

New and existing technologies can be integrated into people's life environments, supporting everyday living and promoting healthier lifestyles and social inclusion. This can be particularly beneficial for the elderly and for people with disabilities, allowing them to continue to live independently in their own homes, in the community and at work.

At the University of Bologna, researchers have a strong expertise in the **design**, **development and real-life testing of smart and adaptive environments**. Multidisciplinary teams are used to work together with a participatory design approach.

Researchers have exploited the potential offered by **Internet of Things** (IoT) technology, wearable sensors, mobiles, biomedical signal processing and Artificial Intelligence for prototyping smart objects and environments capable of identifying, locating, and sensing.

These new environments can lead to new ways of communication with friends, family, caregivers and the objects themselves; can help to identify, monitor, and learn daily living activities in order to provide personalized advice (e.g. on sleep, diet, physical activity) and prevent functional decline or injuries, for an active and healthy aging; can be used to stimulate the user by making life mentally and physically more challenging but without losing comfort.

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Active & Healthy Ageing: the University of Bologna has a consolidated track record of projects aimed at improving health and safety in order to support active aging through digital tools, mobile technology and wearables (e.g. FP7 FARSEEING; H2020 PreventIT; IMI-2 MOBILISE-D; ROP-ERDF HABITAT). The FARSEEING project has been selected by the European Commission as one of the top 3 most influential and high-impact projects of the last 11 years in the field of ICT for Active and Healthy Ageing, and two of its results have been recognized as 'key innovations' by the EC Innovation Radar.

Home care systems: the University of Bologna has strong experience in domestic rehabilitation based on bio-feedback, exergames and virtual reality, regularly designing and clinically validating personal health systems that, like personal managers, aim at empowering older persons or patients and at preserving their health (e.g. EIT Digital <u>Vital@Home</u>).



The University of Bologna has a long-lasting expertise in the **integration of omics data** with genomic characterisation and with higher levels of complexity, including lifestyle and environmental data, in order to obtain a better understanding of clinical phenotypes.

In particular, integrative or systematic approaches along with the development of supporting ICT tools and platforms are a strong academic asset, in order to leverage on the large availability of patient cohorts and big biological data owned by multiple research groups across different departments.

The research of the University of Bologna is based on extensive expertise on the utilisation of **Big Data software** (Cloudera, Hadoop, Talend and Tableau, among others), the development of big data integration methods based on complex networks, convolutional neural networks and machine learning methods.

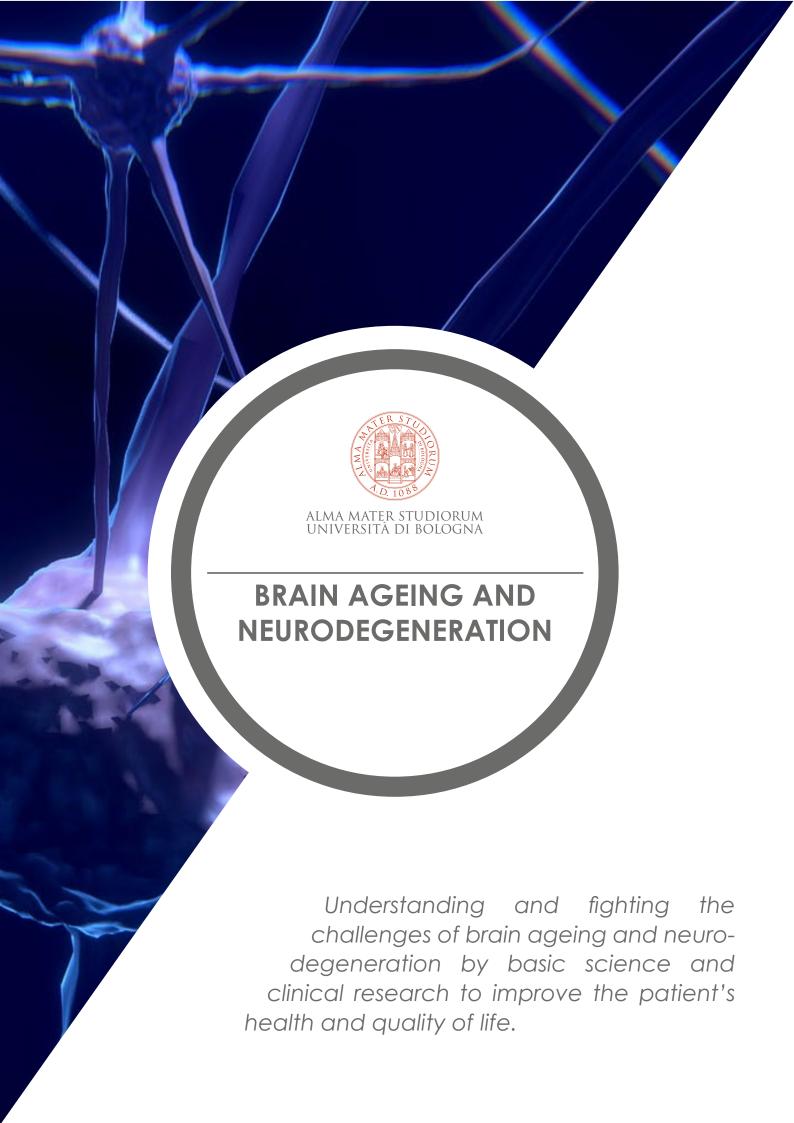
Furthermore, other relevant research activities encompass the mapping of the available clinical and biological information **into networks of a** *priori* **biological knowledge** (Protein-protein interaction networks, Human metabolic networks, KEGG networks, transcription networks, disease databases, drug databases), and the creation of **network propagation algorithms** for the identification of the so called "Diseases Modules".

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Big data analytics and training: the researchers of the University of Bologna have strong and internationally renowned expertise in the field of big data analytics, reflected in the participation in a number of EU-funded projects both in the field of research and innovation (e.g. IMI-2 <u>HARMONY</u> and <u>HARMONY PLUS</u>; H2020 <u>GenoMed4AII</u> and <u>ORCHESTRA</u>) and training (e.g. H2020 <u>IMforFuture</u> - Innovative training in methods for future data).

Medical textual diagnosis classification: the University of Bologna has a long experience on text analytics, driving to the development of ICD-9-CM search engine, which is a remote service able to provide the most relevant ICD codes while the medical record is being typed.

Cognitive impairment: ongoing studies cover the development of web-based application for early screening assessment of cognitive impairment, such as **COGITAB**, which is an easy and highly sensitive web-based test that can detect critical cognitive profiles. It is conceived to carry out mass screening of people over 50 years old.



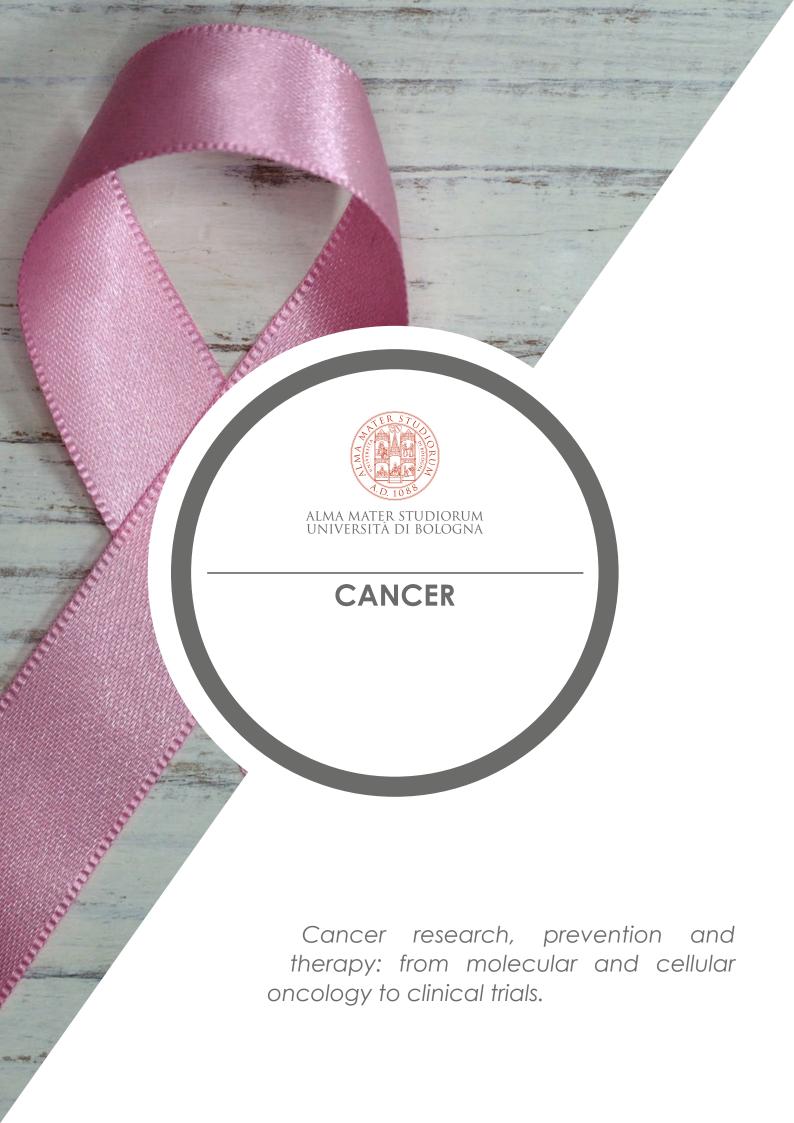
The University of Bologna has a wide network of research groups focusing on basic science and clinical research tackling central and peripheral nervous system disorders.

- The main research areas in neuroscience include neurodegeneration with special reference to prion and rare mitochondrial and neuro-genetic diseases, movement and neuromuscular disorders, disorders of the autonomic nervous system, headaches, sleep medicine with particular focus on narcolepsy, epilepsies, epidemiology of neurological diseases and innovative aspects of neurosurgical and neuroimaging procedures, as well as Parkinson's disease, Alzheimer's disease, Autism Spectrum Disorders and brain longevity
- Research expertise across different departments also includes the harmonization of healthcare data collection, the development of tools for population-level detection of cognitive impairment and the investigation of animal models of addiction, neuropathic pain, and brain-related diseases
- Research expertise are not only related to biological and biomedical skills, but
 encompass also psychophysiology of sleep and dream, chronobiology and
 chrono-psychology for the identification of individual differences in circadian
 rhythms, psychosomatic medicine and psycho-neuroendocrinology

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Excellence in neurosciences at the University of Bologna strongly lies on the close relationship with the **Institute of Neurological Sciences** (ISNB), whose laboratories host facilities for cell and molecular biology, microscopic imaging, next generation sequencing, with large collections of brain pathology, muscle and skin biopsies, cell lines, DNA/RNA, cerebrospinal fluid and plasma/serum repositories from patients with rare disorders. The University also encompasses a **Joint Research Laboratory** provided with an animal facility authorized to operate as medical laboratory and a bio-molecular diagnostic facility.

Neuroscience research activity is reflected in several EU funded projects, e.g. H2020 PROPAG-AGEING - The continuum between healthy ageing and idiopathic Parkinson Disease within a propagation perspective of inflammation and damage: the search for new diagnostic, prognostic and therapeutic targets, JP Neurodegenerative Disease Research ADAGE - Alzheimer's disease+AGEing, IMI-2 JU PRISM and PRISM 2 - Providing quantitative biological measures to facilitate the discovery and development of new treatments for social and cognitive deficits in Alzheimer's disease, schizophrenia and depression.



At the University of Bologna cancer studies are developed in collaboration with the St. Orsola-Malpighi Hospital, a general hospital housing the School of Medicine and the Interdepartmental Center for Cancer Research; the Bellaria Hospital, with a center of excellence for neurological sciences; and the Rizzoli Orthopedic Institute, a world-class center in the field of bone diseases.

Altogether, several thousand oncological patients, from the Emilia-Romagna region, from other Italian Regions and from European and African countries, are diagnosed and treated each year. Large clinical series are being accrued for what concerns frequent cancers and also for many types of rare tumors.

- Preclinical research is developed within university laboratories and in collaboration with clinicians, in areas ranging from subcellular organelles of tumor cells (mitochondria, ribosomes), to cancer vaccines, to cancer predisposition genes, to the use of cancer genomics and transcriptomics to discover and target novel cancer genes, to studies of preventive components of the diet
- The clinical oncologists coordinate and participate in numerous clinical trials, in particular for what concerns pediatric oncohematology, cancer immunotherapy, leukemias and lymphomas, bone tumors and gastroenterological tumors

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Pediatric oncohematology: the University of Bologna is **a Reference Center** at National (GITMO - Italian Group for Bone Marrow Transplantation) and European (**EBMT**) level, for autologous and donor hematopoietic stem cell transplantation, with a leading role in the national networks that coordinate clinical trials in pediatric acute leukemias and solid tumors.

Hematology: The University of Bologna is at the forefront of experimental and clinical hematology, with <u>a wide portfolio of clinical studies</u> and several EU projects (eg. <u>HARMONY</u>, <u>HARMONY PLUS</u> and <u>GenoMed4AII</u>) on neoplastic hematological disorders.

Cancer immunology and immunotherapy: ongoing studies range from the preclinical design of preventive vaccines for non-infectious tumors to clinical studies exploring predictive biomarkers in lung cancer and other solid tumors.

Gastrointestinal cancer: the University of Bologna is at the forefront of gastrointestinal oncology, leading to a sizeable number of clinical cases even for such rare tumors as gastrointestinal sarcomas (GIST) and cholangiocarcinomas. Since 2009, the Medical Oncology Unit is certified as European Centre of Excellence for the integration of cancer therapy and palliative care.





Research activities spans from the application of virtual/augmented reality (VR/AR) and digital diagnostics and care, to the use of health informatics and mobile technologies.

The research of the University of Bologna covers a wide range of issues:

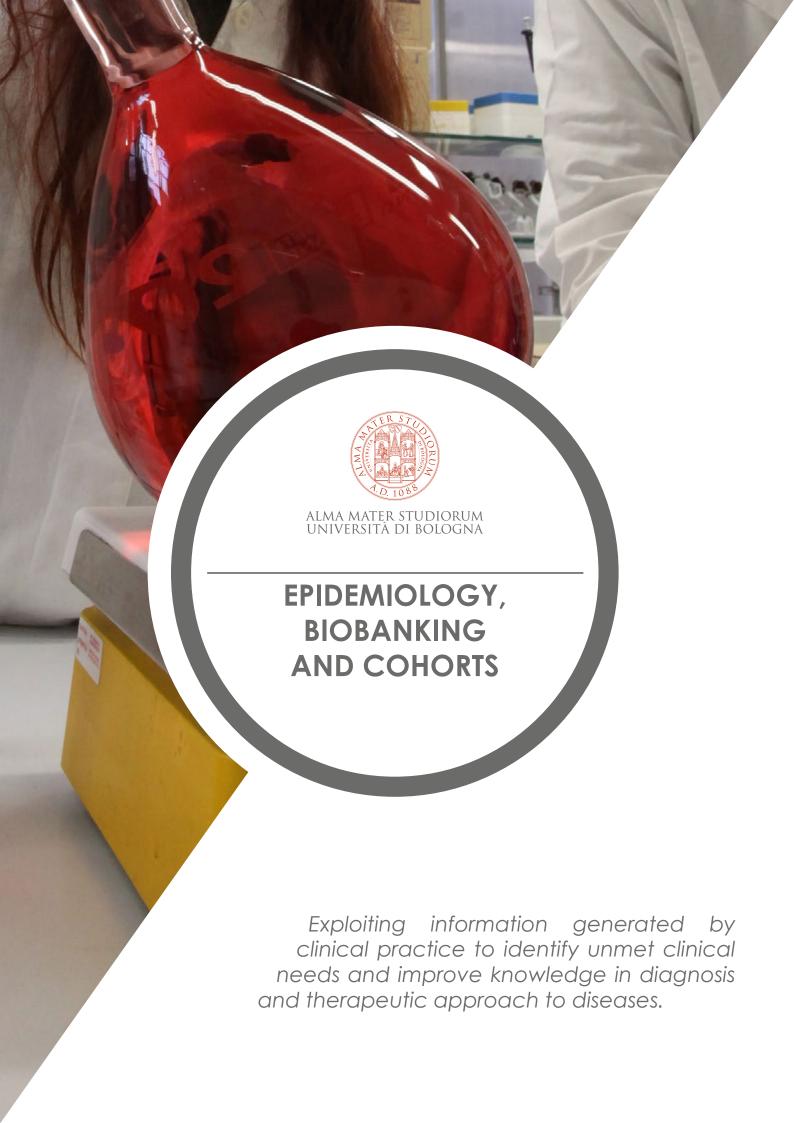
- Integration of biological systems modelling and medical imaging for the development of innovative diagnostic systems and more effective care practices
- Robot-assisted surgery integrating VR and AR technologies in the operating room
- 3-D kinematic tracking for human movement analysis, artificial vision and gesture recognition
- Motion analysis and physical activity monitoring via wearable systems
- Motor and cognitive assessment in neurological disorders through mobile platforms
- Prevention and rehabilitation platforms for the neuromotor and cognitive domains, neurostimulation, VR/AR and biofeedback-based interfaces for neurorehabilitation
- eHealth/mHealth solutions for digital health, personalised medicine and risk stratification aimed at a better prevention of different pathologies

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These skills allowed the funding of a number of EU projects (eg. ISW, PreventIT, ONCORELIEF, RETENTION) and the release of innovative products addressing several aspects of eHealth.

Researchers are also involved in the **National Technology Cluster OPLON** - oPportunities for active and healthy LONgevity: a national flagship program on health and life sciences, aimed at preventing frailty and functional decline and promoting the health of the elderly, planning and developing early diagnosis, care and cure.

Innovative research led to the filing of patents (e.g. Augmented reality glasses for medical applications and corresponding augmented reality system) and the launch of the academic spin-off mHealthTechnologies SrI, specialised in CE-marked medical devices, movement analysis, signal processing, algorithm development, wearable sensors, and data mining.



The **excellence in clinical activity** that for decades has characterized the University of Bologna and the hospitals connected with it provides large opportunities for observational research: several longitudinal collections of clinical data, biological samples and digital images are available and continuously enriched; they cover frequent clinical conditions with still unsolved diagnostic and therapeutic questions (e.g., inflammatory bowel diseases), as well as rare diseases (e.g., mitochondrial neurological diseases).

Longitudinal collections frequently include data on diet and lifestyle habits, and focus on longevity and healthy aging. In addition, data on psychological and psychiatric status are collected in specific cohorts of patients. Clinical expertise that characterise all relevant research groups and departments are complemented by **ICT excellence**, which provides updated support in data storage, protection and linkage, as well as in innovative datamining and analysis.

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Biobanks and cohorts of neurological diseases: biological samples and clinical data from the Neurogenetics Laboratory; record-linkage of healthcare data of patients with Parkinson Disease (**ParkLink**); biological samples and clinical data on mitochondrial disorders from the neurological services of the Emilia-Romagna region (**ER-MITO**).

Biobanks and cohorts of gastrointestinal/hepatic diseases: samples and clinical data for the study of microbiota and related diseases; liver disease biobanks; whole genome studies of rare tumors.

Longitudinal population-based investigations: Brisighella Heart Study (BHS), started in 1972 and involving 3000 subjects clinically evaluated at baseline and every four years thereafter, by collecting an extensive amount of clinical and laboratory data; H2020 projects, e.g. **ORCHESTRA**, aiming at building a pan-European cohort in response to the COVID-19 pandemic, and **ENLIGHTENme**, a population study on the impact of urban lighting on health and wellbeing.



Non-Communicable Diseases (NCDs) are now the leading cause of preventable morbidity and related disability, and thus significantly affect the wellbeing of many individuals.

All different NCDs are studied in the different Departments of the University of Bologna, and **translational medicine approaches** are put in place thanks to the strong cooperation with clinical departments.

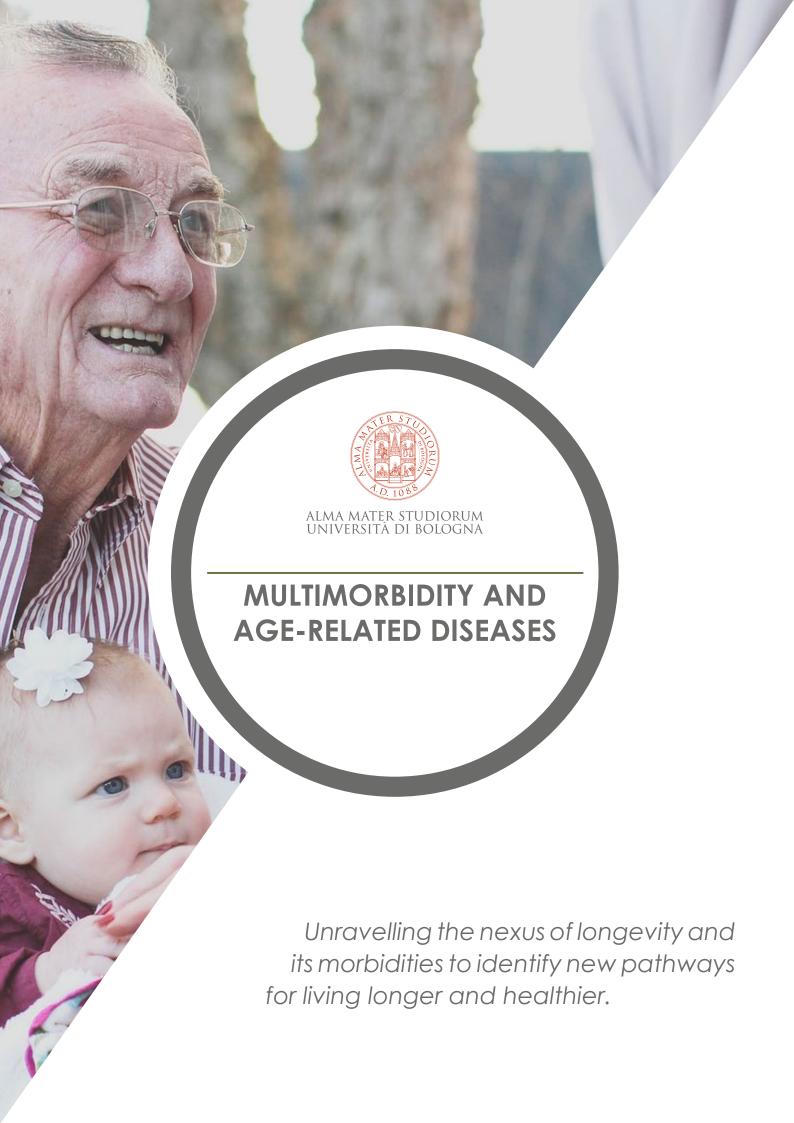
- In relation to liver diseases, researchers have strong expertise in the
 understanding of pathogenetic basis of hepatitis and novel therapies,
 treatment of hepatic cancer, unravelling of the onset mechanisms leading
 to NASH and NAFLD as well as autoimmune liver diseases and their treatment
- In relation to gut disorders, research teams have strong research interest in the prevention and treatment of autoimmune chronic diseases, inflammatory bowel diseases, and the gut surgery. Furthermore, there is also an emphasis on research on biomolecular, therapeutic and social aspects of functional gastrointestinal disorders, neurogastroenterology, intestinal infectious and inflammatory bowel diseases. Last, the study of colon cancer and the role of the microbiome in its development is gaining particular attention

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A number of EU-funded research projects reflects the international standing of research groups working in the field of NCDs, e.g. H2020 <u>GlyCoCan</u> which aims to develop new methods to investigate the role of glycosylation in different aspects of colorectal cancer; <u>LIVERHOPE</u> which aims to evaluate a novel therapeutic strategy for patients with cirrhosis; <u>DECISION</u> for the identification of new combinatorial therapies for decompensated cirrhosis.

Organ transplantations is historically a major research and clinical excellence at the University of Bologna due to the number of clinical cases and its successful track record, especially for split liver and kidney transplants, as well as the development of novel methodologies to preserve the quality of the donor organs, which made Bologna an internationally renowned center for transplantation.

Biomedical research: in 2000 the **Center for Applied Biomedical Research** was funded to provide the scientific community of the St. Orsola-Malpighi University Hospital with an interdisciplinary research facility, a unique location for sophisticated instrumentation aimed at foster collaborative interactions among different research teams, in order to speed up the transition from basic research discoveries to new treatments.



The University of Bologna has a long-lasting experience in studying the ageing multi-factorial process and its associated non-infectious co-morbidities. In particular:

- Cardiovascular diseases and hypertension: Researchers in this sector have broad experience in the organization and conduction of all phases of clinical trial research, as well as morbidity and mortality trials in hypertension and coronary artery disease
- Pulmonary Hypertension: Research areas of interest are the study of pulmonary arterial hypertension, pulmonary embolism, chronic heart failure, and heart transplantation, as well as treatments connected to the endothelin pathway, the prostacyclin pathway, the nitric oxide pathway
- Diabetes and obesity: Researchers in this sector have large experience in glucose and amino acid metabolism; nutrition in patients with cirrhosis, diabetes, obesity, and in normal ageing; quantification of liver function; insulin resistance; non-alcoholic fatty liver disease; disease management of the metabolic syndrome, obesity and eating disorders across the life span; epidemiology, treatment and outcome assessment

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The integration of preclinical and clinical research with therapeutics and care is a strong asset of the University of Bologna. The first double blind, placebo-controlled study on the effect of the endothelin receptor antagonist (bosentan) on the echocardiographic and Doppler parameters in PAH patients has been conducted.

A number of clinical studies and EU funded projects have been carried out in these areas, such as: CARBALIVE - Clinical evaluation of carbons of controlled porosity as a new therapeutic for the treatment of liver cirrhosis and non-alcoholic fatty liver disease; ESCAPE - Evaluation of a patient-centred biopsychosocial blended collaborative care pathway for the treatment of multimorbid elderly patients; PAPA-ARTIS - Paraplegia prevention in aortic aneurysm repair by thoracoabdominal staging with 'minimally- invasive segmental artery coil-embolization': a randomized controlled multicentre trial; DECISION - Decompensated cirrhosis: identification of new combinatorial therapies based on systems approaches.





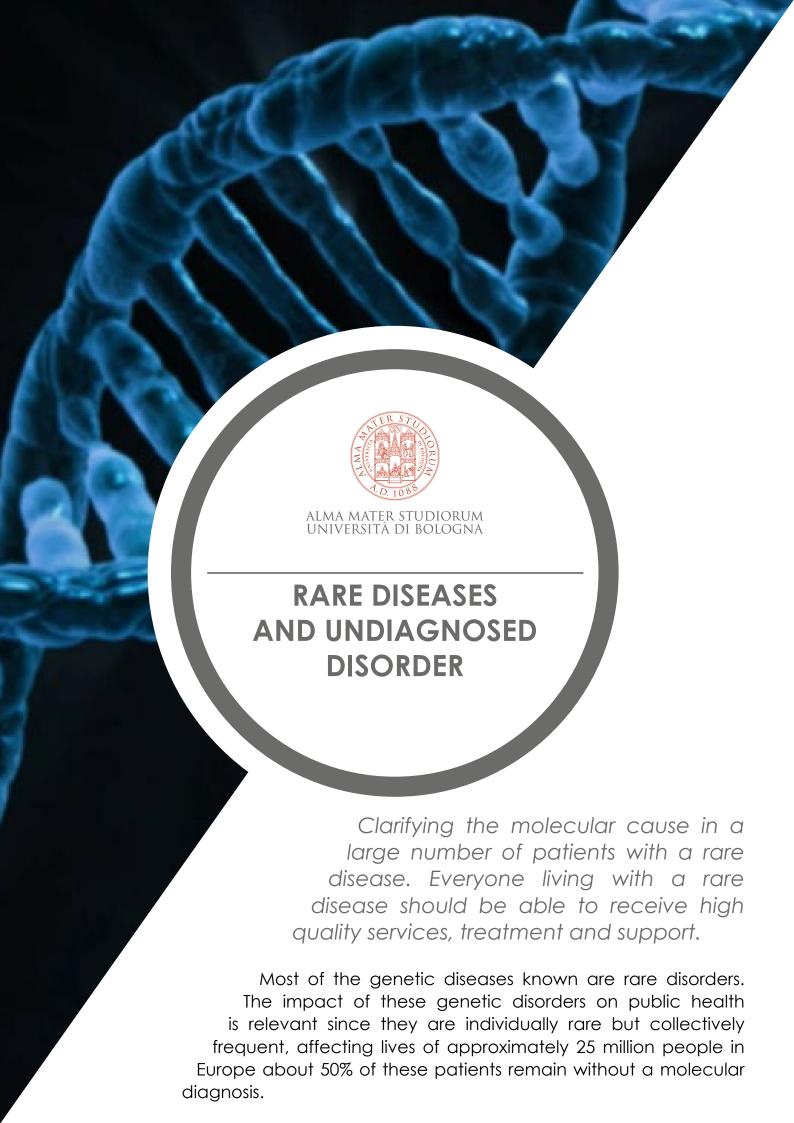
The research of the University of Bologna covers a wide range of issues:

- Development of preventive cancer vaccines through viral reprogramming
- Isolation, expansion and differentiation of stem cells of different human and animal origin, including Induced Pluripotent Stem Cells IPS: a platform of cell production, characterization and their exploitation towards therapy
- Development of cell biosensors based on genetically engineered cells (e.g., bacterial, yeast and mammalian cell lines) for diagnostics, drug screening and clinical applications
- Development of molecular (nano) biosensors towards molecules of interest for pharmaceutical industry and for clinically-relevant biomarkers (also at the point-of-care)
- 2D and 3D in vitro and in vivo models for testing of safety and efficacy of potential drugs and bioactive molecules (also in compliance with Replacement Reduction Refinement RRR principles and Good Laboratory Practice GLP)
- Development of new precision-medicine tools based on omics (transcriptomics, metabolomics, epigenomics, gut microbiota through Next Generation Sequencing NGS, bioinformatics, advanced analytics) and on advanced imaging (electron, confocal, optical, atomic force microscopy, live-animal imaging)
- Development and application of computational methods for drug-target interactions and in silico screening of molecular libraries
- Separation and purification of pharmaceutical products and recombinant macromolecules through chromatography techniques

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The University of Bologna contributes to the international research progress working on funded projects at European level and by developing and making available innovative solutions:

- Laboratory Animal Facilities for mice (transgenic or not), rats, guinea pigs and zebrafish; breeding, primary cultures, treatments, behavioral and ex vivo tests, also operating in GLP
- A distributed **microbiological collection** of more than 200 bacteria and yeasts strains, including human pathogens (e.g. food or water-borne) and non-pathogens (e.g. microbiota)
- <u>WellMicro</u> spin-off provides the analysis of one's personal gut microbiota and nutritional/therapeutic personalized counseling based on one's own 'microbiopassport'
- <u>StemSel</u> spin-off provides innovative instrumentation for regenerative medicine for selection and sorting of stem cells
- IMI 2 <u>HARMONY</u> and <u>HARMONY PLUS</u>
- H2020 <u>ORTHOUNION</u>, <u>QSPainRelief</u>, and <u>DECISION</u>



The University of Bologna have traditionally been interested in understanding the molecular causes leading to different genomic and genetic disorders. This commitment resulted also in the **active participation in several European Reference Networks** (ERN), aimed at facilitate discussion on complex or rare diseases that require highly specialised treatment: ENDO ERN, ERN LUNG, ERN ITHACA, ERN SKIN, ERN BOND and ERN EURACAN, through the St. Orsola-Malpighi University Hospital and the Rizzoli Orthopaedic Institute.

Several research group have exploited the use of **NGS approaches** to identify causative mutations in patients with a range of different rare Mendelian phenotypes, including syndromic and non-syndromic neurodevelopmental disorders. A list of the main diseases studied includes: intellectual disabilities, neurodegenerative disorders (such as Hereditary spastic paraplegias), Rare Skeletal Diseases (Osteochondrodysplasias), focal epilepsies and epileptic encephalopathies, rare pediatric dermatology diseases, rare endocrine conditions such as Turner Syndrome and lipodystrophies, myelodysplastic syndrome, hereditary optic neuropathies and several neuromuscular disorders among others.

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Different research groups have established an extensive network of collaborations with clinical and research centers across major research strengths, such as NGS sequencing of germ-line and somatic DNA from patients with genetic diseases and the implementation of methods for statistical assessment of disease-gene associations of rare variants for rare Mendelian/complex disorders (trio analysis, gene collapsing analysis).

Gene-editing tools for functional assessment of the genetic variants identified through NGS high-throughput data is also a major area of excellence of the University of Bologna.

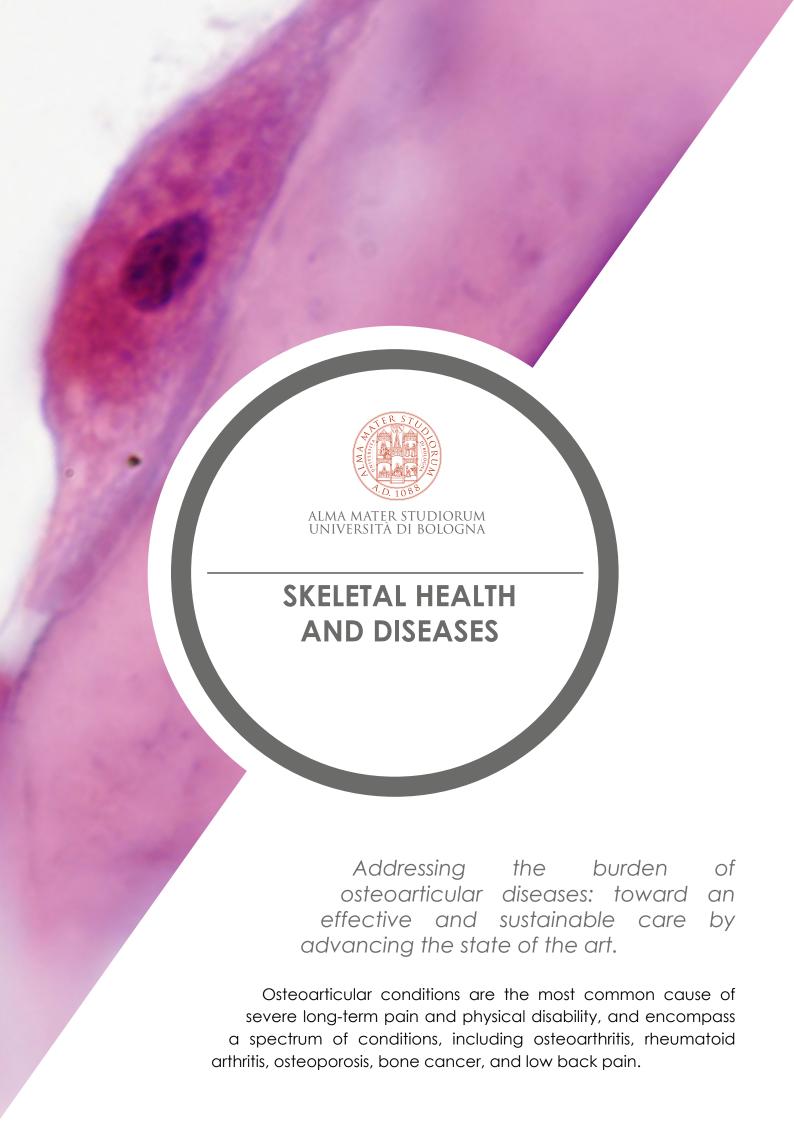
The University of Bologna participates to a number of national and international consortia for the analysis of rare variants in the general population (*Network for Italian Genomes - NIG*) and in diseases (Epi25: a collaborative project aimed to exome sequence as many as 25,000 patients with epilepsy and the Epilepsy Genome Initiative - EGI).



- Preclinical research develops regenerative medicine approaches based on the combination of polymeric and ceramic biomaterials, cells, physical energies, and bioactive drugs for in vivo applications (self-repair stimulation) and for developing implantable devices (controlled release of drugs, cells and cell derivatives such as exosomes)
- The clinical targets of preclinical investigations include Central Nervous System repair following neonatal hypoxia and traumatic injuries or stroke, with a primary focus on myelin repair, repair of chronic and diabetic ulcers, the differentiation of human amniotic epithelial cells into insulin-producing cells, and the reconstruction of musculoskeletal tissues following surgical or traumatic loss
- A Good Laboratory Practice (GLP) facility for preclinical validation of processes/products is currently being implemented. Clinical application of regenerative medicine and tissue engineering are already routine at the Istituto Ortopedico Rizzoli, a research and teaching hospital connected to the University of Bologna, for orthopaedic applications and at the University Hospital S-Orsola Malpighi for maxillofacial reconstruction

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Excellence at the University of Bologna encompasses a number of EU-funded projects in the regenerative medicine sector, such as H2020 ORTHOUNION, which aims at combining expanded cells with ceramics to promote bone healing in non-unions of long bones, and H2020 ADIPOA-2, which consists in a clinical trial of autologous adipose-derived mesenchymal stromal cells in the treatment of mild to moderate osteoarthritis.



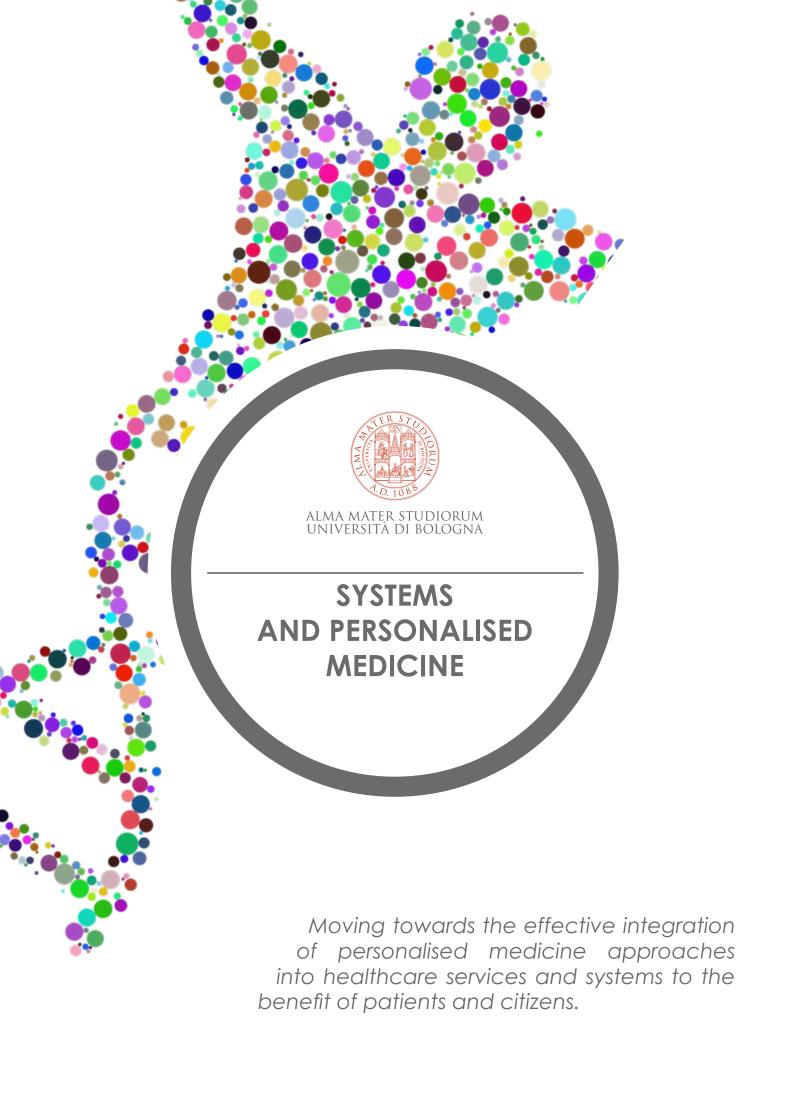
The research of the University of Bologna applies biological and biomechanical tools, through a multidisciplinary approach, to the most common and impacting osteoarticular conditions, as:

- Paediatric orthopaedics and rare diseases: genomic profile and phenotypic features of collagenopathies and muscle diseases
- Bone cancer: genomic and metabolomic profile of sarcomas, drug resistance, biomarkers (miRNAs, exosomes) photodynamic therapies, tumor microenvironment in sarcomas and bone metastases, biomarkers, clinical impact of gut microbiome
- Articular implants: tribology of devices, advanced imaging (radiostereophotogrammetry, dynamic MRI), objective measurement of results by gait analysis and wearable devices, infection
- **Tissue engineering and regenerative medicine**: biocompatibility, surface modifications by chemico-physical approaches, platelet derivatives, advanced therapies
- 3D printed orthotics and implants for foot diseases and bone reconstruction
- **Inflammation and articular damage**: genomic profile of hand osteoarthritis, biomarkers in rheumatic diseases, chondrocyte damage in osteoarthritis
- Osteopenia and osteoporosis: pathophysiology of osteopenia and prevention of fractures

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The excellence of the University of Bologna lies in the skeletal health and disease lies on the close link with the **Istituto Ortopedico Rizzoli** (IOR), a leading European center for orthopaedic science and care. Research facility of IOR include 15 laboratories, covering the spectrum of orthopaedic science and an in vivo facility for experimental surgery, a platform for genomic data analysis, and an advanced microscopic imaging platform are also available. Orthopaedic rare disease and bone cancer biobanks, together with several collections of serum and tissue material, are fully integrated with clinical information.

Excellence in the field is reflected in the participation to the **European Reference**Network (ERN) on Rare Bone Disorders <u>ERN-BOND</u> and in a number of EU funded projects, e.g. IMI-2, <u>ITCC-P4</u> - ITCC Pediatric Preclinical POC Platform, H2020 <u>FURTHER</u> and <u>MCDS-Therapy</u>.



Taking into account specific risk factors, genetic phenotype, pharmacokinetic characteristics, and other specific features unique to each patient, personalized medicine approaches are studied at the University of Bologna. They are mostly based on systems biology research and on the rapid development of omics and high-throughput technologies, at the edge between bed and bench side. Major clinical areas of relevance are chronic diseases such as hypertension, age-related comorbidities and neurological disorders.

Furthermore, advanced skills in complex networks, deterministic and stochastic modelling of physiological systems with multiscale approaches, advanced data-driven techniques based on machine and statistical learning methods are strongly present in several research groups across the University.

Other points of excellence are the **big data analytics methods**, including the integration of heterogeneous data sources leveraging on the computing resources and cloud environment owned by the University. This has led to improve and evaluate **preventive strategies** and to identify the personalised and precision medicine, with particular relevance for **early diagnosis** and to predict clinical outcomes like falls, frailty, depression, and functional decline in older people.

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Ageing and systems medicine: the University of Bologna has a long-lasting experience on applying a systems medicine approach to age-related diseases and other issues, and this is reflected in a number of EU funded projects, e.g. H2020 **PROPAG-AGING**, **ESCAPE**, **QSPainRelief**.

Personalised medicine in haematology and oncology: the University of Bologna is involved in several projects related to data analytics and big biomedical data integration for personalised medicine in the haematology and oncology areas, e.g. IMI-2 <u>HARMONY</u> and <u>HARMONY PLUS</u>, H2020 <u>GenoMed4AII</u>, and <u>PRIMAGE</u>.