and 11th in Europe for projects funded by the European Commission. With the Horizon 2020 Framework Programme (2014-2020), funds were granted to 437 projects (of which 34 ERC and 24 MSCA Individual Fellowships) for a total of 189 M€. So far, 58 projects (including 7 ERC and 6 MSCA Postdoctoral Fellowships) worth more than 27 M€ have been funded under the 2021-2027 Horizon Europe Programme. Furthermore, at national level, in the last 10 years POLIMI ran 146 projects funded by the Italian Ministry for Research under the National Interest Research Projects program (PRIN), 32 as coordinator, with about 19 M€ of funding. POLIMI also ran several grants financed under the Operative National Program (PON) and Operative Regional Program (POR), with a total financial contribution of more than 15 M€.

POLIMI carries out research activities with several public and private bodies. Recently, it signed important partnerships with major national and international companies. The main public partners are: Ministries, Lombardia Regional Government, Municipality of Milan, Chamber of Commerce, CNR, ASI, Enea.

National and international collaborations

At POLIMI, a high number of research project are carried out through national and international collaborations mainly in the frame of ERC (European Research Council), MSCA (Marie Skłodowska-Curie actions), European Projects, National technology clusters, Call Hub Research and Innovation, Joint Research Centre (JRC), Smart Cities and Fondazione Cariplo initiatives. Many international collaborations have been established with European and international universities in order to become capillary even out of national borders in the field of research and innovation. Besides the active cooperation in 19 EU countries, POLIMI is active in many other extra EU areas, including Asia, USA, Australia. Furthermore, POLIMI is part of wide research and education networks, such as: IDEALeage (ETH-Zurich, TU-Delft, RWTH Aachen, Chalmers University); ALLIANCE4TECH (CentraleSupélec in Paris, Technische Universität Berlin and University College London) and ENHANCE (Chalmers University of Technology, Norwegian University of Science and Technology, RWTH Aachen, TU-Berlin, Universitat Politècnica de València and Technical University of Warsaw).

POLIMI is also part of several EIT KICs (Knowledge and Innovation Communities) partnerships that bring together businesses, research centres and universities on key strategic topics: Climate; Digital; Urban

Mobility; EIT Raw materials; EIT Manufacturing

Collaborations with ANTHEM participants

POLIMI - UNIMIB: Digital Health and Therapeutic adherence. Technological platforms for the study and improvement of workers' safety and wellbeing (MUSA - (National Recovery and Resilience Plan - NRRP) Project). Amperometric sensors, L-NESS (Epitaxial nanostructures on Silicon and Spintronics)



(<https://lness.como.polimi.it/index.php>). 3D devices and microfluidic platforms. Network on sociological italian departments (CIDAS)
 POLIMI - UNIBG: Imaging and diagnostic methods for chronic diseases (lung). 3D in vitro advanced systems to mimic organs and tissues. Biomechanical characterization of arteriovenous fistulas.
 POLIMI - HUNIMED: Advanced imaging analyses in oncology. Development of diagnostic tools for lung cancer and lymphoma. Development of artificial organs, wearable devices, predictive analyses in cardiology. **MEDTEC** School (training of new professional figures capable of integrating and enhancing the typical skills of the physician with basic skills and the typical application of Biomedical Engineering).
 POLIMI - UNICT: Network on sociological italian departments (CIDAS)
 POLIMI - ABM: wearable devices for multichannel EEG. Development of software EEG evaluation during robot assisted rehabilitation.
 POLIMI - UNICAL: Agreement with Department of Mathematic and IT on surgery applied AI. POS2 Project Fa.Per.Me on the development of analytical data for personalised medicine. Cal.HUB.Ria project POS grant (Health Field - Goal 4).
 POLIMI - CHIESI: microCT imaging for diagnostic applications. Innovative systems for not-invasive drug administrations and selection of methodologies for neonatal applications.
 POLIMI-NEGRI:Lung image analysis by analytical and AI techniques in COVID-19 patients
 POLIMI-INFN: Memorandum of Understanding of the Ebrains Italian Community; Agreement on the Quantum Initiative

Educational activities including the activation of research doctorates

POLIMI offers study programmes at all levels (26 Laurea Courses, equivalent to Bachelor of Science, 44 Laurea Magistrale Courses, equivalent to Master of Science, specialising masters and postgraduate programmes, 19 Ph.D. Programmes) in Architecture, Design and Engineering. In particular, the PhD programme in Bioengineering trains graduate students through a strong interdisciplinary education in engineering methodologies and technologies to develop research on biological systems and health sciences. Methods, devices, and systems are developed with a multidisciplinary approach, from the molecular and the cellular levels to living organisms up to biomedical systems, with the purposes of improving diagnosis and therapy as well as health and daily life structures and services.
 POLIMI also organises degree programmes (both BSc and MSc) in collaboration with other universities. In particular, MEDTEC School, the new single-cycle Master's Degree course (6 years), activated by Humanitas University in agreement with the Politecnico di Milano, aims to train a new professional figure capable of integrating and enhancing the typical skills of the physician with basic skills and the typical application of Biomedical Engineering.

International bibliometric indicators

For researchers participating in ANTHEM, H-index/number of publications/number of citations are reported (source: Scopus): A. Aliverti (42/274/5.836); P. Taroni (45/313/6.071); L. Capelli (24/108/1.950); F. Ieva (13/104/757); D. Loiacono (20/72/1.010); C. Paganelli (18/57/855); R. Dellaca' (30/146/2.848); G. B. Fiore (25/137/1.814); A. Redaelli (45/316/7.269); M. Soncini (24/86/5.836); E. G. Caiani (31/241/7.846); M. Ferrario (19/91/1.373); M. G. Signorini (27/171/3.040).

Humanitas University (HUNIMED)

HUNIMED is an international higher education institution, established in 2014 and recognized by the Italian Ministry of University and Research (MUR). HUNIMED research interests focus on basic and translational research in life sciences. An essential feature of our strategy is a close, direct, bidirectional interaction between research and clinic. A major thrust in development in areas including: inflammation and immunity; cardiology; oncology and neurosciences. These areas of work represent the fingerprints of Humanitas University in a highly competitive context in which it is essential to have critical mass. In addition, complementary areas are being developed, which will stand on their own and will integrate into the existing lines. These will include imaging in its various facets; Public Health and epidemiology; genomics and epigenomics; biomaterials and their relationship to bioengineering; orthopaedics and regenerative medicine. A major effort is towards technology transfer. The mission of HUNIMED is also to train **globally-oriented medical doctors** through **state-of-the-art interactive teaching methods** and close integration with the clinical community at the Humanitas Research Hospital.

Research activities at HUNIMED are supported by cutting-edge technological units. Our students, researchers and physicians have access to an area of up to 20.000 smq. Research activities are carried out by 350 researchers and physicians (from 16 countries spanning over four continents), divided into more than 24 research groups including several prestigious, top-level groups covering many research areas: Immunology, Cardiovascular Research, Neuroscience, Oncology. The group operates in close collaboration with the hospital's 700 physicians, to facilitate

translation, i.e. the direct application of the most recent advances in healthcare through a systematic and ongoing process of innovation. A gender equality plan (GEP) has been developed and implemented. HUNIMED GEP is published on the official website of the institution (<https://www.hunimed.eu/it/organizzazione-e-governance/documenti-ufficiali-di-ateneo/>).

Scientists and researchers from 16 countries spanning over four continents are involved in studies on high impact non-communicable diseases, e.g. cancer, myocardial infarction, stroke, and autoimmune diseases.

HUNIMED provides its researchers with laboratories, fully equipped with instruments for molecular and cellular biology research, for clinical imaging and for clinical research, including a phase 1 unit. The research centre is equipped with facilities at the forefront of technological innovation, outstandingly supporting preclinical and clinical research.

Single participating groups

Medical School and MedTec School, belonging to the Department of Biomedical Sciences.

Leading scientific activity in the last 10 years

The Scientific Production of HUNIMED has constantly increased during the last 5 years. In 2021 HUNIMED published 907 manuscripts with a raw Impact Factor of more than 7,516 points. Here are some recent publications.

- TS Meyhoff et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. **New England Journal of Medicine** 386 (26).
- The Severe Covid-19 GWAS Group* Genomewide association study of severe covid-19 with respiratory failure. **New England Journal of Medicine** 383 (16).
- G Grasselli et al. Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardia Region, Italy. **Journal of the American Medical Association** 323 (16).
- E Kyriazopoulou et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. **Nature Medicine** 27 (10).
- D Clark et al. Casemix, management, and mortality of patients receiving emergency neurosurgery for traumatic brain injury in the Global Neurotrauma Outcomes Study: a prospective observational cohort study. **Lancet Neurology** 21 (5).
- S Fanti et al. Consensus on molecular imaging and theranostics in prostate cancer. **Lancet Oncology** 19 (12).
- S Aliberti et al. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. **Lancet Respiratory Medicine** 10 (3).
- G Grasselli et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. **Lancet Respiratory Medicine** 8 (12).
- A Shoemark et al. Characterization of Eosinophilic Bronchiectasis A European Multicohort Study. **American Journal of Respiratory and Critical Care Medicine** 205 (8).
- JS Smolen et al. Effectiveness of IL-12/23 inhibition (ustekinumab) versus tumour necrosis factor inhibition in psoriatic arthritis: Observational PsABio study results. **Annals of the Rheumatic Diseases** 80 (11).
- IF Hall et al. rs41291957 controls miR-143 and miR-145 expression and impacts coronary artery disease risk **EMBO Molecular Medicine** 13 (10).
- M Sollini et al. State-of-the-art of FAPI-PET imaging: a systematic review and meta-analysis. **European Journal of Nuclear Medicine and Molecular Imaging** 48 (13).
- M Kirienko et al. Radiomics and gene expression profile to characterise the disease and predict outcome in patients with lung cancer. **European Journal of Nuclear Medicine and Molecular Imaging** 48 (11)
- M Sollini et al. Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. **European Journal of Nuclear Medicine and Molecular Imaging** 48 (10).
- AR Patel et al. SCMR level II/independent practitioner training guidelines for cardiovascular magnetic resonance: integration of a virtual training environment. **Journal of Cardiovascular Magnetic Resonance** 23 (1).
- B Foldyna et al. Quality and safety of coronary computed tomography angiography at academic and non-academic sites: insights from a large European registry (ESCR MR/CT Registry). **European Radiology** 32 (8).

Ability to manage and implement excellent projects



<p>HUNIMED, with the internal Grant Office Department, manages more than 100 financed research projects (>30 M€) funded by all the major funding agencies (European Commission, MoH, Lombardia Region, Charities, etc.). Researchers involved in the proposed project have an outstanding track record.</p> <p>HUNIMED has a vast experience in managing and supervising research projects. From 2014 on, the portfolio includes more than 100 externally funded competitive research projects, 12 of which financed by EU funding programs (FP7 and H2020). Three research grants have been granted by the ERC to HUNIMED researchers. HUNIMED is also coordinator of 1 project funded by Innovative Medicines Initiative – IMI with 21 partners and a budget of 15,5 M€. HUNIMED has received funding for about 8,7 M€ from the European Community, 17,3 M€ from Charities and 2,7 M€ from Italian agencies and institutions. HUNIMED has a Technology Transfer Office, that supports and conducts the innovation process, adding value to the outstanding research developed at HUNIMED in the life science field, including biomedical, medtech and digital health. Humanitas patent portfolio comprises 18 patent families belonging to 44 patent applications and 19 granted patents covering several fields, e.g. immunology, oncology, markers for diagnosis and medical tech devices.</p>
National and international collaborations
<p>Main international collaborations include the Wuhan Renmin Hospital (CN), Western University (CA), University of Helsinki (FI), Paris Diderot University - Paris VII (FR), Haifa Technion (IL), Cooperatie Medisch Specialisten Rijnstate (NL), University of Lausanne (CH), Queen Mary University of London (UK), Vanderbilt University and University of Wisconsin (USA).</p>
Collaborations with ANTHEM participants
<p>HUNIMED-UNIMIB: Smart medical devices with antibacterial properties. Virgilio Program</p> <p>HUNIMED-UNIBG: Wearable devices for remote monitoring of chronic and frail patients.</p> <p>HUNIMED-POLIMI: Advanced imaging analyses in oncology. Development of diagnostic tools for lung cancer and lymphoma. Development of artificial organs, wearable devices, predictive analyses in cardiology. Microbiome characterization in healthy and chronic diseases. MEDTEC School (training of new professional figures capable of integrating and enhancing the typical skills of the physician with basic skills and the typical application of Biomedical Engineering).</p> <p>HUNIMED - UNISALENTO: Agreement on international strategic collaboration and technology transfer in the biomedical and social sciences. Microbiome characterization in healthy and chronic diseases.</p>
Educational activities including the activation of research doctorates
<p>HUNIMED is running 2 PhD programs: Molecular and Experimental Medicine and Data Science in Medicine and Nutrition to provide training in various fields of life sciences and molecular medicine offering a stimulating environment with access to state-of-the-art technology and clinical case lists for translational studies. Two masters are available, in Advanced Technologies in Rehabilitation and in Radioligand Therapy.</p>
International bibliometric indicators
<p>For lead researchers participating in ANTHEM, H-index/number of publications/number of citations are reported: Arturo Chiti (48/274/9.413); Maria Rescigno (68/200/33.086); Marta Scorsetti (42/316/6.691); Maurizio Cecconi (59/338/21.853); Stefano Aliberti (49/317/10.603); Carlo Selmi (67/403/14.998).</p>

University of Calabria (UNICAL)
<p>UNICAL is a public institution whose institutional mandate is to pursue research, teaching and third mission activities, contributing to the social, cultural and economic development of society. The organisational structure of the University, which recalls the provisions of Law 240/2014, is divided into a service structure, the General Management, and academic structures represented by 14 Departments, Specialisation Schools, Research and Research Centres service and several Poles. Departments are responsible for carrying out scientific research, teaching and training activities. Since 2003, UNICAL, equipped with an office in charge of Technology Transfer activities, has implemented numerous actions to strengthen credibility and relationships within the regional and national innovation network and link research activities with industrial applications and spin-off creation. UNICAL research structure includes several research teams in many scientific areas that produced a very large array of research results: the most recent data count 166 research groups, 127 laboratories, 1.500 research lines, 39 active patent families, 43 spin-offs (150 employees with high training profiles) and 1 incubator (Technest, with an area of 2.000 m²). Spin-off companies, which were created from the enhancement of research products, on average have 6 innovative products (or services) and generate an annual production value of more than 7.0 M€. UNICAL has in recent years developed a dense network of relationships with all the players in the development of the territory. Project: Tech4You - Technologies for climate change adaptation and quality of life improvement. The researchers involved in the program belong to all departments. The involved expertise includes ICT, agri-food, sustainable and</p>

renewable energy, risk assessment and management, life science, manufacturing, green energy, confirming the interdisciplinary and complementary skills. Involved participants can claim outstanding scientific track records, with highly-cited publications appearing in high-impact journals and prestigious international venues. Among the laboratories, the participation of: The Scalable Computing and Cloud Laboratory of DIMES is highlighted, which researches high-performance computing systems, cloud computing systems, Big Data analysis systems and applications, scalable and distributed systems, and The Modelling & Simulation Centre - Laboratory of Enterprise Solutions (MSC-LES) of DIMEG which aims at the acquisition and deepening of knowledge and skills in the field of Modelling and Simulation. It is worth mentioning that in the ICT sector, UNICAL holds 6 patents.

Single participating groups

The team includes researchers from the Dept. of Pharmacy, Health and Nutritional Sciences, and from the Dept. of Economics, Statistics and Finance; Environmental Engineering; Biology, Ecology and Earth Sciences.

Leading scientific activity in the last 10 years

Selected publications:

- Rigiriacciolo et al. Focal Adhesion Kinase (FAK)-Hippo/YAP transduction signaling mediates the stimulatory effects exerted by S100A8/A9-RAGE system in triple-negative breast cancer (TNBC). **J Exp Clin Cancer Res.** 2022 41(1):193.
- De Francesco et al. Triple-negative breast cancer drug resistance, durable efficacy, and cure: How advanced biological insights and emerging drug modalities could transform progress. **Expert Opin Ther Targets.** 2022.
- Scordamaglia et al. Metformin counteracts stimulatory effects induced by insulin in primary breast cancer cells. **J Transl Med.** 2022 20(1):263.
- Cirillo et al. Estrogen receptor variant ER α 46 and insulin receptor drive in primary breast cancer cells growth effects and interleukin 11 induction prompting the motility of cancer-associated fibroblasts. **Clin Transl Med.** 2021 ;11(11): e516.
- Lappano et al. The IL1 β -IL1R signaling is involved in the stimulatory effects triggered by hypoxia in breast cancer cells and cancer-associated fibroblasts (CAFs). **J Exp Clin Cancer Res.** 2020; 39(1):153.
- Cirillo et al. AHR and GPER mediate the stimulatory effects induced by 3-methylcholanthrene in breast cancer cells and cancer-associated fibroblasts (CAFs). **J Exp Clin Cancer Res.** 2019;38(1):335.
- Santolla et al. GPER Mediates a Feedforward FGF2/FGFR1 Paracrine Activation Coupling CAFs to Cancer Cells toward Breast Tumor Progression. **Cells.** 2019;8(3).
- Feng et al. A Platform of Synthetic Lethal Gene Interaction Networks Reveals that the GNAQ Uveal Melanoma Oncogene Controls the Hippo Pathway through FAK. **Cancer Cell.** 2019. pii: S1535-6108(19)30043-1.
- Rigidacciolo et al. Focal adhesion kinase (FAK) activation by estrogens involves GPER in triple-negative breast cancer cells. **J Exp Clin Cancer Res.** 2019;38(1):58.
- Lappano and Maggiolini M. G protein-coupled receptors: novel targets for drug discovery in cancer. **Nature Drug Discovery.** 2011, 10, 47-60

Ability to manage and implement excellent projects

The University is the referent of two large Infrastructural projects of national and international importance such as the MATERIA-STAR infrastructure project which opens new investigations in all fields of Materials Science and a project linked to an integrated system of laboratories and research infrastructures for the provision of scientific and technological services dedicated to the monitoring, control and protection of the environment, called SILA (Integrated System of Laboratories for the Environment).

Project activities: UNICAL has shown an impressive capability to attract regional (n. 21 POR), Italian (n. 20 PON, PRIN) and European funds (n. 9, FP7, H2020). In the last three years, the University has been the coordinator /leader of 20 EU research projects for a total amount of about 14 M€.

National and international collaborations

There are currently 251 international cooperation agreements with institutions from 54 countries. UniCal is counted among 30 Italian universities selected to participate in the world's largest Higher Education fair, NAFSA-USA.

Collaborations with ANTHEM participants

UNICAL - UNIMIB - INFN: X-Ray Star Facility, 3D Digital Pathology.

UNICAL - UNIBG: 3D Digital Pathology.

UNICAL - POLIMI: Agreement with Department of Mathematic and IT on surgery applied AI; POS2 Project Fa.Per.Me on the development of analytical data for personalised medicine; Cal.HUB.Ria project POS grant (Health Field - Goal 4).

UNICAL - UNICT - UNIMIB: Innovative technology for minimally invasive sampling (FISR 2019-04543) UNICAL - INFN: Star-2 Infrastructure
Educational activities including the activation of research doctorates
There are currently 12 PhD Courses (including: Translational Medicine, Mathematics and Computer Science, Life Science and Technologies, Information and Communication Technologies, Physical, Chemical and Materials Sciences and Technologies) and 13 Master Degrees.
International bibliometric indicators
For each team member, H-index/number of publications/number of citations are reported: Marcello Maggiolini: (56/192/10.400); Vincenzo Pezzi (41/115/4.770); Luigi Pasqua: (22/51/1.175); Antonella Leggio (24/86/1.625); Catia Morelli (24/57/1.801); Michele Galluccio (27/63/2.421); Sabrina Giordano (9/22/215).

University of Campania “Luigi Vanvitelli” (UNICAMP)
<p>UNICAMP was established in 1991 and counts nearly 30.000 students with 16 departments located in 5 territorial areas (Aversa, Caserta, Santa Maria Capua Vetere, Capua and Napoli) and a teaching staff of about 1.000 professors and researchers. The University supports quality research, favours the start of new business initiatives born from research groups, in a constant perspective of multi-disciplinarity, internationalisation and cultural exchange with other universities and research institutions. It has invested significant resources for research enhancement with programs dedicated to basic and applied research and the transfer of technological innovation to the economic and social system, helping to meet the development needs of society through its scientific and professional skills. From 2014 to 2020, the UNICAMP has adopted a self-financing research program for a total value of 41 M€. Currently, UNICAMP ranks 19th among all 63 Italian state universities for the quantity and quality of research and has been quoted for QS world ranking universities. The University encourages international access to its research and training activities also through international degrees. In 2020, UNICAMP joined the Advanced School of Public Health, Epidemiology and Biostatistics (SPES), with the goal of creating an integrated system ensuring the training of highly skilled professionals. The University has activated a Gender Equality Plan.</p> <p>Through technology transfer, UNICAMP pays particular attention to the development of the territory through many investments, the activation of agreements and Job placements, patents, Spin-Offs (counting 14 operating companies). UNICAMP has also contributed to the genesis of some important Technological Districts in Campania including: Smart Power System High Technology District in Campania, Campania Aerospace Technological District (DAC S.c.ar.l.), Campania BioScienceS.C.a.R.L. and High Technology District for Cultural Heritage S.c.ar.l."(DATABENC S.c.ar.l.). The patent portfolio of UNICAMP consists of 23 already approved patents and 9 submitted patent requests. Among the approved patents UNICAMP includes 6 international patents (1 related to Medicine) , 4 new patents related to Medicine (Question no. 102020000031991 (IT), title "Prevention of cellular senescence in conditions of stress"; Question no. 102020000029084 (IT), title "Portable vessel scanner"; Question no. 202021000001052 (IT), title "Full suit"; Question no. 102021000014054 (IT), title "Orthopaedic bust"; Question no. 102021000015755 (IT), title "Nanoparticles and their uses"). Another service in the area of Relations with the Production and Territory is that of the University Job Placement which, in addition to managing the procedures relating to the activation of non-curricular internships, supports graduates, for the purpose of entering the world of work, with training tools and moments of confrontation with companies useful for building one's professional identity and planning one's career; It also offers companies and institutions multiple services aimed at encouraging innovation and the intersection of demand and supply of work.</p>
Single participating groups
UNICAMP participates with the Dept. of Advanced Medical and Surgical Sciences, Dept of Precision Medicine and Dept of Mathematics and Physics. Overall, 15 researchers with proven expertise in the different aspects of cell biology, radiobiology and radiology and cancer biology, and clinical cancer.
Leading scientific activity in the last 10 years
<p>Selected publications:</p> <ul style="list-style-type: none"> • Del Gaudio et al. CBX2 shapes chromatin accessibility promoting AML via p38 MAPK signaling pathway. Mol Cancer. 2022;21(1):125. • Carafa et al. RIP1-HAT1-SIRT Complex Identification and Targeting in Treatment and Prevention of Cancer. Clin Cancer Res. 2018 ;24(12):2886-2900. • Martinelli et al. Cetuximab Rechallenge Plus Avelumab in Pretreated Patients With RAS Wild-type Metastatic Colorectal Cancer: The Phase 2 Single-Arm Clinical CAVE Trial. JAMA Oncol. 2021;7(10):1529-1535. • Derby et al. Griffithsin carrageenan fast dissolving inserts prevent SHIV HSV-2 and HPV infections in

<p>vivo. Nature Comm. 2018;9(1):3881.</p> <ul style="list-style-type: none"> • Macedo-Silva et al. Epigenetic mechanisms underlying prostate cancer radioresistance. <i>Clin Epigenetics.</i> 2021;13(1):125. • Sardu et al. Pre-Menopausal Breast Fat Density Might Predict MACE During 10 Years of Follow-Up: The BRECARD Study. JACC Cardiovasc Imaging. 2021;14(2):426-438. • Andreuzzi et al. Colorectal cancer development is affected by the ECM molecule EMILIN-2 hinging on macrophage polarization via the TLR-4/MyD88 pathway. J Exp Clin Cancer Res. 2022;41(1):60. • Fogli et al. The expanding family of c-Met inhibitors in solid tumors: a comparative analysis of their pharmacologic and clinical differences. Crit Rev Oncol Hematol. 2022; 172:103602. • Steenstrup et al. Telomeres and the natural lifespan limit in humans. Ageing (Albany NY). 2017 ;9(4):1130-1142.
Ability to manage and implement excellent projects
<p>The promotion of financing and planning opportunities concerns also managed European funds, such as Horizon 2020, FP7 – MidFrail Project-, thematic programs such as Life, but also the so-called mixed funds, as they are jointly managed by the national authorities and the European Commission (e.g.: ERANET). Numerous projects currently active have been financed under the National Operational Plan (PON) on the ministerial announcement PRIN (Research Projects of Relevant National Interest) and on the Regional Operational Program POR / FSE 2014-2020. Starting from 2017, the University has launched the VALERE PROGRAM (ADVANTAGES FOR RESEARCH)</p>
National and international collaborations
<p>The University maintains collaborative relationships with: Okan University - Istanbul; Pyatigorsk University (Center for Russian Language and Culture “A.S. Pushkin”); Université des Sciences Humaine et Sociales 3 de Lille; Institut Galilée de l’Université de Paris 3; Beijing Institute of Fashion and Technology Shanghai East China Normal University; Universidad de JAEN; Universidad de Castilla; La Mancha Universidade Municipal de Sao Caetano do Sul. Since 2010 more than 450 Visiting Professors have been involved in teaching and research activities. The University “L. Vanvitelli” is member of 7 International Networks and Joint-Undertaking: NETVAL; PNI CUBE; C.R.U.I. Foundation; A.P.R.E.; SVIMEZ; R.U.I.A.P.; CINI. Moreover, the university is part of 7 Knowledge Innovation Communities (KIC): Netval (Netval Research Universities Network); Knowledgeshare; Techshare; TRANSDAIRY; IFKAD (International Forum on Knowledge Asset Dynamics); Research & Entrepreneurship Foundation; Research Exchange.</p>
Collaborations with ANTHEM participants
<p>UNICAMP-INFN-: Proton Boron Fusion Therapy, boron concentration measurements in biological samples (PBFT - Project NEPTUNE) UNICAMP-BIOGEM: Tumour diagnosis and characterization. UNICAMP - UNIME: Regulation of autophagy by N-acylethanolamines as a promising approach for the treatment of inflammatory-based diseases: from neurodegeneration to metabolic disorders. 2020 -2023 (PRIN- code 2020SEMP22) UNICAMP-BIOGEM: CONNECT CA19127 “Cognitive decline in Nephro-Neurology: European Cooperative Target” of the COST Action; iCURE project (Identification, characterization and significance of colorectal tumorigenesis: cause, prevention and cure) POR CAMPANIA FESR 2014/2020 ASSE I UNICAMP - UNICT: project PRIN 2020 (2020LM8WNW_004):Metabolic aspects of vascular disease: relevance for atherosclerosis development and identification of new therapeutic targets and companion biomarkers UNICAMP - INFN- UNICT: Project PRIN2017 “PBCT Proton Boron Capture Therapy” (2017XKWWK9)</p>
Educational activities including the activation of research doctorates
<p>UNICAMP PhD programmes include Translational Medicine, Biotechnology and Biochemical Science, Biomolecular Science, and Experimental and Clinical Science; the master degrees offered include Pain therapy, Oncologic Dermatology, and Neuroradiologic Diagnosis.</p>
International bibliometric indicators
<p>The main participants have the following H indexes: Barbieri Michelangelo (49), Cappabianca Salvatore (32), Capuano Annalisa (34), Carafa Vincenzo (26), Docimo Ludovico (26) Gialanella Lucio (32), Martinelli Erika (44) and Paolisso Giuseppe (87).</p>
University of Messina (UNIME)
<p>The University of Messina was founded in 1548 and has an ancient tradition going back more than 500 years. The</p>

University of Messina (UniMe) has always been characterised by the quality of research and teaching by its international vocation. Today the University offers a wide range of training possibilities, with numerous degree courses, both three-year and specialist, capable of intercepting and adequately responding to the demands of the world of work. The University has 12 departments covering the chemical, physical, biological, medical, economic and humanities disciplines (<https://www.unime.it/it/dipartimenti>) and two decentralised offices in Priolo and Noto. Thanks to its geographical position in the centre of the Mediterranean, UniMe is a place where different cultures meet. In 2020, the University ranked seventh in Italy for the increase in enrollments in three-year, single-cycle and master's degrees, registering + 27,4% increase in enrollments compared to the previous year against + 7% at the Italian level + 6,6% in the South, + 9,9% in the Centre and + 5.1% in the North. The University also has the highest research productivity among the Universities of the Sicilia Region in terms of citations per researcher (4.1 of absolute value), as well as the highest number of patents (45 patents).

Single participating groups

Department of Chemical, Biological, Pharmaceutical and Environmental Sciences; Department of Biomedical, Dental, Morphological and Functional Imaging Sciences.

Leading scientific activity in the last 10 years

UNIME has undertaken several important proposals in the field of public-private partnerships by setting up joint research laboratories and platforms with important companies in the area such as STMicroelectronics, S.I.F.I, I.O.M. and synergy with the most important research infrastructures in Sicilia, such as the CNR "Beyond – Nano" within which UniMe hosts one of the important research relating the advanced in terms of materials research, processes and nanotechnologies and in the sensor sector. In this regard, from 2020 a collaboration has already been underway with European House Ambrosetti, to strengthen the processes of technology transfer and research. The University also has the highest research productivity among the Universities of the Sicilia Region in terms of citations per researcher (4.1 of absolute value), as well as the highest number of patents (45 patents). The Scientific Production of UNIME has constantly increased during the last 5 years. In 2021 UNIME published 2.449 manuscripts. Selected publications:

- Campolo et al. TAK1 Inhibitor Enhances the Therapeutic Treatment for Glioblastoma. **Cancers** (Basel) 2020;13(1):41.
- Scuderi et al. TBK1 Inhibitor Exerts Antiproliferative Effect on Glioblastoma Multiforme Cells. **Oncol Res.** 2021;28(7):779-790.
- Casili et al. TLR-4/Wnt modulation as new therapeutic strategy in the treatment of glioblastomas. **Oncotarget** 2018;9(101):37564-37580
- Scuderi et al. KYP-2047, an Inhibitor of Prolyl-Oligopeptidase, Reduces Glioblastoma Proliferation through Angiogenesis and Apoptosis Modulation. **Cancers** (Basel). 2021;13(14):3444.
- Calabrese et al. Carbon Dots: An Innovative Tool for Drug Delivery in Brain Tumors. **Int J Mol Sci.** 2021;22(21):11783.
- Nocito et al. Physicochemical characterization and antibacterial properties of carbon dots from two Mediterranean olive solid waste cultivars. **Nanomaterials** (Basel) 2022;12(5):885.
- Aguenouz et al. MicroRNA-10 and -221 modulate differential expression of Hippo signaling pathway in human astroglial tumors. **Cancer Treat Res Commun.** 2020; 24:100203.
- Aguenouz et al. Serum levels of miRNA-21-5p in vitiligo patients and effects of miRNA-21-5p on SOX5, beta-catenin, CDK2 and MITF protein expression in normal human melanocytes. **J Dermatol Sci.** 2021;101(1):22-29
- Visalli et al. miRNA expression profiling regulates necroptotic cell death in hepatocellular carcinoma. **Int J Oncol.** 2018;53(2):771-780.
- Siracusa et al. Anti-inflammatory and anti-oxidant activity of Hidrox in Rotenone-induced Parkinson's Disease in mice. **Antioxidants** 2020, 9(9), 824

Ability to manage and implement excellent projects

UNIME has more than 50 active national and international projects, in the last three years, in the field of Health such as: projects of significant national interest (PRIN), National Operational Program (PON), Research & Mobility Program, The special supplementary fund for research (FISR), and AIFA call. At the UniMe there are: 5 active PRIN 2020; 5 active FISR; 2 active Research & Mobility 2017; 16 active PRIN 2017; 11 PON Research and Innovation 2014/2020; 4 active PO FESR Sicilia 2014/2020 and more.

Examples of PRIN: LINEA A 2017 MIUR 2017MYJ5TH_004 "Identification and validation of COmmon pathways at the CrOssroads of neurodegeneration and Neuroprotection" LS7 - Diagnostic Tools *PI: Esposito Emanuela* J44I19000740006. 2) PRIN 2020-2021 MIUR 202039WMFP_001 "New interventional approaches on

multiple inflammatory pathways involved in regeneration after trauma and aging- associated diseases” LS7-Diagnostic Tools. *PI: Cuzzocrea Salvatore* J45F20000310001. 3)PRIN 2020-2021 MIUR 20202THZAW_004 “Targeting functional and structural plasticity in Alzheimer disease. From diagnosis to treatment” LS7-Diagnostic Tools *PI: Esposito Emanuela* J45F20000320001. 4)PRIN 2020-2021 MIUR 2020SEMP22_001 “Regulation of autophagy by N-acylethanolamines as a promising approach for the treatment of inflammatory-based diseases: from neurodegeneration to metabolic disorders” LS7 - Diagnostic Tools *PI: Paterniti Irene* J45F20000340001.

Examples of PON “Ricerca e Innovazione”: PON “Ricerca e Innovazione” 2014 – 2020 1735 2017 MIUR ARS01_00144 MOLIM ONCOBRAIN LAB “Metodi innovativi di imaging molecolare per lo studio di malattie oncologiche e neurodegenerative” Salute *PI: Baldari Sergio* J66C18000330005. 2) PON “Ricerca e Innovazione” 2014 – 2020 1735 2017 MIUR ARS01_00492 BiLiGeCT “Biopsie liquide per la Gestione Clinica dei Tumori” *PI: Piperno Anna* B96G18000590005. 3) PON “Ricerca e Innovazione” 2014 – 2020 MIUR BONE++ “Sviluppo di Micro e Nanotecnologie per la Predittività, la Diagnosi, la Terapia e i Trattamenti Rigenerativi delle Alterazioni Patologiche dell’Osso e Osteo-Articolari” *PI: Cuzzocrea Salvatore* J66C18000340005. Piano Operativo Salute (POS), Ministero della Salute: Traiettorie 3 “Medicina rigenerativa, predittiva e personalizzata”, Azione 3.1 “Creazione di un programma di medicina di precisione per la mappatura del genoma umano su scala nazionale” T3-AN-13.

National and international collaborations

The University of Messina (UniMe) has undertaken several important proposals in the field of public-private partnerships by setting up joint research laboratories and platforms with important companies in the neuroscience area such as STMICROELECTRONICS (www.st.com), S.I.F.I (<https://www.sifigroup.com/>), I.O.M. (<https://www.gruposamed.com/it/istituto-oncologico-del-mediterraneo>), Epitech Group (https://www.epitech.it/project/linea_neuroscienze/it), Department of Pharmacological and Physiological Science, Saint Louis University, Saint Louis, MO, USA

Collaborations with ANTHEM participants

UNIME - IOM: Drug delivery and therapies. Research platform on oncological research. Drug Delivery, veicoli per un'innovazione sostenibile” funded by the Ministry of Education, University and Research PON – Ricerca e Competitività 2007-2013; Agreement for scientific research.

UNIME - UNICAMP: Regulation of autophagy by N-acylethanolamines as a promising approach for the treatment of inflammatory-based diseases: from neurodegeneration to metabolic disorders. 2020 -2023 (PRIN- code 2020SEMP22)

UNIME - UNICT: SAMOTHRACE foundation; Network TT of Complementary National Plan of Health Ministry.

UNIME- INFN-UNICT: Memorandum of Understanding for Collaboration in the Construction, Maintenance and Operation of the ALICE Detector

Educational activities including the activation of research doctorates

Master in Preparation Techniques Of Antitumor Drugs And Assessment Of The Safety And Effectiveness Of Medical Device; PhD in Applied Biology and Experimental Medicine; PhD in Bioengineering Applied to Medical Sciences.

International bibliometric indicators

For researchers participating in ANTHEM, H-index/number of publications/number of citations are reported: Mhammed Aguenouz (28/86/2.465); Maria Caffo: (18/90/1.010); Michela Campolo (29/91/1.872); Sabrina Conoci (29/150/2.373); Irene Paterniti (36/141/3.431); Emanuela Esposito (53/214/8.859); Rosalba Siracusa (32 /126/2.486).

University of Salento (UNISALENTO)

UNISALENTO manages the processes and activities of teaching, research and connection with the territorial reality through a precise organisation and division of roles and functions starting from the Government Bodies, which have the task of defining the strategic guidelines, economic and educational institutions of the University, to the Central Administration which has the task of achieving the objectives defined by the governing bodies, to the teaching and research structures. The University is made up of a total of 789 Professors and Researchers, 544 units of Technical-Administrative Staff who supervise and manage 61 Degree Courses and 150 International Partners. In 2021, 40 new fixed-term researcher positions of type a) were approved and, precisely 27 for the Innovation theme and 13 for the Green theme to give maximum support to research activities aimed at the territory. Teaching and research are divided between departments and research centres: 1) Cultural heritage; 2) Innovation Engineering; 3) Mathematics and Physics; 4) Economics; 5) Biological and Environmental Sciences and Technologies; 6) Legal Sciences; 7) History of society and human studies; 8) Humanities studies. From a financial point of view, UNISALENTO,

manages operating income for 97 M€ against operating costs for 93,3 M€ (2020 data). This situation guarantees the correct management of all university processes and the coverage of teaching and research needs. The management body of large projects is in particular the University Centre for large projects, dedicated to the management of complex initiatives with high budgets. The UNISALENTO also has over 980 agreements and contracts with public and private bodies, of which over 70 with international bodies.

Single participating groups

The **Department of Biological and Environmental Sciences and Technologies** (DiSTeBA) consists of 35 Research Laboratories involved in prestigious international programs and is part of some national consortia, European thematic consortia, National Competence Centers, and Networks of Public Research Laboratories, of 1 European network of excellence. In 2018-2020 it was selected as a "Department of Excellence" and beneficiary of additional funds from the MIUR. Furthermore, the DiSTeBA includes structures in agreement with the ASL of Lecce, such as the diffuse laboratory of interdisciplinary research applied to medicine (DReAM) and the Clinical proteomics laboratory which host staff from the University of Salento and support studies in the bio-medical field. The DiSTeBA laboratories mostly involved in the current proposal are: Laboratory of General Microbiology (Head: Pietro Alifano); Laboratory of Cell Biology (Head: Cecilia Bucci); Laboratory of Molecular Biology (Head: Luisa Siculella); Laboratory of Comparative and Applied Physiology (Head: Michele Maffia); Laboratory of Applied Physiology (Head: Tiziano Verri); Laboratory of Endocrinology and Molecular Oncology (Head: Bruno Di Jeso); Laboratory of General and Inorganic Chemistry (Head: Francesco Paolo Fanizzi); Laboratory of Physical Chemistry (Head: Ludovico Valli);

The **Department of Engineering for Innovation** focuses on new technologies and aims at promoting and disseminating technology innovation. The Department is active in the research fields of Civil Engineering, Computer Science, Controls and Robotics, Industrial Engineering and Management, Materials Science, Mechanical Engineering, Nanotechnology and Telecommunications. The Department has a research permanent academic staff of 150, most of them are affiliated with the Schools of Engineering and Science, a technical/administrative staff of 15, 17 non-permanent researchers, 15 administrative and over 100 PhD students and collaborators working in several research projects. Involved laboratories include the Biomaterials Laboratory and the Laboratory of Nanomedicine, Nanobioelectronics and nanobiotechnology.

The Departments of History of society and human studies and of Legal Sciences will collaborate.

Leading scientific activity in the last 10 years

- Di Salvo et al. The Microbiome of the Maculea-Myrmica Host-Parasite Interaction. **Sci Rep.** 2019 ;9(1):8048.
- Guerra et al. (2019) Modulation of RAB7A protein expression determines resistance to cisplatin through late endocytic pathway impairment and extracellular vesicular secretion. **Cancers** (Basel) 11(1) pii: E52.
- De Santis et al. Dysbiosis Triggers ACF Development in Genetically Predisposed Subjects **Cancers** (Basel) 13(2) pii: E52 (2021)
- Sandriet al. Fabrication and pilot in vivo study of a collagen-BDDGE-elastin core-shell scaffold for tendon regeneration. **Frontiers Bioeng Biotechnol** 4:52, 2016.
- Marra et al. (2018). A gap analysis methodology for product lifecycle management assessment. **IEEE Transactions on Engineering Management**, 65(1), 155-167.
- Picca et al. Older Adults with Physical Frailty and Sarcopenia Show Increased Levels of Circulating Small Extracellular Vesicles with a Specific Mitochondrial Signature. **Cells.** 2020;9(4):973.
- Aloisiet al. Anti-aggregating effect of the naturally occurring dipeptide carnosine on $\alpha\beta$ 1-42 fibril formation. **PLoS One.** 2013;8(7): e68159.
- I Fasolino et al. Osteoinductive And Anti-Inflammatory Properties Of Chitosan-Based Scaffolds For Bone Regeneration, **Material Science and Engineering C**, 2019. 105, 110046.

Ability to manage and implement excellent projects

In addition to the departmental structures, UNISALENTO has a Fundraising and Research enhancement office for the participation and management of project initiatives. The management body of large projects is in particular the University Center for large projects, dedicated to the management of complex initiatives with high budgets. Projects are located in the following areas: education (60%), research and innovation (34%), environment (3%), culture and tourism (1%), employment (1%), social inclusion (1%). UNISALENTO has in its portfolio multiple active participations within **292** national and international cooperation programs, notably PON and PON FESR. UNISALENTO has also coordinated **34** national and regional programs. In addition to these projects, UNISALENTO is active in many European and international research programs with a coordinating or partner role in about **70** approved projects: CIP (2 projects), CREA (3), CREA2027 (1), EPLUS 82), EPLUS (2),

ERASMUS2027 (1), FP7 (18), H2020 (37), HORIZON (4), SOCPL (2) for a Total Budget of almost **303 M€**, out of which 13 as coordinator.

National and international collaborations

UNISALENTO has relations with 190 international centres of high scientific quality under 300 agreements. In addition, 590 agreements were born on the basis of the research activities carried out on RS & t themes and around specific research projects. Concerning ANTHEM themes, main previous activities were funded by i) MUR, including PRIN, PON, FISR, MUR-FAR (D.M. 593, D.M. 488); ii.) the Ministry of Economic Development; iii.) Istituto Superiore di Sanità (ISS) (Multicentric studies); iv.) Puglia Region (Strategic projects), in addition to foundations (Telethon and AIRC) and pharmaceutical companies (Sanofi, Gilead Science). The most relevant international collaborations are: **NO**: Prof. H. Stenmark and Prof. C. Progida, University of Oslo. **UK**: Prof. G. Schiavo, University College London; Prof. Matteo Santin, University of Brighton; Prof. Federica Masieri-University of Suffolk; Dr. Leandro Castellano, University of Sussex. **USA**: Prof. C. Wu, UC San Diego; Fabio Cominelli, MD, PhD, Chief, Division of Gastroenterology and Liver Disease, School of Medicine, Cleveland; Alessio Fasano, MD, Division Chief, Pediatric Gastroenterology and Nutrition; Director, Center for Celiac Research and Treatment, MassGeneral Hospital, Boston; Prof. Robert Langer, Prof. I.V. Yannas, Massachusetts Institute of Technology, Cambridge; Prof. Myron Spector, Prof. Paolo Fiorina, Harvard Medical School, Boston; Prof. Lee Kaplan, Massachusetts General Hospital and Harvard Medical School, Boston. **IL**: Prof. H. Eldar-Finkelman, Tel Aviv University. **AU**: Prof. R. Eri, University of Tasmania. **DE**: Prof. H. Daniel, Technische Universität München; Prof. U. Wenzel Justus Liebig University Giessen. **FR**: Prof. J Vizioli, Université Lille.

Collaborations with ANTHEM participants

UNISALENTO - HUNIMED: Agreement on international strategic collaboration and technology transfer in the biomedical and social sciences. Microbiome characterization in healthy and chronic diseases
 UNISALENTO - UNICT: PON Ricerca e Innovazione 2014-2020, Asse II - Progetti Tematici, Azione 2 - Cluster Tecnologici: Avviso D.D. 1735 del 13 luglio 2017 per la presentazione di progetti di ricerca industriale e di sviluppo sperimentale nelle 12 Aree di specializzazione individuate dal PNR 2015-2020. Integrated approach to tackle the interplay among adaptation, stressful conditions and antimicrobial resistance of challenging pathogens (PRIN 2017)
 UNISALENTO-ABM: ab medica and UNISALENTO are involved in a joint MISE project for the creation of advanced sensors for EEG monitoring
 UNISALENTO-INFN: Agreement on co-funding of fixed-term researchers

Educational activities including the activation of research doctorates

I level courses (three-year degrees): Biological Sciences; Biotechnology; Environmental Sciences and Technologies; Sustainable Development and Climate Change; Motor and Sport Sciences; Viticulture and Enology; Nursing; Optics and Optometry; Industrial Engineering; Information Engineering; Engineering for Sustainable Industry; Biomedical engineering. **II level courses (two-year master's degrees)**: Coastal and Marine Biology and Ecology; Experimental and Applied Biology; Medical biotechnologies and nanobiotechnologies; Environmental Sciences; Sciences and techniques of preventive and adapted motor activities; Communication Engineering and Electronic Technologies; Computer engineering; Mechanical Engineering; Management Engineering; Materials Engineering and Nanotechnologies. **Single-cycle courses**: Medicine and Surgery. **PhD**: Biological and Environmental Sciences and Technologies; Material, Structure and Nanotechnology Engineering; Engineering of complex systems; Mathematics and IT; Physics and Nanosciences; Nanotechnology. **Master Courses (II level)**: Accreditation of health and social-health structures; Applied data Sciences; Molecular Biomedicine; Expert in neuro-cognitive assessment and rehabilitation of developmental age, adults and the elderly; Psychosocial intervention for the promotion of community well-being; Scientific programming

International bibliometric indicators

For researchers participating in ANTHEM, H-index/number of publications/number of citations are reported: C. Bucci (46/142/10.117); A. Sannino (40/138/5.028); L. Valli (35/182/4.081); M. Chieppa (33/84/9.837); T. Verri (27/116/2.483); C. Demitri (24/69/2.149); F. Guerra (20/41/1.646); A. Corallo (15/165/1.079).

National Institute for Nuclear Physics (INFN)

INFN is the Italian research agency dedicated to the study of the fundamental constituents of matter and the laws that govern them, under the supervision of the Italian Ministry of University and Research (MUR). It conducts theoretical and experimental research in the fields of subnuclear, nuclear, astroparticle and applied physics, at its own national laboratories in Italy and at major laboratories worldwide (CERN, FNAL, KEK, LAB, BNL, IHEP, et al.). Fundamental research in these areas requires the use of cutting-edge technology and instruments, developed by the INFN at its own laboratories and in collaboration with industries. Thanks to this capacity building and

knowledge transfer INFN has always been attentive on the social impact and fallout of its research, notably in the health sector. The portfolio of medical physics related activities includes (but is not limited to) development of accelerators for innovative therapies (hadrontherapy, BNCT), dosimetry, radiobiology, PET/SPECT/MRI, imaging, production of radioisotopes. Many of these are conducted in strict collaboration with national and international centres like CNAO, GSI, ELIMED. Medical applications of nuclear physics are a growing sector of INFN assets as testified by the many projects funded by its own Committee on Technological and Inter-disciplinary Research (currently around 40 active projects in the interdisciplinary area) and the involvement in other medical research installations. Another relevant field for INFN is the ICT area, with more than two decades of open innovative solutions for advanced distributed computing and software applications, including AI techniques from ML to cutting edge DL.

For human resources, a major asset of INFN is its pervasive presence throughout the whole country, thanks to the strong collaboration with Universities. Its structures are in most cases co-located with physics departments, and university researchers are associated and funded by INFN (4.000 people, including students). INFN employs more than 1.000 staff researchers and technologists, whose work is recognized internationally for their contribution to various European laboratories and research centres worldwide.

Single participating groups

INFN National Laboratories of Legnaro (LNL), INFN National Southern Laboratories (LNS), INFN Units of Catania, Napoli, Pavia.

Leading scientific activity in the last 10 years

INFN has a large and heterogeneous scientific production, with over 3.000 peer-reviewed papers published per year, including major scientific breakthroughs such as the discovery of the Higgs boson in 2012 or the first detection of gravitational waves in 2016. INFN ranks third in the global Nature Index for physical sciences, and first (for the third time) in Italy in the last evaluation of research by the MUR Agency ANVUR.

Medical physics applications mentioned above, and fields like Monte Carlo simulations of treatment planning, breast CT, dosimetry for new therapies and most recently studies on the evolution of Covid-19 pandemia and its effects on lung diseases are producing many papers on several high IF journal, e.g.: 1) MUNES a Compact Neutron Source for BNCT and Radioactive Wastes Characterization. **Proceedings of LINAC 2014**, Geneva, CH. 2) TRASCO RFQ. **XX International Linac Conference 2000**, Monterey, US. 3) IFMIF/EVEDA beam commissioning at nominal 125 mA deuteron beam in pulsed mode. **IPAC2020**, invited. 4) High power RF conditioning of the TRASCO RFQ. **Proceedings of Linac 2012** Tel Aviv, IL 5) Microdosimetry of an accelerator based thermal neutron field for Boron Neutron Capture Therapy, **Applied Radiation and Isotopes 2022**. 6) The Hallmarks of Glioblastoma: Heterogeneity, Intercellular Crosstalk and Molecular Signature of Invasiveness and Progression. **Biomedicine**, 2022. 7) Novel Approach to Design and Evaluate BNCT Neutron Beams Combining Physical, Radiobiological, and Dosimetric Figures of Merit, **Biology**, 2021. 8) Multimodal evaluation of ¹⁹F-BPA internalization in pancreatic cancer cells for boron capture and proton therapy potential applications, **Physica Medica** 94, 2022.

Ability to manage and implement excellent projects

Given the relevant scientific, technological and applicative results, characteristic of its mission, the last years have seen INFN strengthening further its international DNA, both by participating in an organic way to European research infrastructures (such as those of the ESFRI Road Map) and looking for to transform some of its infrastructures into ERICs. Success stories include KM3NeT, the distributed research infrastructure for neutrino telescopes in the sea depth, EuPRAXIA for new plasma acceleration, Einstein Telescope, the successor of EGO-Virgo. For internally funded projects, INFN acts in most cases in international contexts in large and long-lasting collaborations (up to ~5.000 members) with complex management structures. For internal projects INFN has a yearly budget of over 50 M€, with over 1.000 scientists directly involved, and a total number of initiatives exceeding 100. INFN collaborates with leading funding agencies for space activities, like ASI (IT), ESA (EU) and NASA (US). INFN is a key player in initiatives (such as the Italian Computing and Data Infrastructure, National Competence Centres (such as BI-REX, the Competence Centre on Big Data and Industry 4.0), multiple PON projects, state-of-the-art POR-FESR and Technology Transfer initiatives, collaborations with HPC centres such as CINECA, and with many IRCCS and health centres and institutions, public and private. In addition, UNICT, INFN and CANNIZZARO are already realising a preclinical facility for ultra-flash proton therapy thanks to the BCT program funded by the Sicilia region. This facility will be upgraded for electron ultra-Flash preclinical studies in the framework of this proposal. INFN is also a member of ALISEI, the national technological cluster for advanced life science, where it represents all the public research organisations inside the Directive Council, and whose mission is to coordinate and boost the knowledge transfer from basic research to industry and society in that field.

INFN also competes for and wins EU and national “one-shot” project funds, ranging from ~10-100 M€/yr. Within Horizon 2020, for the ERC instrument, INFN got five Starting, eight Consolidator (one of which with a re-entrant PI from abroad) and one Advanced Grants. This adds up to the 36 MSCA projects and 55 Infrastructures granted in the previous programme. To manage external funds, INFN has a dedicated Unit, assisting activities related to the application, management and reporting of the Institute research funding from external national and international sources. Moreover, INFN has a National Committee for Technology Transfer: a strategic scientific-technological body that promotes INFN Knowledge Transfer activities.

National and international collaborations

INFN, as one of the top worldwide research institutions devoted to fundamental research, has deeply rooted collaborations with national and international peers, at all levels. INFN is delegated by the MUR to coordinate Italian activities at CERN. INFN participates and funds experimental activities at major laboratories worldwide (US: FNAL, BNL, JLAB; JP: KEK; CN: IHEP, et al.) and is a founding member of the European Gravitational Observatory Consortium. Of particular note are also the experiments ATLAS, CMS at CERN (which discovered the Higgs boson in 2012) and VIRGO (which discovered gravitational waves in 2016). A non-exhaustive list of internally funded projects includes ATLAS, CMS, LHCb, ALICE, BELLE2, VIRGO, G-2, AMS, FERMI. All of these are multi million € experiments, involving international collaborations, in which INFN has a prominent role in the design, construction, operations and management. In most of them INFN has been a leading party in the design, deployment and operations of the software and computing infrastructure, with large scale efforts resulted in the realisation of e-Infrastructure such the GRID, the Cloud, the integration with the HPC centres and the development of specialised AI based algorithms.

A significant part of INFN activities is related to the thematic areas of ANTHEM. In the high-technology field INFN has designed and is commissioning the biggest accelerator based on Radio Frequency Quadrupole in the world, at the IFMIF facility of Rokkasho, in Japan (120 mA current, 5 MeV energy), whose objective is the production of very intense neutron beams to test the critical parts of fusion reactors. Fusion is indeed another field where INFN is active, contributing e.g. to the International Thermonuclear Experimental Reactor. INFN participates with active and leadership roles also in several health-related projects and collaborations: full membership to the association “Alleanza Contro il Cancro” on oncology-related research; participation in ELIXIR-Italy as part of the Italian Joint Research Unit (with the development of turnkey solutions such as Laniakea, for the automatic deployment of virtual Galaxy environments for life science); coordination of the NRRP National Center on HPC, Big Data and Quantum Computing, contributing to data analysis and management to the spoke on “In-silico medicine and Omics data”. Several collaborations are active in the field of BNCT with foreign Institutions located in Argentina, China, Spain, UK.

Collaborations with ANTHEM participants

INFN-UNICT-CANNIZZARO: BCT (Breast Cancer Therapy) funded by Sicilia Region

INFN-UNICAL-UNIMIB: STAR-2 Infrastructure

INFN - UNIMIB: Agreement for the activation of the PhD programme in Physics; agreement for the management of the cryogenics laboratory; 3D Digital Histology

INFN - UNIBG: 3D Digital Histology; Agreement for the Italian participation in the GASP: General AntiParticle Spectrometer

INFN- UNICT: Agreement for the activation of the PhD programme in Physics

INFN- UNIME - UNICT: Memorandum of Understanding for Collaboration in the Construction, Maintenance and Operation of the ALICE Detector

INFN- UNICT - IOM: “DiOncoGen: Innovative diagnostics” project, funded through POR FESR Sicilia 2014/2020

INFN- POLIMI: Memorandum of Understanding of the Ebrains Italian Community; Agreement on the Quantum Initiative

INFN-UNISALENTO: Agreement on co-funding of fixed-term researchers

INFN- UNICT - UNICAMP: Project PRIN2017 “PBCT Proton Boron Capture Therapy” (2017XKWWK9)

INFN-UNICAL-UNIMIB: X-Ray Star Facility

INFN-UNICAMP: Proton Boron Fusion Therapy, boron concentration measurements in biological samples (PBFT - Project NEPTUNE)

Moreover, several partners of ANTHEM participate in scientific activities which belong to the INFN Scientific Committees and are scrutinized by a referee panel on a yearly basis, like the ones listed below (in parentheses the experiment acronym):

- Research line on particle physics: UNIMIB (LHCb), UNICT (CMS, LHC_F), UNICAL (ATLAS, KLOE), UNIME (KLOE), UNISALENTO (ATLAS)

- Research line on astroparticle physics: UNIMIB (AMS_2, LSPE, CUORE, HOLMES_2, NU_AT_FNAL, LITEBIRD, GERDA, QUBIC), UNIBG (DARKSIDE), UNICT (AUGER, DARKSIDE), POLIMI (AUGER, DARKSIDE, SUPREMO), UNISALENTO (AUGER, NU_AT_FNAL)
- Research line on nuclear physics: UNICT (CHIRONE, NUMEN_GR3, N_TOF), POLIMI (ASACUSA, CHIRONE), UNIME (CHIRONE)
- Research line on interdisciplinary physics: POLIMI (ASTAROTH, NEPTUNE, PRAGUE), UNICAMP (NEPTUNE), UNISALENTO (AT_SVB, BOLAS_NEXT)

Educational activities including the activation of research doctorates

Thanks to agreements stipulated with Universities, INFN researchers carry out teaching activities mainly in the MSc courses in Physics: in 2021, 47 INFN staff were supervisors or co-supervisors for degree theses that fall within the scope of the research carried out by the institution. INFN is particularly active in the third-level education, thanks to a funding program of PhD scholarships and the activation of joint doctorates. The Institute counts 13 PhD programs as co-owner with a growing trend in the last five PhD cycles. INFN funds over 60 PhD scholarships yearly and annually about 170 PhD theses in the INFN area are discussed. The tip of the iceberg is the extraordinary success of the Gran Sasso Science Institute, the doctoral school located in L'Aquila, of which INFN has been the implementing body and of the PhD School for Accelerators in Rome.

International bibliometric indicators

Metrics for key participants (H-index/publications/citations): G. Cuttone (33/382/10.165, Scopus); A. Pisent (13/140/849, Scopus); V. Vercesi (111; 1166; 60.525, Web of Science).

Azienda Socio Sanitaria Territoriale Bergamo Est (ASST BGEST)

ASST BGEST has a reference area that can be identified with the eastern area of the Bergamo province. The natural basin extends from the south-eastern outskirts of Bergamo to the entire basin of the Bergamo lakes and valleys, which includes 103 Municipalities, with a total population of 385.902 inhabitants out of the 1.116.384 of the Bergamo Province. The reference area identified includes as a territorial extension almost 50% of the Province of Bergamo, while the total population is 35% of the total. The Health Trust operates in a very diversified geographical and demographic context, ranging from the metropolitan belt, with a rich industrial area and a large agricultural area, to the lakes area, characterised by strong tourist seasonality, up to the high mountains, with its access difficulties. ASST Bergamo Est is structurally characterised by the distribution of its multiple structures, both hospitals and territorial, over a wide geographical area of belonging, which responds to a logic of proximity and which also nourishes a sense of particularly accentuated, shared between citizens and operators. An important demographic data is the ageing of the Bergamo population: 21,36% of the population is over 65 and both the old-age index and the ageing index have undergone an increasing trend in recent years.

The ASST includes HOSPITAL CENTER and TERRITORIAL CENTER: “Bolognini” hospital in Seriate; “M.O.A. Locatelli” of Piario; “Pesenti Fenaroli” hospital in Alzano Lombardo; Gazzaniga “Briolini” hospital; Hospital “SS. Capitanio and Gerosa ” of Lovere; “Passi” Hospital of Calcinato; “S. Isidoro ”of Trescore; “P.A. Faccanoni ”of Sarnico; Health District of Albino; Health District of Seriate; Health District of Trescore Balneario. There are four directly managed hospitals for acute patients (Seriate, Alzano Lombardo, Piario and Lovere), one with direct management rehabilitation activities (Gazzaniga). The Calcinato Hospital is characterised both as a hospital for low-risk patients, which houses both hospitalisation departments (Subacuti - Hospice and Alcohol Rehabilitation - the latter two managed through the form of public-private Management Trials) and operating sales for small interventions, both Community Hospital as defined by the NRRP and Community House.

The Trescore and Sarnico Hospitals are managed by private entities under concession. The corporate services of nephrologists are also managed under concession to private subjects and an excellence Centre for Alzheimer’s disease. The Hospitals are managed considering their territorial distribution, and assigned to three distinct structure departments: Hospitals of Seriate and Calcinato, Hospitals of Alzano Lombardo and Gazzaniga, and Hospitals of Piario and Lovere.

Key persons and expert groups

Dr. Keim R, Dr. Nastasi G, Dr. Piti A, Dr. Manelli F, Dr. Tedeschi A, Dr. Ranieri A, Dr. Patelli G, Dr. Novel L, Dr. Giudici V

Key infrastructures

Dept. Medicine, Dept. Cardiology, Dept. Surgery, Dept. ER, Dept. Quality and Safety, ICT, Bio-engineering

Ability to manage clinical trials and research projects

Project leader of disease management for frail and chronic patients (CREG project, services centre for transitional

care, tele-health, e-health
Involvement in Regional, National and international working groups or Medical / Scientific Societies
Collaborations with FIASO, SIMM, Slow Medicine, Green Hospital Network; Collaborations with CARD (confederation regional association of health districts); Involvement in Telemechron project (national/regional); Mirato Project (regional); Telecovid (with University of Bergamo) Involvement in Multidisciplinary group for automated processing Lab. (Calcinatè Hosp.): Multiply Lab. Of Stanford, Porsche Consulting, Politecnico Milan, University of Milan, University of Bergamo, R.I.
Collaborations with ANTHEM participants
ASST BGEST - UNIMIB: 3D Digital Pathology ASST BGEST - UNIBG: Telemedicine technologies and process management; agreements for the development of research and educational activities. AI-based tools for genomic diagnosis for precision medicine. AI-based tools for genomic diagnosis for precision medicine. GBM Diagnosis.3D Digital Pathology. ASST BGEST - UNIBG - FERB: Concept study of the MyTravelCare platform, a support to foreign travellers in Italy ASST BGEST - NEGRI: Genomic analysis of rare diseases by precision medicine. SARS-CoV-2 genotyping
Educational activities including research doctorates and specialisation courses
Collaborations with University of Milan-Bicocca, University of Bergamo, University of Brescia, Politecnico of Milan and University of Milan for post-graduate doctor, nurses, technicians
International bibliometric indicators
For researchers participating in ANTHEM, H-index/number of publications/number of citations are reported: Alberto Tedeschi (36/186/4.813); Filippo Manelli (11/25/491); Francesco Locati (9/28/1.488).

Azienda Socio Sanitaria Territoriale Monza (ASST MONZA)
ASST MONZA is a public entity of the Lombardia Regional Social-Health Service (SSL). It has legal personality under public law and organisational, administrative, patrimonial, accounting, managerial and technical autonomy. ASST of Monza provides accredited health and sociomedical services and, in cooperation with UNIMIB, carries out research and teaching activities. In fact, it is a primary Centre of the Department of Medicine and Surgery - School of Medicine and Surgery of the University of Milan Bicocca. It is a 2nd level acute hospital, a reference centre for major trauma (CTS) and part of the high speciality network (neurosurgery, cardiac surgery, thoracic surgery, vascular surgery, haemodynamics). The ASST has started the process at the Ministry of Health for recognition as a public-law IRCCS Foundation 'Fondazione IRCCS San Gerardo dei Tintori', the process of which is almost complete.
Key persons and expert groups
Pathology and diagnostic unit: Matteo Garancini, Vincenzo l'Imperio Neurology unit: Laura Brighina, Simone Beretta
Key infrastructures
ASST MONZA, San Gerardo hospital, after processes developed in recent years with the progressive increase in the capacity and quality of care and research, is currently the seat of second level facilities recognised by the Lombardia Region, such as: <ul style="list-style-type: none"> • Highly Specialised Emergency Department (EAS) - The Emergency Department is a complex organisational structure afferent to the Department of Urgent Emergency Care (POA with DGR N° X/6295 Session of 06.03.2017); • Centre for highly Specialised Traumas (CTS) Greater Trauma Network - Decree of General Directorate for Health – Lombardia Region n. 8531 of 1.10.2012; • Level II Reference Centre in the Complex Hand and Upper Limb Trauma Network - Decree of General Directorate for Health - Lombardia Region no. 358 of 23.1.2014 and Decree of General Directorate for Health - Lombardia Region no. 4825 of 6.6.2014; • Level IV Stroke Centre of the ST-Elevation Myocardial Infarction (STEMI) network - Regional Decree no. 1962 of 6.7.2011; • Level II Stroke Centre - Decree of General Directorate for Health - Lombardia Region no. 10068 of 18.9.2008; • Level III Centre for the Digestive Haemorrhage Network - Decree of General Directorate for Health - Lombardia Region no. 5168 of 11.6.2012;

- National Centre (on a total of 16) ExtraCorporeal Membrane Oxygenation (ECMO) for the treatment of severe acute respiratory failure syndrome and refractory cardiogenic shock or cardiac arrest - DGR 2562 of 2.12.2019;
- Hub Centre for time-dependent ST-Elevation Myocardial Infarction (STEMI), Interventional Cardiology and STROKE - DGR 2906 of 8.03.2020;
- Hub centre for pneumology, infectious diseases and intensive care - DGR 3264 of 16.06.2020;
- The Verri GMP Laboratory has been an AIFA-authorized centre for cell production since 2009. The GMP Facility named "Stefano Verri Laboratory for cell and gene therapies" is one of the first GMP facilities approved by AIFA (2007) that received in 2018 the extension to the authorisation for the production of genetically modified somatic cells by non-viral methods, the first and only facility in Italy. Since the date of approval, the quality of its activities and results has been confirmed by the positive results of the two-yearly inspections carried out by AIFA, the numerous clinical research protocols with advanced therapy medicinal products (somatic cell therapy products, gene therapy and tissue engineering), and the development and production commissions for authoritative Research Institutions in Italy. The Verri Laboratory works in close synergy with the Tettamanti Foundation.
- Preferential pathway (short track) at specialist outpatient clinics for ophthalmology, dermatology and otorhinolaryngology, where users who present a clear specialist need and a stable clinical condition at emergency room triage are sent directly for examination:
- AIFA-accredited Phase 1 trial centre of ASST Monza (self-certification in accordance with AIFA Determination no. 809/2015);
- Reference centre for rare diseases in adults; Eye Bank; Cornea and vitreo-retinal surgery transplant centre; Adult Bone Marrow Transplant Centre; Child Bone Marrow Transplantation Centre; Centre for the Study and Treatment of Arterial Hypertension; Epilepsy Centre; Centre for Multiple Sclerosis; Centre for the diagnosis and treatment of autoimmune liver diseases in adults and children

Ability to manage clinical trials and research projects

The research activities of ASST Monza rely on a solid organisation that is strongly integrated with the University. As confirmation of the strong integration between ASST Monza and the University, it should be noted that for "early phase" studies, the Institution has set up a Unit for Phase I/2 studies (under the direction of a contracted University doctor), in accordance with AIFA Determination no. 809/2015, which enables, both from a data management and clinical point of view, to support the conduct of early phase studies, generally of a profit nature. Furthermore, the University supports ASST Monza through the Bicocca Clinical Research Office (BiCRO) structure, which promotes non-profit research, providing researchers, including hospital researchers, with adequate support (agreement between ASST Monza and UNIMIB in 2018); BiCRO has been part of the European Clinical Research Infrastructures Network (ECRIN) since 2020.

In the year 2021, a total of 259 profit and 403 non-profit studies were conducted. A number of research projects funded by several agencies are ongoing, including: Multidisciplinary (Ministry of Health, Infectious Diseases); Standlow (Ministry of Health, Neurology); Muse (RF-2016-02364584- Ministry of Health, Infectious Diseases); Albioss (Ministry of Health, Anaesthesia and Intensive Care); GR-2018-12366471 (Ministry of Health, Gastroenterology); RF-2018-12366471 (Ministry of Health, Pathology); GR-2018-12365988 (Ministry of Health, Neuro-surgical Intensive Care); FINAL-TIR (Ministry of Health, Pathology); Inaction (Ministry of Health, Infectious Diseases); COVID-2020-12371808 (Ministry of Health, Pneumology); Mereafaps 5.0 (Lombardia Region, Pharmacy); Metarel (Lombardia Region, Pathology); Strokovid (Lombardia Region, Neurology); COVitaminD (Lombardia Region, Oncology); Interceptor (AIFA, Neurology); Plagencell (FRRB, Verri Laboratory); Transcan-2 (FRRB, Pathology); Neurospheres (San Raffaele service, Verri Laboratory); FRA-ASC Annoni (Cariplo, Geriatrics); CCP-ITALY (covid-19) (AREU, SIMT); Optimising the care of patients with Multiple Sclerosis (ROCHE, Neurology); Hercoles (Roche, Surgery I); FIL_FLAZ-12 (Roche, Haematology); Nutritional assessment in idiopathic pulmonary fibrosis: a pilot study' code 'NUTRIPF (Roche, Pneumology); SECURE (European Commission, Cardiology); Fellowship 2015, 2016 and 2017 (Gilead, Infectious Diseases).

Involvement in Regional, National and international working groups or Medical / Scientific Societies

Asst Monza is the first non-IRCCS facility in Lombardia (second only to the IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation in Milan) in terms of number of active Therapeutic Plans in the field of rare diseases, with a continuous increase. The multi-specialist skills of ASST Monza make it possible to manage patients with multifactorial and complex pathologies from both a medical and surgical point of view.

In line with this clinical activity, the San Gerardo Hospital has the following 'European Reference Network' centres (ERN): i) craniofacial malformations on a genetic basis (ERN Cranio); ii) rare haematological diseases

(EuroBlooNet); iii) liver diseases (Rare-Liver) iv) congenital metabolic diseases (MetabERN).
Collaborations with ANTHEM participants
ASST MONZA - UNIMIB Joint Training and Specialization Courses in Medicine and Surgery. Joint Translational Research in chronic and frail diseases (i.e. excellence centres and research collaborations on neurological diseases, endocrine diseases, cancer diseases etc.)
ASST MONZA - UNIMIB: Grant Fondazione Cariplo 2021 “Networking, ricerca e formazione sulla sindrome post COVID” (Networking, research and training on post COVID syndrome), funded project: "The Post-Covid-19 Syndrome: network building and innovative management to address a new public health emergency”.
Educational activities including research doctorates and specialization courses
ASST MONZA is highly involved in medical specialisation programmes: most of the medical specialisation schools are indeed present in the UNIMIB-HSGerardo agreements.
International bibliometric indicators
For researchers participating in ANTHEM, H-index/number of publications/number of citations are reported (source: Scopus): Mattia Garancini (18/63/925); Vincenzo L’Imperio (9/50/257); Laura Brighina (24/58/1.352); Simone Beretta (23/86/1.951).

Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII (ASST PG23)
ASST PG23 is a public hospital and a national centre of excellence with advanced specialities in all areas of medicine and surgeries, particularly for organ and tissue transplant. It is one of the largest Tertiary Public Health Hospital in the north of Italy, extending over an area of 320.000 m ² , comprising more than 900 beds, including 108 beds in intensive and subintensive care and high dependency unit, 36 surgery theatres, 226 outpatient clinics, 9.000 m ² dedicated to diagnostics and 4.000 m ² dedicated to the Emergency-Urgency, with a heliport working 24 hours a day. ASST PG23 performed 18.374 emergency hospitalizations, 41% of the total of admitted patients. Operational transplant programs include heart, kidney, liver, lung, pancreas, paediatric bowel, with combined heart/lung, and heart/kidney. ASST PG23 is a tertiary level reference centre for heart failure patients with the Cardiovascular Department conducting heart transplants since 1985.
Key persons and expert groups
Operational Unit (OU) Pathology: Dr. A. Gianatti, MD OU Medical Genetics: Dr. M. R. Iacone, Geneticist OU Cardiology 1 / Prof. M. Senni, MD, Prof. at UNIMIB, affiliated Head of Unit OU Endocrine Diseases 1/Diabetology: Prof. R. Trevisan, MD, Prof. at UNIMIB, affiliated Head of Unit
Key infrastructures
Pathology Unit: Laboratories deal with preparation of histological and cytological samples, immunohistochemistry, molecular biology and cytogenetics of solid tumours and flow cytometry, offering over 400 different types of exams. Main activity areas: examination of biopsies for organ transplant; monitoring histological examination on biopsies and surgical pieces; extemporaneous examination in the cryostat; sentinel lymph node examination; vaginal and extravaginal cytological examination (urine, effusions, fine needle aspirations); seminal fluid analysis; immunophenotype for lymphomas in flow cytometry; FISH - CISH (EWSR1, SS18, DDIT3, MDM2, FKHR, EBV-EBER); HPV-RNA; breast cancer markers (ER, PGR, c-erbB-2, Ki67); FISH for target therapy (HER2, ALK); diagnostic finding. Techniques used: Immunohistochemistry; "Thin layer" method for Pap Test; Flow cytometry; FISH-CISH; NASBA; OSNA test. Medical Genetics Unit deals with the diagnosis and prevention of constitutional and acquired genetic diseases through chromosome and DNA analysis. It carries out genetic tests for the identification, before and after birth, of constitutional anomalies (heritable) and tests for the identification of anomalies in tumours. The activity is aimed at outpatient users, hospitalised users, external and private entities. Genetic tests are analysed with peculiar characteristics and included in a multidisciplinary process of taking charge aimed at informing and providing pre- and post-test indications, in collaboration with clinicians. Techniques used: Cytogenetics (chromosomal analysis and FISH) on peripheral blood, bone marrow, chorionic villi, amniotic fluid and other tissues; CGH arrays on peripheral blood and in the prenatal period); Molecular genetics (DNA mutation analysis; polymorphism analysis; gene sequencing; NGS of gene panels; methylation test exome analysis (WES) in the trio). Cardiology 1 Unit is specialised in: i) acute and chronic ischemic heart disease, through coronagraphy and imaging studies, coronary interventional procedures and individualised antithrombotic therapy; ii) acute or chronic heart failure, with individualised multi-drug therapies, respiratory and/or circulation assistance systems, ultrafiltration or dialysis techniques, electrical therapy; iii) cardiac arrhythmias using specific drug therapies and interventional transcatheter processing procedures; iv) hypertrophic cardiomyopathy in a multidisciplinary approach with cardiologists, paediatric cardiologists, cardiac surgeons, electrophysiologists, specialists in advanced

heart failure / heart transplant, anaesthetists and geneticists. **Endocrine Diseases 1 - Diabetology Unit** is specialised in diagnosis and treatment of: type 1 and type 2 diabetes (T1D/T2D); chronic complications of diabetes (retinopathy, nephropathy; cardiovascular); hypoglycemia and dyslipidemia; obesity and associated complications; insulin resistance; endocrine pathologies. It follows about 300 children and 1.500 adults with T1D, and about 6.000 T2D providing accurate care, optimising glycometabolic control and implementing a multimodal strategy for treatment and long-term complication prevention. It also provides all patients with a program for the correct follow-up of the endocrine/metabolic pathology and for the prevention of complications.

Ability to manage clinical trials and research projects

Pathology - Dr. Gianatti. Involved for more than 10 years in clinical trials in the onco- hematological field of which he is responsible for the pathological-anatomy part in almost 100 experimental trials in phase I, II and III studies relating to the experimentation and validation of therapeutic protocols. **Diabetology - Prof. Trevisan.** More than 50 international clinical trials related to the treatment of T1D/T2D patients. In particular we participated in clinical trials related to the effectiveness of new technologies in the treatment of type 1 diabetic patients. **Cardiology - Prof. Senni.** More than 50 trials in Cardiology (out of which 16 as National Leader and and 1 as Global Lead Investigator) on Heart Failure, HF and Diabetes, Acute Coronary syndrome, Myocarditis, Dyslipidemia, Myocarditis, Amyloidosis, Pulmonary Hypertension, and more than 10 trials more than 10 trials related to acute and chronic heart failure, cardiorenal syndrome, ventricular dysfunction. Among the research projects, the units participate in the subproject "Schelectric pumps" of the ICAROS project on the following field: "Experimental preparation for the study of the dynamic cardiomyoplasty" and "Ventricular Assist Device with muscular pump". Other research themes: canine model of pressure overload hypertrophy and pacing heart failure at Cardiorenal Laboratory of Mayo Clinic (Rochester-MN, USA); echocardiographic field at Echocardiographic and Hemodynamic Laboratory of Mayo Clinic (Rochester-MN, USA); left ventricular remodelling. **Medical Genetics - Dr. Iascone.** In the last five years: 1) Co-I "Sequencing of the newborn genome: feasibility and clinical, ethical, psychological and economic implications", Telethon Foundation (lead partner) in partnership with ASST PG23 and UNIAMO Federation Italian Rare Diseases Onlus; 2) PI of "Responsible Implementation of Newborns Genome Sequencing: a technical and interpretative feasibility study" GSP21003-Telethon; 3) PI "GENE - Genomic analysis Evaluation Network-Prospective multicenter cost-effectiveness study of whole exome sequencing (WES) as the first genetic test in pediatric patients with suspected genetic disease" Innovation projects in the field of health and social health of the Lombardia Region; 4) "RARE: Rapid Analysis for Rapid care - Evaluation of the clinical utility of whole exome sequencing (WES) for the urgent diagnosis of rare genetic diseases in critically ill pediatric patients in neonatal and pediatric intensive care", ASST PG23.

Involvement in Regional, National and international working groups or Medical / Scientific Societies

Prof. Trevisan is member of Italian Society of Diabetology (SID). Previous. Member of the SID scientific Committee, past SID president of Lombardia Region and member of SID national board. Involved in several trials related to the use of technology in Type 1 diabetes. **Prof. Senni** is Fellow of the Mayo Clinic; Fellow of the European Society of Cardiology from 2000; Fellow of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) from 2001; Associate Editor of European Journal of Heart Failure; Chairman of Heart Failure Working Group of ANMCO in 2009-2010; Member of Committee - HFA Working Group of Heart Failure preserved Ejection Fraction of Heart Failure Association of ESC; Member of the Study Group on Diabetes and Hypertension of Heart Failure Association of ESC. Member of the technical commission for the experimental introduction of new therapies and new technologies in the Cardiovascular field General Welfare Department. **Dr. Iascone** is Member of Italian Society of Human Genetics and of European Society of Human Genetics; Member of Section I Working Group of the Consiglio Superiore di Sanità: "Transfer of Omics Techniques in clinical practice." (2020-2021). **Dr. Gianatti** is Member of the Italian Society of Pathological Anatomy (SIAPEC); Regional coordinator of the SIAPEC lymphoma study group; Coordinator of the technical table of pathology of oncological screening programs of the Lombardia Region.

Collaborations with ANTHEM participants

ASST PG23 - NEGRI Data for clinical decision support and data management. Genomic analysis of rare diseases by precision medicine.

ASST PG23 - UNIBG: 1) Artificial intelligence algorithms for the development of critical care evaluation of AKI; 2) Development of a no-SQL database for the management of genetic data and effective diagnosis of rare diseases; 3) Data-driven design of MPC controller for artificial pancreas; 4) XR for tele-rehabilitation. In addition, stable agreements for the development of research and educational activities. 5) Clinical decision support system and data management. AI-based artificial Pancreas and endocrinological therapies. AI-based tools for genomic diagnosis for precision medicine. Remote physical therapy and telemedicine

Educational activities including research doctorates and specialisation courses
<p>ASST Papa Giovanni XXIII hosts the School of Medicine and Surgery. It is a six-year MSc degree Course in Medicine and Surgery in English language of UNIMIB in partnership with the UNIBG, the University of Surrey, and ASST PG23. Based in Bergamo, the program has a revolutionary new medical curriculum integrating a rigorous program of basic science education with intensive clinical mentoring right from the second year onwards. The program offers a multidisciplinary and inter-professional educational experience fostering the integration of knowledge and skills, open-mindedness, scientific and critical thinking, a caring attitude, and a holistic approach to health care needs. Prof. Trevisan is Associate Professor in the specialisation school of Endocrinology and Metabolism. Among the main interests in teaching and research: the advantage of advanced hybrid closed loop systems for the treatment of type 1 diabetic patients. Prof. Senni: National Scientific Qualification Associate Professor 1st and 2d level - Diseases of the Cardiovascular System and Diseases of the Respiratory System MUR. Postgraduate school of Cardiology. Dr. Iascone is tutor for the specialty school in medical genetics at the University of Milan, thesis supervisor in medical genetics, professor of medical genetics for Course in Medicine and Surgery in the English language of Milano Bicocca University, and lecturer of cardiovascular medical genetics for the IHS-UniBg Master. Dr. Gianatti is Adjunct Professor for the degree course in medicine and surgery at UNIMIB.</p>
International bibliometric indicators
<p>For key researchers participating in ANTHEM, H-index/number of publications/number of citations are reported (source: Scopus): Roberto Trevisan (47/185/10.525); Michele Senni (62/354/21.439); Maria Iascone (20/129/1.592); Andrea Gianatti (25; 110; 3.579).</p>

Azienda Ospedaliera Cannizzaro Catania (CANNIZZARO)
<p>CANNIZZARO is a public hospital and the emergency hospital for the eastern Sicilia (II LEVEL emergency department). It is a centre of excellence with advanced specialities several areas of medicine and surgeries, particularly for neurosurgery with gamma knife, burnt unit (reference unit for eastern Sicilia), stroke unit, gynaecology, thoracic surgery, vascular surgery, haemodynamics and nuclear medicine. The hospital has an area of 160.000 square metres, comprising more than 540 beds, including beds in intensive and subintensive care, 22 surgery theatres. CANNIZZARO has a heliport and CO118. The hospital performed around 20.000 hospitalizations (more than 60%, represented by emergency patients). The Advanced technological department, hosted in CANNIZZARO, has several high technology equipments, such as Cyclotron and PET. PET imaging is a crucial step towards precise medicine for the assessment of oncological patient outcome and response after chemo or radio treatment. Metabolic parameters are often faster changing and more indicative of therapy effects than morphological changes allowing an early prediction of therapy response at interim of treatment. For this reason, PET imaging possesses an enormous potential to improve clinical cancer treatment decision making and clinical testing of novel cancer therapy protocols to minimize risk of treatment failure and side effects allowing the discrimination of patient responders from non-responders to treatment. Moreover, molecularly targeted agents focusing on cancer hallmarks in combination with radiotherapy are becoming an increasingly important component in the treatment of tumours. Characterising the tumour microenvironment before and after treatment could help to optimise the outcome of these combined effects. At this scope, preclinical imaging studies represent a potential approach to evaluate therapeutic strategies using agents targeting molecules and radiotherapy.</p>
Key persons and expert groups
<p>Nuclear Medicine Unit: Dr. Ippolito Massimo, MD; Dr. Sebastiano Cosentino, MD; Dr. Fabrizio Scopelliti, Pharmacist PhD Medical Physics Unit: Dr. Maria Gabriella Sabini, Medical Physicist MD</p>
Key infrastructures
<p>The Unit of Nuclear Medicine at CANNIZZARO is the first public centre operating in Sicilia for the production and use of positron emitter radiopharmaceuticals for the diagnosis of pathologies, mainly in the oncological field, but also cardiological and neurological. The centre is equipped with 2 PET scanners, one of which is equipped with CT 16 slices Biograph Horizon (Siemens company), and the other equipped with CT 64 slices (GE Healthcare company), both with 4D and TOF system. All these equipments represent the latest generation of scanners that the centre has been equipped with, from July 2005 when its diagnostic activity began: starting from a single PET scanner, in 2007 the first PET/CT tomograph was added, and subsequently, in 2010, a new PET/CT 64 slices 4D-TOF (first installation in Italy) was installed, as a replacement for PET not equipped with CT. Finally, in 2017, the Centre updated its technologies with</p>

the addition of a second hybrid tomograph to replace the older PET/CT, now having a fleet of cutting-edge machines in the early diagnosis of oncological diseases.

In addition to the diagnostic instruments, the Center also includes a Radiopharmacy Laboratory, which is equipped with the following instruments: i) 18MeV cyclotron for the production of positron emitting radioisotopes, placed inside a shielded bunker with concrete walls over 2,5 metres thick; ii) 5 synthesis and manipulation hot-cells, used for the production, to date, of 6 tracers for clinical use (18F-FDG, 11C-Choline, 11C-Methionine, 68Ga-DOTATOC, 68Ga- and 18F-PSMA); iii) Laboratory to perform quality controls on radiopharmaceuticals produced. All this makes the Nuclear Medicine Unit of Cannizzaro Emergency Hospital the only centre in Sicilia and one of the few centres in Italy to produce several specific radiopharmaceuticals for the diagnosis, follow-up and response to the treatment of different tumour histotypes.

The **Medical Physics** Unit provides adequate answers in the field of management, control and clinical use of radiological equipment and radioactive sources used for diagnostics, therapy and research, as well as physical surveillance for protection from risks from ionising radiation for patients, operators and individuals of the population, in compliance with Italian and European laws.

The main activities carried out by the Medical Physics team concern Radiation Protection, Radiotherapy, Gamma Knife, Radiodiagnostics, Nuclear Medicine, Non-Ionizing Radiation, and Health Technology Assessment.

Recently, a brand-new laboratory has been created in an area nearby the existing one. This laboratory consists of a dedicated production room (where 4 hot cells and 3 synthesis modules are installed) and a quality control room (where HPLC, Mass Spectrometry, Gas Chromatography, TLC and other controls can be performed) entirely dedicated to research projects, finalised to preclinical studies on mice and small animals in cooperation with Catania University and CNR-IBFM.

Ability to manage clinical trials and projects

CANNIZZARO is involved in two H2020 projects (EXA MODE and BIGPICTURE) and is leading a research project funded by Regione Sicilia named Breast Cancer Therapy (BCT). In 2015, CANNIZZARO was awarded a project funded by the National Healthcare Plan (Piano Sanitario Nazionale), aimed to develop a high technology radiopharmacy laboratory. Other activities include:

- Phase-III randomised study (double blind) with Pembrolizumab (MK-3457) and Enzalutamide versus Enzalutamide with placebo in patients affected by Metastatic Castration-Resistant Prostate Cancer;
- Phase-III randomised study (double blind) to test security and effectiveness of Pembrolizumab in combination Lenvatinib versus Pembrolizumab and placebo in patients affected by Urothelial Carcinoma;
- A Phase 3, Randomised, Double-Blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Tafasitamab Plus Lenalidomide in Addition to Rituximab Versus Lenalidomide in Addition to Rituximab in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma Grade 1 to 3a or R/R Marginal Zone Lymphoma;
- Imaging protocol for NGS-negative MDR patients. In addition, UNICT, INFN and CANNIZZARO are already realising a preclinical facility for ultra-flash proton therapy thanks to the BCT program funded by the Sicilia Region. This facility will be upgraded for electron ultra-Flash preclinical studies in the framework of this proposal.

Involvement in Regional, National and international working groups or Medical / Scientific Societies

All the activities involving these branches are “by definition” transversal, because all these clinical activities are strictly and firmly connected to each other. Starting from 2010, a Multidisciplinary Unit of Senology is operating at CANNIZZARO. The inpatient department is made of 6 beds for breast cancer disease, as ordinary hospitalisation, day hospital and day service. The diagnostic and therapeutic pathway is shared with the Nuclear Medicine Unit regarding the sentinel lymph node and PET, with the Radiotherapy Unit and with the University Plastic Surgery Unit regarding breast reconstruction. The activity, the number of cases treated per year, the clinical pathways, are perfectly aligned with guidelines from European Society of Mastology.

Medical Physics Unit cooperates with INFN LNS for the study and clinical implementation of dosimetry techniques with thermoluminescence and radiochromic detectors (GAF) - Scientific collaboration with the Institute of Bioimaging and Molecular Physiology (IBFM) of the National Research Council (CNR) for the development of diagnostic and therapeutic research protocols, for the implementation in the clinical routine of innovative PET/CT and MRI image processing techniques, for the study of new biomarkers that correlate multimodal data from diagnostic and therapy techniques with clinical follow-up.

This interest of the community in preclinical research has led to establish a collaboration with UNICT, Centre for Advanced Preclinical *in vivo* Research, INFN-LNS, and IBFM-CNR in Cefalù. To formalise the collaboration, a Memorandum of Understanding was signed in 2017. The main aims of this network are to build a strong research

collaboration on small animal research and to create a user-orientated preclinical facility where dedicated *in vivo* researches to be translated into clinical practices can be performed.

Collaborations with ANTHEM participants

CANNIZZARO - UNICT: Preclinical research

CANNIZZARO-UNICT-INFN: BCT (Breast Cancer Therapy) funded by Sicilia Region

Educational activities including research doctorates and specialization courses

Tutoring and teaching activities have been carried out for different schools and students of UNICT: Degree in Radiology, Degree in Radiology technician, Specialisation in Medical Physics, Specialization in Hospital Pharmacy. Tutoring and teaching activity also involved postgraduate students of Master degree in Clinical Pharmacy: oncologic compounding and Molecular and translational Imaging: from preclinic to clinic, held by Messina and Catania Universities. Additionally, several courses have been performed within regional orientation projects for high-school students.

International bibliometric indicators

For team members H-index/number of publications/number of citations are provided (source: Scopus): Ippolito Massimo (15/46/542); Sebastiano Cosentino (7/22/125); Fabrizio Scopelliti (1/4/4); Maria Gabriella Sabini (18/69/987).

Agency for Health Protection of the Milan Metropolitan Area (ATS MI)

ATS MI n is a Public Health Agency of the Lombardia Region. Its mission is to concretize the health planning of the Lombardia Region in its catchment area and to guarantee the provision of essential health services (Essential Levels of Assistance - LEA) through services delivered by health-care facilities, both public and private. They also oversee the integration of health and social services provided by the public authorities. ATS MI covers 193 municipalities in the Northern Italian region of Lombardia, with a total population of 3,48 million inhabitants. The ATS manages an organised data warehouse, where demographic and health administrative information on the population is stored.

Key persons and expert groups

Antonio Giampiero Russo, Director of the Unit and of the Cancer Registry, having a long-term experience in Epidemiological and Statistical analysis of chronic diseases and their management, using both clinical and administrative databases. Anita Andreano, Responsible of the Hospital performance and Monitoring Unit, including taking care of chronic patients by general practitioner and territorial health services. Sara Tunesi, expert in biostatistic and environmental epidemiology, with long-term experience in epidemiological and statistical analysis of chronic diseases.

Key infrastructures

The Epidemiology Unit of ATS MI manages 3 population registries, collecting clinical information at the individual level: i) Cancer register (about 30.000 new cancer cases detected/year) accredited to the International Cancer Agency of Lyon; ii) Register of Causes of Death (coding the main cause of death for about 35.000 deceased residents/year); iii) Register of congenital malformations accredited as full member at EUROCAT.

These registers are integrated with the data warehouse and allow the integration of individual information derived from the patient contact history with the nodes of the Health System with clinical information, pathology data and information relating to the treatments received by the included subjects.

The Epidemiology Unit of the ATS of Milan has availability of all data needed for the project within its catchment area, and has experience in constructing algorithms for chronic disease classification and predictive models in public health contexts, as well as visualisation of health profiles in publicly available websites.

Ability to manage clinical trials and research projects

The Epidemiology Unit has participated, and is at present involved, in national research projects on epidemiology and clinical pathways of chronic diseases, and has experience in applied research based on administrative health data, which will be used to coordinate and realise part of the project:

- CARIPLO Foundation: 2021-4388 (9/2022-9/2024): The Post-Covid-19 Syndrome: network building and innovative management to address a new public health emergency". (Partner)
- CARIPLO Foundation: 2020-4269 (10/2021-04/2023): Enhancing healthcare and well-being through the potential of big data: an integration of survey, administrative, and open data to assess health risk in the City of Milan with data science. (Project Coordinator)
- Ministry of Health Ricerca Finalizzata: RF2011-02348959, CUP: E42114000120003 (11/2014-11/2017): From the Measure Of Guidelines Adherence In Oncology To The Assessment Of Health System Performance. (Project Coordinator)

- Regione Lombardia - DG Health - Innovative Project 2011 (field of innovative research): (2011-2013): Integration of tumor registries with DIPO, ASL Milano1, Cremona and Monza Brianza. (Project Coordinator)

Involvement in Regional, National and international working groups or Medical / Scientific Societies

The Epidemiology Unit has been identified by the Lombardia Region as the reference ATS for epidemiology, with particular reference to the area pertaining to the Diseases Prevention of the Lombardia Region. Its Cancer registry is included in the network of AIRTUM (Italian Association of Cancer Registries) performing, as a member, collaborative studies on epidemiology of cancer, also in relation to other chronic diseases. The register is also accredited to the IARC and has participated to numerous international studies, including the CONCORD programme for world-wide surveillance of trends in cancer survival, led by the London School of Hygiene & Tropical Medicine and the BENCHISTA International benchmarking of population-based childhood cancer survival by stage at diagnosis.

Collaborations with ANTHEM participants

ATS MI - UNIMIB:ATS is involved in the Residency Program in Biostatistic and Medical Epidemiology

Educational activities including the activation of research doctorates and specialization courses

The Epidemiology Unit of ATS MI is included in the network of the Residency programme in Biostatistic and Medical Epidemiology of the UNIMIB.

International bibliometric indicators

For team members H-index/number of publications/number of citations are provided (source: Scopus): Antonio Giampiero Russo (56/227/12.272); Anita Andreano (18/62/1.135); Sara Tunesi (18/45/1.877).

BIOGEM scarl (BIOGEM)

BIOGEM is a consortium between universities and research centres. Scientific research carried out at Biogem has a strong translational vocation, aiming to contribute to the development of new and more effective diagnostic and therapeutic applications, particularly in the nephrology and oncology fields, also making use of a very advanced facility for the generation of animal models of several pathologies (i.e., mouse, rat, rabbit, and zebrafish). An important role is played by preclinical research, aimed at testing new drugs, for which Biogem has recently got the GLP (Good Laboratory Practice) certification, the only Research Centre in Southern Italy for toxicity and biocompatibility studies. Biogem is also active in higher education and dissemination of scientific culture: it organises MA and PhD programs in relevant scientific disciplines and has a Museum of the History of Earth and Life.

Key persons and expert groups

Capasso Giovambattista is Full Professor of Nephrology at University of Campania “Luigi Vanvitelli” - Napoli and since 2014 the scientific director of Biogem institute. He has a long experience in precision and personalised medicine with translational approach in the area of rare diseases, kidney pathophysiology, onco-nephrology and brain-kidney interaction.

Michele Caraglia is Full Professor of Biochemistry at University of Campania “Luigi Vanvitelli” - Napoli, director of the molecular oncology and precision medicine lab at Biogem, and since 2019 chair of Covid-19 Molecular diagnostics at Biogem institute. He has a consolidated experience in the study of the signal translation in human cancer cells achieving many important accomplishments in the field of cancer research, thanks to the numerous national and international collaborations.

Concetta Ambrosino is Associate Professor of Biology at the University of Sannio and Head of Gene & Environment laboratory at Biogem Research Institute. She has a large experience on Development and study of zebrafish and mouse models of human pathologies to identify alternative models for the dissection of signalling pathways. She has conducted landmark studies to verify the environment toxicity on gene function.

Key infrastructures

BIOGEM is organised in 6 research laboratories: Molecular Oncology and Precision Medicine, Translational Nephrology, Stem Cells and Tissue Regeneration, Genes and Environment Interaction, Epigenetics, and Computational Biology labs. The most relevant technologies and infrastructure are:

- Computational infrastructure (1000 CPU cores, 10 GPU units, 5TB RAM, and 500TB storage).
- Software tools and ready to use pipelines to perform typical large scale genomic, transcriptomic, and proteomic analyses from sequencing data.
- Genomics equipment such as, Ion S5 system, Ion Chef, Illumina next 550, FACS cell sorter.
- Mass spectrometry interfaced with HPLC to allow hyphenated analytical schemes: like LC/MS and LC/MS/MS; alternatively, nano-LC chromatography for high sensitivity or specific proteomics type of

analysis.
Ability to manage collaborative projects
<p>BIOGEM has a longstanding experience in managing both national and international scientific projects, such as: European projects (FP6-LIFESCIHEALTH - Focusing and Integrating Community Research programme 2002-2006 - Silencing RNAs: organisers and coordinators of complexity in eukaryotic organisms SIROCCO; FP6-LIFESCIHEALTH - Focusing and Integrating Community Research programme 2002-2006 - European transcriptome, regulome and cellular commitment consortium - EuTRACC; Marie Curie PIRG-GA-2008-239519 - Pancreatic stem cell PIRSES-GA-2012-318981- RNA REGULOMICS: the role of non coding RNA in human health and disease; Marie CurieFP7-PEOPLE-2007-ERG-246680 SepiaCartilage.</p> <p>Recently, Biogem has been involved in the European CanServ project, aimed at the creation of a network for Cancer Research Infrastructures.</p>
Collaborations with ANTHEM participants
<p>BIOGEM - UNICAMP: CONNECT CA19127 “Cognitive decline in Nephro-Neurology: European Cooperative Target” of the COST Action; iCURE project (Identification, characterization and significance of colorectal tumorigenesis: cause, prevention and cure) POR CAMPANIA FESR 2014/2020 ASSE I</p> <p>BIOGEM - UNICT R&S activities on biomarkers identifications and development of new diagnostic methods (Project “Identificazione di biomarcatori e sviluppo metodi diagnostici e terapeutici nel campo dell’oncologia e della biologia vascolare”, funded by MIUR PON – Ricerca e Competitività 2007-2013)</p>
Patents, granted technologies and/or International bibliometric indicator
<p>BIOGEM has 3 start-up entities: CAREBIOS Campus Regi Biologia Srl was established in 2008, promotes and supports scientific research in biotechnology field; IMMUNOMICA SRL, an innovative start-up founded in 2021, aimed at launch on the market two analytical platforms dedicated to precision medicine in Oncology; CaWUR s.r.l. conceived to generate cancer patients-derived organoids to improve personalised therapies.</p> <p>Biogem has contributed to the development of several patents, such as Cyclopentanone and cyclopentenone derivatives as potent activators of HSF-1/Improvements in Pharmaceutically Useful Compounds (“4-aza”) International number: WO 04/013077; US 7,183,440; UK 0218261.6 6; EU 3766493.5; Improvements in Pharmaceutical Compositions (“Thiol Adducts”); Improvements in Pharmaceutical Compositions (“208”), 2009 International number: WO 08/012583; US 12/375,208; UK 0515573.4; JP 2009-521352, HK 09111176.4; EU 07789358.4 26; Synthetic Method and Novel Chemical Compounds Internazionale Numero: WO 03/080552; US 7,304,186; UK 207028.2; Methods for Inhibiting IKK, 2006 International number: US 60/167,090; 60/186,023; 7,053,119; 7,399,606; RETINOID DERIVATIVES WITH ANTITUMOR ACTIVITY, 2017 Number: EP16191348.8.</p> <p>Bibliometric Indicators (H-index/publications/citations, source Scopus): Capasso Giovambattista (40/341/7.422); Caraglia Michele (65/509/18.952); Concetta Ambrosino (29/59/3.016).</p>

Fondazione Europea di Ricerca Biomedica Onlus (FERB)
<p>FERB is a non-profit organisation (ONLUS) founded in 2001. It was founded by four European foundations with the common goal of successfully managing healthcare facilities with particular attention to the care and rehabilitation field. FERB Onlus identifies its mission in the viability of assistance, social assistance and social health projects against acute diseases and complications emerging from post-acute care and in respect of the various systems whatever is the cause of the alteration, impairment and eventual disability.</p> <p>To achieve these goals the Statute provides that FERB Onlus can establish and manage care facilities directly or by agreements with companies or Public or Private Hospitals as well as forms of public-private collaboration, according to the legal provisions in force.</p> <p>Along the years FERB Onlus focused its attention to the research field, thanks to agreements with the main Italian Universities and other healthcare facilities, thus investing several resources to research and innovation. FERB Onlus adapted the activities performed in its facilities to the changing health needs through an ongoing commitment to innovation and improvement. Through the research, it has been able to develop new procedures of Rehabilitation Interventions in intensive care and increase the rehabilitation treatment of chronic diseases. Results were outstanding (see the following sections), in several fields such as the after-effects of the cerebrovascular and neurodegenerative diseases, chronic rehabilitation and all the aspects related to patient assistance after the hospitalisation (caregivers).</p> <p>FERB Onlus research department is currently working on different fields. One of the most important ones is the</p>

‘REcage project’, which is an European project that aims to tackle one of the most challenging problems arising during the clinical course of dementia: the so-called Behavioural and Psychological Symptoms of Dementia (BPSD). The major objective of the project is to assess the effectiveness of an intervention, through a special medical care unit for patients with BPSD. This treatment looks promising for both short and long-term efficacy (alleviating BPSD and improving quality of life of patients with dementia).

Moreover, FERB Onlus is working on the Parkinson disease field, studying the application of new neurophysiological techniques in its facilities. Five different double-blind clinical trials are currently underway with the aim of improving gait and balance disorders in Parkinsonian subjects through transcranial direct current stimulation (TDCS) and repetitive magnetic stimulation (rTMS) techniques.

Interventional experimental protocols designed to evaluate the efficacy and brain changes related to rehabilitation aided by cortical stimulation with rTMS focused on rehabilitation and neurostimulation treatment for stroke patients have been activated.

Finally, an important aspect of FERB Onlus research is about ‘coma state’ patients: from studies conducted in collaboration with the University of Milan and the Coma Science Group at Liegi University, through the application of TMS/hd-EEG, it was possible to distinguish the vegetative state from the minimally conscious state; that is of paramount importance to guide future therapeutic and rehabilitation strategies.

Key persons and expert groups

The Units involved in ANTHEM are the Rehabilitation Unit and the Special Care Unit for Alzheimer. For key persons see CVs.

Key infrastructures

FERB Onlus is currently managing four healthcare facilities, following public tenders, three with the Bolognini Hospital of Seriate (BG) for the management of St. Isidore Hospital of Trescore Balneario, the Excellence Centre for the treatment and rehabilitation of people with Alzheimer at the Briolini Hospital of Gazzaniga, a Hospice at the Passi Hospital of Calcinante, and one with the Melegnano Hospital in Cassano d’Adda (MI). The active ordinary beds are 87 in Trescore Balneario (15 General Practice, 57 Specialistic Rehabilitation and 15 General Geriatric Rehabilitation) in addition to 4 technician beds dedicated to macro-rehabilitation specialist (day hospital); 46 ordinary beds of Specialistic Rehabilitation and 2 technicians beds dedicated to macro-rehabilitation specialist in Gazzaniga, 14 beds in Calcinante and 60 beds in Cassano d’Adda, 12 of them dedicated to Alzheimer patients.

Ability to manage clinical trials and research projects

FERB Onlus has a solid research organisation, which involves Physicians, Therapists (physiotherapists, speech and language therapists, occupational therapists, etc.), Professors, Phd students, which made outstanding results along the years, mostly through the synergies between the healthcare facilities managed and the partner Universities. In the Alzheimer Excellence Centre of Gazzaniga (BG) operate physicians (including FERB Onlus Scientific Director Prof. Defanti) and therapists who have long time experience in the Neurology field; the Centre is also the research site of the ‘ReCage project’, that involves 18 organisations, covering all the necessary components of the ecosystem and of the innovation chain, to reach the project objectives (clinical partners, government organisations, etc.).

All the healthcare facilities have state-of-the-art medical devices, including robotics equipment, mostly to perform rehabilitation techniques for inpatients, which is used for research activities as well.

On the website <https://www.ferbonlus.com> is a section called ‘Ricerca’ with all the publications in which FERB Onlus contributed.

Involvement in Regional, National and international working groups or Medical / Scientific Societies

International:

- Belgium: Université Européenne du Travail (U.E.T) de Bruxelles, about EMS EEG measurements of data and population analysis as part of studies with TMS EEG equipment; Coma Science Group at Liège University (Prof. Steven Laureys); Université Libre de Bruxelles and Université Catholique de Louvain.
- Germany: University Hospital Würzburg Josef – Schneider, about the role of investigating the pathophysiology of movement disorders by means of high-density electroencephalogram, trans cranial magnetic stimulation, biomechanical analysis, brain imaging studies including by clinical neurophysiological assessments and rehabilitation protocols.
- National:
- Cognitive Neuroscience Section, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia;
- Department of Medicine and Surgery, Section of Neuroscience, University of Parma;
- Center for Mind/Brain Sciences- CIMEC, University of Trento about the application of rTMS for cognitive enhancement in Alzheimer's disease;
- University of Milan, about EMS EEG studies;

- University of Genova DIBRIS (Department of informatics, Bioengineering, Robotics e System Engineering);
- University of Brescia, about studies on the rehabilitative treatment of Parkinson's disease, progressive supranuclear palsy by means of repetitive transcranial magnetic stimulation and measurement by sensors of posture improvement and instability reduction;
- Neurological Centre 'Carlo Besta' in Milan;
- University of Bergamo, Management Engineering Department;

Collaborations with ANTHEM participants

FERB - UNIBG: Digital health e data analytics. Digital triage. Wearable devices for remote monitoring of chronic and frail patients.

FERB- UNIBG - ASST BGEST: Concept study of the MyTravelCare platform, a support to foreign travellers in Italy

FERB - UNIMIB: Framework Collaboration for activities in the disability motor, cognitive and behavioral sector.

Educational activities including research doctorates and specialisation courses

- FERB Onlus is internship site for Physicians and Psychologists coming from several Italian Universities, such as Milano Bicocca School of Medicine and Surgery, University of Roma Tor Vergata, University of Bergamo, University of Parma.

- Partnership with the University of Bergamo for internship Level I Master's degree in "management for health and social work professions - coordination and organisation of hospital, home and community-based services"

- Internship site for Rehabilitation Therapists (University of Brescia, Milano Bicocca, ASST Papa Giovanni XXIII, IRCCS Eugenio Medea Bosisio Parini)

International bibliometric indicators

For the lead researchers, the bibliometric indicators are (source: Scopus) Patrizio Sale: H-index: 34; number of publications: 104; number of citations: 3.672.

Istituto Oncologico del Mediterraneo (IOM)

IOM is an highly specialised, 3rd level oncology department, one of the few in Sicilia, which together with IOM Ricerca Srl and REM Radioterapia Srl, constitutes the Oncology Pole of Viagrande. This pole was created with the aim of reaching a critical mass of high scientific level professionals at the service of therapeutic and research needs in the oncology sector.

The centre aims to personalise diagnosis and therapy through the integration of scientific research and clinical practice, to improve current diagnostic and treatment processes. Since its foundation, the Institute, in its entirety, has operated both in the field of oncological assistance and in scientific research applied to the treatment of cancer, making use of professionals from different specialties (highly qualified doctors and researchers) who operate across the board by participating in clinical and research activities (basic research and molecular research), discussing therapy and clinical pathways and, with the support of advanced diagnostic structures, following the patient towards recovery or towards treatments that can guarantee better living conditions.

The centre was born from the idea of developing research paths particularly oriented towards clinical output and effectively transferring the research results to the patient's bed. To increase technology transfer from basic to clinical research, the IOM is strongly dedicated to translational research and focuses on the excellence of clinical practices, with a strong push towards scientific research and technological innovation.

R&D activities are designed and implemented under the direction of the Institute's Scientific Director. By virtue of the strong propensity for research, the Oncology Center boasts a very modern research centre equipped with cell biology laboratories, imaging laboratories, experimental radiotherapy laboratories, biorepository, biobank and cryogenic conservation, technological platforms and a modern animal facility specialised in housing of rodents (mice and rats), laboratories for preclinical experimentation and an internal OPBA for the evaluation of research projects and support to submit authorization requests to the Ministry of Health.

The laboratories have been designed and equipped following the highest technical and scientific standards and; together with the clinical activity, they are constantly engaged in research and development as evidenced by the participation in numerous research projects funded by the Ministry of Education, 'University and Research or from the Sicilia Region. The laboratories are equipped with equipment dedicated to molecular investigations, allowing efficiency and automation for pre-analytical processes (extraction and purification of nucleic acids through automated extractors, evaluation of concentrations and quality through microfluidic electrophoresis on chip) and analysis (NGS sequencing, real time PCR High -throughput). The research laboratories are structurally designed to minimise interference between operational flows by separating the purification operations from the amplification

and characterization phases (extraction, pre-PCR, post-PCR) and the procedures used follow the quality standards required by UNI EN ISO 9001: 2015 regulation. The pathology unit acts as a contact point between clinical activities and research laboratories, and has invested considerable efforts in streamlining the flows of biological samples. The unit also has extensive research experience in the topics of molecular diagnostics and biobanking, and over the years has created an organised collection of biological materials (fresh and waxed), annotated with clinical information. The IOM biobank is part of the European network of biobanks BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) thanks to the high standardisation of the procedures applied in the operational process of the structure.

The idea of developing research paths particularly oriented towards clinical output, and of effectively transferring the research results to the patient's bed, led the IOM to create a qualified research laboratory equipped with advanced technical-scientific equipment: IOM Ricerca Srl. IOM Ricerca has developed a series of innovative tests with the aim of bringing routine diagnostics to new levels of innovation and quality. In addition, IOM Research has been engaged since its establishment in R&D projects that allow the improvement, update and enhancement of its biotechnological services offer; thanks to the solid experience IOM Research offers a wide range of biotechnological services and customised solutions for the realisation of various research projects or to validate new scientific protocols. Finally, the research centre is structured as a Campus open to the establishment of other research entities, public and private, which share this vision and has been identified by the Sicilia Region as a technological Campus that offers skills at the service of technological, strategic innovation, organisational and commercial of SMEs (the Campus has been included in the catalogue of innovation service providers of the Sicilia Region). IOM will make use of the expertise of IOM Ricerca Srl (spin-off of the Institute with inter-interest relationships) to carry out part of the project activities.

Key persons and expert groups

IOM Integrates different high-level professionals with covering different aspects of medical care and research. IOM comprises different multidisciplinary oncology groups (Breast Unit, GI Cancer, Molecular Therapy board). Key persons are: Prof. Giorgio Stassi (Scientific Director of the Institute), Prof. Dario Giuffrida (Oncologist - Director of the Oncology Department), Prof. Giorgio Giannone (Director of GI Surgery), Dott. Paolo Fontana (Director of the Breast Unit), Dott. Lorenzo Memeo (Director of Pathology), Dott. Stefano Forte (Director of the in vivo and in vitro Research laboratory), Dott. Gianluca Ferini (Director of Radiotherapy), Dott. Luigi Castorina (Director of Nuclear Medicine).

Key infrastructures

Involved in ANTHEM: omics and NGS facility (with its bioinformatics unit), experimental radiotherapy facility, the animal models facility, the experimental oncology Unit and the pathology Unit.

Ability to manage clinical trials and research projects

The Institute has an internal division dedicated to R&D activities, of high competence and professionalism, equipped with modern facilities, able to carry out highly innovative and wide-ranging activities, as demonstrated by the participation in numerous research projects financed by the European Community, the Ministry of Education, University and Research, the Ministry of Economic Development and the Sicilia Region, and a considerable number of scientific publications of international relevance.

For several years now, IOM Spa has participated, as leader, partner or supplier of know-how, in numerous funding programs for scientific research in the life science field, with the ambitious goal of enhancing its expertise in the topics of molecular oncology and translational medicine. The management of R&D projects is the responsibility of the "Management of R&D projects" office which carries out the planning, monitoring, auditing and scientific and administrative management of the projects, in line with the relevant legislation and according to the procedures of quality that foresee internal SOPs prepared for the management of R&D projects. In recent years, in particular, research activities of the IOM have focused on the increasingly topical issue of precision medicine (aiming to identify new and superior technological solutions, and implementing synergistic systems to support clinical decisions that favours the personalization of the diagnosis also in a pro-therapeutic sense), on the theme of digital pathology and on the theme of experimental radiotherapy.

Finally, the Institute manages several clinical trials of both phase 2 and phase

Leading scientific activity in the last 10 years

- Puglisi C et al. Ex Vivo Irradiation of Lung Cancer Stem Cells Identifies the Lowest Therapeutic Dose Needed for Tumor Growth Arrest and Mass Reduction In Vivo. *Front Oncol.* 2022 May 12;12:837400. doi: 10.3389/fonc.2022.837400. PMID: 35646627
- Castorina P et al. *J Pers Med.* 2022 Mar 26;12(4):530. doi: 10.3390/jpm12040530. PMID: 35455646
- Puglisi C et al. Radiosensitivity of Cancer Stem Cells Has Potential Predictive Value for Individual

Responses to Radiotherapy in Locally Advanced Rectal Cancer. *Cancers (Basel)*. 2020 Dec 7;12(12):3672. doi: 10.3390/cancers12123672. PMID: 33297488

- Forte S et al Gene expression analysis of PTEN positive glioblastoma stem cells identifies DUB3 and Wee1 modulation in a cell differentiation model. *PLoS One*. 2013 Dec 12;8(12):e81432. doi: 10.1371/journal.pone.0081432. PMID: 24349068
- She QB Integrated molecular pathway analysis informs a synergistic combination therapy targeting PTEN/PI3K and EGFR pathways for basal-like breast cancer. *BMC Cancer*. 2016 Aug 2;16:587. doi: 10.1186/s12885-016-2609-2. PMID: 27484095
- Di Franco S et al. Adipose stem cell niche reprograms the colorectal cancer stem cell metastatic machinery. *Nat Commun*. 2021 Aug 18;12(1):5006. doi: 10.1038/s41467-021-25333-9. PMID: 34408135
- Pagliuca A et al. Analysis of the combined action of miR-143 and miR-145 on oncogenic pathways in colorectal cancer cells reveals a coordinate program of gene repression. *Oncogene*. 2013 Oct;32(40):4806-13. doi: 10.1038/onc.2012.495. Epub 2012 Nov 5. PMID: 23128394.
- Vigneri P et al. High BCR-ABL/GUSIS Levels at Diagnosis of Chronic Phase CML Are Associated with Unfavorable Responses to Standard-Dose Imatinib. *Clin Cancer Res*. 2017 Dec 1;23(23):7189-7198. doi: 10.1158/1078-0432.CCR-17-0962. Epub 2017 Sep 19. PMID: 28928163.

Involvement in Regional, National and international working groups or Medical / Scientific Societies

IOM has implemented a vast area of research involving all the skills operating within the Institute, and the establishment of scientific collaborations with research bodies of national and international relevance. IOM is part of a structural and stable network of public and private subjects and institutions operating in the field of culture and scientific research and oncology, including: the IRCCS San Martino Hospital in Genoa, the Rizzoli Orthopaedic Institute, the Istituto Superiore di Sanità (ISS), CNR, UNIME, UNICT, IFOM, Cloud Pathology Group, Alphagenics Biotech Srl, Vera Salus Ricerca Srl, the Research Consortium in Oncology and Molecular Medicine, the main Sicilian and Italian cancer institutes (both public and private), the University of Genoa, various patient associations, AIL, Alleanza Contro il Cancro, the University of Perugia and biotech companies and pharmaceuticals (Nerviano Medical Sciences, Pfizer, Bracco).

Furthermore, the IOM collaborates with Touro University and Roseman University (Las Vegas, USA) on the topic of liquid biopsy and exosomes; on a stable basis with the department of haematology, oncology and molecular medicine of the ISS, as evidenced by the numerous publications produced and the establishment of the Consortium for Research and Innovation in Oncology and Molecular Medicine; is a full member of the Organisation European Cancer Institute; collaborates with several national universities (the University of Rome La Sapienza); has activated a framework agreement between IOM and UNICT that allows joint research on strategic issues, facilitating operational and scientific interaction between the two bodies.

Collaborations with ANTHEM participants

IOM - UNIME: Drug delivery and therapies. Research platform on oncological research. "Drug Delivery, veicoli per un'innovazione sostenibile" funded by MIUR - PON Ricerca e Competitività 2007-2013

IOM - UNICT: Drug Delivery for cancer. Research platform on cancer research. Joint training program for postgraduate students. Drug Delivery, veicoli per una innovazione sostenibile" funded by MIUR - PON - Ricerca e Competitività 2007-2013

IOM - INFN - UNICT: "Dioncogen: diagnostica innovativa", funded by POR FESR Sicilia 2014/2020 (IOM is Project Leader).

Educational activities including research doctorates and specialisation courses

IOM participates in industrial and executive PhD programs with the University of Messina and with the University of Catania. IOM also participates in the training of medical doctors for the residency programs of the University of Catania. Finally, the Institute has planned a training course of excellence relating to the issues of precision medicine, translation research and total quality management in the healthcare sector. This II level Master, already approved by the University of Messina, will start at the end of the year 2022.

International bibliometric indicators

For researchers participating in ANTHEM, H-index/number of publications/number of citations are reported: Lorenzo Memeo (44/106/9.207); Stefano Forte (26/70/2.110).

Istituto Mario Negri (NEGRI)

The Istituto di Ricerche Farmacologiche Mario Negri IRCCS (IRFMN) is an Italian private, not-for-profit organisation for the research and education in biomedicine established in Milan, Italy in 1961 with the main aims to improve human health and wellbeing. Today, beside the original Milan headquarters, IRFMN has two other sites

in Bergamo, namely the Anna Maria Astori Centre and the Clinical Research Centre for Rare Diseases “Aldo e Cele Daccò” (CRCRD), dedicated to the basic research and to the application of basic research into clinical practice, respectively.

About 750 among the researchers and support staff are active at the Institute’s three main sites.

IRFMN’s research programs, distributed among 11 departments, span from the genetic and molecular level to the whole human being. The main research headings are the fight against cancer, nervous system and mental illnesses, cardiovascular and kidney diseases, rare diseases, toxic effects of environmental contaminants, food safety, mother and child’s health. IRFMN also evaluates the efficacy of health interventions through clinical studies in several medical areas, collaborating with clinical groups, academia or private companies.

Parallel to its biomedical investigations, IRFMN is dedicated to graduate and doctorate training, through Ph.D. and specialisation programs. IRFMN has been formally recognized by the Italian Ministry of Health as IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico – Scientific Institute for Research, Hospitalisation and Health Care) in 2013, with particular reference to pharmacological studies related to neurological, rare and environmental diseases. IRFMN will be represented in this project by the Departments of Rare Diseases and Biomedical Engineering.

Single participating groups

Key persons: Marina Noris and Anna Caroli from the Rare Diseases and Biomedical Engineering Department.

Key infrastructures

The 9500 sqm Clinical Research Centre for Rare Diseases has a day hospital ward with 10 beds and several outpatient consulting rooms. Inter-connected computerised systems allow management and recording of clinical data, biological samples, radiographic and microscope images and statistical data. The Centre's investigators (biologists, geneticists, pharmacologists, bioengineers, informatics, statisticians, nurses and technicians) are involved in pathophysiology, genetic and pharmacology studies on rare diseases and multicentre trials. Data from about 31.500 patients with over 1.000 different rare diseases are recorded in the Centre's database. The Centre leads the International Registry of HUS/TTP and the Italian Registries of MPGN and SRNS. Maintenance of a certified centralised biological sample bank ensures availability of clinical material for new investigative approaches as they get developed.

The Laboratory of Immunology and Genetic of rare diseases equipment include two next generation sequencers with all tools for automatized NGS workflow, Sanger sequence machines, light and fluorescence microscopes, confocal laser scanning microscope, transmission and scanning electron microscopes for tissue and cell imaging, microCT system (SkyScan 1076, Bruker-microCT), software for digital image processing software and workstations and quantification of 3 dimensional structures, cryostat and microtome, spectrophotometers, Trans-Blot Turbo transfer system, Odyssey Licor Imaging System, and all standard laboratory instruments. The Department of Biomedical Engineering has an extensive track record in the delivery of IT service infrastructure to support clinical trials, in the development of dedicated electronic CRFs for data collection, in leading infrastructure operation and maintenance, and in medical imaging analysis, using both analytical approaches and artificial intelligence techniques. Labs are also equipped with the latest equipment for cutting-edge technology embedded with a computer system-based infrastructure for data collection and analysis and combined data and image processing.

Ability to manage and implement excellent projects

This project will be carried out at the CRCRD within the Departments of Rare Diseases and Biomedical Engineering. Since 1992 when CRCRD began its activities, more than 110 clinical studies mainly in the fields of kidney diseases, renal transplant, diabetes and rare diseases have been performed. In these trials the CRCRD has always acted either as promoter or as coordinator. This is made possible because this location offers all the facilities for the design, preparation, conduction and evaluation in a single place.

BENEDICT (NCT00235014), DEMAND (NCT00157586), VALID (NCT00494715), VARIETY (NCT00503152), CRESO (NCT01213212), ATHENA (NCT00494741), ALADIN (NCT00309283), ALADIN2 (NCT01377246), SIRENA (NCT00491517), SIRENA2 (NCT01223755) as well as by the REIN Study whose results are still used by clinicians worldwide to slow the progression of chronic kidney diseases are just few examples of clinical trials designed, coordinated and carried out at the Center.

As for research projects, IRFMN has managed and coordinated numerous national and international research projects. At the EU level, it has been involved in about 160 EU-funded grants (FP5, FP6, FP7, LIFE, H2020, Horizon Europe, etc), in more than 30 of them as Coordinator, and its researchers are still active in initiatives funded under the major EU funding schemes.

Selected EU research projects carried out at the two Bergamo sites in the last 10 years are: EUREnOmics (FP7-HEALTH-2012-INNOVATION-1-305608); STELLAR (FP7-HEALTH-2012-INNOVATION-305436); KidneyConnect (FP7-HEALTH-602422); TranCYST (FP7-PEOPLE-MCA-ITN-317246); NICHOID (ERC-CoG-

2014-646990); NEPHSTROM (H2020-PHC-2014-634086); CKD-AKI (H2020-MSCA-IF- 2015-703226); COBRA (LIFE13 ENV/IT/000492); LAWBRASYS 636592-H2020-MG-2014-2015).

Projects currently active are: nPETS (H2020-MG-2018-2019-2020-954377); TrainCKDis (H2020-MSCA-ITN-2019-860977); DECODE (ERAPerMed 2020-151); RESPECT (ERAPerMed 2020-326); REASON (EuroNanoMed 2019-049); BEAt-DKD (H2020-JTI-IMI2-2015-115974).

National and international collaborations

Over the years, the Mario Negri Institute has created a large network of collaborations, involving clinical centres, general medical associations, hospitals and universities.

Here it is worth mentioning the “GISSI-Italian Group” for the study of myocardial infarction survival, which represented a milestone for cardiovascular diseases. Currently, IRFMN manages the ongoing networks of “GiViTi-Italian Group” for the Evaluation of the Interventions in Intensive Care Units involving more than 560 Intensive Care Units and the “Fenice-Italian Group” for Clinical Research in Emergency Medicine.

The Institute is also characterised by its full and active inclusion in the international scientific community thanks to stable collaborations with numerous international institutions, such as the World Health Organisation, the Organisation of European Cancer Institutes (OEI), the European Medicines Agency (EMA), the European Chemicals Agency (ECHA), the European Food Safety Authority (EFSA), the American National Institutes of Health (NIH). IRFMN is also a partner of the EU infrastructures EATRIS and ECRIN.

As for the CCRD since 2001, it has been the Coordinator Centre of the Regional Network for Rare Diseases in Lombardia and collaborates with the Istituto Superiore di Sanità within the National Network for rare diseases. It also participates in the Italian Network Project for Listening & Information Centres on Rare Diseases – RICA.MaRE, promoted again by the National Network for rare diseases.

CRCRD also leads the GBD Genitourinary Disease Expert Group.

From 2017 to 2021 the Laboratory of Medical Imaging of the Bioengineering Department has been part of the leadership of the COST action PARENCHIMA (Magnetic Resonance Imaging Biomarkers for Chronic Kidney Disease - CA16103) and it is now coordinator of the RESPECT project (EraPerMed-2020-326). Dr A. Caroli has been a member of the European Imaging Biomarkers Alliance (EIBALL) ESR research committee, and is currently past-chair of the EU renalMRI network.

Collaborations with ANTHEM participants

NEGRI - UNIMIB. Multiple research collaborations. Neurological disorders diagnosis and therapy. Theranostic nanoformulation for neurological disorders (i.e. EU NAD Large Project).

NEGRI - UNIBG Clinical decision support system and data management. Computational investigation of morphologic and hemodynamic vascular changes and their role in vascular disease onset. Computational and AI-based tools for vascular access outcome prediction. AI-based tools for genomic diagnosis for precision medicine.

NEGRI – POLIMI: Lung image analysis by analytical and AI techniques in COVID-19 patients

NEGRI- ASST BGEST: Genomic analysis of rare diseases by precision medicine. SARS-CoV-2 genotyping.

NEGRI- ASST PG23: Data for clinical decision support and data management. Diagnostic image analysis in Chronic Kidney Disease, neurological diseases, and COVID-19. Nephrology trials. Genomic analysis of rare diseases by precision medicine.

NEGRI - UNIBG: Modelling and computational fluid dynamics, AI-based Medical imaging

Educational activities including the activation of research doctorates

The Institute runs training courses for graduate researchers, including a national and an international PhD program in collaboration with the Open University UK.

IRFMN also promotes initiatives for the diffusion of scientific culture in biomedicine, in general and as specific backing for healthcare practice, and rational use of drugs.

International bibliometric indicators

The results obtained by researchers at the Institute are set out in more than 16.400 scientific publications in international journals; these have aroused such interest that in 2003 four of the top 50 Italian researchers in all scientific disciplines most cited throughout the world had worked at the Institute. For team members H-index/number of publications/number of citations are provided (sources: PubMed and Scopus): Marina Noris (68/220/16.495); Anna Caroli (32/68/3.125).

AB Medica (ABM)

ABM is a leading company in developing and distributing innovative medical devices and minimally invasive technologies, to more than 400 hospitals in more than 14 European countries. Its mission is to make available



advanced medical technologies able to reduce risks, operative trauma and recovery times, thus significantly improving both the quality of care and the quality of life of patients. ABM, working in partnership with over 50 of the world's most innovative companies in healthcare and fostering on sales force of more than 60 people, has successfully introduced, in the last 30 years, an impressive range of revolutionary technologies in several market segments (i.e. the DaVinci System in Robotic mini-invasive Surgery by Intuitive Surgical Inc, the CyberKnife System in Stereotactic Radiosurgery by Accuray Inc, the Mako System in orthopaedic surgery by Stryker and the Telemedicine and Remote Presence robot by InTouch Health). ABM offers a continuous presence for the client, with an innovative clinical and technical support model.

ABM invests heavily in Research, Development and Innovation, in the fields of health innovation and enabling technology. It is also promoting research projects in the field of rehabilitation, telemedicine and ambient assisted living solutions for the development of advanced medical devices for people affected by neurological diseases.

Key persons and expert groups

Research & Development Department: Marco Nalin, Giovanna Macrì, Mauro Picciafuoco, Irene Del Chicca

Key infrastructures

Maia Connected Care

ABM developed a proprietary telemedicine platform called Maia Connected Care, which is a cloud platform certified as a class IIA Medical Device, in compliance with the directive 93/42/CEE. This platform is the central tool for the virtualization and remotization of several services between the healthcare centres and the patients, allowing a complete management of the care pathways.

Maia allows the definition of a personalised care plan and the monitoring of patients' clinical conditions, the acquisition and storage of physiological data recorded from medical devices, both from the patient and a formal/informal caregiver (or healthcare professional).

The tool is modular, based on a central communication core and a high application flexibility. The main modules are:

- **Tele-monitoring:** through an app, it is possible for the patient to upload data and personal parameters in the platform and manage the monitoring. The tele-monitoring can be discrete (i.e., spot measurement taken by the patient) or continuous, even in real-time, thanks to the Winpack device (and its evolution Winpack HB, described below).
- **Tele-visit:** the tool provides an audio/video connection to open a communication channel between the patient and the clinician. This module can be used simultaneously with the tele-monitoring tool, enabling the possibility to issue a referral and provide guidance on the patient's clinical pathway.
- **Tele-rehabilitation:** the tool allows to design a personalised rehabilitation plan (PRI – Piano di Riabilitazione Individuale), integrating the modules described above and external dedicated tools/contents, opening the participation in the rehabilitation process to different actors/therapists.

Maia allows the creation of different accounts and roles for patients and clinicians, which can be acquired directly from existing legacy platforms, if these are interoperable and open to the data exchange. Furthermore, it allows the creation of a network of healthcare professionals operating on the same patient and clinical pathway, and the collection of epidemiologic data useful for diagnostic purposes.

The Maia platform embeds by design with a technology that enables the integration with the main hospital information systems, at least those compatible with the main communication standards (including HL7/PHIR). Moreover, the platform is open for the integration of external devices, both available by third parties and designed internally to ab medica.

Because of its design rationale and being completely developed in-house, the Maia platform is a tool which is dynamic, flexible and in continuous evolution both from the perspective of the offered services and usage models. Main characteristics: a) Class IIA Medical device; b) General Data Protection Regulation (GDPR) compliance; c) multi-tenancy; d) Integrability with public and private IT systems; e) Interoperability: the platform can collect, share and exchange data, making them available to any system; f) Modularity, with the different modules available on demand based on the different clinical needs; g) Clinical and Technical Service Centre available 24/7 to answer directly to the patients' needs.

Winpack HB

The WINPACK HB system is a medical device for the continuous real-time monitoring of physiological parameters and diagnosis support. The device is targeted for patients in non-critical conditions, and it will be certified as Class IIa medical device in.

The system includes a wearable central unit, able to continuously record (through specific applied parts) and wireless transmit the following physiological parameters: body temperature, SpO2, ECG (with 12 and 7 leads),



Heart Rate, Respiratory Rate, body position and fall detection.
 The central unit has a wireless connection to one or more secondary units, able to perform measurements of further vital signs. One of these units (NIPB) is a wearable device able to measure systolic and diastolic pressure continuously and non-invasively through oscillometric measurement. Such measurement is sent wireless to the central unit, so it can be aggregated with other parameters and transmitted to the central monitoring station. All the units are battery powered, able to provide continuous patient monitoring for 24 hours. The batteries can be extracted from the device and charged through ad-hoc multiple charging pods.
 The Winpack HB has a flexible and expandable architecture to other auxiliary units, making the overall system modular, flexible, and interoperable. Furthermore, all the units are equipped with displays and keys, so to ease the usage of the devices in the different usage scenarios, including real-time monitoring both in hospital and at home.

Ability to manage collaborative projects

In the last 3 years, ABM was involved in 6 funded projects from Regional, National and International public bodies, for an overall budget of approximately 1,3M€. In these projects, in collaboration with other companies and Universities, ab medica worked on research and development of innovative products and services in the lifescience domain. In particular, in 3 of the 6 projects, ABM was project coordinator.

Collaborations with ANTHEM participants

ABM - UNISALENTO: ab medica and UNISALENTO are involved in a joint MISE project for the creation of advanced sensors for EEG monitoring.

ABM -UNIMIB: ABM and UNIMIB participated to various project funded by Lombardia Region on tele-rehabilitation, including Ability, ReAbility and SideraB.

ABM – POLIMI: ABM and PoliMI collaborated in two projects related to tele-rehabilitation, in particular Ability and SideraB, both funded by Lombardia Region.

ABM - UNICT: The two partners were involved in the joint project SMART HEALTH

ABM – CHIESI: The two partners were involved in the IRMI project.

Patents, granted technologies and/or International bibliometric indicator

Patents:

- Electrocardiograph; International Publication WO2015107465, Patent Granted in Europe EP3094237 B2, USA US9314554B2.
- ECoG – Implantable Device for Acquisition and Monitoring of Brain Bioelectric Signals for Intracranial Stimulation –; International Publication WO2012143850, Patent Granted in Europe EP2699145B1, USA US9031657B2; Japan JP6082942 B2; Canada CA2832520A; Australia AU2012245942 B2; China CN103648367B; India 3101/KOLNP/2013.
- Helmet Wireless EEG – Device for Recording Video-Electroencephalograms; International Publication WO2017055354; Patent Granted in Europe EP3355766B1; USA US10750971B1; Canadese CA2999152.
- Support Device for Sensors And/Or Actuators That Can Be Part Of A Wireless Network Of Sensors/Actuators; Patent Granted in Europe EP2276395B1; USA US9612140B2; Japan JP5637517 B2; Sud Korea KR101589232B1; India 3496/KOLNP/2010; Brasil BRPI0911797B1.
- Wearable Tonometer Structure; Patent Granted in Europe EP2775905B1.
- IMPROVED WEARABLE TONOMETER; Patent Granted in Europe EP3439548B1.
- A Device for Measuring A Plurality Of Parameters In Patient Subject To A Treatment With Radiopharmaceuticals; Patent Granted in Europe EP3107443B1; USA US10722171B2.

Bibliometric indicators (H-index/publications/citations):

Marco Nalin (17/44/900); Giovanna Macrì (4/11/107).

Artemide (ART)

Vision, competence, capacity and production technologies originate the beauty of timeless product design. ART, founded in 1959 by Ernesto Gismondi, is based in Pregnana Milanese.

Historical lighting company, ART has always been synonymous with innovation and Made in Italy, with products considered icons of contemporary design, at an international level both for the consumer and contract world, indoor and outdoor.

ART, the company of “The Human & Responsible Light”, declares its perspective towards the future guided by values, innovative vision and research that are the basis of sustainable projects.

ART is ISO 9001, ISO 14001 and ISO 45001 certified, since 2019 it has joined the United Nations Global Compact and since 2018 it has transparently witnessed its path with the certified Sustainability Report.

ART developed and develops not only luminaires but products with hybrid performances linked to the theme of



<p>environmental quality like for example solutions on the subject of room acoustics properties (by using sound-absorbing materials for the reduction of reverberation for the construction of the body), to arrive at luminaires of the INTEGRALIS family equipped with custom light sources capable of generating containment and reduction actions on given bacterial populations starting from spectra based on the wavelengths of the visible.</p> <p>ART has extended its skills also in the IoT field, thanks to highly specialised internal figures and external collaborations with important partners. Wireless control systems have been developed that allow you to manage extensive networks of lighting devices, devices and sensors that can communicate with environmental variables. This is aimed at ensuring self-determination for the individual user in choosing the most suitable lighting scenario combined with maximising performance both in terms of environmental quality and responsible energy sustainability.</p>
Key persons and expert groups
Research & Development Department: Fabio Zanola, Laura Pessoni, Andrea Gallucci.
Key infrastructures
<p>ART has in-house design skills related to mechanical design, electronic design and optical design. It has the ability to directly generate prototypes using both traditional approaches based on CNC machinery, and rapid prototyping based on 3D printing.</p> <p>It has test laboratories in which it can fully or partially characterise lighting devices or light-sources from an electrical, thermal, optical, photometric point of view, in terms of production it has machinery for sheet and extruded sheet processing, metal processing, surface treatments and painting.</p> <p>It has assembly and gluing equipment as well as inbound and end-of-line control.</p>
Ability to manage collaborative projects
Artemide has been engaged for years in research, both internal, detached from any type of participation in national or international calls and completely self-financed (POLIMI, University of Milan, S. Raffaele, University of Padua), and in research calls funded at the level of the Lombardia region (it participated in several regional calls) and at the national level as Industria 2015.
Collaborations with ANTHEM participants
<p>ART - UNIMIB: innovative sterilisation methodologies and antibacterial methods</p> <p>ART - POLIMI: R&D founded activities (i.e. materials design, prototype production)</p>
Patents, granted technologies and/or International bibliometric indicator
<p>For many years Artemide has been opening important research topics on photonics and new technologies to outline a future vision, a new way of interpreting and experiencing light.</p> <p>The numerous invention patents that accompany the development of ART products and the international awards in the field of innovation and sustainability testify to its design tension towards the future.</p> <p>In the optoelectronic field, ART uses LED sources, designs and internally develops state-of-the-art power supply and control devices, investigates the most innovative technologies for the creation of high-performance optical devices. From the point of view of product development, it researches materials, advanced finishes and sustainable processes with a view to responsible and long-lasting design.</p> <p>In particular ART patented almost 100 lamps of different kinds, 7 fixtures and 13 lightning apparatus, systems or devices. Patents that are particularly relevant for the ANTHEM project are listed among the references of Pilot 2.4.</p>
Chiesi Farmaceutici (CHIESI)
<p>CHIESI is an Italian pharmaceutical company founded in 1935. The Group currently employs 6.389 people, 2.119 of which are in Italy, within a global business consisting of 30 affiliates, 7 research centres located in Italy, France, the US, Canada, China, the UK and Sweden, 3 production sites in Italy, France and Brazil, and a commercial presence in 100 countries. 2020 saw overall revenues totalling 2.229 M€, of which 1.542 M€ were generated in Europe. Expenses in R&D in 2020 amounted to 448,3 M€. Our goal is to combine commitment to results with integrity, operating in a socially and environmentally responsible manner. In 2018, Chiesi became a Benefit Corporation, adopting a new legal form under the Italian and US Law by integrating, into the Articles of Incorporation, four purposes of common benefit, and we are the largest global pharmaceutical Group to be awarded B Corp Certification, a recognition of high social and environmental standards.</p> <p>MISSION & VISION: by 2025 we aspire to be a point of reference for patients affected by chronic respiratory disorders, neonatal pathologies, rare diseases and other health conditions which are difficult to treat. As a family-controlled company, we want to continue to grow sustainably by focusing on key markets such as the US and</p>



<p>Europe, but also expanding patients' access to care in key emerging countries like China. We aim at maintaining a profitability level adequate to support our investments in innovation and development and our internationalisation efforts. As a B Corp, our business purpose has a dual objective: creating value for both shareholders and stakeholders. We use the power of business to build a more inclusive and sustainable economy. We work to embrace state-of-the-art technologies to identify and develop new therapies, to streamline processes, improve efficiency, favour people working proximity and sharing. We believe we can achieve all this only through teamwork, taking care with particular attention to the wellbeing and the excellence of all the people working with us. Leveraging diversity and creativity, we want to promote a working environment that welcomes everyone's contribution and awards personal accountability.</p>
Key persons and expert groups
Experimental Pharmacology and Translational Science Dept., Dr. F. Stellari, Dr. A. Murgo, Dr. G. Federico.
Key infrastructures
<p>Molecular Imaging Facility (MIF) is a core facility focused on the set-up and validation of new robust and reproducible animal models of acute lung inflammation, chronic asthma, COPD and pulmonary fibrosis used to profile new chemical entities generated from the Chiesi R&D pipeline. Moreover, it provides support to researchers working with disease models in small animals, offering a range of technologies and equipment to perform <i>in vivo</i> non-invasive longitudinal imaging study.</p> <p>MIF is integrated in the Specific Pathogen Free (SPF) animal facility of the Chiesi Research Centre based in Parma. The laboratory is equipped with <i>in vivo</i> bioluminescence (BLI; IVIS, LUMUMA II) and fluorescence molecular tomography (FMT; 4500) imaging systems and a micro-CT (Quantum GX) with all the accessory equipment and laboratory space necessary to perform animal studies in a SPF environment. The objective of the facility is to integrate the different <i>in vivo</i> non-invasive imaging modalities with disease models in small animals to visualise physiological and pathological processes <i>in vivo</i>, reducing at the same time the numbers of animals necessary to perform an individual study and minimising the impact of the procedures on animal well-being. The facility also supports translational and basic research programs with the ambition to develop new high-end <i>in vivo</i> imaging approaches that may help to close the gap between preclinical and clinical studies.</p>
Ability to manage collaborative projects
<p>In order to plan and manage complex projects, programs and portfolios of projects, a comprehensive and robust structured framework supporting the whole drug development process end to end is in place, involving a fully dedicated Global R&D which works cross-functionally with all other relevant internal stakeholders such as marketing and sales, manufacturing, medical affairs etc in a matrix structure, with multifunctional dedicated teams. A formalised stage-gate process is in place, with specific governance processes and tools involving dedicated committees such as Pipeline, Portfolio and Investment Committee (PPIC), Technical Committee (TC) and New Product Committee (NPC) supporting decision making on both projects in pipeline or in evaluation as new options to enter the pipeline, and dedicated project or Therapeutic Area (TA) focused multifunctional teams focused in strategizing and executing on specific TAs and projects. Ad-hoc processes, tools and dedicated structures are as well in place to support open innovation and access to a broad innovation network, both public and private, as well as to support co-development and integration of projects, technologies and assets from sources external to Chiesi. More than 45 projects are currently running within CHIESI pipeline across different TAs, development phases, and technological platforms.</p>
Collaborations with ANTHEM participants
<p>CHIESI- ABM: The two partners were involved in the IRMI project.</p> <p>CHIESI-POLIMI microCT imaging for diagnostic applications. Innovative systems for not-invasive drug administrations and selection of methodologies for neonatal applications.</p> <p>CHIESI - UNIMIB: proteomic characterization for lung chronic pathologies diagnosis.</p>
Patents, granted technologies and/or International bibliometric indicator
<p>CHIESI R&D activities are clustered in the areas of respiratory and neonatology, rare diseases, and special care. The pipeline covers the stages from preclinical to, to early and late clinical and post-approval. Approved products include Foster and Trimbow (respiratory area), Curosurf (neonatology cluster), Kengreal and Cleviprex (Cardiovascular), Ferriprox and several others pharmaceuticals for rare diseases.</p>
Diapath Spa (DIA)
<p>DIA, based in Martinengo, Italy, was founded in 1997. We are a private company, family owned, operating independently and distributing its own products worldwide. With our experience in the market, we successfully provide high quality products and customised services to hospitals and laboratories all around the world. Since the</p>



establishment of the business, we have expanded our distribution network to cover Europe, Middle East, Africa (principally North Africa), Asia, United States and South America. We currently have partnerships in more than 90 countries. DIA has a wide range of reagents, consumables and instruments as reported below: we have a mix of technical and business personnel with different fields of expertise; ranging from Biotechnology, Chemistry, Mechanical Design and Mechanical Engineering. Our company departments include: Reagent production, Instrument production, Planning, Quality Control, Innovation Department, R&D Department, Technical Service – SAT, International Sales, Domestic Sales, Marketing, ISO & Regulatory, Information Technology, Finance & Accounting, Management Control and Operations & Lean. Through forming specialised alliances, we have managed to incorporate partners in our supply chain, completing the circle of technical skills and the commercial competence necessary for the launching of our products. We also manufacture a complete portfolio of Instruments, Reagents and Consumables for Pathology. The company is a family business that has an international focus. DIA currently has a turnover of 22 M€ of which more than 30% are export proceeds.

Mission: Innovate to contribute to a better diagnosis. Constantly innovate, evolving existing technologies or redesigning current processes and solutions in a completely original way. Contribute to the best diagnosis for patients, offering our customers a complete range with the best solutions for usability, reliability, safety and respect for the environment.

Vision: Become the most innovative Brand in Pathology, improving life of people involved in the diagnostic process. Offer innovation, quality and reliability with a special attention to the Customer.

Key persons and expert groups

DIA brings together an expert team. The company's management team consists of highly qualified professionals with in-depth knowledge and vast experience in the fields of Histopathology, Biology, Biotechnology, Engineering, Chemistry and Innovation Management, guaranteeing the correct experience for a successful implementation of the project. Key Persons: Dr. Carmelo Lupo, Head Of Innovation, Biologist; Dr.ssa Nadia Casatta, Senior Researcher, Biotechnologist

Key infrastructures

Diapath factory facility in Italy handles the production, Instrument Production, Reagent Production, Quality Control, Technical Services, Logistics and our LaboPath – which is a full-scale pathology laboratory in our headquarters facility where we also test the use of all our products as a matter of routine (see figures below). This ensures a continuous control and improvement in product quality. We are certified ISO 9001 and ISO 13485. DIA also runs an Academy to train distributor service engineers to transfer our expertise and experience thereby guaranteeing that the customer receives exactly the right service

Ability to manage collaborative projects

DIA invests 10% of its annual turnover in innovation, research & development. This in turn has helped in structuring a innovation, research and development departments, which combines the skills of mechanical engineers, electronics and biologists, and to the support of marketing which includes and satisfies the needs of the patient and of the health worker. In addition there are active collaborative projects with Università degli Studi di Bergamo, Politecnico di Torino and University Campus Biomedico in Rome. In 2019, Diapath S.p.A. won the selection for the EIC Accelerator. Diapath participated in the European funding EIC Accelerator, a pilot project of the European Innovation Council which belongs to Horizon 2020 programme, the first largest program realised by EU for Research and Innovation. It is an earmarked funding to support and promote the growth of SMEs during their development phase to promote European global competitiveness focusing on three important “topics”: Scientific excellence, Industrial leadership and Challenges for the Society. The selection of both the projects and the companies was harsh and rigid. Comparing a total of 5.310 projects, 1.852 has passed the final selections and only 75 have been selected by the European Community for the funding with a rate selection of 1,4%. Among the 75 companies, only 3 are Italian and just one comes from Lombardia: DIA. DIA benefits a European funding of 2 M€, as support for a total budget of about 4 M€, for an innovative and revolutionary project regarding diagnostic in Pathology, focusing on safe diagnosis and concerning the precision medicine

Collaborations with ANTHEM participants

DIA-UNIBG-UNIMIB: 1) Investigation with X-ray microCT about the thermofluids dynamical processes in a histologic sample; 2) Mathematical and numerical modelling of biological systems.

DIA-UNIBG: 3D Digital Histology

Patents, granted technologies and/or International bibliometric indicator

As a result of a dynamic research and development centre, DIA created several more than 20 exclusive patents,

such as Ottix, an innovative reagent which is non-toxic and replaces both the Xylene and the alcohol scale in the processing and coloration protocols in pathology. Or Sicura and SafeCapsule, a novel fixative composition for samples of biological material meant to limit the operator exposure to formaldehyde vapours during sampling and storage of formalin. In the annex, the complete list of DIA patents (update July 2022). DIA also has 7 Trademarks.

Scientific Publications:

- G. Gazzato et al. Primitive Cutaneous (P)erivascular (E)pithelioid (C)ell Tumour (PEComa): A New Case Report of a Rare Cutaneous Tumor. **Genes** 2022; 13(7).
- G. Gazzato et al. Review Preferentially Expressed Antigen in Melanoma (PRAME) and Human Malignant Melanoma: A Retrospective Study. **Genes** 2022; 13(3).
- F. Contino et al. Negative transcriptional control of ERBB2 gene by MBP-1 and HDAC1: diagnostic implications in breast cancer. **BMC Cancer** 2013; 13 (81)
- P. Cancemi et al. Differential occurrence of S100A7 in breast cancer tissues: a proteomic-based investigation. **Proteomics Clin Appl** 2012
- L. Minafra et al. Unmasking epithelial-mesenchymal transition in a breast cancer primary culture: a study report. **BMC research notes** 2012
- Presti M.L. et al Myc promoter-binding protein-1 (MBP-1) is a novel potential prognostic marker in invasive ductal breast carcinoma. **PLoS One** 2010
- P. Cancemi et al. Large-scale proteomic identification of S100 proteins in breast cancer tissues. **BMC Cancer** 2010
- G. Pelosi et al. Immunoreactivity for Thyroid Transcription Factor-1 in Stage I Non-Small Cell Carcinomas of the Lung. **American Journal of Surgical Pathology** 2001.
- L. Viganò et al. Embryo/larval toxicity and transcriptional effects in zebrafish (*Danio rerio*) exposed to endocrine active riverbed sediments. **Environ. Sci. Pollut. Res.** 2020; 27, 10729–10747.
- L. Viganò et al. Contamination levels and spatial distribution in the lagoons of the Po River Delta : Are chemicals exerting toxic effects? **Estuar. Coast. Shelf Sci.** 2019.
- L. Guzzella et al. Molecularly imprinted polymers for the detection of benomyl residues in water and soil samples. **J. Environ. Sci. Health, Part B**, 2019
- N. Casatta et al. Hepatic gene expression profiles of a non-model cyprinid (*Barbus plebejus*) chronically exposed to river sediments. **Comparative Biochemistry and Physiology Part – C** 2017.
- N. Casatta et al. Endocrine disrupting chemicals in coastal lagoons of the Po River delta: sediment contamination, bioaccumulation and effects on Manila clams. **Env Sci Poll Res** 2016.
- N. Casatta et al. Tracing endocrine disrupting chemicals in a coastal lagoon (Sacca di Goro, Italy): sediment contamination and bioaccumulation in Manila clams. **Sci Total Environ** 2016; 511C:214–222.
- N. Casatta et al. Lack of Sir2 increases acetate consumption and decreases extracellular pro-aging factors. **Biochim Biophys Acta** 2013; 1833:593–601.



B. CHARACTERISTICS, FEASIBILITY AND CONTROL

B.1 Description of Reference Communities and level of engagement

The ANTHEM Reference Communities have been defined based on territorial and/or pathology considerations, selected according to the project high-level objectives and vision. More precisely, the distribution of pathologies, the socio-geographical conditions and the diversity of Regional Healthcare Systems have been considered as key criteria when selecting the Reference Communities, as explained in Section A.1. The project has the ambition to fill systemic and technological gaps benefiting both communities of patients and communities of citizens living in socio-economic and geographical contexts that are characterised by different needs and capabilities in terms of the healthcare system, but also to tackle some major, still unmet needs in the fields of several high-impact chronic diseases (Figure 7).

	PATHOLOGY	OBJECTIVES	COMMUNITIES	CLINICAL PARTNERS	INDUSTRIAL PARTNERS
SPOKE 1	<ul style="list-style-type: none"> ✓ Cancer diseases ✓ Degenerative diseases ✓ Rare diseases ✓ Metabolic diseases 	<ul style="list-style-type: none"> ✓ People and organisational support systems (25%) ✓ Prevention and screening for early diagnoses (38%) ✓ Diagnostics (25%) ✓ Monitoring and treatments (12%) 	<ul style="list-style-type: none"> ✓ Metropolitan area ✓ Mountain ✓ Pathology-driven 	<ul style="list-style-type: none"> ✓ FERB Onlus ✓ ASST Bergamo Est ✓ ASST Monza ✓ ASST Papa Giovanni XXIII ✓ Istituto Mario Negri ✓ UNIME 	<ul style="list-style-type: none"> ✓ Diapath Spa
SPOKE 2	<ul style="list-style-type: none"> ✓ Chronic diseases ✓ Degenerative diseases ✓ Infection disease 	<ul style="list-style-type: none"> ✓ Prevention and screening for early diagnoses (43%) ✓ Diagnostics (14%) ✓ Monitoring and treatments (43%) 	<ul style="list-style-type: none"> ✓ Metropolitan area ✓ Mountain area ✓ Pathology-driven 	<ul style="list-style-type: none"> ✓ ATS Milano ✓ FERB Onlus ✓ ASST Bergamo Est ✓ ASST Monza ✓ ASST Papa Giovanni XXIII 	<ul style="list-style-type: none"> ✓ Artemide Spa
SPOKE 3	<ul style="list-style-type: none"> ✓ Chronic diseases ✓ Metabolic diseases ✓ Infection disease 	<ul style="list-style-type: none"> ✓ Prevention and screening for early diagnoses (50%) ✓ Diagnostics (25%) ✓ Monitoring and treatments (25%) 	<ul style="list-style-type: none"> ✓ Metropolitan area ✓ Pathology-driven 	<ul style="list-style-type: none"> ✓ Humanitas 	<ul style="list-style-type: none"> ✓ Ab Medica Spa ✓ Chiesi Farmaceutici Spa
SPOKE 4	<ul style="list-style-type: none"> ✓ Cancer diseases ✓ Chronic diseases 	<ul style="list-style-type: none"> ✓ Diagnostics (25%) ✓ Monitoring and treatments (75%) 	<ul style="list-style-type: none"> ✓ Island area ✓ Pathology-driven 	<ul style="list-style-type: none"> ✓ A.O. Cannizzaro ✓ Ist. Oncologico del Mediterraneo ✓ Biogem Scarl 	

Figure 7. Relationship between project structure, objectives, target pathologies and Reference Communities

Accordingly, each Pilot targets a specific Reference Community, whose relevance and size are reported in Tables B.1 through B.4, together with an estimation of the level of engagement of the Communities intended as the number of patients or residents directly involved in the Pilots during the project lifetime. Of course, the vision of ANTHEM in the medium-term, beyond 2026, is to reach and positively impact a much larger number of citizens, as explained in Sections C.1.2 and C.1.3.

For Pilot 1.1, devoted to general AI-models for patient-specific decision making and personalised medicine, the previous consideration on the Reference Communities does not apply, since the Pilot itself is instrumental to the other Pilots of Spoke 1, and hence, it results transversal to all communities. Since the Pilots of Spoke 4 are preclinical and seek to collect sufficient data to plan a Phase I clinical trial in the selected reference populations the project target size is not relevant at this stage.

Gender aspects. A comprehensive analysis of different chronic diseases impact on gender discrepancy is not yet available, limiting also the real personalised care approach for both diagnostic and therapeutic purposes. Gender discrepancy was observed in selected multimorbidity patterns of patients affected by chronic diseases, with some chronic pathologies having major or selective recurrences in the female population.

The female population has a major life expectancy compared to male population, with increased risk of disabilities related to chronic morbidities and comorbidities. Furthermore, different biological determinants and physiological features have an impact not just in chronic disease onset and progression, but also in therapeutic and care response of individuals. In the ANTHEM project, the development of new pathways of care will be realised taking into account not just specific pathological and territorial dimension, but also the gender dimension of the patients and populations selected during project progression. All the developed technologies will be measured and developed taking into account diagnostic, monitoring and therapeutic discrepancies potentially related to gender dimension.

Many factors that impact on medical investigation process in fact can be ascribed to sex, as biological state, and also gender, intended as a psychosocial process involving experimental subjects, researchers, funders and the public. Therefore, consideration of sex and gender aspects of medical research is essential if personalized therapies are to bring benefits to both male, female, or intersex subjects. These aspects span from biological differences that might lead to unexpected responses to medical treatments or, on the other way, to gender dependent attitudes that might, for example, impact the perception or the acceptance of specific treatments or technologies.

Sex and gender dimensions will be therefore tackled through the whole pilots and they will be addressed continuously.

Table B.1. Reference Communities for the Pilots of Spoke 1.

Spoke 1 - Data and technology driven diagnoses and therapies		
Reference Community and relevance	Size of the Community	Size of Project Target (per year)
Pilot 1.2 Digital Triage at the emergency room		
Patients accessing Emergency Departments (ED) in the hospitals of the Val Seriana area (ASST BGEST) in 2023-2026. This area has 4 hospitals with an ED department.	In the period 2011-2021, an average number of 115.000 patients accessed the ED per year. After a slight decrease during the COVID-19 pandemic period, in 2022 (Jan-Mar) ED visits exceed 2019 volumes.	>100.000
Pilot 1.3 AI based Artificial Pancreas for children		
Type 1 Diabete (T1D) patients, particularly in childhood and adolescence in the Bergamo province	1.800 patients - 250 of these patients are less than 18 years old	>50
Pilot 1.4 timely genomic diagnosis for children with rare diseases toward precision medicine		
Paediatric population (0-5 yo) in the Bergamo province. The methods can be exported to other areas/populations.	About 7.700 newborns yearly; 2023-2026 years for a total of about 30.000. In the Lombardia region it is 68.000/year.	>2.000
Pilot 1.5 Mass spectrometry for tissue biopsy investigation		
Lombardia population undergoing Fine Needle Aspiration (FNA) to investigate possible thyroid cancer (just to mention the first example of cancers to be investigated).	Share of population with palpable thyroid nodules 4%. Yearly Lombardia FNA about 20.000. Percentage of FNAs indeterminate for malignancy 15-30%.	>100
Pilot 1.6 Improved multi-source image based diagnostic for early cancer detection		
General Population of the Napoli 3 South and Salerno area.	New cases/year: breast cancer 840; colorectal cancer: 750; thyroid cancer: 150; skin cancer (melanoma): 120.	>100
Pilot 1.7 Genetical insights in neurodegenerative disease		
GD patients or parents accessing Genetic and Pharmacogenetic Unit of Azienda Universitaria Policlinico of Messina (Center for Diagnosis, Treatment and Prevention of Rare Genetic Diseases)	About 50 new patients/year	>30
Pilot 1.8 MicroCT-based 3D digital histology		
Patients with thyroid lesions and GBM in Lombardia Region at first	About 1.000 new patients/year	>100

Table B.2. Reference Communities for the Pilots of Spoke 2.

Spoke 2 - Connecting patients and therapists through adaptive environments and intelligent sensors to enhance proximity medicine		
Reference Community and relevance	Size of the Community	Size of Project target (per year)
Pilot 2.1 Remote physical therapy and sensorized environments		
Population of the Val Seriana	About 130.000 people spread on 38 villages on 55 km of length	>100
Pilot 2.2 Epidemiological study of cardiovascular diseases in a mountain area		
Val Brembana general population 20-60 yo with no particular risk factor.	The Val Brembana population is about 43.000 people	>5.000
Pilot 2.3 Smart wearable and portable sensors to monitor human healthiness and pathological states		
Population of the Val Seriana	About 130.000 people spread on 38 villages on	>100

	55 km of length	
Pilot 2.4 Wide spectrum light and devices to sanitise surfaces and air		
Workers and patients at ASST MONZA (hospital rooms)	About 300.000 outpatients/year, 20.000 admissions, and 4.000 healthcare professionals	>20 hospital rooms
Pilot 2.5 Development of nanosensors for the detection of pathogens and biohazards		
Population of the Val Seriana	About 130.000 people spread on 38 villages on 55 km of length	>200
Pilot 2.6 Remote monitoring of groups and community		
Population of the Val Seriana	About 130.000 people spread on 38 villages on 55 km of length	>5.000
Pilot 2.7 Wearable devices for remote monitoring of Parkinson patients		
Val Seriana area Parkinson patients	More than 5.000 people are suffering from Parkinson's disease in the province of Bergamo.	>100

Table B.3. Reference Communities for the Pilots of Spoke 3.

Spoke 3 - Risk factors monitoring, diagnostic tools and therapies in chronic disease		
Reference Community and relevance	Size of the Community	Size of Project target (per year)
Pilot 3.1 New technologies for air quality and lifestyle assessment		
Residents in metropolitan areas located in Lombardia and Puglia (Milano, Bari, Lecce) with a focus on Taranto, considering the environmental problems.	3.200.000 inhabitant in Milan area; 320.000 inhabitant Bari area; up to 95.000 inhabitants Lecce area; 198.000 inhabitants Taranto area	5% of the population
Pilot 3.2 Environmental determinants of health		
Residents in metropolitan areas located in Lombardia and Puglia (Milano, Bari, Lecce) with a focus on Taranto, considering the environmental problems.	3.200.000 inhabitant in Milan area; 320.000 inhabitant Bari area; up to 95.000 inhabitants Lecce area; 198.000 inhabitants Taranto area	5% of the population
Pilot 3.3 Innovation of diagnostic approaches in chronic heart and lung diseases		
Patients affected by chronic and neoplastic diseases of the lung living in Lombardia and Puglia	Up to 700.000 in Lombardia and 200.000 in Puglia	>250
Pilot 3.4 Innovation of therapeutic approaches in chronic heart and lung diseases		
Patients requiring intensive care treatment for lung disease living in Lombardia and Puglia	Up to 3.000 in Lombardia and 1.000 in Puglia	>50

Table B.4. Reference Communities for the Pilots of Spoke 4. (N.B. the Pilots in this spoke will develop mainly preclinical activities aimed at reaching the possibility within the time limits of the proposal to have sufficient data to plan a phase 1 clinical trial in the selected reference populations - for this reason the size of project target is not predictable at this moment)

Spoke 4 - Preclinical and clinical breakthrough theranostic and treatments for cancer		
Reference Community and relevance	Size of the Community	
Pilot 4.1 Multifunctional materials for advanced theragnostics		
Oncological patients	Up to 377.000 patients, national oncological patients per year	
Pilot 4.2 Optical microsensors		
Oncological patients	Up to 377.000 patients, national oncological patients per year	
Pilot 4.3 Multi-modal correlative microscopy platform		
Oncological patients	Up to 377.000 patients, national oncological patients per year	
Pilot 4.4: FLASH therapy effect on glioblastoma		
GBM patients	1.800 patients, national oncological patients per year, 75% of these patients are 45-70 years old	
Pilot 4.5 Sonoporation and drug delivery for Glioblastoma and melanoma treatment		



GBM and melanoma patients	GBM: 1.800 patients, national oncological patients per year, 75% of these patients are 45-70 years old; Melanoma: 8.000 patients, national oncological patients per year, 80% of these patients are 40-50 years old
Pilot 4.6 Innovative nanoparticles for drug delivery	
Oncological Patients	Up to 377.000 patients, national oncological patients per year
Pilot 4.7 Development of a perfusion-based bioreactor platform	
Oncological Patients	Up to 377.000 patients, national oncological patients per year
4.8. AI-Based Systems Biology Approaches in Cancer Multi-Omics Data Analysis	
Oncological Patients	Up to 377.000 patients, national oncological patients per year
Pilot 4.9 Realisation of a boron neutron capture therapy (BNCT) facility in Caserta	
Patients with Glioblastoma and other aggressive malignant tumours in Italy	GBM: 1.800 patients, national oncological patients per year, 75% of these patients are 45-70 years old. Size of the community will be >100.

The engagement model for the ANTHEM's reference communities was designed and developed during the planning of the project. The agenda setting was co-developed in conjunction with territorial healthcare services ATS (Agenzie di Tutela della Salute-Health Protection Agencies, that are administrative structures of the Region that provide health and social health services through public and private accredited and contracted entities), ASST (Aziende Socio Sanitarie Territoriali-Territorial Social Healthcare Companies that participate together with the other providers, both public and private, in the provision of the Essential Levels of Assistance (LEA) and any additional levels defined by the Region with their own resources, in the logic of taking charge of the person) and hospitals, partners of the project. Model development followed a bottom-up, iterative process completed over three stages. The first stage included a context mapping method of the participating organisations, trial sites, and geographical areas and, where possible, information about the target populations. The contextual, local characteristics and dynamics of services and some of the service users' characteristics were assembled into descriptive portraits of each organisation.

Following this contextual review, the second stage involved consulting the literature on barriers to recruitment and retention of hard-to-reach groups in complex interventions. From this we determined existing barriers to recruitment which are summarised below:

- Geographical factors (Relocation of participants, transportation difficulties)
- Illness-related barriers Fear of relapse as a result of participation, severity of illness.
- Level of support (Lack of support to take part in research, 'no one to go with')
- Fear, suspicion and/or distrust of researchers and/or general distrust of research (Fear that research could be harmful or cause excessive worry for the person, concerns about confidentiality)
- General inconvenience of participating in research (Takes too much time, lengthy process involving transportation and attendance)

The information was combined with our descriptive portrait data, and some recruitment strategies and engagement approaches have been identified :

- Logistic: Organising and communicating with partners to foster conditions for knowledge translation
- Strategic: Raise and maintaining partner interest, facilitation of a participatory research process
- Cognitive : Developing a shared vision and phrasing of the research

At the end, the ANTHEM engagement process has been identified, as shown in Fig. 8. In summary, as a first step, ASST and hospitals will inform teams of clinicians working in their structure about project activities, as well as ATS identifies the population at risk, through the development of specific algorithms, to be included in specific projects involving the use of new technologies, including through Community Homes and Community Hospitals. As a second step, teams of hospital clinicians and GPs will explain project activities to patients in order to engage them after Informed Consent Form signature. Association of patients such as UN RESPIRO DI SPERANZA LOMBARDIA Voluntary Activities, AIMAC (Associazione Italiana Malati di Cancro) and AICARM ONLUS (Associazione Italiana per lo studio e la ricerca delle CARdioMiopatie) can disseminate and give support to divulgation of results'project.

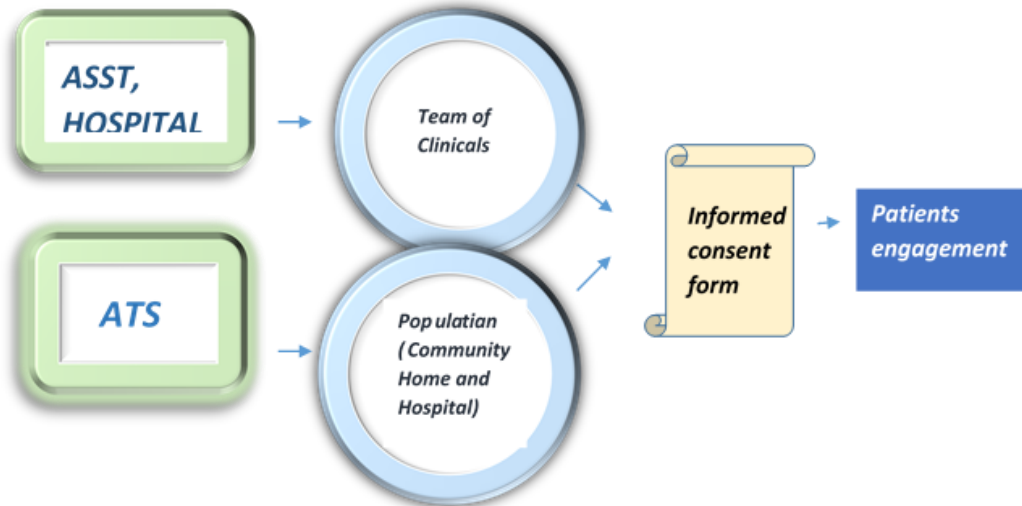


Figure 8: the ANTHEM engagement process following PNRR indications

B.2 Composition of the critical mass

ANTHEM is structured in 4 thematic Spokes led by public Universities with academic organisations, public healthcare institutions, private research & healthcare institutes, and private companies as Affiliates. A total of 23 organisations participate in ANTHEM as Spokes or Affiliates, out of which 12 are involved in 2 different Spokes. The partnership has been built to meet the project's objectives through:

- an academic core guaranteeing complementary expertise, excellence in research in the several disciplines involved, and outstanding educational capacity for the next generation of researchers and professionals;
- the geographical balance among the target territories, both to reach the Reference Communities and to boost the country's innovation capacity;
- the strong engagement with the healthcare systems (hospitals, healthcare agencies, regional entities) allowing to develop solutions in close contact with the operational environment and the real-world needs, and at the same time to effectively access the Reference Communities;
- the involvement of the private sector in the different dimensions and stages of the research and innovation path, from the research carried out by private universities and research institutes, to the collaboration with private healthcare institutions and companies active in the sectors of medical devices, pharmaceuticals, and biotechnologies;
- the capitalization on the previous and existing collaborations between the partners to build a solid network capable of launching and implementing the activities following the tight schedule of the National Plan for NRRP Complementary Investments.

Each subject devotes a number of researchers to the ANTHEM activities for the period 2023-2026 selected on the basis of scientific and technical excellence and favouring the engagement of outstanding young researchers (see also B.7). The existing critical mass will be integrated in the implementation phase through a recruitment programme, dedicated notably to PhD (>50) and fixed-term researchers and technologists (about 80), aimed at attracting the best talents. Table B.5 reports for each Spoke and for each Affiliate the contribution to the critical mass in terms of total number of researchers and total number of researchers devoting at least 3 person-months/year (PM/y) to the project. Overall, the ANTHEM critical mass consists of 208 individuals, out of which:

- 144 (69%) devote a very significant effort to the project (at least 3 PM/y);
- 82 (39%) are women;
- 44 (21%) are young researchers (i.e., up to ten years of experience since the completion of the PhD).

Table B.5 ANTHEM critical mass by Spoke and subject; $\geq 3PM/y$ indicates the no. of researchers devoting at least 3 person-months per year to the project.

Spoke 1 - Data and technology driven diagnoses and therapies			Spoke 2 - Connecting patients and therapists through adaptive environments and intelligent sensors to enhance proximity medicine		
Partner	Role	No. of Researchers	Partner	Role	No. of Researchers

		Tot.	≥ 3PM/y			Tot.	≥ 3PM/y
UNIBG	Spoke	14	14	UNIMIB	Spoke	18	8
UNIMIB	Aff.	12	9	UNIBG	Aff.	7	7
UNIME	Aff.	4	3	UNICAL	Aff.	3	2
UNICAMP	Aff.	3	2	ASST PG23	Aff.	4	2
ASST BGEST	Aff.	2	2	ATS MI	Aff.	2	2
FERB	Aff.	2	2	ART	Aff.	2	2
DIA	Aff.	2	2	ASST MONZA	Aff.	2	2
ASST PG23	Aff.	2	2	FERB	Aff.	2	2
NEGRI	Aff.	2	2	ASST BGEST	Aff.	2	2
ASST MONZA	Aff.	3	2	Total for Spoke 2		42	29
Total for Spoke 1		46	40				
Spoke 3 - Risk factors monitoring, diagnostic tools and therapies in chronic disease				Spoke 4 - Preclinical and clinical breakthrough theranostic and treatments for cancer			
Partner	Role	No. of Researchers		Partner	Role	No. of Researchers	
		Tot.	≥ 3PM/y			Tot.	≥ 3PM/y
POLIMI	Spoke	22	4	UNICT	Spoke	15	13
HUNIMED	Aff.	12	11	UNICAL	Aff.	7	3
UNISALENTO	Aff.	5	3	UNIME	Aff.	5	3
CHIESI	Aff.	3	2	UNICAMP	Aff.	8	8
ABM	Aff.	4	4	INFN	Aff.	13	11
Total for Spoke 3		46	24	CANNIZZARO	Aff.	5	3
				UNISALENTO	Aff.	3	2
				POLIMI	Aff.	4	2
				HUNIMED	Aff.	9	2
				BIOGEM	Aff.	3	2
				IOM	Aff.	2	2
				Total for Spoke 4		74	51

Table B.6 Overall costs of the project: breakdown by Spoke.

Spoke 1	Spoke 2	Spoke 3	Spoke 4	Hub	Total
25.516.253 €	25.934.836 €	22.322.098 €	49.270.317 €	2.180.000 €	125.223.504 €

The breakdown by Spoke of the overall costs of the project are shown in Table B.6, whereas Figure 9 shows the main cost categories. Personnel cost includes both the critical mass and personnel to be recruited to work on the project. About 42% of the total cost concerns southern Regions. Moreover, *open calls* (11% of the total costs) will be devoted to cascade funding for the national research and innovation community beyond the ANTHEM partnership.

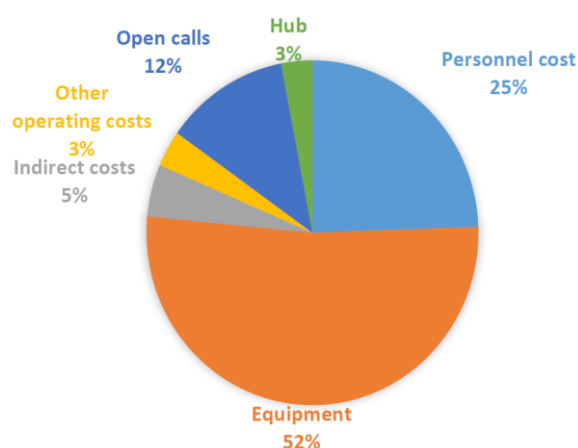


Figure 9 Cost breakdown by category.

B.3 Management and administrative structure

The Foundation “Fondazione ANTHEM” is the Legal Entity managing the Initiative - the Hub - and it will be based in Milan, Italy. According to its purposes, it has the legal nature of a private non-profit foundation and it will

include as members UNIMIB, UNIBG, UNICT, POLIMI, UNICAL, UNICAMP, UNIME, UNISALENTO, INFN, HUNIMED, BIOGEM and CHIESI. The Governance of the foundation will include:

- **General Assembly:** with majority by Public Universities and Public Research Institutions supervised by MUR, and is chaired by the Initiative President. In compliance with the Foundation's purposes, it establishes



the general operational lines of the program's activity and the methods of achieving the objectives; provides recommendations to the Board of Directors on the general lines of the Programme activity and on the related objectives and programs; expresses a mandatory opinion on the annual budget prepared by the Board of Directors and on the reports; it proposes specific initiatives to the Board of Directors within the scope of the program; appoints the members of the Board of Directors. Regular meetings of the General Assembly are held once a semester.

- **President:** it is appointed by the General Assembly on the proposal of the Initiative Proposer. The President chairs the General Assembly assisted by the Director (see below), she/he oversees the execution of the resolutions of the Assembly, exercises the powers delegated to him by the Assembly itself. The President has the right to delegate part of his powers to individual Directors and also has the right, within the scope of the delegated powers, to appoint attorneys determining their powers; maintains relations with authorities, public administrations and other public and private entities.
- **Board of Directors:** it is appointed by the General Assembly, with majority share by Public Universities and Public Research Institutions supervised by MUR, is composed of 7-11 members, of which 3-4 reserved to the Private Companies Promoters, and it is chaired by the Initiative President; The Board of Directors elects the President from among its members. It draws up the multi-year activity plan on the basis of the guidelines defined by the MUR (funding body) as well as the annual activity plan. Approves the budget (forecast economic-financial budget) and the regular or contingency reports of the progress of activities; appoints the Program Manager defining the related duties, powers and salary, as well as the duration of the assignment; elaborates and approves any internal regulations; establishes contingency strategies in case of deviation in the planned progress against planned expenses, objectives, risks and timelines. Regular meetings are held quarterly. Contingency meetings can be called up any time with a minimum forewarning of one week.
- **Director:** it is appointed by the Board of Directors, manages and coordinates the activities of the Initiative and acts as *Program Research Manager*.
- **Activity Coordination Committee:** board of Spokes' coordination, composed by the spoke leaders and chaired by a Coordinator selected among its members, which addresses and monitors the scientific activity plan and the overall performance indicators, shares best practices among spokes and promotes cross contamination through inter-spoke or multi-spoke initiatives;
- **Scientific Expert Committee:** 4 different Expert Committees consisting of cross spokes experts with the aim of pursuing strategic goals and determining working policies for the entire project. The planned committees are as follows: 1) Data expert committee; 2) AI expert committee; 3) NCD expert committee; 4) Health system expert committee;
- **Ethics Committee:** independent committee of 7 outstanding experts in the field, including a Chairperson appointed among its members, which provides guidance and feedback on ethical issues, such as: equity (avoiding disparities), ethical alignment with regulatory compliance, fairness, privacy, risk assessment, social trust and acceptance, sustainability and transparency;
- 3 external **Advisory Boards (AB):** a) an Institutional AB, including the involved Regional Healthcare Institutions; b) a Beneficiaries/Patients AB, including local communities, and patients' associations; and, c) an Industrial AB, including the relevant industrial associations.

Organisational Model. To carry out the management and coordination activities required by the Research Program the appointed Director that acts as Program Research Manager is responsible for the implementation of the planned activities. The Director is supported by thematic operational units, each having specific functions relating to the obligations of the promoting entity (Table B.7). Figure 10 represents the organisational model and the governance of the Hub.

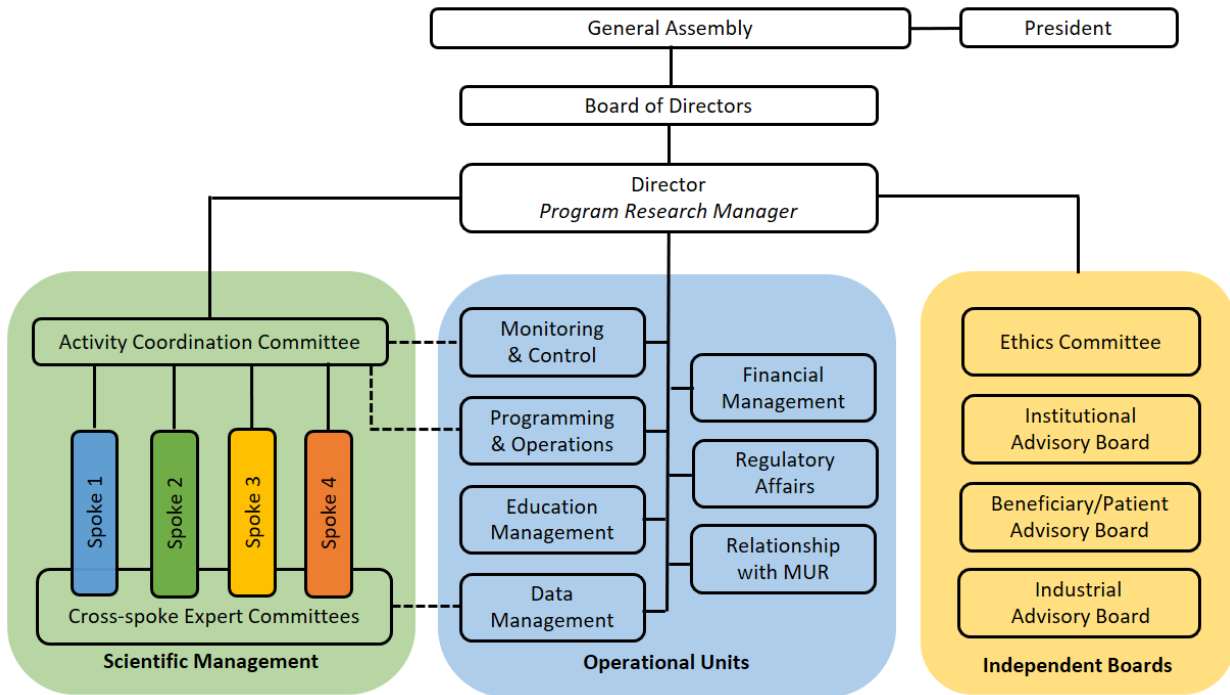


Figure 10. Organisational model and Governance of the Hub.

Table B.7. Role of the Hub Operational Units

Management, Financial Accounting and reporting
<p>Ensuring implementation of the Research Program as approved; Ensure traceability of expenses and avoidance of double funding of operations through specific accounting and information coding procedures; The Hub will be responsible for the implementation of a coordination system capable of evaluating, monitoring and measuring the progress of the expense reporting for each Spoke. The Hub will implement a shared process to standardise collection of financial data from each Spoke and transmit it to the MUR through the dedicated information systems.</p>
Monitoring and control
<p>Carrying out the managerial, administrative and financial controls of the operations as required by law; Facilitating verifications by the authorised bodies, including on-spot verifications, on the beneficiaries of the loans, including on the Hub, the Spokes and the affiliated entities; Guaranteeing a sound conservation of project documentation and of supporting documents relating to expenses incurred to ensure traceability of operations.</p> <p>Monitoring of the progress of the project in relation to the work plan/ chronogram along with monitoring of the continuous financial and technical feasibility of the project will take place through specific controls that will include: reports; criticalities registers; change management; risk monitoring and management; verifying the continued validity and justification of the investment. The project will be monitored in relation to the following tolerances: Times and Costs; Scope; Risks; Quality; Expected Results / Benefits. The controls will be governed by four main modes: delegating authority from one level to the next; dividing the project into manageable steps; by setting "Time-Driven" internal reports (cyclic and/ or deadline driven) and "Event Driven" (produced when specific tasks have been accomplished or in the case of the detection of critical issues that require to schedule a correction actions) to monitor project updates; reporting deviations (from the established plan). Possible responses to any deviation from the established plans might include: adjusting project tolerances; the removal of causes; the definition of a response plan and the restructuring of time and targets.</p> <p>The Board of Directors will ask for regular "highlight reports" that will be used to authorise subsequent phases. The Project progress monitoring will be undertaken in a bottom-up mode according to the established Governance Structure. Following the monitoring results the correction actions will instead be executed in top-down mode according to the expected command flow. The Spoke Leaders will produce monthly Reports (1-2 pages), supervised by the Programme Manager, to update the Board on the progress of the indicators that have been established for each phase of the project.</p>

Regulatory affairs
<p>Ensuring compliance of all activities with relevant EU and national legislation, including on state aid; Guaranteeing compliance with the “Do no significant harm” (DNSH) principle in the assessment and implementation of activities; Adopting measures to ensure compliance with the principles of sound financial management, concerning the prevention of conflicts of interest, fraud, corruption and the recovery of unduly assigned funds; Ensuring compliance with any regulatory provisions, guidelines and technical instructions issued by relevant national and EU entities involved in the implementation of the Research Program.</p>
Programming and Selection of Operations
<p>Selecting relevant activities and promptly starting them not to incur in implementation delays, providing a specific date for the start of the operational phase; Identifying any factors that may affect the timing and expenditure as defined in the time schedule.</p>
Education Management
<p>Identify present and future educational needs, and plan, develop and modify facilities and programs; Networking and building professional relationships with members of the institution and the community.</p>
Data Management
<p>A Data Management System will be in place and a Data Management Plan (DMP) will be defined and distributed to all the partners who will provide their agreement by signing the Plan. The DMP will apply to each original data set and will specify: type of data collected or generated; metadata standards to be employed; access, exploitation rights and privileges levels; back-up and security procedures; disciplinary norms adopted; data-sharing rules and procedures; archiving and preservation; all according to the FAIR principles (Findable, Accessible, Interoperable and Reusable). A Data Protection Officer will be appointed and a Data Expert Committee nominated at the very project start. A first version of the DMP will be delivered to MUR in the negotiation phase by Spokes and Affiliates and subsequently updated.</p>
Relationship with MUR
<p>Producing, on a bimonthly basis, reports on the activities of the Initiative, highlighting the achievement of intermediate and final milestones and target, and reports of expenses incurred by the Initiative; Producing a final technical report detailing the implementation of the Research Program and ensuring transmission of data relating to the lines of activity to allow for the preparation of annual reports; Ensuring the correctness, reliability and consistency of the financial, physical and procedural data of the operations and compliance with the relevant information system requirements; Providing any relevant documentation and information relating to implemented procedures and expenses incurred by the Research Program; Ensuring visibility of the Union funding, by providing coherent, effective and proportionate targeted information to multiple audiences.</p>

As mentioned above, the Hub will be in charge of overseeing that all activities comply with the DNSH principle. In particular, the ANTHEM project does **not** include any “brown” R&I activity pursuant to the Communication of the European Commission 2021/C58/01:

1. fossil fuel related activities, including downstream use;
2. activities under the EU Emissions Trading System (ETS) that result in greenhouse gas emission projections that are not lower than the relevant benchmarks;
3. activities related to waste landfills, incinerators and mechanical biological treatment plants;
4. activities where the long-term disposal of waste may cause damage to the environment.

B.4 Equipment and technologies involved in the deployment of the activities

The participants will make use of existing equipment (Table B.8) and of the available facilities described in A.3, including e.g. certified animal facilities. The most relevant scientific equipment to be acquired and necessary to meet the ANTHEM objectives is described in Tables B.9-B.12, these acquisitions constituting a project objective.

Table B.8. Key equipment to be used for the activities and currently owned by ANTHEM partners.

Spoke	Description
Spoke 1	<ul style="list-style-type: none"> • Mass Spectrometers (TissueTyper MALDI-TOF/TOF MS System and timsTOF fleX, Bruker; 6546 LC/Q-TOF, Agilent) • X-ray absorption based micro-CT facility

	<ul style="list-style-type: none"> • 1 Maxwell RSC Instrument (Promega), a benchtop automated instrument for DNA/RNA extraction from any sample; • 2 Microlab STARlet (Hamilton), liquid handlers; • 1 TapeStation (Agilent), a system for automated electrophoresis for the quality control of DNA/RNA; • 1 3730xl DNA Analyzer (Applied Biosystems), a capillary electrophoresis sequencer; • 1 Ion Torrent PGM (ThermoFisher Scientific), a benchtop next-generation sequencing (NGS) platform; • 1 Ion Torrent S5XL system (ThermoFisher Scientific), a next-generation sequencing (NGS) platform; • 1 Ion Chef (ThermoFisher Scientific), for automated Ion Torrent Ampliseq library preparation, template preparation, and chip loading. 	
Spoke 2	<ul style="list-style-type: none"> • Quadrupole Mass Spectrometer (QMS) Hyden EQP 1000 Analyser (neutrals, ions and ion energy) • <i>In vivo</i> imaging platform (7T MRI, micro-CT, bioluminescence, infrared tomography) • Nuclear Magnetic Resonance (NMR) - Varian 400 MHz • CytoViva Enhanced Darkfield and Hyperspectral Microscopy • Steady State and Time Resolved (ps) spectrofluorimeter Edinburgh FL900 • ULTRAFast fs laser + OPA + Transient Absorption detector (UV-to-IR) • 00/600 MHz High Spinning Speed (35KHz) Solid State NMR (Bruker) • Confocal system for single particle photoluminescence spectroscopy (NIKON) • Transmission Electron Microscope JEOL JEM 2100P 200 kV + Gatan RIO CMOS camera • <i>In vivo</i> animal facility (7T MRI, micro-CT, infrared tomography, bioluminescence) • Microspectrometer for fluorescence correlation spectroscopy and lifetime decay measurements 	
	<ul style="list-style-type: none"> • Multi-photon microscopy system • Zeiss Gemini 360 SBF-SEM microscope • Super-resolution confocal microscope • Peptide synthesiser • Operetta CLS - HTA 	<ul style="list-style-type: none"> • Nanosight NTA • DLS and zeta Potential Malver Zetasizer • Nanosight particle analyzer • CPS differential centrifugal sedimentation • Spectrofluorometer FluoroMax4 (Horiba)
Spoke 3	<ul style="list-style-type: none"> • Agilent HPLC_MS / MS technology; MALDI-TOF-TOF mass spectrometer Bruker Daltonics Ultraflexxtreme • Bruker Avance III 400 MHz NMR spectrometer; AVANCE III HDTM 600 Superconducting • Raman microscope + AFM TERS module Horiba Jobin Yvon Xplora • Langmuir tanks with protective cabin KSV NIMA LB5000 • Class NIR spectrophotometer Agilent Technologies Cary-5000; • Class 100.000 clean room equipped with class 10.000 modules • Accurion EP4 integrated AFM-SPR-ellipsometer system • Integrated system Langmuir tank + Brewster angle microscope + NIMA-NFT-ORIEL reflection spectrophotometer 	
	<ul style="list-style-type: none"> • X-ray diffractometry • Molecular Imaging Facility (MIF) • Agilent gas chromatograph technology 	<ul style="list-style-type: none"> • HPLC_UV / VIS • DLS Z-potential analyzer • Nano-HPLC-MS/MS
Spoke 4	<ul style="list-style-type: none"> • Ultra-high dose rate diagnostic and dosimetry systems • Multimodal integrated system PET/CT (Albira-Bruker) at high-resolution • Optical imaging system/X-ray (Xtreme II - Bruker) for small animals, fluorescence, bioluminescence and X-ray imaging, and the detection of radioisotopes. • Ultrasound Imaging, high-frequency ultrasound system (Fujifilm VisualSonics Vevo-3100) equipped with stage and micromanipulators for echography and ultrasound-guided surgery for small animals • Orbitrap Fusion™ Tribrid™ LC-MS Thermo Scientific Mass Spectrometer combined with • nCounter System NanoString Technologies • Confocal laser scanning microscope Leica TCS SP8 • TrueBeam Novalis STx linear accelerator 	

	<ul style="list-style-type: none"> • Thermo-Fisher QuantStudio 5 Dx (Real-Time PCR) • computational units (1000 CPU cores, 10 GPU units, 5TB RAM) • Cytofluorimeter Sorter BD FACS Aria III (5 laser) • Ion source: the 80 kV 50 mA RF source TRIPS, with all ancillary systems • RF system (5 of the 8 solid state chains, 125 kW each) • Prototype target (nominal power density, low power) • RFQ cooling skid; interface at the heat exchange with the general cooling system • X ray irradiator for <i>in vitro</i> and <i>in vivo</i> studies • RFQ structure (8 brazed modules, 1,1m long) • Seahorse Real-Time Cell Metabolic Analysis 	
	<ul style="list-style-type: none"> • BD FACS CELESTA • Xcelligence ROCHE • Gentle MACS DISSOCIATOR • Novseq6000 ILLUMINA • Laser 45 Tw with interaction chamber • <i>in vitro</i> ed <i>in vivo</i> irradiation beamline • Radiobiology laboratory • Low energy beam transport line • Confocal microscopes • Scanning Electron Microscope 	<ul style="list-style-type: none"> • Pre-clinical lab facility • Ion S5 system • Ion Chef • Illumina next 550 • FACS cell sorter. • Mass spectrometry (Rodano) Q Exactive • HPLC Thermo (Rodano) Ultimate 3000 • Illumina MiSeq Sequencer • UHPLC Dionex UltiMate 3000

Table B.9. Most relevant equipment to be acquired as part of the project objectives of Spoke 1.

Description	Pilot	Cost (€)	Description	Pilot	Cost (€)
Equipment for NGS	1.4	1.800.000	Scintillating crystals	1.6	180.000
ZEISS Xradia Versa	1.8	1.550.000	Digital and Real time PCR system	1.4	160.000
2 x laparoscopic column Indocyanine green	1.6	595.000	Streak chamber	1.6	155.000
Liquid metal Jet X-rays source (Excillum)	1.8		448.000	Mechanics and electronics of the mockup	1.5
Small-animal MRI	1.7	440.000	Ultrasound equipped with laparoscopic and transrectal probe	1.6	137.000
Data storage-disk system-tape and management	1.8	439.000	Silicon Photomultipliers	1.6	125.000
Termofisher Genexus	1.1	415.000	Gene Array reader for SNP genotyping microarray and CNV	1.4	122.000
Next generation sequencing (NGS)	1.7	400.000	Interferometric masks and piezoelectric motors for phase contrast imaging	1.8	122.000
1125 x wearable ECG monitoring system	1.3	360.000	Optical Bench for scintillating crystal characterisation	1.6	105.000
Automated preparer for DNA / RNA libraries	1.7	300.000	Readout electronics	1.6	100.000
MALDI 2 ionisation source for Mass Spectrometry Imaging (Bruker)	1.5	250.000	microGRID for high spatial resolution for Mass Spectrometry Imaging (Bruker)	1.5	80.000
4 powerful workstations with screens	1.8	244.000	X-ray detector (high resolution)	1.8	61.000
Ultrasound scanner	1.4	244.000			
Sanger 8 capillary sequencer	1.7	200.000			

Table B.10. Most relevant equipment to be acquired as part of the project objectives of Spoke 2.

Description	Pilot	Cost (€)	Description	Pilot	Cost (€)
TEM/STEM equipped with FEG, with X-Ray analysis	2.5	850.000	epMotion 5075t ngs	2.3-2.5	120.000
Zeiss Cell discoverer	2.3	700.000	Detection system with IR TCSCP detector, light sources, integrating sphere	2.5	103.00
2000 x wearable ECG monitoring system	2.2	640.000	sputter-coater - SEM/TEM	2.5	100.000
Amnis® Imaging Flow Cytometer	2.5	438.000	NanoAssemblr Ignite Instrument	2.5	100.000

Scanning Tunnelling Microscope with vacuum chamber	2.3-2.5	360.000	Double Tilt Liquid Nitrogen Cryo-Transfer Holder	2.5	100.000
Ultrafast Upconversion Fluorescence Spectroscopy Head	2.5	313.000	2 x ultrasounds	2.2	97.00
Robotic Platform for automated materials production + accessories	2.3	300.000	Laser diffraction AEROTRAC II-granulometer	2.4	95.000
Tunable laser 700-1500 nm	2.4	250.000	Absolute PL Quantum Yield Measurement System C9920-03G		
6000 x blood pressure monitor	2.2	240.000	Hamamatsu	2.5	95.000
Interface for the analysis of plasmas and flames at atmospheric pressure	2.4	204.000	FT-IR spectrometer	2.5	75.000
Droplet digital PCR system (BIO-RAD QX 200 autodg)	2.5	160.000	2 x ergospirometer	2.2	72.000
			3D Printer platform + accessories	2.3	70.000
Automatic ultramicrotome for preparative ultra-thin sections	2.3	150.000	GridION Mk1C and seq kit	2.3-2.5	60.000
			PV Loop analysis system	2.2	57.000
Nanolive 3D Cell Explorer Fluo	2.3	150.000	Rheometer Anton Paar + accessories	2.3	50.000
Cytofluorimeter BD FACSLyric™ System 3 LASER	2.5	150.000	5mm2 Silicon Foundry Chip Manufacturing	2.3-2.5	50.000
			Type 2 Goniophotometer equipped with sensor support	2.4	32.000

Table B.11. Most relevant equipment to be acquired as part of the project objectives of Spoke3.

Description	Pilot	Cost (€)
PET-MRI integrated system equipped with CT for small animals	3.3.3.4	3.710.000
PET/CT digital scanner	3.3	3.660.000
MRI scanner	3.3	1.905.000
Radiopharmaceutical laboratory (small animals)	3.3-3.4	976.000
Computing facility: high performance CPU/GPU servers with NAS backup support and 48-gates 10GB networks with SFP connectors.	3.3	800.000
Platform for developing wearable prototype: electronics, PCB system, welding, microscope, 2x 3D printers, validation devices Cosmed k5, optoelectronic system for motion analysis.	3.1	700.000
Multiparameter wearable devices and SW (100 garments)	3.2	600.000
Optical laboratory: Picosecond pulsed broad band laser sources, High-contrast narrow-bandwidth wavelength selection device, Pulse-picker, Time domain detector with high efficiency over a broad spectral range, Near-infrared photomultiplier, Multichannel acquisition board for time correlated single photon counting	3.3	400.000
Micro-CT	3.3	350.000
Intensive care monitoring instruments A	3.3	180.000

Table B.12. Most relevant equipment to be acquired as part of the project objectives of Spoke 4.

Description	Pilot	Cost (€)
mSEM platform equipped with sample preparation and characterization instruments	4.1-4.3	10.315.000
RF system (3 of the 8 solid state chains, 125 kW each)	4.9	2.100.000
Robotic arm equipped with 2-3D imaging system and radiotrasparent operating table	4.7-4.8	1.600.000
Beam transport line between RFQ and target	4.9	1.500.000
PET Imaging instrument for small animals	4.5	1.200.000
Ancillaries for the RFQ, including power couplers and injector refurbishing	4.9	1.200.000
Linear Accelerator Electron Flash	4.4-4.5	1.000.000
Control system (LLRF, MPS, PPS, General Control System)	4.9	900.000
MACSima™ Imaging Platform - Miltenyi Biotec	4.4-4.5	800.000
SHIELDED Rooms construction	4.9	800.000
Flash Therapy equipment	4.4	766.000
Beam Shaping Assembly	4.9	700.000
Advanced RADIOTHERAPY instrumentations	4.9	700.000

Laparoscopic columns with Indocyanine green x2	4.9	595.000
OXFORD NANOPORE SEQUENCING	4.9	550.000
Agilent BioTek Cytation C10 Confocal Imaging Reader	4.4-4.5	520.000
HPLC-High resolution Mass Spectrometry + radiochemical detector	4.4-4.5	500.000
3D in vitro laboratory platform	4.7-4.8	500.000
Optimization of the laser contrast using a plasma mirror system	4.4	500.000
NGS	4.4-4.5	500.000
High power neutron production target	4.9	500.000
Workflow of circulating tumour cells collection (CTCs)	4.5	420.000
SINGLE CELL SEPARATOR 10XGENOMICS	4.9	400.000
CONFOCAL microscope ZEISS LSM900	4.9	400.000
ZEISS LSM 980 with Airyscan 2	4.4-4.5	350.000
BIOIMAGING EQUIPMENT MICRO-MRI	4.9	350.000
BD CELL SORTER	4.9	350.000
NGS	4.7-4.8	300.000
FIBSEM 3D system, Nanotomography and AI image analysis	4.7-4.8	300.000
MySeq – Illumina	4.9	300.000
Confocal microscopy	4.5	250.000
Cyclotron Target fo Ga-68	4.4-4.5	240.000
Cyclotron Target for Cu-64	4.4-4.5	240.000
NanoString CosMx	4.4-4.5	240.000
Upgrade of the vacuum chamber for electron acceleration	4.4	200.000
Gas jet system for electron acceleration	4.4	200.000
Diagnostics for electron beams: both transverse and longitudinal diagnostics, electron bunch position, dimension, charge and energy	4.4	200.000
Acceleration approach with a capillary	4.4	200.000
HPLC system with DAD detector and 60 mm FLOW CELL, HISENS, + TSQ Altis Plus Triple Quadrupole Mass Spectrometer ThermoFisher	4.4-4.5	200.000
KTAC-4000 SonoPore4000 Sonoporator equipped with SonoPore4000 Ultrasound Probe KP-SS1M Small Straight Probe1 mm and KP-SS2M: 2mm	4.5	200.000
Radioactive waste management	4.9	200.000
Laser Microdissector Leica	4.4-4.5	160.000
MACSQuant® Analyzer 16 Flow Cytometer	4.4-4.5	150.000
Seahorse XFe24 Analyzer	4.4-4.5	150.000
LIVE CELL Analysis Syst INCUCYTE	4.9	150.000
DeepLive™ LC-OCT (Line-field Confocal Optical Coherence Tomography).	4.4-4.5	140.000
IVIS ILLUMINAI In vivo Imaging System	4.9	140.000
MICROSCOPIO THUNDER IMAGER LIVE CELL & 3D ASSAY	4.9	140.000
Ultrasound equipped with laparoscopic and transrectal circular probe	4.9	137.000
Chromium x & Accessory Kit, 12 Mo Warranty	4.4-4.5	130.000
VISUM CytAssist	4.4-4.5	103.000
Synthesis module for radiometals	4.4-4.5	100.000
MGI/Hamilton	4.4-4.5	100.000
digital ultrasound	4.7-4.8	100.000
Long-focusing parabola for laser-gas interaction	4.4	100.000
Quantum-Si Carbon+Platinum next generation protein sequencer	4.4-4.5	100.000
Flow cytometer	4.5	80.000
BenchMark ULTRA IHC/ISH System	4.4-4.5	80.000
IP-Star® Compact	4.4-4.5	75.000
X-ray diffractometer	4.6	70.000
Preparative HPLC system	4.6	70.000
Purification module for radiometals	4.4-4.5	60.000
Quality controls on radiometals (Atomic absorption)	4.4-4.5	60.000



Turbiscan system for evaluation of injectable solutions	4.6	60.000
Ella Automated Immunoassay System bio-techne	4.4-4.5	55.000
Oxford Nanopore GridION+P2Solo	4.4-4.5	54.000
QIAcuity One, 5plex Platform System (Digital PCR)	4.4-4.5	50.000
Tape Station 4200TS	4.4-4.5	40.000
Redundant Storage unit 100TB	4.4-4.5	40.000
10X Genomics Chromium	4.4-4.5	40.000
EZ2 Connect Qiagen	4.4-4.5	30.000
Tissue Microarray platform	4.4-4.5	30.000

B.5 Feasibility of the work plan

The objectives and the methodologies of the different Spokes are planned taking inspiration from the real clinical needs. The objectives of ANTHEM project have been arranged with the clinical partners (hospitals-ASST) and Territorial entities (Regional Bodies) involved and the Spokes organisation aims to make them realisable in the real world. Here we summarise the principal objectives and the related methodologies.

Spoke 1. - Data and technology driven diagnosis and therapies.

Objectives: Development of digital and technical solutions to translate the real clinical needs of the chronic population.

Methodologies: Overall, all the Pilots will be technology-driven and have data mining and AI as a core element for data analysis. The proposed methodologies will be focused on the results obtained from all the planned Spoke, to make usable data obtained from advanced technologies for diagnosis of cancer and chronic diseases. In brief, the objective of the Spoke will be reached employing the following methodologies: a) tools and algorithms for anonymizing and extracting information from clinical, biological, omics and environmental data; b) last generation MS and -omic technologies (single cell MS directly performed on tissues, genomic analysis); c) last generation prototypes of 3D bioptic models (X-ray phase contrast microCT) d) AI methods to collect and evaluated the obtained data from different sources.

Pilot 1.1, Pilot 1.2, Pilot 1.3 will be devoted to manage and treat data obtained from the therapeutic pathway considering selected examples of the care experience in the clinical environment (triage and therapy). Pilot 1.4 and Pilot 1.7, Pilot 1.5, Pilot 1.6 and Pilot 1.8 will be devoted to generate, collect and reengineer respectively genomic, proteomic, imaging and bioptic clinical data obtained in the diagnostic pathways.

Overall significance of the Spoke: Spoke 1 will allow to generate the ideal experimental conditions to manage together -omic, bioptic and patient related data in a functional and effective flux. The Spoke organisation includes the collection of wet data (i.e. -omic and bioptic data) and their use in relationship with information related to the entire patient management process (from the triage to therapeutic plan).

Spoke 2. Connecting patients and therapists through adaptive environments and intelligent sensors to enhance proximity medicine.

Objectives: Development of wearable, portable and environmental platforms to monitor in real time both patients' parameters and environmental risks involved in the onset of pathological conditions.

Methodologies: The Spoke 2 will include technological innovations useful for the early detection of biomarkers related to the relapse of chronic conditions. The proposed methodologies will be adopted to generate AI-driven smart devices and platforms that will allow to follow in real time patient's conditions and environmental risks. In brief, the following methodologies will be employed: a) VR and smart assisted devices (ie. virtual environment and digital motion acquisition); b) e-technologies to monitor cardiovascular disease (i.e ECG wearable T-shirts integrated with AI assisted platforms for patients evaluation); c) smart medical devices and platforms (In/Ga biosensors integrated in functionalized printed patches and biomaterials to detect representative biomarkers (i.e. cholesterol, PCR, glucose); d) point of cares based on multifunctional colloidal nanoparticles (conjugated nanoparticles / lateral flow) and DNA



based -omics (DNA barcoding / metagenomics) to detect and quantify environmental and human biohazards (microbial pathogens) ; e) last generation light – based systems to sanitise environments contaminated by microbial pathogens as identified within the Spoke. All the proposed methodologies will include AI-based systems to collect and make usable in the clinical environment the obtained data.

Pilot 2.1, Pilot 2.4 and Pilot 2.5 will be devoted to the environmental control (home and care centres) and will be focussed respectively on the implementation of home-care pathway and on biohazard quality control of care centres. Pilot 2.2, Pilot 2.3, Pilot 2.6 and Pilot 2.7 will be devoted to generating and collecting patients related data to maximise and make available early diagnostic methods. The activities related to innovative therapies for orphan tumours will integrate from the beginning the methodologies of telemedicine, envisioning the possibility of tele-follow-up after the treatments. All the Pilots will include the assessment and validation of AI-based platforms to generate usable data connected with the healthcare system.

Overall significance of the Spoke: Spoke 2 will allow to generate a platform in which devices and biosensor with different features and roles will be useful to check parameters and biomarkers useful to monitor in real time patients healthiness. The Spoke organisation includes technological innovations directed to the development of wearable and portable devices to control in real time physiological conditions (i.e. patches to control measurable biochemical markers, devices for breath control), point of cares and platforms to control biohazard contamination (i.e. nanoparticles based Point of cares and metagenomic platforms to analyse microbial identities) and their use in relationship with information related to the entire patient management process (from the triage to therapeutic plan).

Spoke 3. Risk factors monitoring, diagnostic tools and therapies in chronic disease

Objectives: Development of diagnostic tools and therapeutic methods to monitor and treat chronic diseases, with particular emphasis on pulmonary and cardiovascular diseases.

Methodologies: The Spoke 3 will include technological solutions to develop and test in significant environments diagnostic tools to detect environmental or lifestyle associated pollutants (PMs, VOCs, ozone, microplastic) that have negative impact in chronic disease progression. Furthermore, target therapies aimed to treat the same diseases will be developed within the Spoke. In brief, the following methodologies will be developed: a) AI - assisted wearable devices will be developed to detect environmental air quality (i.e. PMs, ozone and VOCs); b) lung and gut tissue models will be generated using organ-on-chip assembled in microfluidic devices to mimic organ and tissue complexity and to test microplastic/food contaminants, c) advanced imaging systems already employed in clinic, introducing patient stratification to implement AI based diagnostic; d) advanced system for in vivo imaging e) new *in silico* platforms for drug screening to fasten the development of therapeutic plans and opportunities.

Pilot 3.1 and Pilot 3.2 will be devoted to detect and identify environmental and life-style factors (air pollutants - VOCs, ozone, PMs - and micro- and nanoplastics) that can have negative impact in the maintenance of patient wellness or in the exacerbation of chronic pathological manifestations. Pilot 3.3 and 3.4 will be devoted to generate and validate diagnostic (imaging data and point of cares) and therapeutic approaches (in silico platform to fasten the therapeutic translation) to improve care approaches in patients affected by pulmonary and cardiovascular disease.

Overall significance of the Spoke: Spoke 3 will allow to generate a model system in which patients affected by systemic chronic disease can be followed taking into consideration together environmental risks and early diagnosis and treatment. The Spoke organisation is mainly focussed on cardiovascular and lung disease. Both pathologies can be often correlated and the environmental (air pollutants) and lifestyle factors (diet and food contaminants) play a key role in the relapse of symptomatic phenomena. Patient related activities include diagnostic and therapeutic solutions to optimise both quality of life and care pathways of patients from different territorial realities that can strongly differ in terms of pollutants exposition (i.e Taranto area, Milan).

Spoke 4. Preclinical and clinical breakthrough therapies and treatments for cancer.

Objectives: Development of innovative therapeutic solutions and clinically relevant multifunctional approaches

Methodologies: The Spoke 4 will include therapeutic multifunctional solutions to develop innovative and personalised treatments for cancer. In brief, the following methodologies will be developed: a) multiple multifunctional theragnostic nanoformulations with improved therapeutic outcomes taking advantage of more effective targets; b) new methods to overcome the biological barriers and the current limited efficacy of nanoformulations (i.e. sonoporation US-mediated); c) FLASH therapy; d) boron neutron capture therapy (BNCT).



Furthermore, the Spoke will include methods to implement the validation and the evaluation of the proposed therapies including also the development of new advanced tissue models in bioreactors (i.e. perfused tissues and organoids), new optical diagnostic methods for in depth cancer cells and tissue characterization / drug validation (i.e. niche-on-chip, microfluidic devices) and an AI assisted multi-omics platform to have a complete output of therapeutic efficacy.

Pilot 4.1, Pilot 4.4, Pilot 4.5, Pilot 4.6 and Pilot 4.9 will be devoted to the development of innovative therapeutic solutions for cancer treatment. The selected approaches will allow to generate a platform in which differential therapeutic solutions will be investigated in parallel to maximise the opportunity of combined and personalised therapies for cancers. Furthermore, Pilot 4.9 will allow the establishment of a new boron neutron capture therapy (BNCT) - an emerging treatment to improve the therapeutic outcome for cancers with poor therapeutic response. Pilot 4.2, Pilot 4.3 and Pilot 4.7 will be devoted to generating diagnostic solutions covering the entire cancer of interest (from cells to tissues). This approach will allow us to characterise new targets of interest for patient stratification and to better validate the effect of proposed therapies. Pilot 4.8 will include an AI based system to evaluate and to maximise the efficacy of theranostic platform developed within the Spoke.

These Pilots are tightly interconnected as BNCT and FLASH therapy need to rely on effective treatment planning capacity thus advanced diagnostic methods are required. The potential of therapy innovation depends on solid radiobiological data thus new models and methods are pivotal. Moreover, BNCT is based on a drug administration able to concentrate in tumours, thus theranostic formulations have the potential to improve the therapeutic effectiveness.

Overall significance of the Spoke. Spoke 4 will pave the way for a theranostic platform focussed on cancer treatment. The Spoke will include last generation treatments (i.e. multifunctional nanoformulation with increased target ability, FLASH and ULTRA-FLASH therapy) and a new BNCT facility. The development of multiple multifunctional therapies in the same Spoke will allow to test and validate combinable therapies to overcome the current limitations occurring in poor responsive or untreatable cancers (i.e. melanoma, GBM). The diagnostic platform developed will allow to test and validate in-depth and at different biological levels the developed solutions, considering also patient stratification and personalised approaches.

The Initiative feasibility builds on several factors that ensure the achievement of the project goals:

- The outstanding scientific and technological reputation of all the players – academic and non-academic – involved in the Initiative;
- An efficient management structure for the Hub and Spoke model, combined with the proven high-level managerial capacity of the members of the Hub, Spokes and Scientific Investigators;
- The high level of maturity of the technologies, processes and services employed in the activities and promoted for scale up and transfer to the operational environment;
- Balance of competencies and complementarity of expertise, at the level of each spoke, also favouring cross-fertilization and interdisciplinarity;
- The adequate investment balance between the existing (Table B.2) and future (see C.2) human resources to be selected according to the best practice international criteria;
- The large array of previous successful projects managed by partners, including the joint ones (see A.3);
- The existing facilities and platforms that will be used in the activities, together with newly acquired equipment (see B.5);
- The full engagement of the partners in the Spokes and in the Pilots' activities in a collaborative way across different sectors: the participation is shown in Figure 11.

An additional key element for the project feasibility is a reliable and well-structured work plan, along with a set of indicators to effectively monitor and assess the progress of the whole project (see also B.9). Milestones and Deliverables provide intermediate checkpoints to assess the advancement of each Pilot against quality standards, time, costs and associated risks (a preliminary risk assessment is provided in Table B.43). In the first phases of the project, Pilots will follow parallel although similar paths and therefore a set of initial Milestones (MS) and Deliverables (D) has been defined (Table B.13) that will be relevant for all pilots. However, it is worth stressing that each Pilot will be individually responsible for the achievement of those Milestones and Deliverables. Subsequently, each Pilot will follow an individual Work Plan based on the specific Milestones and Deliverables indicated in Tables B.14 through B.41. Timing information is provided indicating the month (M) of delivery since ANTHEM's start. For the interrelationship among the Pilots, please see Figure 5.

	UNIMIB	UNIBG	UNICAL	ASST PG23	ASST BGEST	ASST MONZA	ATS MI	FERB	ART
Pilot 2.1	✓	✓		✓					
Pilot 2.2	✓	✓		✓			✓		
Pilot 2.3	✓	✓					✓		
Pilot 2.4	✓					✓			✓
Pilot 2.5	✓								
Pilot 2.6	✓		✓						
Pilot 2.7		✓			✓	✓		✓	

	POLIMI	HUNIMED	UNISALENTO	CHIESI	ABM
Pilot 3.1	✓	✓	✓		✓
Pilot 3.2	✓	✓	✓		
Pilot 3.3	✓	✓	✓		✓
Pilot 3.4	✓	✓	✓	✓	

	UNIBG	UNIMIB	UNIME	UNICAMP	ASST BGEST	ASST MONZA	ASST PG23	DIA	FERB	NEGRI
Pilot 1.1	✓	✓								✓
Pilot 1.2	✓				✓				✓	✓
Pilot 1.3	✓						✓			
Pilot 1.4	✓						✓			✓
Pilot 1.5		✓								
Pilot 1.6		✓		✓		✓				
Pilot 1.7			✓			✓				
Pilot 1.8	✓	✓				✓	✓	✓		

	UNICT	POLIMI	HUNIMED	UNICAL	UNIME	UNISALENTO	UNICAMP	INFN	CANNIZZARO	BIOGEM	IOM
Pilot 4.1		✓	✓			✓					
Pilot 4.2		✓	✓			✓					
Pilot 4.3		✓	✓			✓					
Pilot 4.4	✓							✓	✓	✓	✓
Pilot 4.5	✓				✓			✓	✓	✓	✓
Pilot 4.6				✓						✓	
Pilot 4.7				✓							✓
Pilot 4.8				✓							
Pilot 4.9							✓	✓			

Figure 11: participation of the partners in the Spokes and in the Pilots' activities

Table B.13. Planned Milestones and Deliverables relevant for all Pilots.

Milestones
MS1: Hiring new team members for the pilot activity (M6)
MS2: Definition of the requirements for the pilot use cases (M9)
MS3: Definition of data requirements for the pilot: type, size, storage, metadata, FAIRness, privacy management procedures (M9)
Deliverables
D1: Technical report on the literature specific to the Pilot, related to models, best practices, technologies and state of the art (M6)

Table B.14. Planned Milestones and Deliverables relevant for Pilot 1.1.

Pilot 1.1: Leveraging data for clinical decision support system and data management
Milestones
MS1: Approval by partners of other pilots of the defined use cases (M12)
MS2: Testing and evaluation setups approval (M15)
MS3: Release and testing of methodologies for data protection (M18)
MS4: Release and testing of the machine learning models (M20)
MS5: Release and testing of the natural language processing (NLP) models (M28)
MS6: Release and testing of the causal networks models (M36)
MS7: Release and testing of the deep learning models (M42)
Deliverables
D1: Technical report on the testing and evaluation setups (M15)
D2: Prototype and technical report of the developed data privacy structure (M18)
D3: Prototype and technical report of the developed machine learning models (M20)
D4: Prototype and technical report of the developed NLP models (M28)
D5: Prototype and technical report of the developed causal networks models (M36)
D6: Prototype and technical report of the developed deep learning models (M42)
D7: Set of tools for managing the available data (e.g., data security, anonymity, missing data imputation), and a set of algorithms for extracting information from clinical, biological and omics data. Such tools should support

the design of personalised medicine interventions, by leveraging and integrating the heterogeneous data sources mentioned above (M48)

Table B.15. Planned Milestones and Deliverables relevant for Pilot 1.2.

Pilot 1.2: Digital Triage at the emergency room
Milestones
MS1: First release of the multi-lingual hospital triage kiosk (M12)
MS2: Release of the multilingual mobile application recording health historical data (M15)
MS3: Release of the learning system based on up-to date healthcare consumers' information (M18)
MS4: Testing in relevant environment (M24)
MS5: Release of AI-based models (M28)
MS6: Release of data-protection modules (M36)
MS7: Testing of the AI-based developed solutions in a relevant environment (M42)
Deliverables
D1: Technical report and release of the multi-lingual hospital triage kiosk (M12)
D2: Technical report and release of multilingual mobile app recording health historical data (M15)
D3: Prototype and technical report of a multilingual learning system based on up-to date healthcare consumers' information (M18)
D4: Report on the testing of multilingual solutions in a relevant environment (M24)
D5: Prototype and technical report of ML and AI models for patient triage classification and flows (M28)
D6: Prototype and technical report of an integrated, safe ED patient data management system (M36)
D7: Report on the testing of the AI-based developed solutions in a relevant environment (M42)
D8: Advanced patient-centred triage system integrating mobile and kiosk screening devices. The tools will use a set of natural language processing and AI algorithms to efficiently process ED patients (M48).

Table B.16. Planned Milestones and Deliverables relevant for Pilot 1.3.

Pilot 1.3: AI based Artificial Pancreas for children
Milestones
MS1: Release and testing of the control algorithm (M15)
MS2: Release and testing of the meal detection tool to be integrated in the control algorithm. Tools for detecting specific faults (M24)
MS3: Release and testing of patient-tailored model-based alarm systems for hypoglycaemia (M32)
MS4: In-silico testing on UVA/Padova Virtual Patient (M40)
MS5: <i>In vivo</i> testing on Patients from the ASST PG23 (M48)
Deliverables
D1: SW prototype related to M3 plus technical report (M28)
D2: SW prototype related to M4 plus technical report (M38)
D3: SW prototype related to M5 plus technical report (M42)
D4: Technical report on the results of the in-silico experiments (M42)
D5: Technical report on the results of the <i>in vivo</i> experiments (M48)
D6: Patient specific and personalised Learning-Based MPC for completely automated blood glucose regulation in the AP framework (M45)

Table B.17. Planned Milestones and Deliverables relevant for Pilot 1.4.

Pilot 1.4: Timely genomic diagnosis for children with rare diseases toward precision medicines
Milestones
MS1: Hospital and paediatric patient enrollment (M12)
MS2: First release of AI-based decision support models for genomic screening (M15)
MS3: Testing in relevant environment (M20)
MS4: Second release of AI-based decision support model for genomic screening (M24)
MS5: Release of high-volume diagnostic services for rare diseases (M30)
MS6: Third release of AI-based decision support model for genomic screening (M36)
MS7: Testing in operational environment (M42)
Deliverables
D1: Technical report on patient characteristics and needs (M12)

D2: First release of AI-based decision support models for genomic screening: report & source code (M15)
D3: Report on the testing of developed solutions in a relevant environment (M20)
D4: Second release of D2 (M24)
D5: Technical report and source code of of high-volume diagnostic services for rare diseases (M30)
D6: Third release of D2 (M36)
D7: Report on the testing of developed solutions in a operational environment (M42)
D8: Report on the full developed system and on evaluation in a relevant and operational environment (M48)

Table B.18. Planned Milestones and Deliverables relevant for Pilot 1.5.

Pilot 1.5: Mass spectrometry for tissue biopsy investigation
Milestones
MS1: Enrolment of patients and specimens collections (M6)
MS2: Gathering of the requirements for protocols (M9)
MS3: Gathering of the requirements for data management and information exchange (M12)
MS4: Release of protocols for data analysis (M15)
MS5: First release of models for data analysis (M24)
MS6: Testing in relevant environment (M28)
MS7: Second release of models for data analysis (M30)
MS8: Release of molecular signatures specific for the considered disease (M36)
MS9: Testing in relevant environment (M42)
Deliverables
D1: Preliminary database with information about the enrolled patients (according to the diseases) (M9)
D2: Technical report on the optimised analytical protocols with preliminary results of MSI analysis (M12)
D3: Technical report about data analysis, update 1 (M15)
D4: Technical report about the enrolled patients and specimen collections, update 1 (M18)
D5: Technical report about data analysis, update 2 (M24)
D6: Technical report about the enrolled patients and specimen collections, update 2 (M30)
D7: Technical report and molecular signatures specific for the considered diseases (M36)
D8: Technical report on the testing phase (M42)
D9: Technical report and release of the molecular signatures in solid and liquid biopsies able 1) to distinguish not only health subjects from patients but also 2) to correctly classify patients into different subtypes of their diseases (e.g. in the case of thyroid to distinguish pre-malignant from benign) (M48)

Table B.19. Planned Milestones and Deliverables relevant for Pilot 1.6.

Pilot 1.6: Improved multi-source image based diagnostic for early cancer detection
Milestones
MS1: Setup of the territorial screening activity (M3)
MS2: Set up of the partnership (M6)
MS3: Gathering of the requirements of medical and data acquisition methodology (M9)
MS4: Integration of the activities with oncological ambulatorial activities (M12)
MS5: First release of developed AI models (M12)
MS6: Testing in relevant environment (M15)
MS7: Study submitted to our University Hospital Ethical committee (M18)
MS8: First release of developed AI models (M24)
MS9: Testing in relevant environment (M28)
MS10: Intelligent screening activity beginning (M30)
MS11: Third release of developed AI models (M36)
MS12: Release of devices, hardware, SW dedicated to Innovative Surgical Process enhanced by ICG (M40)
MS13: Testing in relevant environment (M42)
Deliverables
D1: Technical reports on the database with information about the enrolled patients (M9)
D2: Technical report on the predictive models (M12)
D3: Technical report and prototype of the developed CAD and its integration with data, 3D augmented reality image procedure (M15)
D4: Technical report on the testing phase (M18)

D5: Technical report and source code of the AI models (M24)
D6: Technical report on Multiparametric Imaging (M30)
D7: Technical report on Territorial Intelligent Oncological Screening and Telemedicine activity (M36)
D8: Technical report and source code of the AI models (M40)
D9: Technical report on the testing phase (M42)
D10: Report on the entire developed system and on all the evaluations in a relevant environment (M45)

Table B.20. Planned Milestones and Deliverables relevant for Pilot 1.7.

Pilot 1.7: Genetic insights in neurodegenerative disease
Milestones
MS1: <i>In vivo</i> model of PD induced by Gaucher syndrome (M2)
MS2: Evaluation of PD markers, Nrf-2 antioxidant pathway and Gaucher syndrome parameters at the different time points (qPCR, staining, western blot, ELISA kits) (M8)
MS3: Gathering of the requirements for data analysis protocols, for data management and information exchange (M8) and release of protocols for data analysis (M15)
MS4: Array Comparative Genomic Hybridization and Next-generation sequencing (NGS) (M36)
MS5: CNVs and SNVs collection and interpretation, by <i>in silico</i> analysis (M36)
MS6: Testing in relevant environment: Clinical evaluations of patients and genotype correlations (patient enrollment, clinical manifestations) (M36); Evaluation of antioxidant, GCase activity (beta-glucosidase leukocyte assay) and inflammatory parameters in patient's serum (M42).
MS7: Release of molecular signatures specific for the considered disease (M44)
Deliverables
D1: new predicting target to slow down the progression and the onset of PD in GBA mutated patients.
D2: better characterised allele risk and estimate possible genotype-phenotype correlation (M15)
D3: Intermediate report on results of data analysis collection of integrated genomics and clinical data (M24)
D4: Final report on implications of GBA mutation and oxidative stress in an <i>in vivo</i> model of GD and on GD patients, in the evolution of PD (M40)

Table B.21. Planned Milestones and Deliverables relevant for Pilot 1.8.

Pilot 1.8: MicroCT-based 3D digital histology
Milestones
MS1: Call for tender for the procurement of a state-of-the-art laboratory X-ray micro-CT facility (M6)
MS2: Installation and commissioning of the X-ray micro-CT equipment (M12)
MS3: Call for tender of the instrumentation for building the custom-made apparatus (M12)
MS4: Report of the first X-ray “virtual histology” application on non-human brains (M18)
MS5: Report of the first X-ray “virtual histology” application on human specimens (M30)
MS6: Installation and commissioning of the prototype of optimised sample preparation system (M36)
MS7: Publication of experimental results on X-ray phase-contrast imaging using the custom system with application of the AI analysis (M48)
Deliverables
D1: Development of a novel method to estimate the diffusion coefficient in a histological sample (M10)
D2: Report of the complete commissioning of a state-of-the-art laboratory X-ray absorption based micro-CT facility and of 2D and 3D image segmentation and federated learning approaches (M12)
D3: Report of the optimised protocol for X-ray CT sample preparation (M18)
D4: Publication of the experimental results on application of AI analysis on pilot datasets (M18)
D5: Delivery of the SW for instrument control and data acquisition for the custom-made X-ray phase-contrast micro-CT imaging (M24)
D6: Publication of the first X-ray “virtual histology”-based manuscript (M24)
D7: Report on commissioning of custom-made X-ray phase-contrast based micro-CT mock-up (M36)
D8: Realisation and installation of a sample preparation system optimised for X-ray CT imaging (M48)

Table B.22. Planned Milestones and Deliverables relevant for Pilot 2.1

Pilot 2.1: Remote physical therapy and sensorized environments
Milestones
MS1: Gathering of the UX requirements for design of new devices and SW applications (M9)

MS2: First release of modular SW architecture for developing (tele)rehabilitation platforms (M12)
MS3: Testing in a relevant environment and definition of the medical protocols (M12)
MS4: Release of AI-based models for data and signal analysis (M18)
MS5: Testing of the prototypes in relevant environment (M24)
MS6: Second release of the rehabilitation platform (M36)
MS7: Testing of prototypes in relevant environment by involving both public and private hospitals(M42)
Deliverables
D1: Technical reports and source code of the platforms for rehabilitation and telerehabilitation for each category of patients (M15)
D2: Technical report on the testing phase: usability and functional properties (M18)
D3: Documentation & release of APIs and SDKs with AI-based models with high level of modularity (M21)
D4: Guidelines and methodological approaches to evaluate the level of confidence of clinicians and patients with new solutions (M27)
D5: Prototypes of innovative devices and sensors for rehabilitation (M28)
D6: Prototypes of devices and sensors to measure vital sign in specific rehabilitation processes (M34)
D7: Final technical report, source code, prototypes and sensors developed within the pilot (M48)

Table B.23. Planned Milestones and Deliverables relevant for Pilot 2.2.

Pilot 2.2: Epidemiological study of cardiovascular diseases in a mountain area
Milestones
MS1: Gathering requirements for implementation of territorial activity (M18)
MS2: Study submitted to Ethics committee (M24)
MS3: Setup of the territorial activity (M30)
MS4: Testing in relevant environment (M36)
MS5: Completion of enrollment of the representative population (M42)
MS6: Evaluation of risk factors prevalence (M48)
Deliverables
D1: Technical report and release of the mobile application for data collection (M12)
D2: Technical report on territorial activity (M18)
D3: Report on Ethics committee approval (M24)
D4: Technical report on the testing phase: usability and functional properties (M30)
D5: Report on GPs adhesion and feedback from the population (M36)
D6: Proposal for cardiovascular risk control strategy at regional level, based on geographical needs and design of multi-technology system (device+data management system) for use with general population(M48)

Table B.24. Planned Milestones and Deliverables relevant for Pilot 2.3.

Pilot 2.3: Smart wearable and portable sensors to monitor human healthiness and pathological states
Milestones
MS1: Definition of device properties for transdermal biosensors (M12)
MS2: Technical report on the testing phase (M15)
MS3: Definition polymers for breath biosensors (M18)
MS4: Definition of functional biomarkers (M24)
MS5: Decision on platform functionalities (M30)
MS6: Testing of the prototypes in relevant environment (M36)
Deliverables
D1: Technical report and Prototype of wearable biosensor (M12)
D2: Technical report and source code of the platform for data integration and data processing(M15)
D3: Technical report on the testing phase (M20)
D4: Technical report and Prototype of transdermal biosensor (M24)
D4: Technical report and Prototype of breath biosensor (M28)
D5: Technical report and source code of the AI-based algorithms (M30)
D6: Integration of wereable/transdermal prototypes with system platform (M36)
D7: Technical report on the testing phase (M42)
D8: technical reports, source code and prototypes developed within the pilot (M48)

Table B.25. Planned Milestones and Deliverables relevant for Pilot 2.4.

Pilot 2.4 Wide spectrum light and devices to sanitise surfaces and air
Milestones
MS1: Definition of the experimental set up, and of analysis protocols, for air sanitation and surface disinfection using different technologies (M12)
MS2: Definition of a methodology for real-time evaluation of bacterial load (M18)
MS3: Study of the efficiency of the different air sanitation and surface disinfection technologies on a model bacterium (<i>Escherichia coli</i>), as a function of the operational parameters (M24)
MS4: Study of the air sanitation and surface disinfection technologies on different pathogens (M30)
MS5: Design and construction of pilot devices for air sanitation and surface disinfection equipped with environmental and biological sensors with remote data acquisition systems (M36)
MS6: Development of feedback systems for the optimization of pilots with a view to environmental and energy sustainability in specific fields of application (M36)
MS7: Test of the pilot devices in real-life conditions (ASST MONZA) (M36)
Deliverables
D1: Technical reports on the experimental set-up and protocols for air sanitation and surface disinfection, lab scale prototypes (M12)
D2: Platform for on-line bacteria detection (M24)
D3: Technical reports on the real-time diagnostic platform (M24)
D4: Technical report on the study of the efficiency of the different air and surface disinfection technologies on the model bacteria <i>Escherichia coli</i> and definition of the operational parameters (M30)
D5: Technical report on the study of the efficiency of the air and surface disinfection technologies on different pathogens (M42)
D6: Prototypes for air sanitation and surface disinfection with sensors and acquisition systems (M36)
D7: Technical reports on the prototypes and the data acquisition systems (M36)
D8: Feedback systems for remote control and real-time optimization of pilots for sustainable applications (M36)
D9: Technical reports on the pilot performances in real-life conditions (M48)

Table B.26. Planned Milestones and Deliverables relevant for Pilot 2.5.

Pilot 2.5 Development of nanosensors for the detection of pathogens and biohazard
Milestones
MS1: Identification of molecular signatures for skin environment related to human skin conditions (Report) (M6)
MS2: Scalability framework for the application from controlled conditions to local scale (Report) (M36);
MS3: Universal method for SPD conjugation to different types of nanoparticles and optimization of the protocol for the colorimetric test in liquid samples (Prototype and/or publication/patent) (M12)
MS4: Set-up of protocol for test application with different samples (Report and/or publication/patent) (M24)
MS5: Universal method for the oriented conjugation of antibodies to semiconductor quantum dots (QDs) (Prototype) (M36)
MS6: Set up of a strip-test for the specific pathogens detection (Demonstrator kit) (M48)
MS7: Identification of cells and/or cellular aggregates and their sorting <i>in vitro</i> using a microstructured devices (protocols/documents) (M12)
MS8: Photoacoustic and photothermal detection of cells based on magnetic nanoparticles/antigen aggregates within <i>in vitro</i> detection chambers (protocols/ documents/ prototype) (M24)
MS9: Near field interferometric detection of gold nanoparticles/antigen aggregates within the detection chamber based on cooling condensation of breath (protocols/ documents/ prototype) (M36)
Deliverables
D1: Baseline setting of skin micro-environment conditions (M10)
D2: Identification of microbial patterns associated with perturbations (M15)
D3: Prototype for efficacy test to assess the presence of pathogens, based on SPD nanoconjugates (M22)
D4: Prototype for efficacy test for the identification of 5 representative pathogens in a sample, including bacteria and viruses (M27)
D5: Photoacoustic and photothermal systems for cell detection and sorting in aqueous or gas media based on magnetic or gold nanoparticles/antigen aggregates coupled to microstructured chambers (M42)

Table B.27. Planned Milestones and Deliverables relevant for Pilot 2.6.

Pilot 2.6: Remote monitoring of groups and community
Milestones
MS1: Definition of the system modules to be implemented (M18)
MS2: Updating of the current SMARTCAMPUS architecture (M24)
MS3: System implementation (back-end and front-end development) (M30)
MS4: System experimentation by involving both sick and healthy people in remote locations (M36)
Deliverables
D1: Technical report on system architecture (M18)
D2: Technical report on SMARTCAMPUS upgrading (M27)
D3: Technical report on system implementation (M35)
D4: Report on the developed system and on all the evaluation in a relevant and operational environment. Beta version release of the app (M42)

Table B.28. Planned Milestones and Deliverables relevant for Pilot 2.7

Pilot 2.7: Wearable devices for remote monitoring of Parkinson's disease and frail patients
Milestones
MS1: Specification definition of the sensor integrated garment (M12)
MS2: Release of mathematical models for data interpretability (M15)
MS3: Definition of the rehabilitation protocols for testing in relevant environment (M18)
MS4: Release of the integrated structure for patients' remote physiological monitoring (M24)
MS5: Deployment (test and qualification) of sensorized garment and data management system (M36)
MS6: Testing in operational environment (M42)
Deliverables
D1: Procurement of a high-quality smart sensorized garment (M12)
D2: Technical report on the AI-based algorithms (M15)
D3: Report on the testing of developed solutions in a relevant environment (M18)
D4: Technical report of the integrated structure for patients' remote physiological monitoring (M24)
D5: Technical report on integration of sensorized garment in data management integrated system (M36)
D6: Report on the testing of the developed solutions in an operational environment (M42)
D7: Report on the entire developed system for remote monitoring of Parkinson's and frail patients, including sensors for the daily quantification of neurological motor symptoms; a data management system for healthcare professionals; early disease detection and timely response to neurological health threats (M48)

Table B.29. Planned Milestones and Deliverables relevant for Pilot 3.1.

Pilot 3.1 New technologies for air quality and lifestyle assessment
Milestones
MS1: First release of the device wearable personal system (WearAQ) able to monitor air quality, subject's activity and physiological parameters and to be part of a Community Sensor Network (M12)
MS2: Release of the mobile application for WearAQ (M15)
MS3: Testing in relevant environment (M24)
MS4: Data collection in relevant environments (M38)
MS5: Final analysis of the results (M42)
Deliverables
D1: Technical report on the design of the wearable personal system WearAQ (M6)
D2: Technical report on the use cases to be studied with the wearable systems (M6)
D3: Technical report and release of the device WearAQ and its mobile application (M15)
D4: Report on the testing in relevant environments (M24)
D5: Report on data collection and methods for data analysis (M42)
D6: prototype of wearable systems (air quality, physiological and subject parameters, Risk prediction for cardiovascular and respiratory diseases) (M48)

Table B.30. Planned Milestones and Deliverables relevant for Pilot 3.2.

Pilot 3.2: Environmental determinants of health
Milestones

MS1: Design and development of several gut-on-chip models and configurations (M12)
MS2: Identification of micro- and nano-plastics in aqueous matrices, in fish and meat (M12)
MS3: Design and development of 3D lung-on-chip model (airway epithelium) and configurations (M18)
MS4: Microbiome transplantation on a selected chip model (M24)
MS5: Set-up of fully integrated analytical platform based on microscopy/spectroscopy techniques (M24)
MS6: Multi-Parametric analysis to identify the effect on specific bacteria strains on gut health (M36)
MS6: Design and development of 3D complete lung-on-chip model (vascularized) and configs(M40)
MS7: Biological evaluation of micro-nanoplastics (M44)
Deliverables
D1: Technical report on the design of the gut-on-chip device (M12)
D2: Report on novel physico-chemical approaches for the identification of micro- and nanoplastics (M12)
D3: Mastermold for the fabrication of the 3D lung-on-chip model (M12)
D4: Technical report on protocol for microbiome transplantation on the gut-on-chip model (M24)
D4: Report on chemical composition of the samples and their structures, also by collecting physico-chemical data from the same spatial region of the sample (M24)
D5: Optimised protocol for the <i>in vitro</i> co-culture of epithelial and endothelial cells (M24)
D6: Technical report on the different effects on microbiome viability, and gut properties (M36)
D7: Report on <i>in vitro</i> and <i>in vivo</i> effects of different micro-nanoplastics (M36)
D8: lung-on-chip and gut-on-chip models and functional analysis of biotic component of atmospheric particulate, micro-nanoplastics and identification of specific bacteria strains (M48)
D9: tools to monitor air pollutants and identify microplastics in food (M48)

Table B.31. Planned Milestones and Deliverables relevant for Pilot 3.3.

Pilot 3.3: Innovation of diagnostic approaches in chronic heart and lung diseases
Milestones
MS1: Definition of the experimental set up for implementing an innovative imaging system (IS-NCD) for diagnosis and follow-up of patients with n pulmonary NCDs (M6)
MS2: Definition of the detailed system requirements specification (SRS) for the PoC device for exhaled breath biomarkers analysis by electronic noses (PoC-EN) (M6).
MS3: Diffuse optics (DO)system with hand-held probe for time domain multiwavelength to monitor tissue composition: definition of basic system requirements (M6)
MS4: Data collection on lung fibrosis animal models by PET, CT and fluorescence imaging, and pathology and gene expression analysis (M12)
MS5: development of AI tools for increasing the quality of LDCT and Magnetic Resonance Imaging of the chest by artificial intelligence (M18)
MS6: Clinical application of innovative radiopharmaceuticals for PET imaging of lung nodules
MS7: Production of the PoC-EN prototype of sensor chamber, gas sampling and recirculation system and microcontroller-based electronic circuits for data acquisition and control of the e-nose module (M18).
MS8: Development, testing and validation of image processing and AI tools for lung functional evaluation (regional ventilation maps) (IS-NCD system) based on the integration of CT, MR, PET imaging to predict lung fibrosis trajectory (M24)
MS9: DO system: Definition of the system architecture and final specifications (M24)
MS10: Implementation and validation of the data processing algorithms for PoC-EN device: 1) dedicated pre-processing algorithms to correct gas sensors response for gas conditions and ageing and 2) specific AI-based machine learning algorithms need to be developed for odour pattern analysis and recognition, including approaches for incremental improvement of the training when new data become available. (M28)
MS11: development of radiomics and AI models to predict lung nodules malignancy from LDCT, PET and MR data (M36)
MS12: System integration of the PoC-EN: a demonstrator prototype of the device will be assembled by combining and integrating all components/modules for allowing system validation.
MS13: Validation and application of image processing and AI tools for lung functional evaluation (CT, PET, MR) in the clinical scenario for evaluation of lung diseases (ILD, COPD and bronchiectasis) (M40)
MS14: Final results analysis of image processing and AI tools for lung functional evaluation (M48)
MS15: DO System validated in laboratory environment (M48)
Deliverables

<p>D1: Technical report the experimental set up for implementing the innovative imaging system (IS) for diagnosis and follow-up (M6)</p> <p>D2: Technical report of the system requirements specification of the PoC-EN device (M6).</p> <p>D3: DO System requirements for specific clinical applications (M6)</p> <p>D4: Technical report on the data collection on lung fibrosis animal models by PET imaging, CT imaging, fluorescence imaging, vital signs, pathology and gene expression analysis (M12)</p> <p>D5: Report on Tissue parameters estimated <i>in vivo</i> by DO system (M12)</p> <p>D6: E-nose working prototype of the e-nose module of the PoC-EN device (M18).</p> <p>D7: Implementation of a dedicated SW for increasing the quality of LDCT by AI (M20)</p> <p>D8: Report on System architecture and final specifications (M24)</p> <p>D9: Technical report on the development, testing and validation of image processing and AI tools for lung functional evaluation (regional ventilation maps) (M26)</p> <p>D10: Technical report on algorithms and processing SW definition and validation (PoC-EN device) (M28).</p> <p>D11: Technical report on demonstrator/working prototype ready for testing and validation (PoC-EN) (M36)</p> <p>D12: Dedicated SW to predict lung nodules malignancy from LDCT, PET and MR data (M38)</p> <p>D13: Interim report on feasibility of AI tools for lung functional evaluation in clinical scenario (M42)</p> <p>D14: Demonstrator of a DO Portable system with handheld probe (M42)</p> <p>D15: Final report on overall results of image processing and AI tools for pre-clinical and clinical lung functional evaluation (M48)</p> <p>D16: DO system: Report on system performance tested on tissue phantoms (M48)</p> <p>Final deliverable (M48): A set of innovative diagnostic approaches in chronic heart and lung diseases, namely: a) innovative image processing methods for patients' follow-up and prediction of disease progression and response to treatment; 2. a CAD system including tools for AI models able to increase the quality of low dose CT and manage lung cancer screening and early diagnosis; 3. a novel device for PoC diagnostics based on innovative exhaled breath biomarkers analysis by electronic noses; 4. A portable system with hand-held probe for time domain multiwavelength diffuse optics, able to monitor tissue composition (water, lipids, collagen) and blood parameters (total blood volume oxygenation level).; 5. Image-based quantification of cardiovascular biomechanics to support early diagnosis, patient selection and patient stratification; 6. Augmented and extended reality tools for therapy planning and treatment</p>
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Table B.32. Planned Milestones and Deliverables relevant for Pilot 3.4.

Pilot 3.4: Innovation of therapeutic approaches in chronic heart and lung diseases
Milestones
<p>MS1: Definition of the experimental set up for implementing an innovative imaging system (IS-NCD) for the evaluation of novel imaging modalities and drugs, based on precision medicine, enabling <i>in vivo</i> methods based on 3R principles (M6)</p> <p>MS2: Definition of detailed system requirements specification (SRS) for the non-invasive ventilator (M6)</p> <p>MS3: Identification of the design strategies for the development of a versatile bicompartamental and dynamic culture system for lung in vitro model (M6)</p> <p>MS4: Data collection on lung fibrosis animal models by PET, CT and fluorescence imaging, and pathology and gene expression analysis (M12)</p> <p>MS5: Production of the prototype of the turbine-based ventilation module, of the sensors module for measuring patient flow, pressure, respiratory gases (O₂ and CO₂) and respiratory mechanics. (M15)</p> <p>MS6: Implementation and validation of the close-loop controllers and data processing algorithms for the ventilator including: 1) dedicated signal pre-processing algorithms to estimate unintentional leaks and patients laryngeal closures; 2) algorithms for estimating respiratory mechanics and gas exchange performance of patient's lungs; 3) system identification algorithms for assessing the physiological conditions of the lung to be provided as input to the ventilation patient tailoring module (M24)</p> <p>MS7: Identification of allometric scaling and fluidic connection to replicate the physio-pathological lung and multi-organ cross-talk (M24)</p> <p>MS8: Assessment of the putative pathways involved in patient deterioration and identification of potential target for therapy in critical ill patients (M24)</p> <p>MS9: Identification of biomarkers for accurate and earlier diagnosis, prognosis of critical ill patients (M36)</p> <p>MS10: System integration: a demonstrator prototype of the ventilator will be assembled by combining and integrating all components/modules for allowing system testing and validation. This device will also include the automatic ventilation tailoring module (M40).</p>

MS11: Engineering of the multicompartmental logic towards integration into an all-in-one culture platform for advanced therapies (M40)
Deliverables
D1: Technical report the experimental set up for the pre-clinical evaluation of new drugs, based on precision medicine, enabling <i>in vivo</i> methods based on 3R principles (M6)
D2: Technical report of the system requirements specification of the mechanical ventilator (M8)
D3: Working prototype of the ventilation and sensors hardware platform (M10)
D4: Technical report on the data collection on lung fibrosis animal models by PET imaging, CT imaging, fluorescence imaging, pathology and gene expression analysis (M12)
D5: A data structure with the metabolite MS peak intensities cleaned and aligned (untargeted metabolomics) and/or metabolite concentrations (targeted metabolomics) (M18)
D6: Release of a bicompartmental Micro Physiological System to model lung barrier tissue dynamics (M18)
D7: Technical report on the definition and validation of algorithms and data processing software (M24)
D8: Algorithms developed in standard language (e.g. Python, Matlab) for the preprocessing and analysing of metabolomics data and for their integration with clinical and laboratory data (M24)
D9: Release of multicompartmental device enabling the lung and multi-organ cross-talk (M30)
D10: Technical report on the demonstrator and working ventilator ready for testing and validation (M36).
D11: 1. innovative image processing methods for the preclinical evaluation of new drugs; novel technologies for personalised non-invasive respiratory support in newborns and small children. 2. Micro Physiological System platform integrating <i>in vitro</i> models of lung tissue barrier replicating a complex physio-pathological response to advanced therapies. 3. Machine learning and data mining techniques for metabolomics data analysis and multilevel integration to identify putative biomarkers able to track changes in the conditions of critical ill patients such in the intensive care unit (M48)

Table B.33. Planned Milestones and Deliverables relevant for Pilot 4.1

Pilot 4.1: Multifunctional materials for advanced theragnostics
Milestones
MS1: Production of biocompatible building blocks via de novo synthesis and/or modifications (M12)
MS2: Assembly of hybrid nanostructured materials and their extensive characterization through complementary techniques (M24)
MS3: Assessing of biological properties of the hybrid nanostructured materials by <i>in vitro</i> 2D/3D GBM models (M36)
MS4: Production of radio-nanoparticles via microfluidics (M36)
MS5: Quality assurance of the labelling procedure (M42)
Deliverables
D1: Report on different innovative building blocks with specific physical-chemical properties (M12)
D2: Report on different formulations of hybrid nanostructured materials (M24)
D3: Prototypes of microfluidic reactors for the production of radio-nanoparticles (M24)
D4: Biological validation in GBM model of the best hybrid nanostructured materials (M36)
D5: Report on production of radio-nanoparticles in microfluidic reactors (M36)
D6: Report on stability of the radio-labelling (M44)

Table B.34. Planned Milestones and Deliverables relevant for Pilot 4.2

Pilot 4.2 Optical microsensors
Milestones
MS1: Selection of the building blocks for fabrication of optical sensing platforms (M10)
MS2: Development/characterisation of sensing platforms based on nano-/microparticles and scaffolds (M20)
MS3: Validation of the sensing platforms in <i>in vitro</i> disease models (M30).
MS4: Validation of the sensing platforms in <i>in vivo</i> disease models (M44).
Deliverables
D1: Report on the properties of pH- and O ₂ -sensing platforms for <i>in vitro</i> studies (M12)
D2: Report on computational analysis and metabolic heterogeneity in selected <i>in vitro</i> disease models (M24)
D3: Updated version of D.2 (M40)

Table B.35. Planned Milestones and Deliverables relevant for Pilot 4.3.

Pilot 4.3: Multi-modal correlative microscopy platform
Milestones
MS1: Deployment of HCI local cloud resource (M12) MS2: Federation of existing equipment with newly acquired instruments (M18) MS3: Implementation of commercial SW packages for correlative analysis of optical/electron microscopy and clinical imaging datasets (M18) MS4: Deployment of ad hoc developed AI-based correlative microscopy toolboxes (M30) MS5: Qualification of the correlative microscopy infrastructure through relevant case studies (M42)
Deliverables
D1: Correlative microscopy infrastructure (M24) D2: Ad hoc developed AI-based correlative suites (M24) D3: Assessment and finalisation of AI suites (M34) D3: Report with the results of correlative microscopy approaches to selected case studies (e.g., brain connectomics, tumour microenvironment, micro-/nanoplastic contaminants) (M42)

Table B.36. Planned Milestones and Deliverables relevant for Pilot 4.4

Pilot 4.4: FLASH therapy effect on glioblastoma
Milestones
MS1: <i>In vitro</i> response to FLASH therapy (M12) MS2: Radiomic, metabolomic and genomic <i>in vitro</i> results and pathway reconstruction by an artificial intelligence approach (M18) MS3: <i>In vivo</i> response to FLASH therapy (M24) MS4: Radiomic, metabolomic and genomic <i>in vivo</i> results and pathway spatial reconstruction by an artificial intelligence approach finalisation (M36) MS5: Development of pharmacological strategy to increase Flash therapy efficacy and/or improve the patient's quality of life, finalisation of the treatment (M44)
Deliverables
D1: Full reconstruction of pathways involved in the biological response of tumour in response to FLASH therapy compared to healthy tissue. Such results will allow a better understanding of the biological mechanisms underlying the efficacy of FLASH therapy to further implement the treatment and increase its efficacy. In particular, the better understanding of this biological response will serve to develop specific cancer support therapy to increase the patients' overall survival and quality of life (M8) D2: Establishment of the optimal dose to achieve most effective therapy with a concomitant significant reduction of adverse reactions (M15) D3: Comparative analysis of Flash therapy vs conventional radiotherapy approach (M22) D4: Full reconstruction of pathways involved in the biological response of tumour in response to ULTRA-FLASH therapy compared to healthy tissue. Such results will allow a better understanding of the biological mechanisms underlying the efficacy of ULTRA-FLASH therapy to further implement the treatment and increase its efficacy. In particular, a better understanding of this biological response will serve to develop specific cancer support therapy to increase the patients' overall survival and quality of life (M28) D5: Establishment of the optimal dose to achieve most effective therapy with a concomitant significant reduction of adverse reactions (M34) D6: Comparative analysis of ULTRA-Flash therapy vs Flash Therapy and conventional radiotherapy approach (M42)

Table B.37. Planned Milestones and Deliverables relevant for Pilot 4.5.

Pilot 4.5: Sonoporation and drug delivery for Glioblastoma and melanoma treatment
Milestones
MS1: Synthesis of sonoporation-inducible liposomes (M10) MS2: Release of <i>in vitro</i> tests on healthy and melanoma and GBM cell lines of ultrasound-inducible liposomes and combination with radiotherapy (M18) MS3: Release of evaluation of sonoporation-inducible liposomes in murine model of orthotopic GBM and melanoma (M32) MS4: Release of <i>ex vivo</i> samples analysis for conventional neuropathological, metabolomic, transcriptomic analyses and gene expression profile (M42)

Deliverables
D1: Early detection and assessment of treatment response combining focus/unfocus ultrasound and controlled release by sonoporation mediated delivery method for enhanced tumour uptake (M8)
D2: Synthesis of sonoporation-inducible liposomes (M15)
D3: Analysis of <i>in vitro</i> and <i>in vivo</i> tests on healthy and melanoma and GBM cell lines of ultrasound-inducible liposomes and combination with radiotherapy (M24)
D4: Evaluation of sonoporation-inducible liposomes and radiotherapy combination in murine model of GBM and melanoma, using live multi-imaging analysis, including both Photoacoustic, μ PET/CT scanning and Xtream to track drug/carrier distribution pre- and post-sonoporation (M32)
D5: <i>Ex vivo</i> samples analysis for conventional neuropathological, metabolomic, transcriptomic analyses and gene expression profile (M42)

Table B.38. Planned Milestones and Deliverables relevant for Pilot 4.6.

Pilot 4.6: Innovative nanoparticles for drug delivery
Milestones
MS1: Development of MSN-based/ MIPs-based joint /parallel/alternative nanodevices (M12)
MS2: <i>In vitro</i> testing 3-4 Nanostructure optimization/ <i>in vitro</i> validation (M18)
MS3: Investigation <i>in vitro</i> of the relationship structure/properties (M34)
MS4: Completion of <i>in vivo</i> studies (M42)
Deliverables
D1: Engineering of the administration and delivery of chemotherapeutic agents by means of nanocarriers and/or MIPs-based plastic antibodies to improve the antitumor efficacy, by increasing drug specificity and/or bioavailability and reducing unwanted side-effects as Photo/sonotherapies add a non-specific physical necrotic agent (heat or ROS action) to the specific chemical agents (M24)
D2: Development of nanodevices (general term) able to recognize, bind targets and therapeutically treat related tumours (M42)

Table B.39. Planned Milestones and Deliverables relevant for Pilot 4.7.

Pilot 4.7: Development of a perfusion-based bioreactor platform
Milestones
MS1: Development of platform for 3D TNBC cells (M12)
MS2: Development of platform for freshly excised TNBC tissues (M15)
MS3: Genomic, proteomic and metabolomic results of TNBC samples on different conditions (M22)
MS4: Pathway reconstruction by an artificial intelligence approach (M28)
MS5: Results on effectiveness of oncotherapeutics on 3D TNBC cells (M38)
MS6: Results on effectiveness of oncotherapeutics on samples from TNBC patients (M44)
Deliverables
D1: Development of a perfusion-based bioreactor platform for TNBC tissues (including TME) (M24)
D2: Implementation of xenotransplantation of cancer specimens in immunodeficient animals that result in TME alterations (M30)
D3: Reconstruction of pathway involved in developing TNBC cells and its relationship with TME (M36)
D4: Report on the mechanisms of resistance to oncotherapeutics and the metastatic dissemination of TNBC and strategy definition for the development of innovative therapies (M40)

Table B.40. Planned Milestones and Deliverables relevant for Pilot 4.8.

Pilot 4.8: AI-Based Systems Biology Approaches in Cancer Multi-Omics Data Analysis
Milestones
MS1: Database design and multi-omics data acquisition (M8)
MS2: Design of a risk score based on the XAI analysis (M20)
MS3: DL-based identification of a genomic-based score to predict prognosis of cancer patients (M24)
MS3: DL-based identification of genomic profiles able to predict response to specific treatment (M44)
Deliverables
D1: Design and development of AI models for the prediction of the multi-omics risk score (M15)
D2: Explainable AI (XAI) analysis to evaluate the predictive power of the omics parameters on the prognosis of the patients (M22)

D1: DL-based software to compute the genomic-based score using cancer cells genetic data (M28)
 D2: DL-based platform for the prediction of the patient's response to the available treatments (M44)

Table B.41. Planned Milestones and Deliverables relevant for Pilot 4.9.

Pilot 4.9: Realisation of a boron neutron capture therapy (BNCT) facility in Caserta	
Milestones	
MS1:	Executive project of the installation (M4)
MS2:	Call for tender for the procurement of three solid state amplifier for RFQ cavity (M9)
MS3:	Construction of gas-detector for microdosimetric characterisation of clinical beams for BNCT (M12)
MS4:	Proton beam nominal parameters obtained at the end of the LEBT (M15)
MS5:	RF power amplifier system for RFQ cavity complete, high power couplers successfully tested at nominal power (M24)
MS6:	RFQ cavity tuning accomplished (M24)
MS7:	Biological evaluation of BNCT, proteome and interactome characterization, immune response, study of organoids (all with neutron facilities already available) (M24)
MS8:	Bunker completion with services (M30)
MS9:	MPS, LLRF and LINAC control system successfully tested (M30)
MS10:	High power Be target ready for proton test (M30)
MS11:	Accelerator/neutron source ready for installation (M32)
MS12:	BSA characterised and ready for installation (M34)
MS13:	Accelerator and ancillaries installed at Vanvitelli Caserta bunker (M42)
MS14:	Production of the first neutron beam at low power (M42, INFN)
MS15:	characterization of the final epithermal radiation field in air and phantom (M48)
MS16:	Start CE marking procedure as a medical device (M48)
Deliverables	
D1:	Report on novel gas-detector construction (M12)
D2:	Report on beam transport optimization through LEBT (M15).
D3:	Report on RFQ coupler production and test (M24)
D4:	Report on RF system production and test (M24)
D5:	Report on cavity bead pulling and final optimization (M24)
D6:	Report on MPS, LLRF and LINAC control system design and production (M24)
D7:	Report on control system off-site test (M30)
D8:	Report on Be target production (M30)
D9:	Report on RFQ conditioning and accelerator beam commissioning (M41)
D10:	Report on accelerator and BSA installation (M42)
D11:	Report on final epithermal radiation field in air and phantom (M48)

Type of Data collected

The nature of ANTHEM requires an illustration of a strategy for the data to be collected. The main output of the project is in line with a recent initiative called Data-centric AI led by Andrew Ng, professor of Artificial Intelligence at Stanford University and one of the world's leading researchers in AI. Data-centric AI is the discipline of systematically engineering the data used to build an AI system that works in different directions, for example: data collection, data quality, data labelling, data augmentation, data deployment and so on.

The traditional supervised AI pipeline involves a data definition and collection phase and a model definition phase. Typically, the most established AI approach has been model-centric, whereby researchers spend much more time, given the set of data available, on studying the mathematical model, e.g., deep neural networks, than on data definition and collection. The computational complexity of the mathematical models typically used in AI combined with the need to deploy in real-world settings the AI models studied by researchers creates a bottleneck related to the quantity and quality of available data.

Data in use by AI technologies must be in digital format, properly labelled by domain experts so as to ensure a high level of data quality and, most importantly, must be protected. WHO Regional Office for Europe recently drafted a guidance document to support member states in strengthening their health information systems. The purpose is "Helping countries to produce solid health intelligence and institutionalised mechanisms for evidence-informed policy-making has traditionally been an important focus of WHO's work and continues to be so under the European



Programme of Work 2020–2025”²⁹.

The ANTHEM project will implement a cross-spoke initiative for the organisation of processes related to the collection, management and protection of health data. This initiative will be coordinated by a committee of experts that we will call the Data Expert Committee and will consist of: data experts for AI applications, data technologies experts, and medical experts.

Health data are of different types: structured data e.g., related to the patient's socio-demographic and clinical characteristics; time series e.g., related to the 24-hour recording of a multichannel ECG trace made with a Holter device; X-ray images; audio and video signals e.g., related to recordings of telemedicine sessions; genetic sequences, etc.

To address such heterogeneity, different data representation technologies will be used in the project. For example, traditional relational databases for structured information like socio-demographic data, time series databases to hold, e.g., physiological parameters, no-sql databases for unstructured information such as genetic sequences, geographic databases to hold geo-referential information on communities of interest, etc.

The Project will develop methodologies for heterogeneous health data management thus ensuring protection of the data and direct access to the AI algorithms.

B.6 Promotion of equal gender opportunities

From a programmatic point of view that looks to the next five years and beyond, the actions and activities that the ANTHEM intends to promote, to favour equal gender opportunities and the enhancement of other variables such as age, culture, physical ability, sexual orientation, are presented here, contributing to the creation of a frank, inclusive and effective research environment.

The presentation is divided into 4 sections and areas of intervention:

- Gender balance in top positions and in decision-making bodies;
- Gender balance in recruitment;
- Integration of the gender dimension and intersectionality in research;
- Actions to contrast stereotypes in the organisation's culture.

For each intervention area, specific objectives, actions and indicators are provided in Table B.42.

It is also worth noting that 39% of the researchers already composing the ANTHEM critical mass are women. This value refers to the team members whose CVs have been attached, and it does not include researchers to be recruited.

Table B.42. ANTHEM action plan to promote equal gender opportunity and monitoring indicators.

Gender balance in top positions and in decision-making bodies	
Objective	Achieve gender balance in top positions and in decision-making bodies.
Actions	Setting up of elective mechanisms for governing bodies providing for balance in candidacies and the constraint for voters to express a double preference, in compliance with the gender variable. Identification of gender balancing measures in management roles and research groups.
Indicators	At least 40% presence of the minority gender in governing bodies. Alternation in decision making roles.
Gender balance in recruitment	
Objective	Increase the percentage of women in the recruitment to guarantee gender balance.
Actions	Provide the members of selection committees with information material about unconscious bias in recruitment. Foresee gender balance in selection committees. In case of draws foresee balanced lists. Publication of a Call for Interest to attract female candidates in view of direct appointments. Foresee direct appointments addressed exclusively to female scholars and researchers for sectors with female population lower than 40%. In particular, concerning engineering, physics, material science and informatic that are not yet in gender balance.
Indicators	Recruitment of at least 40% of female staff.
Integration of the gender dimension and intersectionality in research	
Objective	Integration of the gender dimension and intersectionality in research.
Actions	Organisation of dedicated sessions on gender equality, inclusion and well-being in Health care research, during ANTHEM events. Mentoring programs for female researchers (building relationships between

²⁹<https://apps.who.int/iris/bitstream/handle/10665/349091/WHO-EURO-2021-2661-42417-58838-eng.pdf?sequence=1&isAllowed=y>

	senior and junior researchers) that identify suitable strategies for overcoming obstacles in career paths. For sex and gender dimensions in the Pilots, see B.1.
Indicators	Organisation of an annual workshop. Setting up mentoring programs.
Actions to contrast stereotypes in the organisation's culture	
Objective	<ol style="list-style-type: none"> 1. Strengthening a shared culture on the importance of gender equality and the effectiveness of gender balance. 2. Integration of the gender balance in the organisation of the Initiative and in the management of its activities.
Actions	<p>For Obj. 1: Annual redaction of a gender balance document containing qualitative and quantitative data for the entire community of the HUB initiative, identifying indicators and indices for a context analysis, also in relation to the European panorama. Publication of the document through the communication channels of the HUB initiative.</p> <p>For Obj. 2: Examine context analysis of gender balance and its indicator. Form a working group.</p>
Indicators	<p>For Obj. 1: Annual approval of the gender balance document by the governing bodies and monitoring of the indices.</p> <p>For Obj. 2: Preparation and approval of a Gender Equality Plan in 2023 by governing bodies.</p>

B.7 Involvement of early-stage researchers and international attractiveness

Regarding the international vocation of the Initiative, the involved Universities will put in place institutional strategies to increase **international attractiveness**, specifically for students and young researchers. These will include mobility and exchanges for Master and PhD students as well as international programmes (e.g., MSCA Doctoral Networks and Erasmus+ actions); international offices and vademecum for newly enrolled international students and researchers; degrees/classes in English; support to excellent Postdoctoral Scholars willing to participate in the distinguished MSCA Postdoctoral Fellowships; exploitation of National laws and allowing to recruit winners of prestigious grants, such as ERC and Rita Levi Montalcini grants.

A key goal of the Initiative is to create an environment for the growth of human capital and research that leverages the best skills and young people. This objective will be guaranteed both by the specific commitment of the various Universities to recruit new research staff and, as specified in the previous paragraph, through active networks and partnerships that will be activated at the European level.

In particular, an appropriate modality of advertising vacancies will attract researchers from other countries, both by enhancing existing international relations (see section A.3) and by direct dissemination actions in partnership with leading universities in Europe and in the world working on specific topics.

Specific actions for international attractiveness

- Publication of vacancies on the Euraxess portal
- Informative material published in English
- Competitive remuneration for Postdoctoral researchers
- Fully digital application process and, whenever possible, remote interviews
- Informal networking through the many already established collaborations
- Engagement in the network of companies with international dimensions or networks

ANTHEM will represent an excellent **career boosting opportunity for young researchers**, who – committed to the various research tasks – will largely profit from the exceptionally fertile environment provided by the Initiative. The strong intersectoral flavour, with continuous interactions among the academic and the non-academic environments, the ‘training-by-doing’ approach, the responsibility of task execution, together with the dedicated ANTHEM training opportunities for the academics will equip young researchers with a novel set of technical and soft skills (e.g. communication, management, entrepreneurship, ethics, and data management tools), highly valuable for their career evolution, inside or outside academia. Advanced training in Artificial Intelligence, Machine Learning and Data Science will be erogated also through the aforementioned ELLIS³⁰, the centre of excellence for research and training in artificial intelligence and machine learning. Four Milanese universities (UNIMIB, POLIMI, BOCCONI and UNIMI) have in fact recently become one of the Units of ELLIS, the European Laboratory for Learning and Intelligent Systems. Details on the transversal skills can be found in section: *C.1.4 Potential impact on the training of early stage researchers and personnel involved.*

Moments of knowledge sharing at a national and international level will be organised to improve the impact of the

³⁰ <http://ellis.eu>



activities and create valuable networks. Particular attention will be paid to the selection and enhancement of young talents within the working groups by promoting their visibility in dissemination and networking activities and having them as leaders of dedicated tasks.

A total of over 40 young researchers, i.e. with up to ten years of experience after completion of their PhD, are already involved in ANTHEM, corresponding to 21% of the critical mass. Additional early-stage researchers will be recruited, including 81 Junior fixed-term researchers (technologists to in the case of research centres) yet to be hired to reinforce the academic staff of the ANTHEM Initiative. In addition to the research activities, they will carry out teaching activities at all levels of the University education system.

Finally, more than 50 PhD students will be enrolled and engaged in the research activities, also in close collaboration with the industrial sector to open up a variety of career opportunities and realign highly skilled human capital with market needs. In the selection process for Postdoc and researchers, age may also be considered a preferential criterion to facilitate the participation of scientifically young researchers. Doctoral students will receive specific training on topics that are relevant to this project.

In addition to the specific actions to guarantee attractiveness listed above, the ANTHEM partnership will introduce a series of **organisational measures** aimed at the empowerment and at the wellbeing of newly recruited researchers. First of all, it will foster proactiveness of the employed professionals and will guarantee access to all possible resources needed to achieve top class targets and results. Access to advanced facilities (laboratories, infrastructures) and to last generation equipment on the premises of the consortium's partners will be facilitated (accordingly with existing security restrictions) together with great cross institutional visibility. Collaborations and exchanges with main actors on the territory and the strengthening of agreements to undertake joint projects will constitute a flywheel that will enable innovation and personal growth to all personnel involved. Indeed, access to the partners' existing networks will include contacts with research institutions, main actors in the industrial ecosystem, European Strategy Forum on Research Infrastructures and will take place both at national and international level.

Internal calls for ideas and projects will select the most promising ambitions for innovations and will reward since the beginning the selected young professionals with leading roles that will include chances to coordinate small teams and will create for them the conditions to demonstrate their result-oriented mindset with appropriate human resources assigning since the beginning responsibility roles accordingly to advancements in career based on effective merit.

In relation to the working environment and culture, the following aspects will constitute key prerogatives:

- *Flexibility in relation to working hours and work location:* Smart working possibility with great flexibility of working hours will be guaranteed following an objective-oriented productivity paradigm instead of outdated control-oriented models
- *Healthy and motivating working space:* comfortable working places and up-to-date working instruments and services will be guaranteed. Attractiveness of the positions will also be strengthened by the cultural setting that will be fostered throughout the whole initiative, wellness solutions and services will deliver group-level insights to connect individual wellness to organisational outcomes and create a healthy and motivating working community that will respect private spaces and time and support individual inklings and interests also outside workplace and working time. Also engagement in initiatives will be constantly held, office events/programs and healthy food and drink options.
- *Continuous training:* access to advanced training courses (fully covered or partially reimbursed) also upon motivated request of the employees in addition to training packages and certifications planned by the institution to ensure a continuous update of competences in the working environment.
- It is also planned to provide employees with packages and benefits in support to the handling of the day-by-day management of private life, long-term planning and aimed at facilitating the pursuit of personal extra-work aspirations. For these reasons, it will be considered to provide employees with extra-salary benefits such as:
 - *Wellbeing packages/ Health insurance:* physical and mental wellbeing will be protected through the activation of medical, dental, and vision insurance for employees and their families; mental health and wellbeing resources including an in house *Employee Assistance Program*; disability insurance; life insurance
 - *Competitive compensation:* recognition opportunities through annual bonus for outstanding achievements
 - *Personal time off:* Parental leave, adoption and fertility assistance, paid time off (vacation, holidays, sick leave, bereavement)
 - *Transportation benefits:* transports abonements discounts/ travel cards discounts; cycling schemes (rewards in terms of discounts on cycling equipments and bicycles when demonstrated the regular use of bicycle as mean of transport to work)



- *Childcare solutions*: Kindergarten facilities disposal at discounted fees together with other childcare solutions
- *Culture, leisure and sports*: discount schemes and cards to access culture (events, museums etc.), entertainment (concerts, cinemas etc.) and sport activities (gym card etc.)
- Specific provisions concerning work-life balance are formally planned within the Gender Equality Plans of the ANTHEM partner organisations.

The recruitment process will be empowered by the already existing extensive international network of the consortium that will foster the identification of the most promising international talents.

B.8 Involvement of private parties

The ANTHEM partnership has been designed to meet the projects' goals through the involvement of all the relevant actors. Besides Universities, Research Centres and representatives of the healthcare system, the engagement of the industrial sector is deemed crucial to ensure the successful implementation of the project and the future scale-up of the solutions to be developed.

ANTHEM has attracted **leading and locally well-rooted companies** to the project, both as members of the Hub (CHIESI) and as Spoke Affiliates (ABM, ART, CHIESI, DIA). More precisely, the four companies operating in biomedical and diagnostic fields will act as Affiliates participating in research, transfer, and training activities through their existing research departments. They will contribute to the configuration and implementation of the Spokes' activities in the sectors in which they operate, providing key technology, facilities and expertise (see A.3).

In addition to involving partner companies, three other strategies to engage with the private sector have been designed. 1) to guarantee the adherence of the proposed solutions (processes, technologies, methods) to the needs and the capabilities of the market, and to pave the way for successful exploitation, an **Industrial Advisory Board** composed by representatives of the relevant industrial sectors and notably category associations will be set up. The Board will support the ANTHEM governance in the definition of the most effective development strategies by providing the standpoint of the industrial sector. 2) more companies will be involved in the activities through the participation in the **cascade funding grants**, the so-called *open calls*, which will be an opportunity to reach out to Small and Medium Enterprises (SMEs). In the Italian landscape, SMEs represent a strategic component for the competitiveness of the production chain to which they belong and contribute to the territorial economy. Their participation in open calls is thus expected to provide a full coverage of the stakeholders involved in the Innovation process. 3) beyond the duration of the project, the private sector will benefit from the research result thanks to **new services, TT actions** and creation of **startup** or **spin-off** companies and at the same time from the **highly-skilled personnel** that through the education action will form a new basin of human capital of outstanding level.

In this submission phase ANTHEM proposal has already received several endorsement letters and a variety of private companies (active in high tech and health fields) Italian regions, associations and communities that expressed great interest in ANTHEM results. Between these, private companies that endorse the project are: Siemens s.p.a, Rottapharm Biotech s.r.l, Italfarmaco s.p.a, Tensive S.r.l., STMicroelectronics, Huawei Technologies Italia s.r.l., Emotiva s.r.l., Zeiss S.p.A.. Lombardia, Puglia and Calabria Region also endorsed the project together with a few patient and physician associations and communities (such as Aircam, Comunità Val Seriana, Un Respiro di Speranza, Aimac).

B.9 Qualitative-quantitative indicators for monitoring activities and for ex-post evaluation

Note: this section deals with data used to monitor the activities, for data generated by the project see B.5.

Monitoring. The main tool to monitor the advancement of the project with respect to its scientific objectives will consist in the verification of the timely achievement of the Deliverables and Milestones for each individual Pilot as set out in Tables B.14 through B.41. In particular, the indicators will be of both quantitative and qualitative nature and will assess:

- Compliance with the quality standards for Milestone and Deliverable approval;
- Conformity with the expected time schedule for delivery;
- Conformity with the financial plan for each Pilot and each Spoke, including acquisition of major equipment identified in Section B.3;
- Actual increase in TRL of individual Pilots and solutions with respect to the expected increase indicated in Section A.2;
- Advancement in reaching the target size of the Reference Communities as specified in Tables B.1-B.4.
- Indicators of special interest for the ANTHEM Initiative as a whole include:
- Conformity with the recruitment plan of fixed-term researchers and PhD students;

- Conformity with the Dissemination and Communication Plan as set out in Section C.1.5;
- Compliance with the DMP to be provided to the Ministry in the negotiation phase, notably concerning the upload of relevant datasets on trusted repositories respecting FAIR standards;
- Conformity with the overall financial plan to be produced as part of the Full Proposal.

The internal monitoring outlined above will integrate the regular reports to be produced and delivered to the MUR in full compliance with the requirements of the Call for Proposal as detailed in Section B.3.

Monitoring will be based on iterative evaluation processes, allowing for staging and quantifying the progress of all Pilots and providing continuous insight into them, with the opportunity for prompt intervention and/or correction, should the need occur (e.g., underperforming with respect to plans, delays in the schedule, etc).

Concerning the **ex-post evaluation** and the **impact assessment**, specific indicators are provided in the relevant Section C.1 and will be monitored throughout and after the end of the research and innovation activities funded by the MUR. In this case, indicators are defined, according to NRRP guidelines, based on significance, measurability, relevance, and verifiability. In addition to the specific indicators of Section C.1, ex-post evaluation will make use of the following indicators related to Pilots and transversal activities to be monitored after the end of Ministry funding:

- Yearly increase of the size of the target community reached by the Pilot;
- Yearly increase of the TRL of the solution provided by the Pilot;
- Dissemination: no. of citations of ANTHEM papers; no. of third-party's works exploiting ANTHEM publicly available datasets;
- Exploitation: no. of patents, licences, spin-offs;
- Communication: no. of participants to follow-up outreach events; no. of citizens reached by follow-up communication campaigns; increase in share of population showing acceptance towards proposed innovative solutions.

Risk management. A complete identification, assessment, and prioritisation of risks will be performed at the start of the project by all Spokes under the Hub's supervision and the risk register will be continuously updated. At this stage, a preliminary list of management and scientific/technical risks is provided in Table B.43 together with: i) **Qualitative risk evaluation** in terms of likelihood (probability of occurrence) and severity (significance of adverse effects); ii) **Mitigation measures** to reduce a risk likelihood and/or severity prior to its materialisation; iii) **Contingency plans** to be followed in the case a risk actually materialises.

Table B.43. Preliminary risk assessment and management plan.

Risk (type)	Spoke	Likelihood	Severity
Key person leaves ANTHEM (Management)	All	Low	Low
Mitigation: A large and diverse critical mass; the Initiative strengths not relying solely on individuals.			
Contingency: Participating organisations have the workforce to substitute a person if and when needed.			
Difficulties in recruiting highly skilled researchers (Management)	All	Low	High
Mitigation: The attractiveness of the participating Universities along with a relatively large supply of local PhD programs moderate this risk. High-level positions offer very attractive conditions including salaries and career perspective aligned to European standards and competitive at international level.			
Contingency: Several recruitment windows are foreseen and resources can be moved to a subsequent window as needed. Partners' networks can be exploited if needed.			
Delays in planned activities (Management)	All	Medium	Low
Mitigation: The overall work plan allows for parallel advancement, thus reducing the severity of this risk. Continuous monitoring allows for prompt corrective actions. The internal monitoring strategy will be continuously updated to capture any deviation from planned timing, deliverables and costs.			
Contingency: Close interaction with the Ministry of University and Research to facilitate the programme flexibility and rescheduling of activities if needed.			
Insufficient response to Open Calls (Management)	All	Low	High
Mitigation: The attractiveness of the Open Calls will also be directed to top class providers forming a large pool of potential service suppliers and research partners.			
Contingency: Reallocate resources to the next Open Call window, potentiate communication campaign.			
Lack of coordination among different Spokes (Management)	All	Low	Medium
Mitigation: The Hub management minimises the likelihood of coordination problems also through high-profile managers with robust and consolidated experience in the management of complex scientific and industrial projects will be sought through a professional recruiting campaign.			

Contingency: Increase frequency of formal communications and informal events.			
Ineffective integration of different datasets for AI-based analysis (Technical)	1, all	Low	Medium
Mitigation: Cross-disciplinary and cross-sectoral teams devote effort to integration			
Contingency: Proceed on homogeneous datasets while providing feedback for redesigning the integration architecture. Seek advice from Data Expert and AI Expert Committees.			
Technical solutions are underperforming (Scientific/Technical).	All	Medium	Medium
Mitigation: All partners involved have extensive experience in research and development; accurate feasibility assessment has been already undertaken; continuous monitoring will be undertaken to provide prompt corrective technical and scientific solutions. The number of Pilots prevents the delay in a single Pilot development to affect the overall results of the Initiative.			
Contingency: Reschedule development plan to include root cause identification; if root cause can not be removed evaluate redesign of the solution vs acceptance of underperforming solution.			
Failure in reaching the target size of Reference Communities (Scientific/Technical)	All	Low	Low
Mitigation: Strong involvement of hospitals and healthcare agencies in ANTHEM makes the risk unlikely.			
Contingency: Exploit partners' network, including contacts with Regional Health Systems, to plan trials on alternative communities or potentiate engagement of original community with minimum delay.			
Ethical issues are raised (Scientific/Technical)	All	Low	Medium
Mitigation: Partners have consolidated experience in medical research projects, clinical trials, AI-based activities; in addition, they have internal procedures and dedicated people ensuring that highest ethical standards are respected from the project design phase.			
Contingency: Seek advice from the Ethics Committee; stop critical activity while addressing issues and continue with non-ethically-sensitive parts of Pilot activities.			

B.10 Long-term sustainability

Although ANTHEM mainly aims at sharing its results - data, services, standards, tools - for the benefit of the scientific community, the healthcare systems and patients, the maintenance and continuous development of services, standards, and databases and the further development of technologies require economic sustainability. To guarantee such sustainability after the end of the Ministry funding, actions are planned in different directions: 1) exploitation of the results, including Intellectual Property (IP) management; 2) synergies with healthcare and institutional actors; 3) brand identity and communication; 4) fundraising and international networks. The structure and the governance of ANTHEM, specifically the stable constitution of the Hub as a Foundation, also constitute vital elements for long-term sustainability.

Exploitation will consider IP Rights (IPR) protection through patenting or licensing of solutions obtained jointly by the partners during the development of technologies, products or prototypes also through licensing agreements and industrialization agreements with companies (notably in the medical and pharmaceutical sector) to bridge the gap and achieve commercialization TRL. Due to the diversity in the starting and expected final TRL for the different Pilots, the most suitable strategies or schemes for the exploitation of individual final results will be considered. It is worth mentioning that the capacity of the academic partners (e.g. TT Offices) will be complemented by the added value of private partners and of the Industrial Advisory Board (see A.3, B.3 and B.8). In addition to the economic exploitation, part of the ANTHEM results will be exploited in non-economic ways, including standardisation and data-provision free-of-charge (Table B.44).

Table B.44. Specific exploitation strategies and exploitable results.

Specific exploitation strategies	Exploitable results
<ul style="list-style-type: none"> ● IPR protection of the results ● Contribution to the definition of standards for Definition of standards health data acquisition and management according to the recent Proposal for a Regulation on the European Health Data Space³¹; ● Internal product development and consequent marketing (R & D marketing) 	<ul style="list-style-type: none"> ● Raw data: Measurement or test data for insights or future solutions. ● Databases: Structured and searchable data stored in a systematic manner in electronic archives ● Data correlation: Conclusions deriving from the analysis of empirical data ● Theoretical frameworks explaining phenomena

³¹ https://health.ec.europa.eu/publications/proposal-regulation-european-health-data-space_en



<ul style="list-style-type: none"> ● Creation and provision of services under licensing schemes or through dedicated infrastructures ● Joint ventures with other market players using the results as background ● Creation of spin-offs and startups ● Preparation of business plans including market analyses, also through the involvement of Economists active in partner Universities ● IPR sale or agreements of joint exploitation with industries that could guarantee a further development (Intellectual Property Rights) ● Data provision/ sharing through specific data access licensing schemes ● Establishment of exploitation or collaboration agreement with governmental authorities and industrial players accordingly to the triple helix innovation model ● Erogation of high-level training for technicians and professionals 	<ul style="list-style-type: none"> ● New technical solutions to technical and/or experimental problems, including technologies, methods and processes, devices, units and equipment, drawings, configurations and systems ● Methodologies to optimise processes, create components, reducing time, costs, environmental impact. ● New methods of analysis or processing of data ● Views and simulations (static or dynamic) conveying more information content ● Instructions, manuals, algorithms to perform specific procedures ● Softwares: programs to collect and organise specific content; organised data collections; automation of specific tasks or procedures (i.e. queries and routine analysis generation)
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To prevent conflicts, procedures concerning IP will be agreed by all participants and enter the partnership agreement. **IP management** will include description of the ownership of and the access to the background brought by the parties, the foreground developed, possibly jointly, by ANTHEM partners, the sideground (developed in parallel to ANTHEM activities with other resources) and the postground, generated after the end of the project. In particular, for the different possible strategies (through e.g., patents, copyrights, trademarks, design, industrial secrets) procedures, including for IPR sale or licence, will be put in place. In the specific case of patents, key steps will include: i) evaluation of novelty of the invention; ii) formulation of a deposit strategy; iii) filing of a patent application in the selected geographical areas. For specific actions relevant for the economic sustainability of the project and relative indicators, please see Table C.2, specifically the part of the table relative to the economic and technological Key Impact Pathways.

A key ingredient for the future sustainability of ANTHEM consists in the **synergies with the healthcare systems and the institutions**. In this respect, territorial public entities including Lombardia, Puglia, Campania, Calabria and Sicilia Regions will actively contribute to the Initiative as part of the Institutional Advisory Board. They will be involved in the assessment of the advancement of the projects, and contributing to the definition of the project scenario and future strategy. This favours the uptake in different contexts of the results that will be initially co-developed and tested with the healthcare system partners. Finally, patients and patient associations will play a central role during the implementation evaluation of the outcome of the activities, also through the Beneficiary/Patient Advisory Board. The synergies with the healthcare system actors and with the institutions are expected to make the ANTHEM results impactful as detailed in C.1. The interest of private companies active in key sectors (see B.8) constitutes a promising starting point for the successful implementation of the exploitation strategy.

ANTHEM brand identity will allow the project team to be nationally and internationally recognizable especially in the EU that shares many regulations in healthcare. To this end, ANTHEM will:

- **Construct a visual identity:** this action aims at bringing a unique and recognizable visual identity of the project to potential partners, users, and customers. For this purpose, we designed a project logo that contains visual features referring to the analysis of physiological signals, so as to immediately inspire the potential targets about one of the main aims of the project that is the monitoring of human health parameters for the improvement of care, treatment, diagnosis of chronic diseases.
- **Connect to the world:** this action aims at creating a continuous connection between the project activities and citizens/physicians/industries through the communication activities described in C.1.5.

Beyond the end of the funding period, the ANTHEM team will **seek funds from other private or public institutions** to continue the action by further developing and upscaling the technological solutions and producing new ones exploiting the capabilities and expertise of the participants. Thanks to ANTHEM, the outstanding research capacity of the partnership will even increase thanks to the contribution of new human capital, equipment of the highest quality, a systemic multidisciplinary approach and stronger relationships among the partners. This will put ANTHEM in the best position to participate successfully in competitive calls for proposals for grants or tenders, and to integrate relevant European networks as detailed in C.2.



C. INITIATIVE IMPACT

C.1 Potential impacts of results of the research and innovation program

The ANTHEM project will develop activities in adherence to European and National Priorities thus addressing the needs/priorities in health care of the community and in the countries' economy^{32,33}. Specifically, ANTHEM will strongly contribute to strengthening the home-care services for the management of chronic and frail populations. With this aim, orchestrated actions of the project will be directed to:

- improve the quality of digital tools and expand the use of telemedicine instruments to better support patients with chronic diseases introducing last generation diagnostic, therapeutic and digital tools;
- identify a shared model for the provision of home-care integrated with new technologies (i.e. telemedicine, home automation, digitization);
- integrate home-care with interventions to achieve full autonomy and independence of chronic patients reducing the risk of inappropriate or tardive hospitalizations;
- adopt new technologies and AI methodologies to improve early diagnosis thus implementing digital pathology and allowing their scalability at pathology;
- develop new methodologies for personalised (human-centred) medicine;
- promote new treatment modalities based on biological data to handle orphan cancers.

Through the interdisciplinary effort to generate the ANTHEM platform will cover the unresolved issues still present in the healthcare systems at European, National and Regional levels:

- ensure and improve the **digital access to the healthcare related data**
- improve the efficacy of **medical devices and sensors assisted by AI systems**
- provide an efficient **set-up of healthcare data** taking advantage of selected end-users and **territorial communities**
- improve the reliability and availability of **“digital pathology” data**

As reported in NRRP, Italy needs innovative actions aimed *“to strengthen both the hospital system and the territorial assistance network: the latter appears, in fact, weak and not homogeneous in the ability to provide integrated responses, not guaranteeing fair access to care and constituting one of the main criticalities of the NHS”*.

Starting from the identified needs in the healthcare field, the intervention of ANTHEM will address the main challenges of NHS, thus fostering the following directions:

- contributing to **reduce the current geographical and territorial gaps** in health care system thanks to the harmonisation of the standards of care by means of technology;
- ensuring a better **"care experience"** for patients and healthcare professionals;
- improving the efficiency levels of regional health systems by promoting **home care and remote monitoring protocols**.
- allowing innovative diagnostic processes based on **“digital pathology” data**

ANTHEM project will be developed as a functional and modular care platform, whose validation will be optimised with the participation of heterogeneous partners so as to fully cover the healthcare ecosystem ranging from scientific research, technology transfer to stakeholders. In particular, Universities (UNIMIB, UNIBG, POLIMI, UNICT, UNICAMP, UNICAL, UNIME, UNISALENTO, HUNIMED) and research centres (INFN, NEGRI, FERB, IOM, BIO) will generate new knowledge and innovative tools directed to detect, monitor and treat the major pathologies affecting chronic patients. ASST and ATS (ASST Monza, ASST PG23, ASST BGEST, ATS MI, CANNIZZARO) will support the functionality of the produced tools in the real reference healthcare system. Industrial and private partners (ABM, ART, CHIESI, DIA) that will be involved in technology transfer and joint development of innovative solutions applied within the project. To generate an operative environment the referral Regional Entities (Lombardia, Puglia, Campania, Calabria, Sicilia) will be involved in ANTHEM project research activities.

The approach described above is functional to the impact-oriented vision of the project. Table C.1 summarises the expected impacts of the project, which will then be discussed in more detail in the following sections.

³² https://health.ec.europa.eu/funding/eu4health-programme-2021-2027-vision-healthier-european-union_en

³³ <https://www.governo.it/it/approfondimento/pnrr-salute/16707>

Table C.1. Summary of the ANTHEM impacts.

Expected Impact	Impact of the ANTHEM project
<p><i>Scientific and technological contributions to the consolidation of innovative technologies and potential for societal and economic innovation</i></p>	<p>ANTHEM will generate a new platform for early diagnosis, monitoring and treatment of chronic and frail patients. Scientific and technological contributions to the consolidation of innovative technologies. The multidisciplinary approach is based on a bottom-up approach in which digital tools, sensors and diagnostic/therapeutic solutions will be designed starting from the patient needs and features, by taking into account the major limitations in the home-care management of chronic patients. This approach has been selected to improve the feasibility of the planned activities and to reduce tentative approaches not applicable in the real world. With this aim ANTHEM project includes activities and Pilots with different parallel TLRs (from 2 to 8). Potential for societal and economic innovation. ANTHEM will have a relevant social and economical impact reducing the burden of chronic diseases. Furthermore, the project will have a direct impact on a) ethics and geographical equity of healthcare access also across different territorial areas; b) public health expenditure. With this aim, the ANTHEM project obtained the support of Regional Entities and mountain communities, to be functional across representative communities during the entire project progress. The ANTHEM project will analyse the economical sustainability of project activities and proposed innovation on the healthcare system.</p>
<p><i>Build-up of a goal oriented interdisciplinary community (within and beyond the Initiative).</i></p>	<p>The ANTHEM project will combine the efforts of partners with different expertise to reach a social and economic objective requiring multiple competences. As a matter of fact, the project requires a continuous dialog between scientists with very heterogeneous expertise, from clinicians to informatics, passing through material scientist, physics, cell biologists, engineers, bio-organic chemists. The ANTHEM project will open the way to a well-run platform that will be active also beyond the project completion.</p>
<p><i>Emergence of an innovation ecosystem around a future technology in the theme addressed from outreach to and partnership with high potential actors in research and innovation, and from wider stakeholder/public engagement, with due consideration of aspects such as education, gender differences and long-term societal, ethical and legal implications.</i></p>	<p>UNIMIB, UNIBG and POLIMI are located in the North Area (Lombardia Region) that is already involved in long-term projects aimed to increase the healthcare platforms in parallel with digital transformation. UNIMIB is involved in the future realisation of the “City of Health”, which will bring together expertise in chronic disease early diagnosis, monitoring and treatment. UNISALENTO is located in Puglia Region, which constitutes the Health Innovation Network and the Health Marketplace for the promotion of care pathways and lifestyle of citizens. Other relevant Innovation Hub include for UNICAMP the Hi-HealthTech Innovation Hub “Circular City of Health” and for UNICT and UNIME UNICAL the Harmonic Innovation Hub, Gender aspects. Gender balance will be guaranteed. The selection step of the personnel to be hired in the project will ensure a 50-50 female-male participation. ANTHEM will also ensure that gender balance is addressed at the level of decision-making when implementing the project. Specific measures regarding women role/participation in the project will include i) to phrase and distribute the call properly, women will be encouraged to apply, ii) creation of a good team spirit, better tolerating family needs and obligations better, iii) allocation of tasks to allow temporary replacement of each person by another in case of unexpected events this will help parents with children. Gender balance will be ensured at the level of the Supervisory Board. Training and Education. The project will finance the training and research of PhD students and early stage researchers. It will be a unique opportunity for a translational and multidisciplinary training. Furthermore, specific training will be organised for professional figures and caregivers involved in the healthcare pathways. Ethical and legal implications. The technologies and the tools developed within the ANTHEM project will allow us to obtain data and information useful to standardise defined protocols and pathways of care. These outputs will be useful in the implementations of standards useful to define possible legal or ethical constraints not yet identified or considered.</p>

<p><i>Environmental Impact</i></p>	<p>Telemedicine, and, more comprehensively, e-Health strongly contributes to the reduction of CO₂ emissions and therefore the carbon footprint of medical services by diminishing the necessity of travels to hospitals or PoC to the ones that remain strictly necessary. Routinary controls in fact, allow to establish when a deeper medical exam in an appropriate medical facility is to be recommended. Monitoring systems and remote communication with Medical Doctors that remotely collect and support the evaluation of the patient conditions and parameters in real time also contribute to the reduction of not necessary hospital admission. This has an effect on the reduction of plastic waste resulting from the packaging (plastic envelopes but also the tests themselves, not to mention syringes, nails etc.) and of a variety of chemicals (e.g. reagents and plastic labwares) that are usually associated with clinical tests and that need appropriate disposal. The use of digital pathology diagnostics will allow to reduce the use of chemical pollutants required for samples fixation, preparation and embedding in conventional histology</p> <p>In spite of the advantages, while telemedicine undoubtedly contributes to reducing greenhouse gas emissions, it still has an impact on the environment due to, for example, the higher energy consumption needed to keep monitoring devices functioning and continuous communication with the systems in place. For this reason a Life Cycle Assessment will be evaluated during the project.</p>
<p><i>Quality of Life (QoL) of patients</i></p>	<p>e-Health systems provide advantage in the early detection of pathological phenomena or comorbidities, continuous monitoring of frail and chronic patients allowing therefore prompt and timely interventions. On top of these aspects several studies demonstrate that telemedicine has also a strong impact on QoL of patients not limited to clinical assistance but inclusive of psychological aspects. While patients have the possibility to open a channel with medical personnel without going through a process of reservation of a clinical appointment, also the perception of the received care and results also in a higher confidence in the received assistance: “Telemedicine has been proven to be an effective intervention for patients with several chronic diseases. The results showed that the telemedicine group had significantly higher QoL than the usual care group [...]. In addition, the telemedicine group had lower anxiety [...] and depression scores [...] than the usual care group”³⁴. Actions taken in Spoke 4 for innovative cancer treatment aim at promoting a patient-centred medicine based on a more participative approach, and on a deeper awareness of patients to the treatment strategy. Moreover, patient comfort, number and duration of sessions, aesthetic and psychological quality of life after treatment are specific goals.</p> <p>Care services vehiculated through ICT technologies therefore constitute a safe, cost-effective and time-saving kind of intervention and “<i>it has emerged in the last two decades as a non-invasive surveillance and follow-up method for patients discharged from hospital</i>”.</p>
<p><i>Reference communities</i></p>	<p>The activities exploited during the ANTHEM project will take into consideration patients affected by the major chronic conditions. Patients affected by tumours, cardiovascular diseases, lung diseases and degenerative diseases will be considered to validate and optimise the diagnostic, monitoring and therapeutic approach applying the ANTHEM project pathways also after project conclusion.</p> <p>Furthermore, the project will be focussed on very well-defined territorial communities that are representative of the major typical national communities (i.e. mountain, metropolitan cities, islands). The availability of new therapeutical options located in the South of Italy may also become an attractive opportunity also for other communities in the Mediterranean area.</p>

Due to the complexity and multidisciplinary aspects of ANTHEM, to better analyse and quantify the impact of the initiative, different aspects have been considered:

- Scientific, societal and technological impact of the Initiative *as a whole*, following indications of the Horizon

³⁴https://www.researchgate.net/publication/346141861_The_effects_of_telemedicine_on_the_quality_of_life_of_patients_with_lung_cancer_a_systematic_review_and_meta-analysis

- Europe Framework Program (C.1.1);
- Potential impact of results on “Reference Communities” directly involved in the Initiative (patients QoL and well-being, C.1.2);
- Potential impact of results on “Healthcare System” as a whole (reduction of hospitalisation, reduction of costs, reduction of invasive and expensive medical procedures, C.1.3);
- Potential impact on the training of early stage researchers and scholars (C.1.4);
- Measures to maximise the impact (C.1.5).

C.1.1 Scientific, societal and technological impact of the Initiative as a whole

As highlighted by the EU in the Horizon Europe Framework Program, the assessment of the impact of research and innovation projects has to consider Key Impact Pathways (KIPs) towards:

- Scientific Impact
- Societal Impact
- Technological/Economic Impact

Table C.2 illustrates the KIPs together with the description of the ANTHEM actions and targets, the latter expressed in terms of Key Performance Indicator (KPIs).

Table C.2. Key Impact Pathways as declined by ANTHEM and corresponding targets: Column “KPI-Project LifeSpan” indicates Key Performance Indicators that will be considered to assess the impact during the project while column “Dimensions considered for evaluation of impacts 5+y after project’s end” summarizes the impact dimensions that will be measured up to at least 5 years after the project end to assess medium and long term impact of project’s results and actions.

Type	KIP	Description	KPI - Project LifeSpan	Dimensions considered for evaluation of impacts 5+y after project’s end
Scientific Impact	Creating high-quality new knowledge	Papers Publications	At least 100 publication on top class journals and conferences (during project years) accordingly to the national research quality assessment (ANVUR-VQR) scientific production recommendation	-Publications: Number of peer reviewed scientific publications -Citations: Field-Weighted Citation Index of peer reviewed publications -World-class science: Number and share of peer reviewed publications from projects that are core contribution to scientific fields
		Conferences organisation	Organisation of 5 international conferences (held in the five cities of Milan, Catania, Lecce, Rende, Napoli)	
		Attendance of major conferences/ workshops/ fairs/ Expo events organised by big players and leading scientific and industrial game changers	Attendance of at least 20 international major events per year by spokes’ team members	
	Strengthening human capital in research and innovation	Recruitment of researchers	At least 80 researchers and more than 50 PhD students will be recruited and trained during the project and the establishment of a permanent collaboration will fostered after project funding by	

			academia or by the assistential and industrial partners	of upskilled researchers with more influence in their R&I field
		Training on hard and transversal/soft skills	At least 2 core skills and 2 soft skills courses will be held per project year	-Working conditions: Number and share of upskilled researchers with improved working conditions (assessed through WHOQOL, a quality of life assessment developed by the WHOQOL Group with fifteen international field centres, simultaneously, in an attempt to develop a quality of life assessment that would be applicable cross-culturally) ³⁵ . -New jobs: numbers of phd students obtaining new industrial doctorate title working in healthcare systems.
	Fostering diffusion of knowledge and Open source	Sharing of Open Data (accordingly to GDPR requirements)	At least 5 Data Sets (e.g. on Medical Imaging; Medical devices; Health Records) will be shared on Open Data platforms (e.g. EOSC, Open EHR)	-Shared knowledge: Share of research outputs (open data/ publication/ software etc.) shared through open knowledge infrastructures -Knowledge diffusion: Share of open access research outputs actively used/cited after project's end -New collaborations: Share of beneficiaries having developed new transdisciplinary/ trans-sectoral collaborations with users of their open R&I outputs
Societal Impact	Addressing EU policy priorities and global challenges through research and innovation	The project is aligned and will foster the objectives of: <ul style="list-style-type: none"> • Horizon Europe Mission 2 Cancer • Sustainable Development Goal #3 of the United Nations • EU proposal known as “Artificial Intelligence Act”³⁶ 	The consortium will establish at least 5 formal collaboration agreements with international actors/ stakeholders/ organisation to foster the pursuing of project goals also after the funding period	Outputs: Number and share of outputs aimed at addressing specific EU policy priorities (including meeting the Sustainable Development Goals - SDGs) Solutions: Number and share of innovations and scientific results addressing specific EU policy priorities (including meeting the SDGs)
	Delivering	Expanded Chronic	A reduction of burden of	-Benefits: Aggregated

³⁵ <https://www.who.int/tools/whoqol>

³⁶ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52021PC0206&from=EN>

	benefits and impact through research and innovation missions	Care Model (CCM) improves health outcomes and patient care experience and reduces costs. CCM application leads to better QoL, improved adherence to therapeutic approaches, reduction of hospitalizations and costs.	chronic diseases that translate into higher quality of life of patients and patients' families and caregivers is expected together with a potential reduction of costs, time, and management on the side of the National Health System.	<p>estimated effects from use of the project's funded results on tackling specific priorities, including contribution to policy making and legislation. These will include the measurement of the % of tackled communities of patients reached and that actively employ solutions developed during and after the project.</p> <p>-Impact: Quality of Life Scale (QOLS)³⁷ <u>adapted for use in chronic illness groups</u> will be used in collaboration with patients's association to assess improvements both for patients and families/ caregivers</p> <p>-environmental impact (reduction of CO2 emissions, reduction of plastic waste, reduction of energy consumption)</p>
	Strengthening the uptake of research and innovation in society	Involvement of patients, care givers, MDs and relative associations	It is expected to establish at least 5 agreements with association during the project and with additional 5 within the year after project ending	<p>-Number and share of initiatives where citizens and end-users contribute to the co-creation of R&I content</p> <p>-Societal R&I uptake: Uptake and outreach of scientific results and innovative solutions co-created</p>
Technological/Economic Impact	Generating innovation-based growth	Patent filing	It is expected to file at least 2 patents during the project	<p>-Innovative outputs: Number of innovative products (e.g. medicaments; instruments), processes or methods from Intellectual Property Rights (IPR) applications commercialized after the project</p> <p>-Economic growth: Creation, growth & market shares of companies having developed a portfolio of services and products from project's results (also in partnership with other actors in the market) that fill a</p>
		Start Up Creation	It expected to fund at least 2 start up companies to exploit and transfer to the market services and technologies developed during the project	
		Joining consortium specialised in innovation and tech transfer	At least 4 Project partners are expected to join the "to-reach" partnership ³⁸ to foster technology transfer	

³⁷ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC269997/>

³⁸ <https://to-reach.eu/the-project/partners/>

			<p>demand existing in the market</p> <p>-A 10% reduction of burden of chronic diseases (costs, time, management, patient experience) is expected per pathology considering the samples involved in the project. Improvement is therefore expected if solutions are transferred to the national system.</p> <p>-number of increasing home care and remote monitoring protocols (number of patients)</p> <p>-Number of Hospital, (& similar) using technological solutions developed during the project</p> <p>-Geographical distribution of solutions adopted : north-south comparison</p>
Creating more and better jobs	Professionals employed in Academy, Industry and Health System	At least 10 high profile researchers, technicians and professionals in Digital Medicine will be trained	<p>-Supported employment: Number of FTE (Full Time Equivalent) jobs created, and jobs maintained in beneficiaries entities as a result of the Project's actions</p> <p>-Total employment: Number of direct & indirect jobs created or maintained due to diffusion of project's results (by type of job)</p>
Leveraging investment in research and innovation	Industrialization agreement	At least 4 Industrialization and exploitation agreements are expected to be signed with big industrial players to bring to maturity (high TRL) technological solutions developed during the project	<p>-Amount of public & private investment mobilised with the initial project's investment - Amount of public & private investment mobilised to exploit or scale-up results</p>
	Signed Non-Disclosure Agreements (NDA)	At least 10 NDA are expected to be signed with Industrial Actors during the 4 years of the project	

In addition to the overall scientific, societal and economic impacts, specific trends for healthcare transformation have been identified for the activities within the ANTHEM project (see Table C.3) in accordance with the analysis of key critical trends in life science elaborated from the EU Megatrends Hub³⁹ and Frost&Sullivan Visionary Innovation Groups, Health Megatrend⁴⁰.

³⁹ https://knowledge4policy.ec.europa.eu/foresight/tool/megatrends-hub_en

⁴⁰ <https://www.frost.com/research/industry/healthcare-life-sciences/>

Table C.3. ANTHEM Positioning with respect to Megatrends in Life Sciences.

<i>Critical Trends for Healthcare Transformation</i>	<i>Health Data Science</i>	<i>Medical Technology Disruptors</i>	<i>From Hospital to Home</i>	<i>Precision Medicine</i>	<i>Future of Industries & Outlooks</i>	
<i>Population Health Management</i>	✓	✓	✓	✓	✓	<i>Digital Health</i>
<i>Artificial Intelligence</i>	✓	✓	✓	✓	✓	
<i>Internet of Medical Things</i>	✓	✓	✓	✓	✓	
<i>Telehealth</i>	✓	✓	✓	✓	✓	
<i>Electronic Health Records (EHRs)</i>	✓	✓	✓	✓	✓	
<i>Digital Workflow Solutions</i>	✓	✓	✓	✓	✓	
<i>Chronic Care Continuum</i>	✓	✓	✓	✓	✓	<i>Advanced Medical Technologies</i>
<i>Patient Management</i>	✓	✓	✓	✓	✓	
<i>Regenerative Medicine</i>	-	✓	-	✓	✓	<i>Pharma 2.0</i>
<i>Targeted Therapeutics</i>	-	✓	-	✓	✓	
<i>Life Sciences IT</i>	✓	✓	✓	-	✓	
<i>Molecular Diagnostics & Companion Diagnostics</i>	✓	✓	-	✓	✓	<i>Clinical Diagnostics & Research Tools</i>
<i>PoC Testing & Smart Genomics</i>	✓	✓	✓	✓	✓	
<i>Laboratory Automation</i>	✓	✓	-	-	✓	
<i>Contract Development & Manufacturing</i>	✓	✓	✓	✓	-	<i>Emerging Markets</i>
<i>Business Models & Services</i>	-	-	✓	✓	-	

C.1.2 Potential impact of results on “Reference Communities”

The principal aim of ANTHEM project is to identify and apply a shared functional model in which **home is the first care place** to improve patient’s quality of life and to reduce the physical and social burden of chronic diseases.

With the development of innovative solutions aimed at remote diagnostics and treatment centred on patients, ANTHEM will have a direct impact on the reduction of costs and increase of diagnostics and therapeutic/care pathway success improving patients’ quality of life. ANTHEM project will have direct and substantial impact on reference communities increasing and improving:

- the equity of access to the healthcare system;
- the quality and continuity of care;
- the effectiveness, efficiency, appropriateness of patient care.

The National Plan of Chronicity (NPC) indicates that the most representative pathologies or co-morbidities in the chronic and frail population are represented by cardiovascular diseases as a whole (32,8%), followed by chronic respiratory diseases (24,5%), diabetes (20,3%) and tumours (12,7%). According to the available data, the main causes of death reported in chronic and frail populations are related to cardiovascular disease (37,35 per 100.000 inhabitants), tumours (29,2 per 100.000 inhabitants) and diseases of the respiratory system (6,64 per 100.000 inhabitants).

Starting from these numbers, ANTHEM will validate and optimise the planned theranostic approaches on selected pathologies related to these major pathological conditions. To resolve the current limitations related to the interoperability between digital systems, available data and territorial inequalities, ANTHEM will validate diagnostic, monitoring and therapeutic solutions for the early and real time detection of patients affected by selected tumours (such as GBM, melanoma, thyroid and lung cancer), cardiovascular and lung diseases (i.e. heart failure, fibrosis), degenerative, autoimmune diseases (i.e. neurodegenerative diseases, diabetes).

The ANTHEM project will improve the entire care pathway of patients affected by chronic conditions. The specific actions of the project will generate: 1) last generation digital, biomolecular and imaging diagnostic technologies for early diagnosis; 2) new home care digital tools and medical devices to follow the patient in real time, limiting co-morbidities and tailoring hospitalisation/MDs intervention; 3) a well organised and structured territorial network to



follow and manage the patients with innovative solutions; 4) personalised advanced therapeutic solutions with reduced side effects and increased therapeutic efficacy.

In the following we detail the impact related to specific pathologies by focusing on the incidence rate in Italy and on the ANTHEM directions of intervention.

Patients affected by tumours

The ANTHEM project will provide more sensitive and smart diagnostic methodologies assisted by digital tools to increase the diagnostic potential and the early detection of the selected tumours in the Italian population. Furthermore, personalised therapies will be developed to improve quality of life of patients and to induce tumour remission. **Selected pathologies.** *GBM* is the most common malignancy among brain neoplasms - with an overall incidence of about 3-4 cases per 100.000 people per year (1.500/year in Italy). More frequent in men than in women, it occurs mainly in the age group between 55 and 75 years, with random territorial distribution but with a greater incidence in the Caucasian population than in African or Asian populations. *GBM* is asymptomatic until it reaches important sizes, and the progression of this tumour without symptoms prevents any early diagnosis, which on the other hand is performed by invasive bioptic methods in the patients affected. The latest advances on molecular pathogenesis that is at the basis of *GBM* progression has not yet translated into significant therapeutic progresses, with impact in patient life outcomes. The therapy against *GBM* is multimodal, and usually involves a combination of surgery, radiation, chemotherapy, and immunotherapy. Despite the many efforts devoted in the last 20 years to the study of *GBM* pathophysiology and the research of new biomolecular targets to develop more efficient therapeutic strategies, *GBM* recur with poor prognostic outcomes. *Melanomas* are the cancers that recorded the highest average annual increase, both in men (+ 8,8% in total, + 9,1% in over 70s) and in women (+ 7,1% in total, + 7,6% in under 50s) and in all age groups. These increases, and the recent availability of increasingly accurate diagnostic techniques, indicate the need to implement timely primary prevention interventions to reverse this trend in the coming years. Also, the increases in the incidence rates of *lung cancers* found in all women (+ 3,4%) and in the over 50s (+ 2,1% annual average in the 50-69 age group and + 2,8% in the 70+ age group) require attention and preventive interventions. An increase in incidence rates was also reported for *thyroid cancers* (+ 4,6 % in men and + 3,5% in women), an increase attributable to the spread of "opportunistic screening" in both males (+ 4,4% in over 70s) and in females (+ 3,5% in age groups up to 69 years). During the screening campaigns, a remarkable number of "non-negative" biopsies lead to thyroidectomy, but most of these cases eventually turned out to be benign lesions: this diagnostic limitation could be overcome by the optimization of new diagnostic processes based not only on conventional histology but also on the lesions "molecular signature" through mass spectrometry. X-ray-based "digital pathology" will also contribute to better management of the tumour biopsies since it allows fine imaging without the need for destroying the samples, thus making them available for subsequent analysis even if of very small size.

Patients affected by cardiovascular and lung diseases

The ANTHEM project will provide digital tools and medical devices to improve the home-care monitoring of patients affected by cardiovascular and lung diseases, to offer functional diagnostic methods and innovative intensive care treatments of patients affected by lung diseases. **Selected pathologies:** *Cardiovascular diseases* include, ischemic heart diseases (acute myocardial infarction, acute coronary syndrome, and angina pectoris), cerebrovascular diseases and peripheral arteriopathies. In Italy in recent years, the incidence and the mortality rate of cardiovascular diseases has progressively reduced. This reduction is related to the improvement of diagnostic, therapeutic and rehabilitative options, however the population ageing favours an increase in the prevalence of cardiovascular chronicity in the population, with an increasing burden for patients, society, and the NHS. Globally, it is estimated that in 2019 these diseases were responsible for 18,6 million deaths (239,8 deaths per 100.000). In 2018, a total of 220.456 deaths from diseases of the circulatory system were recorded in Italy (96.017 males and 124.439 females); of these, 62.434 deaths were attributed to ischemic heart diseases (32.765 males and 29.669 females), including 20.739 cases of acute myocardial infarction (11.792 males and 8.947 females), while 53.901 were attributed to the other heart diseases (22.863 males and 31.038 females) and 55.430 to cerebrovascular diseases (22.062 males and 33.372 females). Ischemic heart diseases, other heart diseases and cerebrovascular diseases represent the top three causes of death in Italy (27,1% of the total deaths in 2018). *Lung Diseases:* in Italy around 10 millions of patients are affected by lung diseases, among them more than 8 millions patients are affected by chronic respiratory diseases that need continuous treatments and diagnostic investigations. In industrialised countries, Chronic Obstructive Pulmonary Disease (COPD) is the 5th cause of death in the diseased population. In Italy, 43,4% of the 37.782 deaths attributed to respiratory diseases are related to asthma and COPD, for which the mortality per year varies between 13.849 and 16.786 subjects. COPD has shown a significant increase in prevalence



and mortality in females and recent evidence underlines the role of different susceptibility to risk factors for the development of COPD, such as a different clinical expression of the disease. COPD leads to substantial disability and loss of productivity which significantly affects the patient's quality of life with a substantial economic impact linked to the cost of prolonged treatments and repeated hospitalizations.

Patients affected by degenerative, autoimmune diseases

The ANTHEM project will provide digital tools, medical devices, early diagnostic and rehabilitation solutions assisted by digital tools for patients affected by neurodegenerative diseases and diabetes. **Selected pathologies: Neurodegenerative diseases.** Neurodegenerative diseases are expected to quickly become one of the most significant problems in terms of public health management. The global incidence of neurodegenerative diseases is 1,7 cases per 100.000 people / year. The global incidence is currently estimated at 200.000-300.000 cases, with around 5.000 in Italy. The prevalence of dementia in industrialised countries is about 8% in the over 65s and rises to over 20% after the age of 80. In western countries, cases of dementia could triple in the next 30 years. In Italy, according to demographic projections, in 2051 there will be 280 elderly people for every 100 young people, with an increase in all age-related chronic diseases, and among these dementias. Parkinson's disease (PD) is one of the most frequent neurodegenerative diseases. In industrialised countries the incidence is around 12 per 100.000 people/year with a prevalence of about 2 million affected individuals. The disease is slightly more expressed in males than females (60% vs 40%). PD affects about 1% of the population over 60 and 4% of the population among subjects over 85. Besides early diagnosis, PD patients can greatly benefit from long-term physical therapy that allows them to maintain a better quality of life and a lower incidence of comorbidities linked to reduced mobility. Unfortunately, so far the availability of physical therapy centres is very limited, and effective home-based, remote-monitored programs are warranted to enlarge the number of PD patients profiting from the advance of tailored physical therapy programs.

Currently the total number of patients with dementia is estimated at over 1 million and 3 million people are directly or indirectly involved in their care, with consequences also on an economic and organisational level. ***Diabetes.*** 536,6 million people between 20 - 79 years are affected by diabetes and that an additional 1,1 million children and adolescents (0-19 years) have T1D. The number of adults with diabetes is also set to increase to over 642 million in 2030 and 783 million in 2045. In Italy the diabetes incidence is estimated to be 5,9% (5,9% in males, 5,9% in females) corresponding to 3,5 million people.

The reference communities will have direct benefits since the first stages of ANTHEM project. Considering the different pathological aetiology, pathological evolution, patient stratifications and sub-groups and the potential comorbidity associated and territories inequalities, the ANTHEM project will be organised in well defined Spokes, taking into consideration diagnostic tools, monitoring systems and therapeutic solutions which are personalised for selected chronic diseases in well defined geographical/territorial area. In the following we summarise the impact related to specific Spokes by focusing on the selected pathologies, referral communities and territories.

Spoke 1 - Data and technology driven diagnoses and therapies. Innovative diagnostic and monitoring solutions and tools will be generated taking into consideration chronic patients and frail populations of: Lombardia Region, including mountains (Val Seriana and Val Brembana)/metropolitan territories; Campania (Salerno and Napoli) and Sicilia Region (Messina). The reference communities will include patients affected by tumours (thyroid and GBM cancers), paediatric patients affected by diabetes and patients with Gaucher disease and PD. The activities performed in the Spoke 1 will generate and validate more efficient methodologies for the ***early diagnosis*** of morbidities and comorbidities, and digital assisted technologies for the monitoring of pathological progression and therapeutic/treatment efficacy.

Spoke 2 - Connecting patients and therapists through adaptive environments and intelligent sensors to enhance proximity medicine. Wearable, portable devices and diagnostic digital tools will be generated taking into consideration chronic patients and frail populations of: Lombardia Region, including mountains (Val Seriana and Val Brembana) and metropolitan territories. The reference communities will include patients affected by tumours (thyroid and GBM cancers), patients affected by cardiovascular diseases (i.e. Coronary heart and Peripheral arterial disease, stroke), patients affected by neurodegenerative diseases (i.e Parkinson diseases). The activities performed in the Spoke 2 will contribute to validate and optimise the ***remote monitoring*** of chronic pathologies improving the ***home-care*** approach and reducing pathological recurrence and burden.

Spoke 3. Risk factors monitoring, diagnostic tools and therapies in chronic disease. Technologies to identify and treat life-style and environmental determinants of morbidities onset will be generated taking into consideration the chronic population of: Lombardia Region, including metropolitan territories and Puglia Region (Lecce, Bari and



Taranto). The reference communities will include patients affected by cardiovascular (i.e. coronary heart disease, aortic diseases, peripheral arterial disease, stroke), lung (i.e. COPD, asthma, emphysema) and neurodegenerative (i.e. PD) diseases, and tumours (i.e. melanoma, GBM, thyroid and lung cancers). The activities performed in the Spoke 3 will contribute to implement the *monitoring* ability of chronic patients, to develop *diagnostic tools* and to define innovative *personalised treatments* for chronic diseases.

Spoke 4. Preclinical and clinical breakthrough theranostic and treatments for cancer. Preclinical diagnostic and therapeutic strategies will be generated taking into account the chronic population of: Lombardia Region, including metropolitan territories, Puglia Region (Lecce, Bari and Taranto), Sicilia Region (Messina and Catania) and Campania Region. The reference communities will include patients affected by tumours (i.e. GBM and melanoma cancers), in particular in the Campania Region where a dedicated BNCT facility in Caserta will be established. The activities performed in the Spoke 3 will contribute to improve *early diagnostic* approaches and to define innovative *personalised treatments* for cancer.

C.1.3 Potential impact of results on the “Healthcare System” as a whole

The comprehensive annual costs of care and management of the chronic and frail population in Europe are equivalent to 115 billion or 0,8% of Gross Domestic Product (GDP), furthermore the burden of chronic diseases on social benefit expenditures correspond to the 1,7% of GDP⁴¹. In Italy, chronic patients have access to free-of-charge treatments and diagnostic procedures. The Italian per capita costs are in line with the European average. In detail, the total pharmaceutical costs reached 28.100 M€ billion in 2017 (19.500 M€ billion supported by the NHS, 8.600 M€ by patients).

With the planned activities devoted to monitor, diagnose and treat early manifestation of pathological conditions, ANTHEM will have a strong impact on a more efficient, effective and timely prevention thus reducing the impact of disabilities achieving also the Goal 3 - Good Health and Well-Being (“reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being”).

In the WHO European Region, chronic diseases affect 80% of people over 65 years and often are present as comorbidities. It is expected that by 2060, the number of Europeans over the age of 65 will increase from 88 to 152 million. Italy has one of the higher life expectancies in Europe (second after Spain). Chronic and frail patients are often affected by several co- or multimorbidity, and their therapeutic and diagnostic needs are related to both clinical conditions and also to other determinants (social status - family, environmental, accessibility to care). The correct therapeutic approach requires the intervention of different professional figures. However, this intervention is still fragmented, focusing more on the treatment of the disease than on the management of the patient, with possible care duplications that contribute to the increase in health care costs with lower diagnostic and therapeutic efficacy. It is estimated that around 70-80% of the world's health resources are employed for the management of chronic diseases. These data become even more worrying by considering the most recent epidemiological projections, according to which in 2020 they will represent 80% of all diseases in the world. The WHO definition of chronic disease (“health problems requiring continuous treatment over a period of time from years to decades”) is clearly referred to the commitment of human, managerial and economic resources, both in terms of direct costs (hospitalisation, therapies, medical assistance, etc.) and indirect (premature mortality, long-term disability, reduced quality of life, etc.).

ANTHEM will be developed with the full support of Regional Bodies. To maximise the impact on the NHS, ANTHEM will take advantage of Regional Territorial Entities directly involved in the management of Health Systems. This approach will allow us to generate functional platforms that will be integrated at local and national level, strengthening the territorial medicine and the entire care pathway of chronic patients. The Regional entities involved in the ANTHEM project adhere to the PNC, in which specific actions and models have been identified. The efforts, the interventions and the priorities for each Regional entity involved in the ANTHEM project aimed to improve diagnosis, monitoring and remote treatment of chronic population are reported in the Regional Prevention Plans⁴².

Lombardia Region⁴³

The ANTHEM project is in compliance with the **S3 strategy** of Lombardia Region. The priority of Lombardia Region is to define and develop new technologies, models of assistance and provision of services in the health sector to realise **MEDICINE 5P** - participatory, personalised, preventive, predictive, psycho-cognitive towards an approach based on a patient-centred vision. Lombardia Region intends to design and implement a Regional

⁴¹ OECD/European Union (2016), Health at a Glance: Europe 2016: State of Health in the EU Cycle, OECD Publishing, Paris

⁴² <https://www.salute.gov.it/portale/prevenzione/dettaglioContenutiPrevenzione.jsp?lingua=italiano&id=5771&area=prevenzione&menu=vuoto>

⁴³ Credits for the five regional maps: Wikimedia Commons (CC BY-SA 3.0).

Telemedicine platform with the following strategic objectives essential for completing the digital transformation of social and health services, supporting the implementation of the new organisational model defined by the Regional Law 22/2021 and ensuring the achievement of the NRRP objectives:

- Support and improve the telemedicine services already active in the various regional territorial realities;
- Incentive and stimulate the market to produce and make available innovative digital technologies and devices necessary to progressively increase the type and volumes of telemedicine services in the area;
- Simplify the implementation of telemedicine processes throughout the territory and facilitate access to services by health and social workers and citizens.



Puglia Region

The ANTHEM project is in compliance with the Regional Prevention Plan 2021-2025 and the “**Model 3.0**” promoted by Puglia Region and devoted to improving chronic patients' care experience and management. The model is adherent to the actions identified in the National Plan for chronic Diseases and aims to:

- Valorize the care pathway of healthcare services to guarantee the continuity of care introducing a patient personalised approach.
- Introduce a multi- and interdisciplinary approach common to the healthcare professionals involved in the care pathway of chronic patients.
- The improvement of early diagnosis, introducing methodologies and pathways and home-care solutions to anticipate the current timing of chronic disease monitoring.
- The improvement of Chronic Patient stratification related to patients subgroups features and needs.
- The introduction of specific programs dedicated to Patient Associations in order to train chronic patients on the importance of real time monitoring and diagnostic and on home-care concepts and procedures.



Campania Region

The ANTHEM project will favour the major objectives of Campania Region, as reported in the Triennial Plan for the Development of Campania Healthcare Service. As reported in the report, the major aims of the regional programmatic plan are related to the:

- The improvement of organisational structure of the Health System, taking advantage of digital tools and telemedicine instruments.
- The increase of platforms/methodologies able to facilitate patients monitoring and home-care management.
- The reduction of Healthcare costs dedicated to not necessary hospitalizations or healthcare related services.



Calabria Region

The ANTHEM project will favour the major objectives of Calabria Region, in adherence with the quinquennial regional prevention plan - PNP 2020-2025 (DCA n.161 / 2020). As reported in the programmatic document, the management of chronic patients has been defined as priority in order to improve:

- A patient centred approach in which the entire care pathway is patient personalised
- The early diagnosis of morbidities and comorbidities.
- The equity in care access.
- The identification and the promotion of healthy life-styles



Sicilia Region

The ANTHEM project will favour the major objectives of Sicilia Region, as reported in the quinquennial regional prevention plan PPNP 2020-2025. The research focus of flash therapy included in the present proposal among the advanced therapeutic strategies is considered of high regional strategic importance for Sicilia included in the “Regional Development Strategy 3” and for which UNICT has formed a dedicated joint consortium with INFN and CANNIZZARO.

As highlighted in the programmatic document, chronic diseases are reported as regional priority and the actions

provided to improve the management of chronic patients care pathway are focussed but not limited to:

- The development of interdisciplinary synergies at central and local levels to define specific prevention and therapeutic pathways adherent to the national plan of chronic disease
- The improvement of clinical data collection and analysis
- The realisation of an integrated surveillance system related to hospitalisation flux
- The implementation of healthcare professional training



ANTHEM project will consider the identified models to build up well defined pathways with clear structures applicable with both patients and Hospitals in order to avoid timing - consuming activities and to maximise the project activities in the interest of patients. The application of Personalised Assistential Care pathways and the generation of Expanded Chronic Care Model (Expanded CCM⁴⁴) demonstrated advantages for both patient's quality of life and Health Care systems. The healthcare systems that are experimenting with these care and organisation models demonstrated: a) an improved care pathway and experience of patients that are monitored and treated with a personalised approach on the basis of pathological grade and subgroup; b) greater efficiency and about 20% saving for Health systems.

Personalised Assistential Care pathways and Expanded Chronic Care Model.

The activities promoted and performed during the progression of the ANTHEM project will be planned taking inspiration from the *Personalised Assistential Care pathways and Expanded Chronic Care Model (CCM)* as promoted in the NPC. The personalised assistential care pathway, introduces different subgroups of patients with different diagnostic and therapeutic needs. On the basis of illness grade and complication risks, the care pathway can be modulated considering sub-groups suitable for home-care monitoring and sub-groups that will have needs and pathological features that will require hospitalisation or professional care management

(Figure 12, see also WHO, 2016, Integrated care models: an overview⁴⁵). This approach allows us to foresee and standardise the home care pathway defining the entire therapeutic and diagnostic pathway.

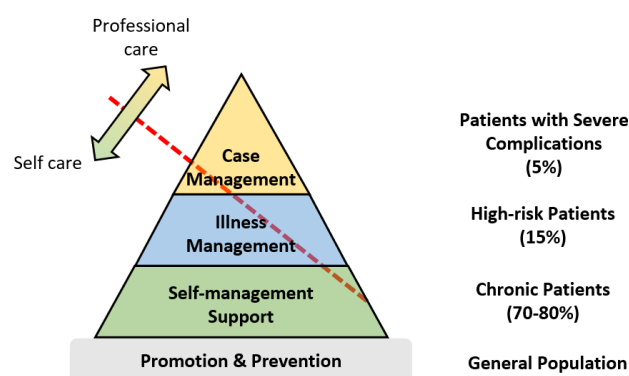


Figure 12. WHO integrated Care Models Overview

This approach allows us to foresee and standardise the home care pathway defining the entire therapeutic and diagnostic pathway.

ANTHEM project will be devoted to direct and validate a personalised “self-care” approach (i.e. C) in which Diagnostic-Therapeutic-Assistance Pathways (PDTA) will be implemented and standardised including different actors in chronic patient management. ANTHEM will introduce new validated and optimised tools to implement and control the intervention strategies, and therefore the care pathways differentiated according to the different needs of the chronic patient sub-groups. The development of new theranostic technologies or devices and the provision of integrated digital tools generated within the project, will validate a new model of assistance with a patient-centric vision in which last generation technologies will be available and applied for the home-care and self-care assistance of chronic patients and high-risk patients.

ANTHEM will adhere to the Expanded CCM (Figure 13, from Barr et al. (2003)⁴⁶) across an integrated care focussed on a) improved health outcomes, b) improved patient care experience and c) costs saving. The application of CCM

⁴⁴ Wagner et al. (1999). *Managed Care Quarterly* 7(3).

⁴⁵ https://www.euro.who.int/__data/assets/pdf_file/0005/322475/Integrated-care-models-overview.pdf

⁴⁶ Barr et al. (2003). *Hospital Quarterly* 1(7).

EXPANDED CHRONIC CARE MODEL

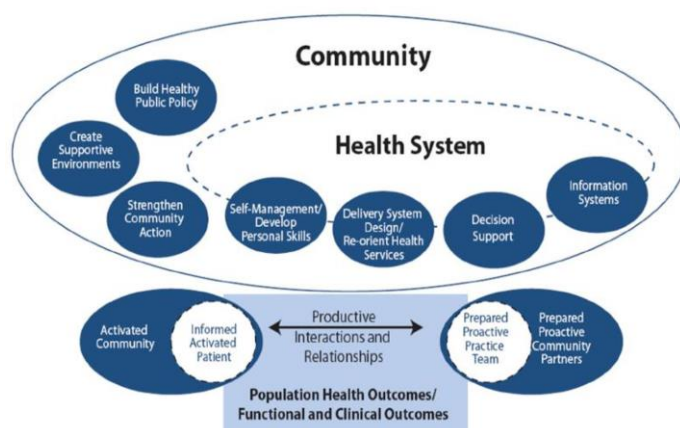


Figure 13 Schematic representation of the Expanded CCM, from Barr et al. (2003).

leads to an improvement of patients' quality of life, an improved adherence to therapeutic approaches, the reduction of hospitalizations and consequently a reduction of healthcare costs.

As planned in ANTHEM, the CCM requires the interactions between multi- and interdisciplinary teams and the use of digital and innovative tools to monitor in real-time patients life-style, the maintenance of healthy states or the early onset of pathological phenomena. Regarding the technological infrastructure, IT standards for interchange and interoperability between data and systems will be used. Regarding data collection and analysis, cutting-edge sensing technologies and innovative methodologies for AI-based data analysis, management and understanding will be used.

Barriers and Obstacles. Even if the advantages related to home-care management of chronic patients are clear for both patient's lifestyle quality and healthcare system efficiency, potential barriers and obstacles to expand and make usable a smart system based on digital care have been identified. Considering the heterogeneity of chronic diseases and the territorial diversity, the following obstacles are still present for the validation of home-care pathways assisted by remote medicine: a) the heterogeneous level of technology competences across population and healthcare professionals; b) the heterogeneous availability of digital infrastructures and pathways in the national scenario; c) the different territorial scenario (same prevention and care goals but with different TRL related to digitalization of healthcare systems). The ANTHEM project will overcome these obstacles introducing during project progression: new and accurate information on chronic diseases patients' groups and sub-groups, interdisciplinary trainings designed ad hoc for the personnel involved in the project and for the final users -including medical doctors, specialised technician, digital managers and patients; new technological platforms that will maximise the continuous operation in different territorial scenario. Such an approach will align with RRI best practices and promote the use of a Social Readiness Level scale in addition to common TRL metrics, economic sustainability analyses, and life-cycle assessments.

C.1.4 Potential impact on the training of early stage researchers and personnel involved.

Training of personnel involved. Specific training will be provided also to the personnel involved in the application of new diagnostic and monitoring technologies (i.e. medical doctors, technicians, nurses, caregivers, patients). The training will include modules devoted to cover the major gaps in the field in order to maximise the remote medicine and digital tools developed within the project. The training will include a selection of transferable skills that will be necessary for both patients and providers of healthcare services. The training of medical assistance providers will be useful also to implement patients' experience and adherence to monitoring and diagnostic protocols developed across the project. Training sessions on telemedicine and remote monitoring and diagnostic will be integrated in medicine and surgery, nursing, biomedical and informatic bachelor of science, taking into account the major needs related to different expertises and needs. The project will use both standardised training methods and will establish new learning technologies according to the innovations and the digital tools introduced for remote monitoring and telemedicine approaches including:

- “in presence” academic and specialisation modules
- synchronous and asynchronous lectures and modules
- faculties-supervised clinical internship
- small groups learning activities
- Furthermore, didactic education of healthcare providers will include the most efficacious methods already in use for sectoral education in the field, including:
 - **experiential simulation learning** to overcome the existing barriers to the diffusion of remote monitoring;
 - **rotation protocols** observing telemedicine services already administered to patients and selected populations;

- **distance learning technologies** including clinical cases presentations, live interactive lectures and tandem presentations;
- **live and interactive clinical sessions** including medical diagnostic and monitoring procedures with the involvement of medical devices and telehealth equipment.
- The topic of interest will include training on:
 - area of interventions of telemedicine and remote medicine (chronic disease management, rehabilitation, intensive care monitoring)
 - telemedicine concepts and applications;
 - telehealth etiquette;
 - correct use of digital and communication technologies;
 - digital triage;
 - medical devices assisted by digital tools;
 - diagnostic and medical procedures using telemedicine equipment and tools;
 - effective interprofessional collaboration and ethical issues and safety issues related to and telehealth and digital tools in medicine;

Training of early stage researchers. The training of highly skilled researchers that will contribute to the innovation of tomorrow in key roles in universities and industries is a target of paramount importance in ANTHEM. During the early phases of the project agreements will be established to implement doctoral programmes in partnerships with the universities involved in the project, but also agreements will be established with research institutions, infrastructures, industrial and socio-economic actors. Multidisciplinary doctoral courses will be designed to respond to precise challenges in medicine and digital health and will train young researchers in multidisciplinary environments that will expose them to a variety of research and innovation sources including academic and non-academic sectors. The research training will include an ample selection also of soft and transferable competences that constitute added value to foster innovation and assure future employability. We will also activate *Industrial Doctorates*, for those PhD candidates that seek to develop robust skills to be exploited in industrial careers. To these candidates will be offered a tailored training, they will be enrolled in doctoral programmes jointly supervised by academic and non-academic partners. In parallel, international Joint Doctorates will also be activated and will also integrate opportunities of international and interdisciplinary collaborations. The project will establish joint doctoral degrees on the basis of already existing programmes and will evaluate to set agreement also for multiple doctoral degrees that will be awarded by the participating institutions to those candidates that will aspire to high profile academic careers. As an example of already existing best practice, UNIMIB and the University of Surrey implemented a dual PhD programme: this increases the capacity and allows students to access excellent R&I environments, e.g. in the case of the University of Surrey and of the ICT field the “5G/6G Innovation Centre”. The project will provide attractive remunerative salaries to the candidates, competitive at European level, and it will provide robust careers perspectives also at international level through paths that will be built since the starting of the PhD programme. All PhD training will also include the following activities on soft and transferable skills:

- **Management skills:** Project Management (not only classical like Prince2 or PMP, but also AGILE Project MgMt methodologies like SCRUM for the development of SW and ICT tools); Strategy Development and Management; Leadership and Team MgMt
- **Personal skills:** Scientific and technical communication (including Communication 2.0 skills and tools, e.g. social networks); Presentation preparation and public speaking; Leadership and Team MgMt; Project Proposal Writing; Language(s)
- **Ethical and legal/regulatory skills:** Privacy issues/GDPR; Ethics; RRI principles and tools; Gender issues; Diversity and inclusion; National and EU legal and regulatory frameworks
- **Business and exploitation skills:** Business Plan definition; IPR Management; Innovation Management; Industry 4.0 Principles and Opportunities
- **Technical skills;** Data Management of structured, semi-structured and unstructured data (e.g. Relational DB, no SQL DB, MongoDB); definition of DMP; Open Data & Open Science (including EOSC-European Open Science Cloud)
- **Budgeting and Financial basics:** Administrative and financial reporting; Artificial Intelligence and Machine Learning (for businesses and other applications); European Research Infrastructures and ESFRI (European Strategy Forum on Research Infrastructures), services and collaboration with private sectors; Innovation in Commercial and Social Enterprises; National and International funding instruments and programmes for SME and collaborative projects

C.1.5 Measures to maximise impact

To maximise the project impact, a plurality of dimensions and actions will be considered (Table C.4).

Table C.4. Dimension and corresponding actions to maximise ANTHEM impact.

Dimensions	ANTHEM measures to maximise impact
<i>Ensuring Scientific Excellence</i>	ANTHEM will be strongly engaged in high-quality research. Its scientific objectives are inspired by international and national guidelines on chronic diseases and the involved research groups are internationally recognized experts in the main area of project development. The usage of the project resources and solutions will be competitive, with the standard criteria of scientific quality expected to be high and monitored by KPIs. Excellence is also guaranteed by the network model. Benchmarking of international labs and centres will be adopted. The enrollment and training of young researchers will be part of the monitoring activities. The adoption of proper and possibly evolving KPIs may help in evaluating the most appropriate configurations for the provision of research infrastructure services.
<i>Attracting, Educating and Training Managers and Users</i>	ANTHEM management structure will allow the selection and progressive enrichment of the skills of its scientific, administrative, managerial, and human resources competences. Managing the activities of the project requires skills that are often not only in the background of the scientists who, having been principal investigators of several international projects, must cope with the complexity of tasks that are not always rewarding from a purely scientific point of view level. An important issue of the project is to attract added value from users, by sharing feedback for designing upgrades and building parts of the infrastructure with selected user groups.
<i>Unlocking the Innovation Potential of Research Infrastructures</i>	Monitoring the innovation potential of access to the research infrastructures is not obvious and only very partially reflected in patents and exploitation, e.g., by industry. ANTHEM can maximise the potential of direct innovation by offering tailored access modes, possibly including dedicated training and, whenever appropriate and legally possible, data exploitation support
<i>Measuring Socio-Economic Impact</i>	The specific activities of ANTHEM specify KPIs that reflect impact on local or general economy, society at large and the local community. Studies on the social cost-benefit analysis of the healthcare systems will be done and reports will be published with the aim of disclosing best practices for future initiatives.
<i>Creating Value from Data Generated by Research through the Open Data Paradigm</i>	ANTHEM will effectively create a National Big Data Value Network. A structural effort will be devoted to make data sets FAIR and to developing interoperable services. It will adhere to best practices in data archiving and retrieval, utilising standards to develop appropriate data management plans.
<i>Framework Conditions for Effective Governance and Long-Term Sustainability</i>	Ensuring sustainability of the investment will concern all stages in the project lifecycle. Accordingly, the development of robust and flexible business plans is key to define the proper governance and identify the stakeholders beyond the reference research community. ANTHEM project is adherent to national and international roadmaps for the improvement of chronic diseases treatment and monitoring. The early identification of shared international and national needs make ANTHEM aligned with planned future funding opportunities.
<i>Structuring the International Outreach of the Initiative</i>	ANTHEM has the ambition to attract international scientists and competences. All the institutes and their staff are already part of the global scientific ecosystem through international collaborations as typical in today's top science initiatives.
<i>Communication, dissemination and exploitation</i>	Communication and dissemination towards the scientific community, stakeholders and final users will be key measures to maximise impact. All Spokes will be proactive in communication, dissemination and public engagement activities. A detailed communication and dissemination strategy will be defined at the start of the project and it will detail: <ul style="list-style-type: none"> • Timeframe of activities • Kind of activities that will be undertaken • What channel will be used to reach which of the specific audiences

	<ul style="list-style-type: none"> • Precise indicators that will allow to measure dissemination and communication activities • Purpose of each dissemination and communication activities and expected result • Communication and Dissemination campaign will aim at guaranteeing the survival of the project after the funding time and maximising the project's impact. Different initiatives and actions will aim at communicating and promoting its objectives, methodology, activities, findings and results, these actions overall targets will aim at: <ul style="list-style-type: none"> • Communicating the project's aims and findings to the general public and to end-users to raise the awareness to the problems/issues tackled by the research and its findings; • Promoting the Project to the scientific, medical and industrial community; • Promoting the Project to patients and stakeholders (e.g., industries; public and private institutions, policy makers; regulatory bodies, caregivers, patient associations) and funding bodies; • Establishing a network of connection between end-users, industries, stakeholders, research and educational institutions and funding bodies, that will guarantee the prosecution of the programme through economic self-sufficiency • The main goal of the dissemination plan is to establish a permanent programme that will be able to scale up in terms of new objectives, methodology, activities, findings and results, in terms of geographical and technical contexts, number of end users, stakeholders and scientific communities involved. • The exploitation strategy will be vital for further developments and future sustainability and it is described in B.10.
<p><i>Communication strategy for the wide public</i></p>	<p>The communication of the ANTHEM objectives and of the research results will be performed to show in a correct and “not illusory” way the perspectives of the research results in future care pathways. Communication to the wide public is becoming more and more important during recent years to demonstrate that the utilisation of the tax-money has a significant relapse on social well being. The activities will be supported by press offices of ANTHEM partners. ANTHEM Network would like to attract the wide public on key interests:</p> <ul style="list-style-type: none"> • The effort in the development of new advanced solutions that are developed to improve early diagnosis, monitoring and therapy of chronic and frail populations. • The innovation of an interdisciplinary approach that involves Artificial Intelligence and digital tools to propose new patient centred solutions. • The scientific curiosity on an attractive matter like the Artificial Intelligence and innovative theranostic and monitoring tools applied to human health challenges. • The potential therapeutic and diagnostic applications of Artificial Intelligence and personalised medicine (drug discovery and testing). <p>The communication instruments will be: a) A dedicated web site the maintenance of which (in regard the content) will be one of the tasks of the Fellows. b) Web 2.0 channels (Facebook, Twitter, Instagram and YouTube) and regular media communications (TV, newspapers). c) Participation to the Regional, National and European events each year d) Participation to patient association events to explain impact, objectives and involvement of patients in the proposed challenge. For further details see B.10.</p>
<p><i>Communication and Dissemination to the stakeholders</i></p>	<p>ANTHEM will interact with the stakeholders organising seminars at the hospital involved in the project and to regional and national healthcare dedicated initiatives. Other hospitals, healthcare providers and the reference Regional Authorities will also be contacted to propose the seminars and workshops related to the project progression. The communication method will be based on power point presentations, round table discussion and videos. Patient associations already connected with ASST involved in</p>

	ANTHEM (i.e. AGO, ALICE, BRIANZA PER IL CUORE, DON GIULIO FARINA, CANCRO PRIMO AIUTO ONLUS) will be directly involved in the communication and dissemination activities.
<i>Communication and Dissemination to the medical/scientific community</i>	Project participants will regularly (at least once a year) take part in major national and international conferences (i.e AACR Annual Meeting, European Society Biomaterials (ESB), Society of Pharmacology (SIF), IEEE Engineering in Medicine and Biology; Expo Sanità). The research results will be promoted also across medical and scientific societies related to the diseases treated in the project (i.e. Society of neuroscience (SfN), European Radiological Society meeting, Società Italiana Biomateriali (SIB), IEEE Engineering in Medicine and Biology Society.). The ANTHEM concept will be promoted in scientific and medical journals (i.e. editorial, perspectives). After careful evaluation of Industrial Valorization, the project results will be published in major scientific peer-reviewed journals.
<i>IP Management and scientific publications</i>	ANTHEM aims to actively disseminate, but also protect concepts and research results where commercial exploitation is a possibility. The members of ANTHEM are actively writing patents to protect the exploitation of newly developed technology. The participation of industrial partners will inspire and catalyse IP protection. The ANTHEM participants will sign a Consortium Agreement defining and detailing the IP matter. The patents will be owned by the institution/company whose employees generated the knowledge. Joint ownership of IP will be applied when collaboration has led to the new knowledge (see section B.10 for further details). All data generated by ANTHEM will be evaluated for IPR protection, and the publication process for data dissemination will start after the clearing of IP and confidentiality issues. The partners of ANTHEM have a high-level track record in publishing in the leading general science and sector specific journals and are internationally recognized in the scientific societies, thus ensuring world-class scientific networking. We expect that the outputs of ANTHEM research (which will benefit from the added value of the network collaboration) will be at least of the same level.
<i>Open Access availability of data</i>	ANTHEM will promote open access by using Open Access (OA) journals or OA release mode, thus allowing a wider dissemination of the scientific achievements and accomplishing the ERA priority on “Open access”. ANTHEM will participate in the Open Research Data pilot, and will implement a DMP. EU policies on Open Access will be adhered to, and the DMP will include procedures on the use of public data repositories. Published papers will be, when possible, in Open Access journals (green/gold model) or publicly available health data storage (such as PhysioNet). The Scientific Board will oversee the process to ensure that all the data from the project remains in searchable open databases, even after the project is completed.
<i>Validation and standards of technologies and devices</i>	The diagnostic, monitoring and therapeutic tools developed within the ANTHEM project will be designed and experimented taking into consideration the entire Total Product Life Cycle (TPLC) to avoid time consuming or not useful experimental activities. With this aim the technological innovations and the developed medical devices and tools will be generated in compliance with the most employed standards (ISO, IEE, IEC). Even if certifications are not mandatory for all the innovative systems and solutions generated during the ANTHEM project, the developed products and technologies will be produced in adherence with the major standards, to improve the management of the entire project activities and to maximise the translational opportunities of the proposed technologies. Furthermore, quality management protocols including the process for risk management, the risk benefit analysis and the clinical evaluation of interest will be generated for the developed digital tools and devices. The innovations and the devices with higher TRL (>5) will be validated in the GMP environment. Common reference standards adopted are listed in Table C.5.

Table C.5. Reference standards relevant for ANTHEM.

Standard	Relevant domains
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ISO/IEC DIS 22989	IT; AI; AI Concepts and Terminology
ISO/IEC TR 24027	IT; AI; Bias in AI systems and AI aided decision making
ISO 12052:2017	Health informatics; Digital imaging and communication in medicine including workflow and data management
ISO/TC 212	Clinical laboratory testing and in vitro diagnostic test systems
ISO 13485:2016	Medical Device quality management systems
ISO 14971	Medical device risk management
ISO 9001:2015	Standard for business quality management systems
ISO 62304:2006	Standard for software used in medical devices
ISO 10993	Standard for biological evaluation of medical devices
ISO 15223	Standard for medical devices' symbols
ISO 11135 / 11137 / 11607	Standard for medical devices sterilisation
IEC 60601	Standard for performance and safety of medical electrical equipment

C.2 Synergy of the research program with programs financed under other Investments (NRRP, Complementary Fund, other national and/or Community resources)

Since it addresses extremely compelling challenges that are priorities for the country and the EU, ANTHEM has natural synergies with a series of programs at the national and international level. These synergies are described below and concern mainly:

- Mission 4 “Education and Research” of the NRRP (C.2.1)
- Mission 6 “Health” of the NRRP, with special reference to the National Telemedicine Platform (C.2.2)
- National Plan for NRRP Complementary Investments (C.2.3)
- Other national and international programs (C.2.4)

For each category, the relevant section illustrates specific programs that share interest with ANTHEM, providing descriptions of the investments and of the elements of synergy and ways to exploit them. Moreover, ANTHEM fully addresses the transversal priorities of NRRP as highlighted in Table C.6. Finally, it is extremely important to note that the synergies mentioned above are characterised by complementarity and thus do not generate a risk of replication nor of overlap of different programs and investments. This is explained in C.2.5.

Table C.6. ANTHEM contribution to the NRRP transversal priorities.

Empower young generations	Reach gender equality	Reduce territorial gap
ANTHEM will give the opportunity to young people to participate in an excellent project, providing them with outstanding training opportunities and fully engaging them in the Initiative (see B.7 and C.1.4). > 40 young researchers are part of the critical mass, > 80 fixed-term researchers will be recruited, > 50 PhD students will be enrolled.	ANTHEM will continuously act to contribute to the achievement of gender equality through the actions described in B.6. Moreover, 39% of the critical mass consists of women; for new recruitments, at least 40% will be women; the project will also be a chance to promote the engagement of young women in STEM disciplines.	The ANTHEM partnership ensures a balanced coverage of different geographical realities of the country. Reducing the territorial gaps is not solely based on the investments in Southern regions (42% of the costs), but mostly on developing common research programs and on positively impacting regional healthcare.

C.2.1 Synergies with programs financed under Mission 4 of the NRRP

ANTHEM is synergistic with Mission 4, Component 2 of the NRRP “From research to business”, and more precisely with a series of research and innovation, collaborative and cross-sectoral projects aimed at reinforcing the Italian R&I landscape through large investments. For thematic and/or territorial reasons ANTHEM has the potential to build synergies - with mutual benefits - with a series of National Centres, Innovation Ecosystems and Extend Partnerships that were recently selected for funding. These are discussed below, however the list may not be exhaustive and could be integrated in the implementation phase. In addition, the significant recruitment program that ANTHEM will implement at the PhD and Junior researcher levels is fully aligned with a number of investments by the MUR within Mission 4 of the NRRP to potentiate the human capital and the capacity of the Italian research system.



National Centre for HPC, Big Data and Quantum Computing⁴⁷

The Centre focuses on the one hand on the infrastructure for HPC and Big Data, and on the other hand on the development of advanced methods, numerical analyses, software and workflow. Among the several application disciplines, the Life Sciences constitute a relevant target field. The Centre is strongly committed towards Open Science and Open Data.

Synergy: Computing methods, including AI, for Health and Life Sciences are a topic of common interest for the National Centre and ANTHEM. Moreover, the Centre could share experience and best practices for Open Data in Life Sciences. INFN coordinates the Centre and five more ANTHEM partners participate in it.

National Centre for Gene Therapy and Drugs based on RNA Technology⁴⁸

The National Research Council's charter for the "Developing Gene Therapy and Medicines with RNA Technology" foundation aims to create and renew research infrastructures and laboratories, including private entities, to develop programs that support entrepreneurial initiatives with sophisticated technological abilities through start-ups and spin-off research programs that enhance specific research results.

The University of Padua is the proponent and leader of the project signed by a charter that includes public, private and business entities from all over the country, and others that are in the process of joining.

Financed by the MUR in the context of the NRRP with 320 M€, the project sees Padua as the national reference centre for the development of therapeutic solutions and treatments in the health sector with particular reference to gene therapies and the development of selective pharmaceuticals using RNA technology.

Synergy: ANTHEM could derive process and product innovations applicable to the territories. 5 ANTHEM partners participate in the National Centre.

Innovation Ecosystem: Multilayered Urban Sustainability Action (MUSA)⁴⁹

Inside the NRRP programme Ecosystem for Innovation UNIMIB coordinates the project MUSA that will scale at regional and national level, starting from Milan, a multi-layered metropolitan city that is undergoing large transformations and that challenges the future to become a European example of excellence.

The project aims at creating an Ecosystem with a synergy of 4 universities of excellence, industries, local government and civil society to become a flywheel to foster innovation, also through Joint and Fab Labs, and enhance competitiveness and business opportunities and models. The ecosystem will focus on urban regeneration and sustainability and it will have impact on the 4 elements of land, water, air and energy through in-depth involvement of the social and digital dimension, health and mobility through science, technology, human sciences and citizenships.

The ecosystem will enhance territorial competitiveness, protect and valorize the territory and citizenship, supporting the achievement of territorial objectives of transformations and thematic objectives of culture, ANTHEM will develop synergy especially with Spoke 2: Big Data-Open Data in Life Sciences, the spoke objectives: Involvement of citizenship on the territory to foster healthy lifestyles and behaviours; Holistic and innovative system for the fast and secure storage and exchange of big data in life sciences; Big data for new technologies for research in the life sciences and for prevention and well being; Personalised and continuous monitoring of the citizen's state of well-being and prevention. Methods employed by the Spoke will include: Co-production of health: the role of the citizen in the collection of big data; Sustainable services to promote citizens' health and well-being (including frail categories); System for the exchange of biological data; governance, management, regulation of access to in silico data services; Technologies for data collection in pharmacological, preclinical, diagnostic, educational fields; digital datasets for the production of artificial organs, planning, surgical training; Digital solutions for the risk stratification and prevention of NCD; Wearable technology to evaluate responses for the prevention of health risks; digital twins for complex systems; Assessment frameworks for AI and ML-based Tech.

Synergy: ANTHEM could share and benchmark patient-volunteer cohorts, and promote synergies with companies and local authorities to bring the resulting pilots into additional operational environments. UNIMIB is the MUSA coordinator, POLIMI is Spoke.

Innovation Ecosystem: Tuscany Health Ecosystem (THE)⁵⁰

The Tuscan project in the context of innovation ecosystems, promoted by NRRP funds. It is one of the 11 nationally funded innovation ecosystems under the NRRP, the only one dedicated to life sciences. It will receive a grant of

⁴⁷ https://www.mur.gov.it/sites/default/files/2022-06/22_06_28%20Scheda_centro%20nazionale%20HPC_PNRR_MUR.pdf

⁴⁸ <https://www.unipd.it/news/gene-therapy-and-rna-technology-future-science-padua>

⁴⁹ https://www.mur.gov.it/sites/default/files/2022-06/22_06_28%20Scheda_ecosistema_MUSA_PNRR_MUR.pdf

⁵⁰ <https://www.toscanalifesciences.org/it/2022/07/nasce-the-tuscany-health-ecosystem/>



110 M€, assigned by the Ministry of University and Research, in reference to Mission 4 (Education and Research) of the NRRP, in particular to component 2 "From research to business".

THE was born from a project proposal presented by the University of Florence, as leader, aligned with one of the strategies of the Tuscany Region relating to life sciences. The ecosystems of innovation, according to the NRRP, in fact arise in areas of technological specialisation consistent with the industrial and research vocations of the reference area, promoting and strengthening the collaboration between the research system, the production system and local institutions.

The ecosystem structure is organised according to the hub & spoke model. The hub function (coordination and management of activities) will be carried out by a consortium company with 12 members: the Universities of Florence, Pisa and Siena, Scuola Superiore Sant'Anna and Scuola Normale Superiore of Pisa, Imt Scuola Alti Studi Lucca, the University for Foreigners of Siena, the Italian Institute of Technology, the National Research Council, Toscana Life Sciences, the National Institute of Nuclear Physics, Confindustria Toscana.

A total of 22 subjects will participate in the THE ecosystem: 7 universities, 6 public bodies and public research bodies, 9 companies or private entities. THE activities will be divided into 10 sectors or research nodes, all linked to advanced topics of life sciences and entrusted to the responsibility of one of the members.

Synergy: due to THE main theme, ANTHEM could benefit from a benchmark for innovative processes in health in a different regional framework, and vice versa for THE.

Innovation Ecosystem: Technologies for climate change adaptation and quality of life improvement (Tech4you)⁵¹

The priority line of the Tech4You ecosystem falls within the "Climate, energy, mobility sustainable" of the National Research Plan (PNR). The main objective is to stimulate the innovation potential of two of the "less developed regions" of Italy, Basilicata and Calabria, currently classified as "Regions in transition", creating a innovation ecosystem in which scientific research carried out by universities and research centres on the territory it meets the needs of citizens and public bodies to be transferred into products marketable developed and exploited by local companies with the support of expert actors of the industrial innovation sector.

To achieve this, Tech4You focuses on the scientific and technological areas which, better than others, represent the intersection between the needs of the territories and skills available in local research centres: adaptation / mitigation of climate change and the improvement of the quality of life.

Synergy: A territorial synergy is linked to the Calabria region and its challenges in terms of QoL, in the case of ANTHEM from the Health perspective. UNICAL coordinates Tech4you.

Innovation Ecosystem: SiciliAn MicronanOTech Research And Innovation Center (SAMOTHRACE)⁵²

The priority line of the Samothrace ecosystem falls within the "Digital, Industry and Space" area of the National Research Plan (PNR). The main objective is to leverage the consolidated vocation of the Sicilian territory in the field of microelectronics and micro and nano technologies to bring it to a higher and more widespread level that can have a significant and tangible impact on the industrial scenario of the island and on the entire society. The set of activities is developed, in fact, around the common thread of micro and nano technologies, microelectronics, materials, microsystems and devices, accumulating methodologies and applications and directing them towards six main areas: energy, health, intelligent mobility, environment, cultural heritage and smart agriculture.

Synergy: The common focus on the Sicilia region is accompanied by the topic of technologies for health. UNICT coordinates SAMOTHRACE and UNIME is a partner of the Ecosystem.

Innovation Ecosystem: Robotics and AI for Socio-economic Empowerment (RAISE)⁵³

The priority line of the RAISE ecosystem falls within the "Digital, Industry, Aerospace" of the National Research Plan (PNR). The main objective is to support the development of a domain-based innovation ecosystem science and technology of artificial intelligence and robotics, focusing on needs of the specific Ligurian context and leveraging existing resources and capabilities to generate new opportunities through effective and efficient knowledge. RAISE wants to improve people's living conditions, defining how explicit objectives are the safety and protection of the territory, the improvement of the levels of inclusiveness of urban environments, the increase in the capacity of remote assistance and remote assistance and care of people, the sustainable development of port environments (engine of the local economy) with a strong attention to workplace safety issues.

⁵¹ https://www.mur.gov.it/sites/default/files/2022-06/22_06_28%20Scheda_ecosistema_Calabria_PNRR_MUR.pdf

⁵² https://www.mur.gov.it/sites/default/files/2022-06/22_06_28%20Scheda_ecosistema_Samothrace_PNRR_MUR.pdf

⁵³ https://www.mur.gov.it/sites/default/files/2022-06/22_06_28%20Scheda_ecosistema_RAISE_PNRR_MUR.pdf



Synergy: research and innovation in AI is a theme of common interest with a person-centred perspective. INFN is a partner of RAISE.

Note that the two Extended Partnerships described below have been selected after the Expression of Interest and will now undergo the Full Proposal and the Negotiation Phases. Information is thus subject to change.

Extended Partnership: Innovative diagnostics and therapies in precision medicine (HEAL)

The partnership is led by University of Palermo and focuses on methods and technologies for the identification of complex diseases. The ultimate goal includes the definition of screening, prevention diagnosis, and precision medicine personalised to the target subject (extract from Annex A to the Call⁵⁴).

Synergy: Common target pathologies and personalised medicine approach. ANTHEM development in operational environments can provide a benchmark to help define and steer the lower TRL HEAL activities.

Extended Partnership: Ageing Well in an ageing society (Age-It)⁵⁵

The project proposal (led by University of Firenze) is dedicated to the consequences and challenges of ageing, the partnership is made up of an aggregation of other Italian universities and companies that will address research on ageing in an integrated perspective, which includes the socio-economic and political-cultural challenges deriving from demographic dynamics and the understanding of the process of ageing and chronic and degenerative diseases. University of Florence (proposing subject) Public notice for the presentation of intervention proposals for the creation of "Partnerships extended to universities, research centres, companies for the financing of research projects basic "- as part of the National Recovery and Resilience Plan, Mission 4" Education and research "- Component 2" From research to business "- Investment 1.3, funded by the European Union - NextGenerationEU.

Synergy: ANTHEM provides a complementary perspective on the elderly, with a focus on empowering the healthcare system to better reach this population range. UNIMIB participates in the Partnership.

C.2.2 Synergies with programs financed under Mission 6 of the NRRP

ANTHEM will also be synergic with initiatives funded under Mission 6, Component 1 of the NRRP, *Private/public partnership proposals for the awarding of the concession for the design, construction and management of enabling services of the national telemedicine platform* and with initiatives funded under Mission 6 Component 2 of the NRRP *Strengthening the technological infrastructure and tools for data collection, processing, data analysis and simulation (Electronic health record)*.

National Telemedicine Platform Enabling Services⁵⁶

The ANTHEM project will implement various telemonitoring activities with consumer and prototype sensors for the purposes of early detection, prevention, treatment, and rehabilitation. The telemonitoring activities have been designed and will be implemented so that there can be, at the technological level, high/full interoperability with existing telemedicine systems at the regional level and telemedicine systems under development at the national level. In fact, there is a national initiative within the NRRP for the design, implementation and management of the National Telemedicine Platform. This initiative includes three groups of services, literally: 1) core services: which includes the essential components for service delivery to patients and health personnel; 2) local complementary service: auxiliary application component that complements the service model of the context in which it is integrated; and 3) innovative experimental service: application component that aims to enrich the local minimal and complementary services with innovative features enabled by new technological paradigms. According to the document defining the methodological aspects of the future national telemedicine platform,⁵⁷ specific local contexts (such as Regions) will be in charge of local complementary services to be integrated with the core services delivered by the national platform by adopting the standard interoperability models defined at the national level. In addition, local contexts will be also in charge of the development and testing of innovative services with the aim, in case of satisfactory results, of integrating them on the national platform. The national plan for telemedicine includes two flagship regions, Lombardia and Puglia, where a minimal set of enabling services will be experimented.

⁵⁴<https://www.mur.gov.it/atti-e-normativa/avviso-n-341-del-15-03-2022>

⁵⁵ <https://www.unifi.it/art-6082-pnrr-partenariato-guidato-dall-unifi-selezionato-dal-mur.html>

⁵⁶<https://www.agenas.gov.it/bandi-di-gara-e-contratti/avvisi-bandi-e-inviti/gare-in-corso/2062-agenas-pubblica-1%E2%80%99avviso-pubblico-per-la-piattaforma-nazionale-di-telemedicina>

⁵⁷https://www.agenas.gov.it/images/agenas/In%20primo%20piano/telemedicina/Allegato_Indicazioni_Metodologiche_di_Perimetrazione_04.05.2022.pdf



ANTHEM project activities will be carried out in synergy with the national telemedicine initiatives mentioned above especially thanks to synergies with local institutions and hospitals. A partnership has been established with the IT&Digital Health Unit of the Lombardia Region that will allow for the entire duration of the project to test prototypes and services that will be deemed to be at a high technology readiness level. For what concerns the interoperability, the project will design health data exchanging REST API interfaces with regional and then national platforms by relying on HL7 FHIR (Fast Healthcare Interoperability Resources), observing all data security principles, and finally by taking into account interoperability with the electronic health record (EHDF) that is being implemented nationwide⁵⁸.

Electronic health record⁵⁹

Sub-investment 1.3.1 of Mission 6, Component 2 of the NRRP aimed at strengthening the technological infrastructure and tools for data collection, processing, data analysis and simulation. The purpose is to extend and standardise the contents of digital health documents, functions and user experience, nutrition and consultation by health professionals at a national level. All ANTHEM products that may be relevant for EHRs will be developed ensuring interoperability with EHR.

C.2.3 Synergies of the research program with programs financed under the Complementary Fund

The MUR is expected to fund four projects under the present Call for Proposal. The ANTHEM team is convinced of the importance of the exchange of information and knowledge and of the coordination among competing projects to make them as impactful as possible. This view is aligned with European practices, e.g. the implementation of “Project Portfolios” by the European Innovation Council in the framework of the Pathfinder programme, or the requirement for projects selected under some calls from the Horizon Europe Work Programme 2021-2022, including notably the Cluster Health, to conduct common networking and dissemination activities. To make the best out of the NRRP and the Complementary Plan, it is most likely that similar good practices will be welcome, if not needed.

Of course, at the submission stage it is impossible to foresee specific synergies since there is no visibility on the themes and approaches of competing projects. Nevertheless, ANTHEM is confident that its original approach, transversal to, and integrating the key themes individuated by the MUR, together with the joint consideration of pathology and territorial aspects in the definition of the Reference Communities, opens up synergy opportunities with any other excellent Initiative that will be funded. For these reasons, ANTHEM is willing to commit to maintain direct communication channels with other funded Initiatives and promote joint networking activities whose precise scope will be defined once the evaluation and selection phases are completed. This will make ANTHEM itself and other selected Initiatives more impactful.

C.2.4 Synergies of the research program with programs financed under other national or EU resources

ANTHEM will also establish synergies with the following initiatives promoted by INFN and Lombardia and Sicilia Regions that have already committed to undertake synergic actions with ANTHEM on the common researches and experimentations of interest. These are the most relevant examples, an exhaustive list of possible synergies with other funding programs going beyond the scope of this document.

FRIDA and BCT

The research activities carried out, in self-financing, by INFN, are divided by thematic areas into National Scientific Commissions. The activities inherent to the application of nuclear physics to the fields of medicine, cultural heritage and development of technologies is part of the national scientific commission 5. Annually, the CSN5 announces internal calls to finance the projects deemed most deserving.

In this context, in 2021, the CSN5 approved and financed the “Flash Radiotherapy with High Dose-rate particle beams (FRIDA)”, dedicated to study and development of radiotherapy in a very high dose rate regimen, using different techniques of acceleration and different particles.

The project involves different INFN offices and laboratories, in particular, the sections of: Catania, Milan, Pisa, Rome 1 and Turin; and the laboratories: Southern National Laboratories (LNS) e Trento Institute for Fundamental Physics and Applications (TIFPA). To INFN units are associated several Italian and foreign universities: Rome "La Sapienza", University of Surrey, University of Pisa, Queen's University Belfast; Italian and foreign research centres: Institut Curie-Centre de Recherche, Helmholtz Zentrum Dresden Rossendorf - Institute of Radiation Oncology-

⁵⁸<https://www.salute.gov.it/portale/pnrrsalute/dettaglioContenutiPNRRSalute.jsp?lingua=italiano&id=5879&area=PNRR-Salute&menu=investimenti>

⁵⁹*Ibidem*



OncoRay, GSI, National Research Council - Institute of Neuroscience, National Research Council - Institute of Bioimaging and Molecular Physiology; And health facilities: Pisan University Hospital.

One of the main objectives of the project is to explore solutions, testing different types of particle beam detectors and monitoring systems, and define a dosimetric protocol for Flash regime beams of both electrons and protons. Solutions that will go, synergistically, to facilitate and positively contribute to the execution of tests in programs within the ANTHEM project and in particular in the facility that will be built at CAPIR centre of UNICT.

Furthermore, among the objectives of the project, there is the biophysical and radiobiological study of the Flash effect on *in vivo* and *ex vivo* models. Also in this case the interaction between the two initiatives is synergistic as the Catania facility will make use of a multidisciplinary and multi-entity collaboration, which includes CANNIZZARO with the nuclear medicine and radiochemistry unit, the institute of bioimaging and molecular physiology of the National Research Council and INFN, being able to carry out studies preclinical on different tumour models obtaining data both of a biological nature with molecular biology and histology, and through imaging techniques, especially imaging PET with different radiotracers and extrapolating a large number of parameters, features, from images (radiomics). Therefore, the Catania site will be able to use the results *in vitro* preliminaries obtained thanks to the FRIDA project by integrating them, synergistically, with a high number of strictly preclinical data available, thanks also to the close collaboration between universities (UNICT), hospital CANNIZZARO and research institutions. This will be even done in the framework of BCT regional program carried out by INFN, UNICT and CANNIZZARO for studying ultra flash effects with proton beams thanks to a 50 TW laser system under realisation at INFN-LNS. Thanks to ANTHEM the system will be upgraded with electron beam acceleration compared with flash therapy for a better understanding of this effect. This integrated facility will be unique in Europe realising a preclinical facility able to guarantee the different particles and radiations covering the full set of dose rates studying in a unique way novel radiation treatment scenario.

Smart&Touch-id⁶⁰

Lombardia Region Telemedicine Project the hub for the creation of innovative-smart rehabilitation systems, connected to needs and territory for strategic research, development and innovation projects aimed at strengthening the Lombard ecosystems of research and of innovation as hubs of international significance. SMART & Touch-ID's mission is to strengthen the dimension of rehabilitation care within the paradigm of "Technology-Enabled Smart Healthcare" in the territory and at home, providing new models and individualised solutions. This mission materialises in the goal of creating a rehabilitation HUB, a technological incubator and aggregator of skills and professionalism that supports the entire process of innovation and development of new technologies: the SMART & Touch-ID. The "SMART & Touch-ID" project promotes, in fact, the activities of a virtuous territorial HUB at the service of the patient-citizen for the creation and validation of treatment paths for chronic NCDs that use technologies enabling (SMART) to respond to the needs of well-being (Touch) and personalization of care (ID).

High-Technology Accelerator Synergies

The specific system proposed, 5 MeV intense proton beam on high power beryllium target, has unique performances. Being able to satisfy BNCT required dose well below the hour treatment. This approach is made possible by two key technologies, high power RFQ, with unique average beam current, and the beryllium target with negligible activation problems. The cutting-edge technology for the realisation of high intensity RFQ (Radio Frequency Quadrupole) and other high intensity linear accelerators structures has been developed and demonstrated by INFN with the participation to many international projects, like IFMIF-EVEDA (realisation of a 125 mA 5 MeV deuteron RFQ for fusion reactor material irradiation, operating at Rokkasho in Japan) and to the European Spallation Source (ESS). IFMIF RFQ, that reached the pulsed beam performances in 2019, is by far the most challenging RFQ in the world, and ESS linac will be the most powerful linac.

The accelerator proposed for BNCT is based on a high power RFQ structure invented and developed by INFN in the first years of this century within the MURST program TRASCO, aimed to the development of key components for accelerator driven nuclear waste transmutation; in 2012, we tested at nominal power in CW the first 2,4 m segment of TRASCO RFQ thanks to CEA infrastructures in Saclay. Lately within the "Progetto premiale" MUNES aspects specific to BNCT application were developed, like the beryllium target and a modular solid-state RF system, better suited for hospital installation.

In particular for the target a Be-V-Cu prototype was developed and tested at nominal power density at INFN electrostatic accelerator CN. Thermal and epithermal neutron moderators were developed and characterised at the same facility. In view of the proposed BNCT facility at Caserta it will be necessary to integrate this accelerator,

⁶⁰ <https://www.openinnovation.regione.lombardia.it/it/b/38399/smart-touch-id-l-hub-per-la-creazione-di-sistemi-riabilitativi-innovat>

approximately 20 m long, in the available bunker, with all the necessary interfaces with the medical part, the electric and water-cooling systems.

The installation of such a system within the clinical environment in Caserta will make such a facility the only one in the world with such performance figures, the only one in Italy with an electrodynamic linear accelerator and the only one invented by a research institution and not bought from a company.

BNCT Radiobiologic and Metabolomic Synergies

A large part of the scientific research in BNCT is concentrated on the molecule capable of acting as a carrier of boron, through studies aimed at highlighting its toxicity profile and, above all, its ability to be internalised at the cellular and/or tissue level. This latter goal is the biggest challenge of BNCT research. In this context, the activities of the researchers of the University of Campania "Luigi Vanvitelli" who, as part of the activities of the NEPTUNE and PBCT Proton Boron Capture Therapy projects, have already developed protocols in cellular metabolomics, to detect and quantify boron-based vectors at the cellular level, using analytical techniques in UHPLC-HR-MS/MS and HPLC-DAD. Cellular metabolomics is a valid method, offering the advantage of exploring the response of the biological system to an external chemical insult and its possible modification from a structural point of view. Techniques such as ultra-performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-ESI-QqTOF-MS), through the accurate measurement of mass and isotope patterns, provide a reliable contribution following a quenching protocol/extraction that takes into account the chemical-physical properties of the carriers analysed.

The researchers of UNICAMP are an active part of the recently presented PRIN project Armonia which aims to optimise a new approach to improve methods for calculating the dose of BNCT in patients. The project proposes a holistic vision of BNCT treatment planning for an improvement of the effectiveness of BNCT in the treatment of GBM, also through the study of more effective boron-based molecules and insights into the effect of subcellular distribution of boron.

Concerning EU funds, since a list of projects synergistic with ANTHEM could hardly be complete, and since many relevant projects will be selected in the future and during the ANTHEM implementation, we focus here on a series of particularly relevant EU programs (Table C.7). The members of the partnership have widespread international networks and ongoing collaborations (see A.3) that will be exploited during the project to build synergies and contribute to future common programs.

Table C.7. European programs particularly relevant for potential synergies with ANTHEM.

Program	Details
Horizon Europe: Cluster 1	The entire "Health" Cluster of Horizon Europe has the potential for synergies with ANTHEM, a specific example being the calls under the Destination "Unlocking the full potential of new tools, technologies and digital solutions for a healthy society" of the Work Programme 2021-2022.
Horizon Europe: Cluster 2	Within the "Digital, Industry, Aerospace" Cluster it will be possible to build synergies with projects funded under the Destination "World leading data and computing technologies" of the Work Programme 2021-2022.
Horizon Europe: MSCA	The Marie Skłodowska-Curie Actions (MSCA) could offer the opportunity to build international networks with excellence centres active in the ANTHEM fields at the European level to: i) strengthen the international training programmes through Doctoral Networks; ii) share knowledge and competencies through exchange programmes for students, technical and research personnel through Staff Exchanges.
Horizon Europe: Mission Cancer	The ANTHEM advancements in diagnostics and therapies for cancer are fully aligned with the objective of the Mission. It could therefore build bridges with EU-funded actions, especially with Coordination and Support Actions.
EU4Health	Synergies could be built with two action lines of the EU4Health program, namely those devoted to "improve medicinal products, medical devices and crisis-relevant products" and to "strengthen health systems, their resilience and resource efficiency", thus moving from the regional and national dimension to a European perspective.
Pilot Projects and Preparatory Actions	Medium-term synergies with actions devoted to the preparation of policies in the fields of health, healthcare system, AI, personal medical data will be sought.



C.2.5 No-overlaps and complementarity

In addition to the formal requirement to avoid double-funding that will be enforced by individual participants and by the Hub (see B.3), ANTHEM prevents *by-design* superpositions and duplications of efforts with other programs funded by the NRRP or the other investments described in C.2.1-C.2.4. Indeed, ANTHEM proposes a complementary approach with respect to the other projects, as detailed below case-by-case:

- National Centres: ANTHEM is complementary to the large investment in infrastructures for RNA technologies for gene therapy and medicine of the National Centre in that RNA-technologies will not be the topic of the ANTHEM Pilots. From the technological and methodological approaches, the two projects tackle different needs. Concerning the HPC Centre, again ANTHEM does not target the HPC infrastructure and the applications of novel computing methods to Health and Life Science are at different development stages for the two projects, with ANTHEM Pilots targeting the operational environment.
- Innovation Ecosystems: the vision of Innovation Ecosystems is to create the conditions to increase the innovation capacity of a given territory, not (or not only) to develop specific technologies. For this reason, the ANTHEM approach will not duplicate the Ecosystem activities, even when they have a focus on health, wellbeing or QoL.
- Extended Partnerships: the activities of the Extended Partnerships concern mainly fundamental research, thus at low TRL. Together with ANTHEM and other programs they cover the whole innovation chain, but without superposition of research content.
- National Telemedicine Platform: ANTHEM is fully complementary, in that it does not address the challenges of developing the platform. It targets instead the endpoints of the platform itself, on the one hand the patients and the monitoring devices, and on the other hand the AI-enabled theranostics.
- Electronic Health Record: with its presence on different territorial frameworks, ANTHEM can provide inputs for the standardisation of EHR on the basis of different needs. However, EHR themselves are not the subject of ANTHEM activities.
- Competing projects on this Call for Proposal: the ANTHEM partnership provides an original contribution. However, should individual, limited aspects of the proposal be considered as overlapping with other selected projects, the Negotiation Phase will allow the applicants and the MUR to avoid effort duplication.
- Other national and international investments: For activities conducted by ANTHEM participants, superpositions have been avoided in the design of the research program. Concerning external future projects, the ANTHEM dissemination activities will make the project well known at the national and European level, thus reducing the risk of potential replication by third parties.

I declare that I have read the information on the processing of personal data provided in the "Privacy" section <http://www.mur.gov.it/it/privacy> of the Ministry of University and Research issued according to article 13 of the Regulation 679/2016 of the European Parliament.

Date: date of the Digital Signature

The Delegate of the Legal Representative of the proposing Entity
(Digital signature)



D. Endorsement Letters

In the following pages are enclosed the received endorsement letters in the following order:

Private Companies:

- *Emotiva s.r.l., Huawei Technologies Italia S.r.l.*
- *Italfarmaco S.p.A*
- *Rottapharm Biotech S.r.l.*
- *Siemens S.p.A.*
- *STMicroelectronics S.r.l.*
- *Tensive S.r.l.*
- *Zeiss S.p.A*

Italian Regions

- *Calabria Region*
- *Campania Region*
- *Lombardia Region,*
- *Puglia Region*

Associations, organizations and Communities:

- *Aimac - Associazione Italiana Malati di Cancro*
- *Aircam Onlus*
- *Comunità Montana della Valle Seriana*
- *Un Respiro di Speranza Lombardia*



Emotiva S.r.l.



Prof Guido Cavaletti, MD
Professor of Human Anatomy
Vice-Rector (Research)
University of Milano-Bicocca
Head, Experimental Neurology Unit
School of Medicine and Surgery
v. Cadore 48, I-20900, Monza (MB) Italy

Milan, October 11th 2022

RE: ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)

Dear Prof Cavaletti,

I have read with great interest the ANTHEM project proposal that contains several aspects of significant industrial interest in all of the spokes presented.

I would be happy to evaluate the progress and the final outcome of the project in order to decide on a possible match with Emotiva R&D strategy and on the potential acquisition of individual results or on additional investments that we might be able to provide to further advance them.

Sincerely,

Emotiva Srl

Andrea Lori
CEO

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Huwei Technologies Italia S.r.l.



Milan 17/10/2022

Prof Guido Cavaletti, MD
 Professor of Human Anatomy
 Vice-Rector (Research)
 University of Milano-Bicocca
 Head, Experimental Neurology Unit
 School of Medicine and Surgery
 v. Cadore 48, I-20900, Monza (MB) Italy

RE: ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)

Dear Prof Cavaletti

I have read with great interest the ANTHEM project proposal that contains several aspects of significant industrial interest in all of the spokes presented. I would be happy to evaluate the progress and the final outcome of the project in order to decide on a possible match with Huawei Technologies Italia R&D strategy and on the potential acquisition of individual results or on additional investments that we might be able to provide to further advance them.

Sincerely

Renato Lombardi
 Head of Italy Research Center
 VP Microwave Product Line



Renato Lombardi
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 Tel.: +39.02.39994.000
 Fax: +39.02.39994.500

Sedi Operative, MILANO

Italy Research Center
 Centro Dir. Milano2
 Pal. Verrocchio 3zo piano
 20090 SEGRATE (MI)
 Tel.: +39.02.39994882
 Fax: +39.02.39994.500

Design Research Center
 Via Santa Margherita 14/via Silvio
 Pellico 7, 20121 MILANO (MI)

CBG Office
 Viale della Liberazione 16/18
 20124 MILANO (MI)

Sede Operativa, ROMA

Via Laurentina 449
 00142 ROMA (RM)
 Tel.: +39.06.64244.000
 Fax: +39.06.64244.500

Altre Sedi Operative

TORINO	Tel:	39. 0239994900
PALERMO	Tel:	39. 0916242090
NAPOLI	Tel:	39. 347 6443804



Italfarmaco S.p.A.



Prof Guido Cavaletti, MD
 Professor of Human Anatomy
 Vice-Rector (Research)
 University of Milano-Bicocca
 Head, Experimental Neurology Unit
 School of Medicine and Surgery
 v. Cadore 48, I-20900, Monza (MB) Italy

Cinisello Balsamo, October 10th, 2022

RE: ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)

Dear Prof Cavaletti

I have read with great interest the ANTHEM project proposal that contains several aspects of significant industrial interest in all of the spokes presented. I would be happy to evaluate the progress and the final outcome of the project in order to decide on a possible match with Italfarmaco's R&D strategy and on the potential acquisition of individual results or on additional investments that we might be able to provide to further advance them.

Sincerely

Christian Steinkühler, PhD
 Chief Scientific Officer
 Italfarmaco SpA
 Via dei Laboratori 54
 20092 Cinisello Balsamo (Milano)
 Italy

Italfarmaco S.p.A.

Sede legale e stabilimento: 20126 Milano – Viale Fulvio Testi, 330 – Tel. 02. 64.43.1 – Fax 02. 64.43.46
 Casella postale 11130 – 20110 Milano Isola

Direzione, Uffici e Centro Ricerche: 20092 Cinisello Balsamo (MI) – Via dei Laboratori, 54 – Tel. 02.64.43.1-Fax 02. 64.24.790
 Capitale Sociale € 13.000.000. int.vers. – R.E.A 273567 – Registro Imprese Milano 38391 – C.F. e P.IVA 00737420158



Rottapharm Biotech S.r.l.



LUCIO ROVATI
Chief Executive Officer
Chief Scientific Officer

Monza, October 13, 2022

To the attention of
Prof. Guido Cavaletti
University of Milano Bicocca

Re: Anthem Project

Dear Prof. Cavaletti,

Thank you for the information regarding the project named Anthem.

I confirm that Rottapharm Biotech is willing to evaluate the projects results for a possible commercial use.

Best regards.

A handwritten signature in black ink, appearing to read "L. Rovati".

Dr. Lucio Rovati
Chief Executive Officer
Chief Scientific Officer
Rottapharm Biotech

Rottapharm Biotech S.r.l. a socio unico

Via Valosa di Sopra, 9 - 20900 Monza (Italy)
Tel. +39 039 9066.104 - Fax +39 039 9066.161
info@rottapharmbiotech.com
www.rottapharmbiotech.com

Cap. Soc. Euro 95.922,50
Cod.fisc. / P.IVA / Registro Impr. Monza e Brianza 12961590150
REA: MB - 1600515



Siemens S.p.A.

SIEMENS

Siemens S p A , Via Vipiteno, 4 - 20128 Milano

Prof Guido Cavaletti, MD
 Professor of Human Anatomy
 Vice-Rector (Research)
 University of Milano-Bicocca
 Head, Experimental Neurology Unit
 School of Medicine and Surgery
 Via Cadore 48,
 20900, Monza (MB) Italy

Milan, October, 14th 2022

RE ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)

Dear Prof Cavaletti,

I would like to thank you for having shared with me the interesting documents related to the ANTHEM project I have read with interest and detail the proposal concerning the ANTHEM project and here below my comments First of all, I think the content is definitively in line with some concepts in terms of digitalization, connected with sustainability of which my interest is devoted The future development of sensors to collect data and therefore allowing their analysis with Artificial intelligent algorithms, from my prospective, will deserve the attention of industrial environment and companies' interest There are several aspects which can be considered of significant industrial interest in all of the spokes presented The future domain of these technologies could be definitively considered in the portfolio of industrial companies that would like to consider the result of your project Therefore, I would ask you to be informed about the progress of ANTHEM project in order to evaluate, after the final outcome of the project, the possible industrial interest for investments in those fields

Sincerely

Siemens S.p.A.

Giuliano Busetto
 Digital Industries Italia CEO &
 Presidente Siemens Industry Software Srl

Siemens S p A
 Digital Industries

Via Vipiteno, 4
 20128 Milano - Italia
 C P 17154 - 20170 Milano

Tel +39 02 243 1
 PEC siemens_spa@pec.siemens.it
 Email infodesk.it@siemens.com
 Sito www.siemens.it

Società a Unico Socio soggetta alla Direzione e Coordinamento di Siemens AG

Capitale Sociale € 65 000 000 i v , N Iscrizione Registro Imprese di Milano Monza Brianza Lodi, Codice Fiscale e Partita IVA IT-00751160151, REA MI 525193

Pag 1 di 1



STMicroelectronics S.r.l.



Prof Guido Cavaletti, MD
 Professor of Human Anatomy
 Vice-Rector (Research)
 University of Milano-Bicocca
 Head, Experimental Neurology Unit
 School of Medicine and Surgery
 Via Cadore 48
 20900 Monza (MB)

Agrate Brianza, 17 ottobre 2022

Subject: letter of support for the ANTHEM (AdvaNced Technologies for Human-centrEd Medicine) project proposal within the call National Plan for NRRP Complementary Investments Law n. 101/2021

STMicroelectronics S.r.l. hereby declares its interest to the Tiny Artificial Intelligence technical activities that University of Milano-Bicocca will perform in the proposal ANTHEM submitted within the call National Plan for NRRP Complementary Investments Law n. 101/2021, should the proposal be funded.

STMicroelectronics' interests on Tiny Artificial Intelligence interests are aligned with the research goals of the proposed ANTHEM project, with reference on Artificial Intelligence research initiative based on STMicroelectronics' sensors, STM32 and others micro-controllers and digital signal processors powered by STM32CUBE.AI (and its derivatives such as ISPU.AI) deep learning deployment toolchain. STMicroelectronics is working on Artificial Intelligent Tiny Cyber Physical Systems based on STM32 NUCLEO CUBE.AI technology, associated sensors, and resource restricted artificial neural networks.

In view of the foregoing, STMicroelectronics S.r.l. is available to consider the possibility of a collaboration with University of Milano-Bicocca within the framework of the ANTHEM project, subject and according to terms to be mutually discussed and defined in writing between STMicroelectronics and the University. This collaboration may include:

STMicroelectronics S.r.l.	STMicroelectronics S.r.l.	Sede legale, direzione generale e amministrativa:
Capitale Sociale € 580.000.000,00 int. vers.	Socio Unico, Direzione e Coordinamento:	20864 Agrate Brianza – Italia
Codice Fiscale 09291380153	STMicroelectronics N.V.	Via C. Olivetti, 2
Partita IVA 00951900968	Amsterdam – Olanda	Telefono: +39 039 603.1 linea passante
VAT Code: IT 00951900968		Telefax: +39 039 6035700
Registro delle Imprese di Monza e Brianza		www.st.com
n. 09291380153		



Tensive S.r.l.



Tensive S.r.l.
Via Timavo 34, 20124 Milano
E-mail: info@tensivemed.com

Milan, 17 October 2022

To: Prof. Guido Cavaletti
Università degli Studi di Milano Bicocca
(Milano)

Subject: **Endorsement letter for the proposal ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)**

To whom it may concern:

I am writing this letter to endorse the proposal ANTHEM submitted to National Plan for NRRP Complementary Investments - Law Decree May 6, 2021, n. 59, converted and modified as to Law n. 101/2021 Research initiatives for technologies and innovative trajectories in the health and care sectors.

Tensive is a biomedical Small and Medium-sized Enterprise (SME) developing new solutions for reconstructive surgery to improve the quality of life for patients. Tensive is committed to bringing into the international market innovative absorbable sterile implants intended to support the ingrowth of the patient's soft tissue to restore the natural appearance of the body.

Tensive is very active in R&D, in particular to find solutions for breast cancer patients. The proposal ANTHEM ("AdvaNced Technologies for Human-centrEd Medicine"), aiming to cover existing gaps in healthcare in scenario like cancers with limited availability of treatments or in presence of clinically relevant diagnostic challenges matches Tensive long-term strategy.

Tensive is interested in the scientific and technological outcome of the proposal and endorses its application.

Sincerely,

Federico Martello (Chief Executive Officer)
Tensive S.r.l.



Tensive S.r.l.
 Via Timavo 34 - 20124 Milano
 Tel 02.5666.0265
 P.IVA 08045870964
 PEC tensivemed@legalmail.it

Tensive Srl - Address: Via Timavo 34 C/O Studio SCG Soc.Traprof.SAS - 20124 Milano (MI) – Italy - Shared Capital Euro 21.177,47 – Vat Number: 08045870964 - Tel. +39 02 56660153 - info@tensivemed.com - www.tensivemed.com - Certified email: tensivemed@legalmail.it - Sdl Code: USAL8PV



Zeiss S.p.A.



Carl Zeiss S.p.A. con socio unico – Via Varesina, 162 – 20156 Milano

Rif.: GLMLOI001
 Tel.: 02 93773.842
 Fax: 02 93773539
 E-mail: giulio.lamedica@zeiss.com
 Data 14/10/2022

To: Prof. Guido Cavaletti
 Università degli Studi di Milano Bicocca
 (Milano)

Subject: Endorsement letter for the proposal ANTHEM (AdvaNced Technologies for Human-centrEd Medicine)

I write to whom it may concern to declare the endorsement of Zeiss to the proposal ANTHEM submitted to National Plan for NRRP Complementary Investments - Law Decree May 6, 2021, n. 59, converted and modified as to Law n. 101/2021 Research initiatives for technologies and innovative trajectories in the health and care sectors.

ZEISS is an internationally leading technology enterprise operating in the fields of optics and optoelectronics. With a portfolio aligned with future growth areas like digitalization, healthcare and Smart Production and a strong brand, ZEISS is shaping the future of technology and constantly advancing the world of optics and related fields with its solutions.

Zeiss is very active in the R&D of Microscopy and Medical solutions for life science Research and Healthcare applications and the proposal ANTHEM ("AdvaNced Technologies for Human-centrEd Medicine"), aiming to cover existing gaps in healthcare of frail and chronic patients through the development of innovative sensors, digital-based advanced diagnostic, systems integrated with AI, matches very well strategy and future plans.

Zeiss is therefore extremely interested in the scientific and technological outcome of the proposal and fully endorse its application.

Giulio Lamedica
 Head of Research Microscopy Solutions
 Carl Zeiss S.p.A.

Carl Zeiss S.p.A. con socio unico
 Sede Legale e Operativa
 Via Varesina, 162
 20156 Milano MI
 Telefono: 02 93773.1
 Telefax: 02 93773.539
 E-mail: info.it@zeiss.com
 Internet: www.zeiss.it
 Soggetta all'attività di direzione e coordinamento di Carl Zeiss Beteiligungs GmbH

Filiale di Novara
 Centro accreditato
 ACCREDIA LAT n° 177
 Via Fleming, 1
 Filiale di Reggio Emilia
 Via Di Vittorio, 14
 Filiale di Rovereto
 Via F. Zeni, 8

Capitale € 4.000.000,00 i.v.
 Registro delle Imprese di Milano n.00721920155
 Codice fiscale n. 00721920155
 Partita I.V.A. n. IT 00721920155
 C.C.I.A.A. Milano: Numero REA 373641
 Certificazione UNI EN ISO 9001:2015
 Iscr.Reg.AEE n° IT0802000000627

Deutsche Bank S.p.A. Sede di Milano
 IBAN: IT91 0031 0401 6000 0000 0033 869
 SWIFT (BIC) CODE: DEUT3333
 Unicredit Banca S.p.A. – Fil. Monza
 IBAN: IT 71 T 02008 05364 000102078313
 BIC: UNCRITMMOLO
Codice destinatario fatturazione elettronica:
UCN410G



Regione Calabria



Azienda per il Governo della Sanità della Regione Calabria
Il Commissario Straordinario

Catanzaro lì, 10 October 2022

to Prof. Guido Cavaletti
University of Milano-Bicocca
ANTHEM Project proponent

Dear Prof. Cavaletti,

I had the opportunity to assess the "ANTHEM" project and I believe the successful completion of the planned activities might really benefit our community, leading to a reduction of disparities and allowing a more efficient and modern approach to care the health of fragile people, especially those who live in remote places.

Therefore, I am glad to endorse the "ANTHEM" project waiting for the possibility to translate the results in Regione Calabria.

Best Regards

Giuseppe Profiti



Regione Campania

GIUNTA REGIONALE DELLA CAMPANIA



Il Presidente

GIUNTA REGIONALE DELLA CAMPANIA
Ufficio di Diretta Collaborazione del Presidente
OAHINHTD

Prot.2022 - 0016848 /UDCP/GAB/CG del 18/10/2022 U
Fascicolo VANTH -

Vice-Rettore dell'Università di Milano Bicocca
Dott. Guido Cavaletti

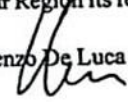
Subject: Project "ANTHEM".

Dear Prof. Cavaletti,

I read the "ANTHEM" project and I believe the successful completion of the planned activities might really benefit our community, favoring the reduction of disparities and allowing a more efficient and modern approach to the health care of fragile persons and oncological patients.

Campania Region is therefore interested in supporting and promoting the Anthem (Advanced Technologies for Human-centred Medicine) project proposed by the Milano-Bicocca University, in collaboration with several Campania Research Centers and glad to endorse the "ANTHEM" project waiting for the possibility to translate and test on-field in our Region its results.

Vincenzo De Luca





Regione Lombardia



Regione Lombardia - Giunta
DIREZIONE GENERALE WELFARE
SISTEMI INFORMATIVI E SANITA' DIGITALE

Piazza Città di Lombardia n.1
20124 Milano
Tel 02 6765.1

welfare@pec.regione.lombardia.it

Guido Cavaletti
Email: guido.cavaletti@unimib.it

Protocollo G1.2022.0041743 del 14/10/2022

Subject : ANTHEM project

Dear Prof. Cavaletti

with reference to the ANTHEM project, having taken note of the defined objectives and the possible concrete effects on citizens, we confirm the interest of Regione Lombardia to positively support your effort.

Best regards

Director

GIOVANNI DELGROSSI

Document referent: FABRIZIO MUSELLA Tel. 02/67652975.

Copia analogica sottoscritta con firma a mezzo stampa predisposta secondo l'articolo 3 del D.lgs 39/1993 e l'articolo 3bis, comma 4bis del Codice dell'amministrazione digitale. Il documento originale è firmato digitalmente e conservato presso l'Ente.

www.regione.lombardia.it



Regione Puglia



**REGIONE
PUGLIA**

**STRUTTURA SPECIALE DI COORDINAMENTO
HEALTH MARKETPLACE
IL DIRETTORE**

To

**Prof. Guido Cavaletti
ANTHEM Project proponent
University of Milano-Bicocca**

**Prof. Fabio Pollice
Magnificent Rector
University of Lecce**

**Prof. Alessandro Sannino
Reserach Delegate
University of Lecce**

Dear Prof. Cavaletti, I had the possibility to assess the "ANTHEM" project and I believe the successful completion of the planned activities might really benefit our community, favoring the reduction of disparities and allowing a more efficient and modern approach to the health care of fragile persons, particularly if living in remote areas.

I am therefore glad to endorse the "ANTHEM" project waiting for the possibility to translate and test on-field in our Region its results.

Yours sincerely,

Bari, 14 ottobre 2022

Dott. Felice Ungaro

A handwritten signature in black ink, appearing to read "F. Ungaro", written over the typed name.



Aicarm Onlus



Florence, 14-10-2022

to: Prof. Guido Cavaletti
Vice-Rector (Research), University of Milano-Bicocca
University of Milano-Bicocca
ANTHEM project proponent

Dear Prof. Cavaletti,

I had the opportunity to evaluate the "ANTHEM project" and I confirm that AICARM onlus is strongly interested and available in being involved in all its activities aimed at improving the health care of the people with cardiovascular diseases.

This might be particularly relevant for patients living in remote areas, but also for the entire population of patients

I am therefore able to guarantee full support to the project.

Prof. Franco Cecchi
President

AICARM ONLUS sede Legale: Via dello Studio 5, 50122 Firenze | Tel 055 291889 cell 371 4533840
Registro Onlus Direzione Regionale Agenzia Entrate n.1052; Registro persone giuridiche RT n.1130
e-Mail : info@aicarm.it PEC: aicarmetsonlus@messaggipec.it www.aicarm.it

**Aimac – Associazione Italiana Malati di Cancro**

Prof. Guido Cavaletti
University of Milano-
Bicocca
ANTHEM project proponent

Rome, 14/10/2022

Dear Prof. Cavaletti,

we went through the full proposal of the "ANTHEM project" and we confirm that the Italian Association of Cancer Patients (Aimac - Associazione Italiana Malati di Cancro) is strongly interested and available in being involved in the activities aimed at improving the health care of the cancer patients living far from their reference cancer centre.

Based on these considerations, we are glad to offer our support to the project.

Best regards.

Laura Del Campo
(Director)

A handwritten signature in blue ink that reads "Laura Del Campo".



Un Respiro di Speranza Lombardia



to: Prof. Guido Cavaletti
University of Milano-Bicocca
ANTHEM project proponent

Dear Prof. Cavaletti,

I went through the proposal of the "ANTHEM project" and I confirm that the patient Association UN RESPIRO DI SPERANZA LOMBARDIA Voluntary Activities, is strongly interested and available in being involved in all its activities aimed at improving the health care of the people with chronic pulmonary diseases, particularly (but not only) if they are living in remote areas.

I am therefore able to guarantee full support to the project.

Our most sincere greetings

the incumbent President
Roberto Adamo

"UN RESPIRO DI SPERANZA LOMBARDIA"
Organizzazione di Volontariato non commerciale
Via Pergolesi, 33 Monza c/o ASST di Monza 20900 (MB)
C.F. 93550020155
info@unrespirodisperanzalombardia.com
www.unrespirodisperanzalombardia.com



Comunità Montana della Valle Seriana



PRESIDENZA

Clusone, 14 October 2022

Guido Cavaletti
MD, Professor of Human Anatomy
Vice-Rector (Research)
UNIVERSITY OF MILANO-BICOCCA

OBJECT: ANTHEM PROJECT

Dear Prof. Cavaletti,

I went through the full proposal of the "ANTHEM project" and I confirm that the Community is strongly interested and available in being involved in all the activities aimed at improving the health care of the people living in problematic areas such as in the mountain and rural parts of Val Seriana. In fact, we are convinced that new technological approaches such as those described in the Anthem project might really benefit our population, as well as be translated into other territories with similar difficult conditions once here tested and validated.

Based on these considerations I am glad to guarantee full support to the project, in close collaboration with the Regional Health Authorities (Regione Lombardia and ASST Bergamo Est) and local General Practitioners.

Looking forward to starting the project as soon as possible, best regards.



THE PRESIDENT
Giampiero Calegari