DARE
DIGITAL LIFELONG PREVENTION

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S3.D2.2

Models preliminary assessment and validation

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S3.D2.2 Models preliminary assessment and validation

Deliverable information	
Spoke number and title	Spoke 3 - Digitally-Enabled Secondary And Tertiary Prevention
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1.0	26/03/2025	Alberto Leardini	Final version

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Personalization and Risk Stratification Tools

The WP2, "Personalization and Risk Stratification Tools", has the aim to deliver digital models of the human body. This is one of the most transversal WP in the DARE project, as it includes Engineers and Physicians.

Mechanistic models such as Digital Twins are applied as modern In-Silico Trials to replace In-Vitro, animal, and human experimentation in assessing the safety and efficacy of new treatments.

Radiomics analysis has been also evaluated for secondary and tertiary health prevention in cardiovascular imaging.

1. Task 2.1 - A Digital Twin technology to monitor the risk of fragility bone fractures in osteoporotic patients

1.1 Task leader

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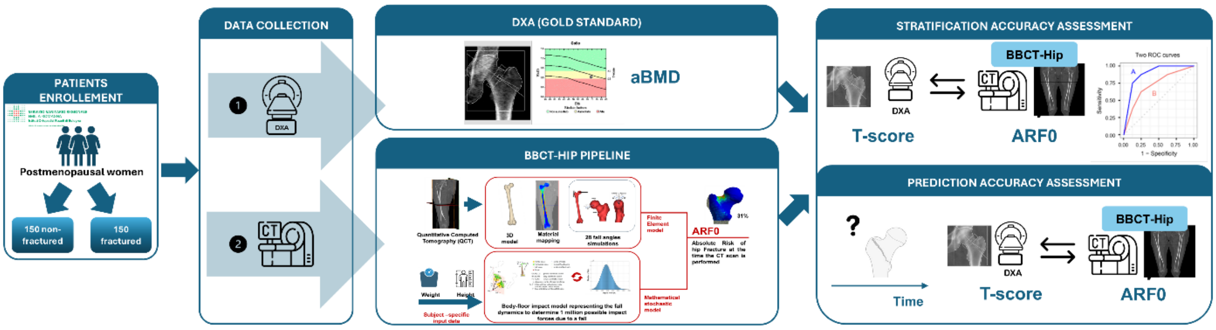
1.3 Graphical abstract



1.4 Task summary

The task involves a clinical study carried out in order to collect clinical validation evidence of the in-silico methodology Bologna Biomechanical Computed Tomography at the hip (BBCT-hip), which predicts the fracture risk at the femur. The study foresees the collection of Computed Tomography (CT) scans and Dual-energy X-ray Absorptiometry (DXA) images for a total of 300 female post-menopausal subjects older than 65 years and therefore at risk of osteoporosis and related fractures. Specifically, these 300 subjects comprise 150 control subjects and 150 subjects with a femoral fracture hospitalized at Rizzoli Orthopaedic Institute. Starting from the CT scans of the enrolled subjects, their height and weight BBCT-hip methodology can be run, and that outputs the risk of fracture at the femur at the time the CT was taken. That outcome, once computed for all 300 subjects, will be compared to DXA-derived T-score, the clinical gold standard, in terms of their stratification accuracy. So far, all the 150 control subjects and 11 fracture subjects have been enrolled and scanned.

1.5 Data used for preliminary assessment and validation

BBCT-hip methodology has already been fully developed within the research group. In addition, the finite element (FE) model it comprises has been validated against in vitro experimental data, and BBCT-hip has also already been validated in a clinical context using a retrospective clinical cohort. Here, 300 subjects, of whom 150 control subjects and 150 fractured subjects will allow 1) stratification accuracy computation and 2) predictive accuracy assessment by following-up the control subjects in time to assess whether the risk of fracture yielded by BBCT-hip can also be predictive of future fracture events.

Subjects will be enrolled in the Rizzoli Orthopaedic Institute, and the following data will be gathered:

- Weight
- Height
- Questionnaire about daily activities to establish risk of falling (only control subjects)
- DXA image
- CT scans

1.6 Devices employed in the study

Not Applicable. Here, clinical images are taken only.

1.7 Developed models/algorithms/platforms

The model object of the clinical study, which is represented by this task is called Bologna Biomechanical Computed Tomography at the hip (BBCT-hip). The model actually orchestrates two distinct models together: one finite element model of the femur to predict the load to failure and one analytical model to estimate the forces due to a fall on the side, the main cause of fractures at the femur. The finite element model of the femur of the subject is based on her CT scan, which allows to build a model with patient-specific geometry and material properties. The femur model is loaded in order to replicate a sideways fall in 28 different orientations, and the load that would fracture the femur (load to failure) is computed based on principal strains for the 28 orientations, resulting in 28 loads to failure. In parallel, a simple analytical stochastic model is used to compute one million possible forces that would be acting on the subject's femur due to a fall on the side based on her height and weight. For each of the 28 orientations mentioned above, the risk of fracture is computed as the number of forces causing fracture (i.e., exceeding the failure load) is extracted and divided by 1 million (i.e., the total number of forces). Hence, a response surface is created with the risk of fracture for the 28 orientations and eventually integrated. Hence, one single value, called ARF0 (absolute risk of fracture at time 0), is obtained for the subject.

1.8 Evaluation metrics and statistical analysis

The number of the subjects to be enrolled was established based on the previous retrospective clinical study, where area under curve (AUC) values related to BBCT-hip derived ARF0 and T-score were obtained on a pair-matched cohort. Based on the hypothesis that similar AUC values would be obtained in this study, researchers established the required number of subjects (equally divided between controls and fractured) such that a statistically significant difference (α=0.05, 1-β=0.9) could be obtained between the two ROC curves.

The outcomes of the clinical study carried out will hence be analyzed mainly through C-statistics (ROC curves), and the difference between the corresponding AUC values will be assessed using the method proposed by Hanley & McNeil.

1.9 Results and discussion

Because a clinical study is still being carried out, the final results will be obtained once all subjects have completed their enrollment. At this moment, the research team is still enrolling the fractured patients (11 subjects enrolled so far), while all the control subjects have been enrolled and have already been scanned. The BBCT-hip pipeline is currently being carried out on the available scans of the cohort of control subjects.

1.10 Next steps

The activities to be carried out in the following 22 months will be the following:

- Completion of the enrollment of the fracture subjects
- Implementation of BBCT-hip pipeline for all the control subjects and extraction of the subject-specific ARF0.
- Implementation of BBCT-hip pipeline for the progressively available fractured subjects and extraction of the subject-specific ARF0.
- Once ARF0 has been obtained for all the 300 planned subjects, ROC curves computation and AUC extraction and comparison → stratification accuracy assessment for BBCT-hip and for the clinical gold standard T-score.
- Yeary follow-up call with the enrolled control subjects for recording any femoral fracture occurrence.

2. Task 2.2 - Predicting the risk of Osteoarthritis and Joint Replacement failure

2.2a. Pilot Predicting the risk of Osteoarthritis and Joint Replacement failure

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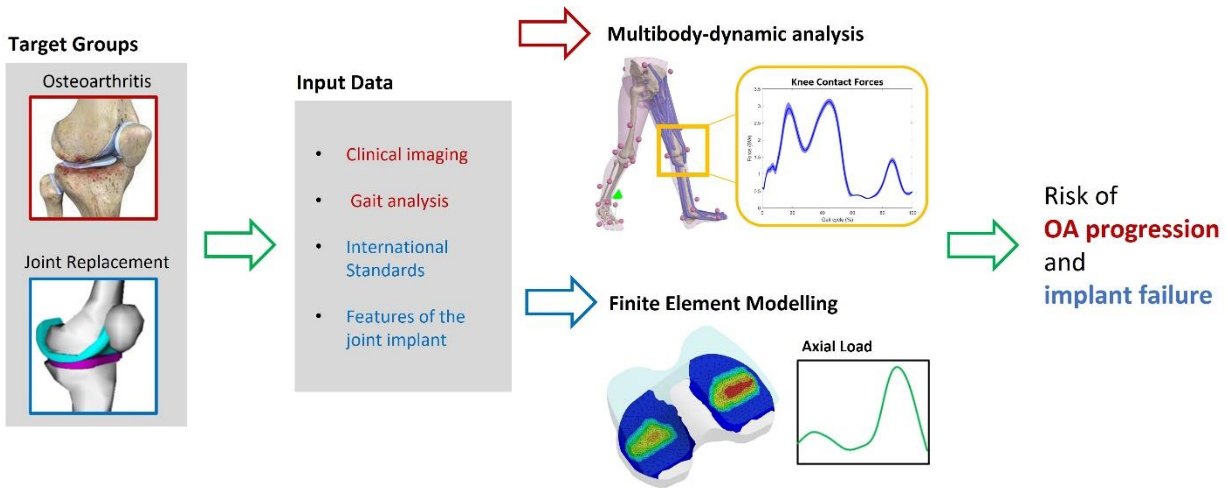
2.3 Graphical abstract



2.4 Task summary

The overall aim of the task is (i) to assess the risk of early osteoarthritis progression, in the perspective of supporting its clinical management, and (ii) to predict the risk of implant failure in patients with joint prostheses due to sub-optimal surgery outcomes.
By focusing on early osteoarthritis, the team will collect data on adult participants with a related diagnosis in the knee joint (clinical study protocol approved by the local Ethical Committee in June 2024). The dataset will include motion capture, force plates, and surface electromyography data synchronously collected while the participants perform various locomotor tasks, along with full lower limb Magnetic Resonance Imaging (MRI) data and information on the quality of the knee cartilage tissue (from a dedicated MRI sequence).

Data will be processed and analyzed to extract information on the functional - i.e., articular loads during locomotor tasks - and health status of the subject's affected knee.
Regarding the Joint Replacement Failure (JRF) assessment, the team developed a first Finite Element (FE) wear model of a Total Knee Replacement using the software Ansys and an open-source CAD model of the implant (Zimmer Natural Knee II Cruciate Retaining). Loading and kinematic conditions defined in ISO 14243 have been implemented to simulate 10 gait cycles. Results in terms of contact pressures on the polyethylene tibial insert have been compared to experimental data extracted from the literature. Verification studies have also been conducted to estimate possible numerical errors in the implementation of the computational model.

2.5 Data used for preliminary assessment and validation

Concerning the early osteoarthritis assessment, the team has been working on the identification of publicly available datasets to test the musculoskeletal modeling pipeline to ensure the planned work can be performed swiftly as their own experimental data has been collected and processed. Public datasets of interest may include gait data from various cohorts of patients and/or healthy participants. The search is currently not restricted to datasets on people with knee osteoarthritis. Regarding the JRF assessment, the team used data from ISO 14243, an international standard that provides protocols for evaluating the wear characteristics of total knee joint prostheses. This standard includes specifications for the conditions and methods used in wear testing to ensure that implants meet specific performance criteria. Initial verification and validation studies were performed by comparing simulation results with literature data on average population metrics.

2.6 Developed models/algorithms/platforms

By focusing on early osteoarthritis assessment, the musculoskeletal models to be used within the study will be developed in OpenSim, a free and open-source platform to perform biomechanical simulations (e.g., of locomotor tasks, activities of daily living, or even sports gestures). The generic template models that will serve as reference anatomy have been validated in the past and are extensively used within the biomechanical community.
Regarding the part of the study related to JRF assessment, the team developed an FE wear model of the Total Knee Replacement (TKR) using the 3D geometry of the Zimmer Natural Knee II implant from the Grand Knee Challenge dataset. The model included a rigid femoral component (Co-Cr-Mo alloy) and a linear, isotropic tibial insert (ultra-high molecular weight polyethylene), both meshed appropriately for analysis. Wear was simulated using Archard's Law with a specified friction coefficient, while boundary conditions followed ISO

14243-1:2004 standards for displacement-controlled testing. The solution process involved two steps: reaching initial loading conditions and simulating 10 gait cycles. Key quantities of interest included maximum contact pressure, volume lost, maximum wear depth, and worn area on both the medial and lateral sides of the tibial insert. The analysis was performed in Ansys Mechanical, utilizing automation for efficiency.

2.7 Evaluation metrics and statistical analysis

For what concerns the early osteoarthritis assessment, the musculoskeletal models' outputs are validated against experimental data (e.g., measurements from instrumented implants and surface electromyography traces), if available. Similarities between model predictions and 'true' values are established by computing the coefficient of determination (R2) and the root mean squared error (RMSE), while statistical significance is determined via Statistical Parametric Mapping (SPM, specifically designed to compare time-variant curves).

Regarding the part of the study related to JRF assessment, the verification workflow proposed follows the generic guidelines described in the ASME V&V 10 and ASME V&V 40 and consists of code and calculation verification. Typical code verification analyses were conducted to identify and quantify possible errors in the code and numerical algorithms implemented in the software. Calculation verification tests that aim at quantifying numerical errors associated with the FE model implementation were specifically adapted to wear simulations.

2.8 Results and discussion

By focusing on the JRF assessment, the first verification phase of the developed computational model primarily involved the different implementation of boundary conditions. The results highlighted the importance of applying the flexion-extension rotation at the femoral component while applying the force on the tibial insert. Convergence analyses were conducted by varying the time step and the mesh, demonstrating that a maximum time step of 0.05 s yields the best results while refining the mesh on the tibial insert produced similar outcomes with lower computational costs. Sensitivity analyses revealed that certain parameters, such as the contact algorithm and penetration tolerance, significantly influence the solutions, particularly pressure and wear depth. The verification tests represent a starting point for developing a more accurate model for predicting wear in knee prostheses, with future developments planned for the automated analysis of multiple parameters and comparison with experimental data over millions of cycles.

2.9 Next steps

Regarding the early osteoarthritis assessment, as soon as the experimental data from the clinical study is available, the team will start the data processing and the model development phases. The developed musculoskeletal models will then be used within the established simulation framework to predict the knee joint contact loads experienced by the participants while performing different locomotor tasks.

Regarding the JRF assessment, in the next 18 months, the team plans to work closely with INFN to refine the porting of the computational model implementation to the secure cloud. With the automation of the simulation workflow using High Performance Computing (HPC), the research group plans to run the model using open-access data from the Laboratory for Movement Biomechanics at the Julius Wolff Institute in Berlin and the Laboratory for Movement Biomechanics at ETH Zürich. Patient data from Clinica Ortopedica e Traumatologica II will also be investigated as input to the simulation framework in the coming months.

2.2b. Pilot Toward the recovery of sport after total knee arthroplasty

2.1 Task leader

PI: Lucia Calbucci (IOR)

2.1 Task keypersons

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Alberto Leardini (IOR)

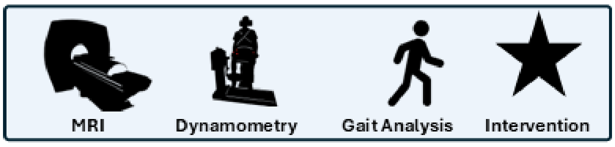
2.2 Graphical abstract

Study Aims:
- Short-term
  - Evaluate the preoperative neuromuscular condition of patients aged between 40 and 65 years who undergo TKA with a pre-opertive history of sports practice
- Long-term
  - Evaluate in these patients the clinical and functional results (quantified through clinical tests, experimental tests, and musculoskeletal modeling techniques), and the degree of return to sports activity following an intensive rehabilitation program

Inclusion Criteria
- Age between 40 and 65 years
- Males and Females
- Patients with a history of sport practice
- Patients who expect to return to sport after TKA
- Primary or post-surgical OA

Exclusion Criteria
- Age between 40 and 65 years
- Males and Females
- Patients with a history of sport practice
- Patients who expect to return to sport after TKA
- Primary or post-surgical OA

Design:
Experimental study, combined with CM&S
20 high activity patients



2.3 Task summary

The incidence of total knee arthroplasty (TKA) in patients aged ≤65 years has recently increased. The majority of these patients have ambitious expectations for post-operative recovery, hoping to return to sports activities. However, these expectations are generally unmet, as the entire clinical pathway is generally designed for older, frailer patients. The aim of the study is to evaluate clinical and functional outcomes in patients aged ≤65 years who underwent TKA with an uncemented implant and functional alignment at the two operative units “Clinica Ortopedica e Traumatologica 1” e “Ortopedia-Traumatologia e Chirurgia protesica e dei reimpianti d’anca e di ginocchio” and were subjected to an intensive rehabilitation protocol aimed at returning to sports activity.

2.4 Data used for preliminary assessment and validation

The pilot study includes 20 patients aged between 40 and 65 who will undergo total knee replacement surgery with an uncemented implant at the Rizzoli Orthopaedic Institute. All patients will follow a specific perioperative pathway aimed at adequate pain management, early functional recovery, and early return to sports activities. Preoperative investigations include magnetic resonance imaging, surface electromyography, clinical and instrumental muscle strength measurements, and Knee Society Score (KSS) administration. Exclusion criteria were rheumatic and/or neuromuscular diseases, extreme knee deformity, compromised bone quality, pregnancy, patients with diseases, or physical conditions incompatible with the use of magnetic resonance imaging. Clinical and functional assessments will be conducted at each follow-up at 1, 3, 6, and 12 months after surgery, while electromyography, dynamometer test, and gait analysis will be repeated at 6 and 12 months. All patients will follow a specific personalized intensive rehabilitation program for the early return to sports activities: they will be hospitalized at the Unit of Physical and Rehabilitation Medicine Rizzoli, and during their stay, they will be trained for a customized telerehabilitation program that will last up to 6 months after surgery. Proprioceptive strength and plyometric protocols will be employed to aid recovery and restore specific sports movements.

2.5 Devices employed in the study

Device #1	
Model	sEMG signals through active probes. Electromyographic recordings will be performed with an electromyography (EMG) system (Sessantaquattro; OT Bioelettronica)
What is it measuring? What is the role of the device in the study?	Surface electromyography to evaluate Knee Extensor and Flexor Muscle Activation from the following muscles: Gluteus Medius (GMD), Rectus Femoris (RF), Lateral Hamstring (LH), Medial Hamstring (MH), Vastus Medialis (VM), Vastus Lateralis (VL) in accordance with the SENIAM (surface EMG for a noninvasive assessment of muscles) recommendations
Total number of devices used in the study	1

Device #2	
Model	Dynamometric chair (COR 1; OT Bioelettronica) instrumented with a load cell (model TF033; CCT Transducers)
What is it measuring? What is the role of the device in the study?	*Maximal Voluntary Isometric Contraction*. Isometric knee extensor and flexor muscle strength will be assessed by means of a maximal voluntary isometric contraction (MVIC) at two knee angles, 30° and 90° of knee flexion. *Submaximal Isometric Contractions*. After the MVIC, submaximal sustained contractions were performed at 20%, 50%, and 80% of the maximal force recorded during the MVIC with the aim of assessing force steadiness and force accuracy

Total number of devices used in the study	1

Device #3	
Model	Home training (Homing Studio, Homing devices) TecnoBody, Italy
What is it measuring? What is the role of the device in the study?	*Homing Studio LCD monitor stands* to manage assessment and training with Homing. To train patients during their functional recovery, to monitor their return to performance, and to prevent injury. *Homing Devices* Device to perform home-telerehabilitation. It allows the best overload, proprioceptive, or balance training to recover from surgery.
Total number of devices used in the study	1+10

2.6 Developed models/algorithms/platforms

The algorithms to process the experimental data have been devised and tested over the years as part of previous research studies and include MATLAB codes to analyze motion capture, force plates, and surface electromyography (EMG) data from the gait assessment [1] as well as synchronized torques and EMG data collected during a maximal voluntary isometric contraction test on a dynamometer [2]. Experimental data processing is conducted according to the guidelines provided by the relevant scientific societies. Musculoskeletal models will be developed in OpenSim [3,4], using the generic Full Body model as a template [5].

2.7 Evaluation metrics and statistical analysis

For each patient, preoperative clinical and functional assessments will be performed, as well as at each follow-up at 1, 3, 6, and 12 months. The investigations include instrumental methods and clinical evaluations. All patients will undergo the FAST rehabilitation protocol. Devices that will be used for instrumental evaluation are supported by published protocols [6,7].

The ITALIAN version of Pre-Op and Post-Op questionnaire will be administered at the proper time points (©by The Knee Society).

All continuous variables will be expressed as mean ± standard deviation (SD) and range. Proper statistical analysis will be used to assess pre- and post-surgery variations. Categorical variables will be summarized in terms of absolute frequency and percentage.

For all tests, the significance level will be set at $p < 0.05$. All statistical analyses will be performed using SPSS 11.0 (SPSS, Chicago, IL, USA).

2.8 Results and discussion

Since the patient recruitment process is underway, the study is in a preliminary phase. Partial results, however, are available from some patients who underwent surgery with an uncemented prosthesis and followed a rehabilitation protocol with FAST characteristics, showing excellent radiographic, clinical, and functional outcomes in the early follow-ups. Returning to sports activities appears to be feasible, as evidenced by these patients progressively resuming running and athletic movements independently, with good results. However, these findings can only be confirmed, including statistically, as the study progresses.

2.9 Next steps

In the next 18 months, the enrolment phase will be completed, all the required preoperative investigations will be performed, and the follow-ups will be structured to collect all the necessary data for the analysis.

3. Task 2.3 – Personalized functional models for preoperative planning of High Tibial Osteotomy

3.1 Task leader

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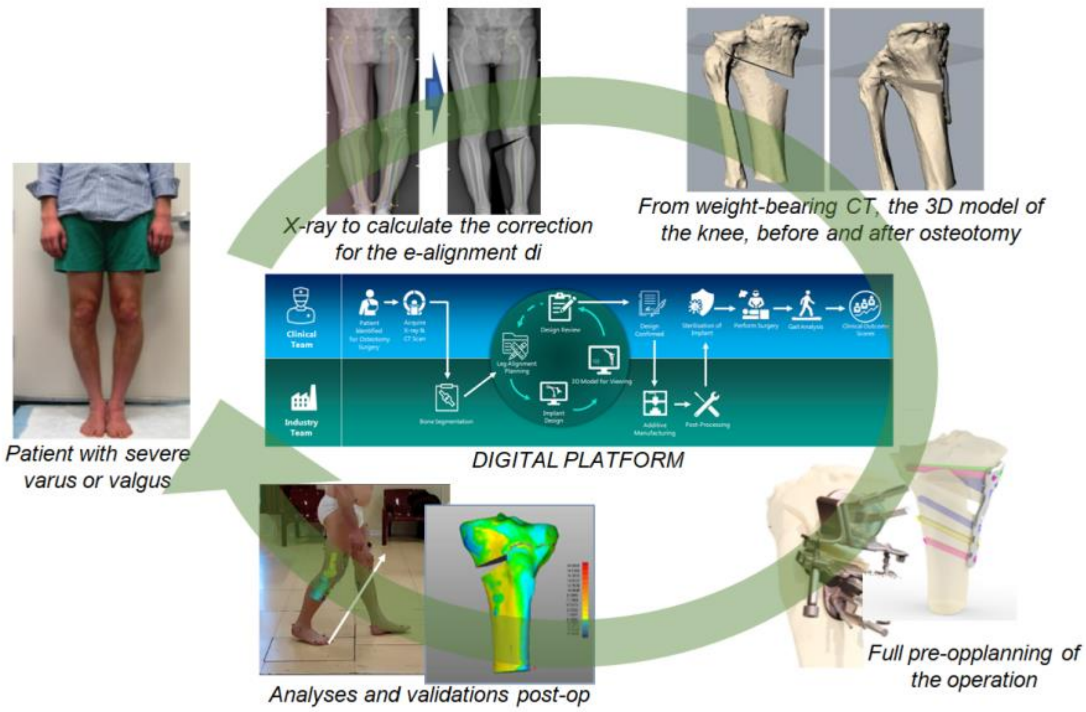
3.3 Graphical abstract



3.4 Task summary

Osteotomy at the human knee aims at treating surgically joint degenerative processes such as osteoarthritis in patients with varus or valgus malalignment; it is meant to slow down the progression of osteoarthritis, and thus to delay other more invasive and expensive interventions such as mono-compartmental or total knee replacements. The degree of interaction between the necessary relevant actors, i.e., surgeons and bioengineers in the hospitals and technologists in industry, is low. Unfortunately, a few digital tools are available to support this fundamental exercise of finding optimized solutions to each single patient, possibly at the point-of-care (POC). This implies critical steps of medical imaging analyses, anatomical modeling, implant design, and overall surgical planning. The development and accessibility to these software tools would definitely enhance surgical treatment, in the case also of remote access for surgeons working in small hospitals, at a distance from big experienced centers with state-of-the-art instruments and skilled surgeons and designers. The major objective of this task is to arrange an accessible platform for 'smart' planning of personalized knee osteotomies, whose operability will be tested in a selected group of distributed specialized surgeons. This "smart" approach for personalized knee osteotomy is expected to have positive effects on the overall workflow of surgical planning, possibly also reducing surgery and hospitalization times, in addition to better clinical outcomes. Design, planning, and complete comprehension of the osteotomy will be supported by biomodels and prototypes to be produced by 3D printers connected with the platform.

3.5 Data used for preliminary assessment and validation

State-of-the-art digital platforms are meant to be used for this sort of medical service to guarantee feasibility, traceability, control, privacy etc., at POC as required for healthcare in medicine. The dataset will be organized and managed according to current rules and legal aspects. These modern general-purpose platforms allow these services but need to be configured very carefully to gather the necessary information in the correct format and deliver the relevant digital products. The various development steps (imaging, modeling, designing, and planning) must be tracked, as well as the necessary checks, authorizations, orders, etc. Operability must be checked, and validation of the process must be performed on real clinical cases. In this respect, a data series of 25 patients operated already with these techniques (for which relevant datasets of medical imaging, implant design etc., are already available) will be processed again, and possible differences with respect to the previous standard tools will be assessed. Training would eventually be given to a number of young and older surgeons. New clinical cases will be eventually analyzed and carefully controlled; these can be from our IOR center in Bologna, but possibly also from other affiliated venues of Rizzoli in Sicily and Emilia-Romagna.

The present activities are now facilitated by the recent start of a unit where IOR has concentrated all the necessary resources, human and instrumental, i.e., the 3Dlab Unit. Because of this further step forward within the context of the present Task, and also because of the complexity of the design and relevant management, an organizational procedure has been recently developed according to the established quality management system ISO 9001/2015; this document is now the reference to guide the full process, from the initial hypothesis of a custom-made implant for a single patient to the implantation in the operating theatre of the corresponding medical device in that patient, including the 3D printing of anatomical biomodels and prototypes for the surgical guides.

3.6 Devices employed in the study

Device #1	
Model	Materialise Mimics FLOW
What is it measuring? What is the role of the device in the study?	Cloud-based collaboration for the surgical cases. Online storage and case sharing with Mimics Flow, including easy access to cloud capabilities like extended reality (XR), a 3D viewer, and AI-enabled segmentation
Total number of devices used in the study	1

3.7 Developed models/algorithms/platforms

Considering the functional specifications needed for the digital platform, a license for the Materialise Mimics FLOW software has been purchased. FLOW is a cloud-based relational database intended for storage, case sharing, collaboration, and process development tracking (Figure 1). When a Clinician – one of the 6 possible user roles in the system, together with Brand Admin, Planner/Engineer, Sales Representative, and Clinician Office Admin – needs a service provided by the unit, a new case is created and defined in FLOW (Figure 2). The exact fields to be filled in the records need to be determined in advance, during the development and validation phase of the software; these can be customized based on the specific request and activity for the surgical case, i.e., 3D Plan only, 3D Plan + printed biomodel/prototype, 3D Plan + surgical guides).

When managing a case that needs a surgical planning and/or a printing phase, Digital Imaging and Communications in Medicine (DICOM) files are directly loaded on the platform or otherwise a Materialise Mimics files containing the images and optionally the segmentation and/or planning, while the second one can be anonymized and linked to an identification code to be used in the existing electronic health records (EHR)/electronic medical records (EMR) system, which is not integrated with the platform. Once the case is created, the different users can manage it based on their role rights. The Planner/Engineer is responsible for preparing plans and design, whereas the Clinician can be designated only as a sharing target; in this case, the Clinician can monitor the evolution of the request, observe the 3D models, plan and design through (in collaboration with the Planner) comments and edits on the viewer (Figure 3). As a matter of fact, the cases can be shared and viewed online regardless of whether the collaborators have Mimics licenses or not.

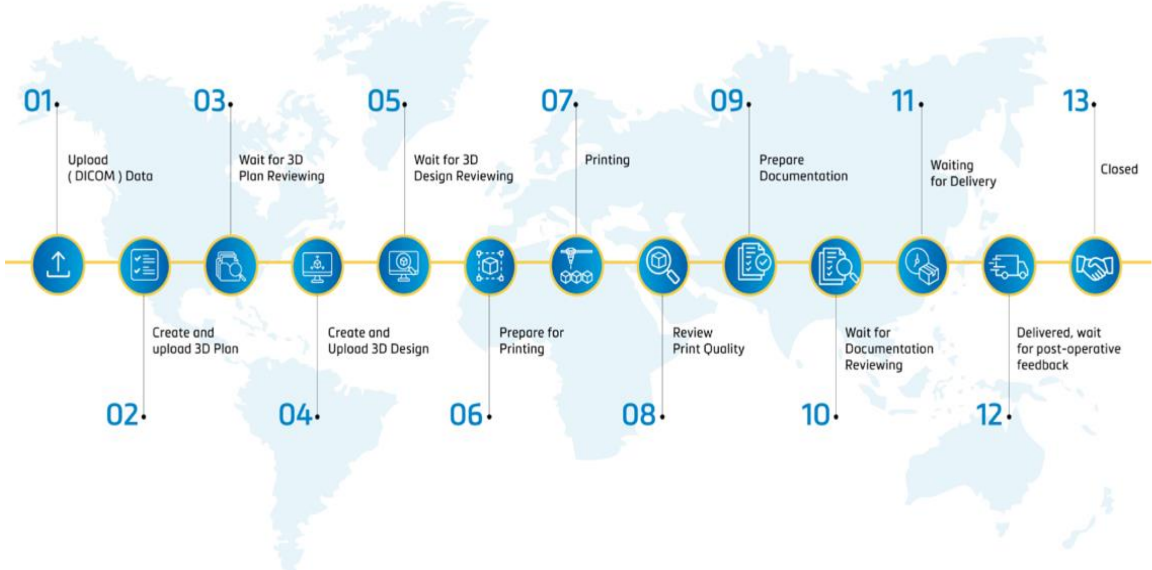


Figure 1. The workflow process defines the sequence of tasks necessary to complete a project or service efficiently.

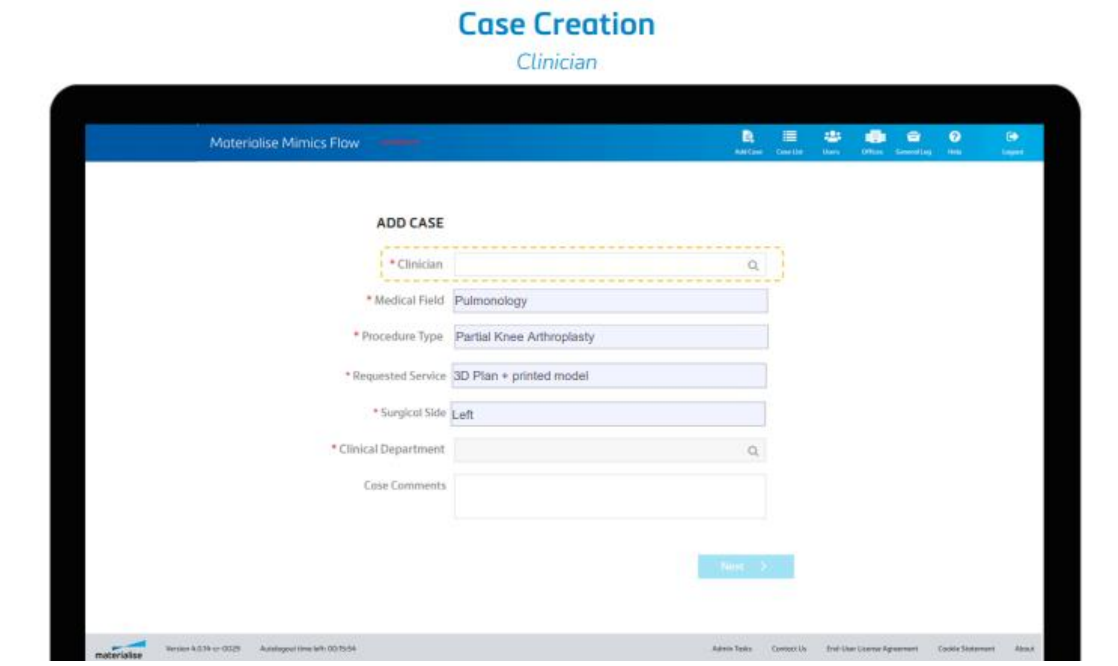


Figure 2. Software interface for the creation of a new case to manage with its relative specifications.

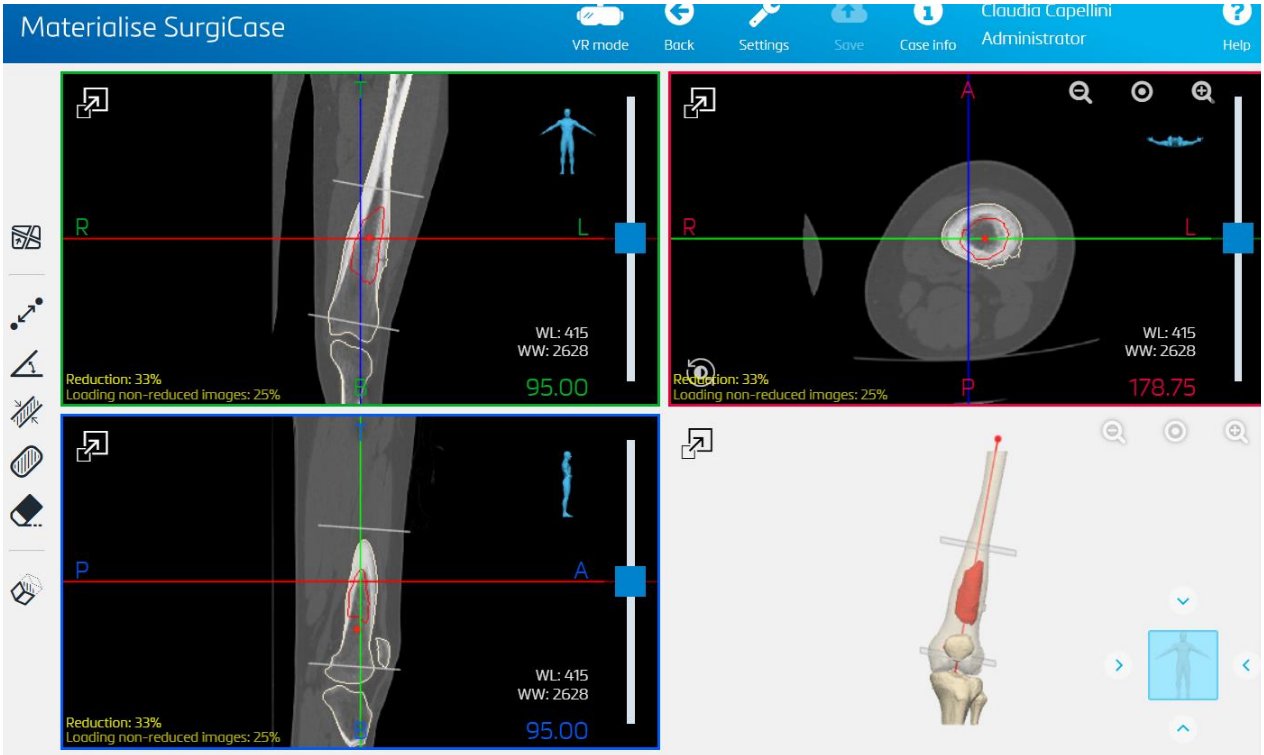


Figure 3. The segmentation process uses the three anatomical views and cutting planes viewer (bottom right). In the case of a bone tumor, indications and measurements can be added at any time.

3.8 Evaluation metrics and statistical analysis

First, starting with the evaluation of two already available platforms (by Adler and Orthoscape), the relative limitations for these pilot purposes were identified, and new steps needed to ensure feasibility, traceability, control, privacy, etc., for personalized orthopedic treatments in POC, were defined and implemented. Measurement of time in medical image uploading and overall data manipulation, as well as quantification of operational steps, were chosen as metrics for comparison with what was already available and for overall monitoring of the activities. As for the web interface, this is being developed according to the new POC-based operational procedure; since it is entirely innovative, there are no other experiences to compare with; thus, feedback from the various practitioners involved is used as an evaluation metric. Second, distance-map analysis is used to compare 3D reconstructions and planning of retrospective cases obtained previously using other platforms and tools with those made with the new platform. Descriptive statistics is used to derive the significance of differences. The overall quality of the digital models is also under investigation by using the corresponding biomodels and prototypes from the 3D printing processes associated with the platform.

3.9 Results and discussion

Comparison of the new smart platform with others available on the market showed no significant differences in image upload time; however, this stage is expected to be faster in the new smart platform after the direct connection between the new platform and the Vue-Pacs system for medical image storage is fully established. Also, from this comparison, it became clear the high number of operational steps (requests, approvals, monitoring, etc.) required to comply with the above-mentioned novel procedural process to regulate the various professional figures involved in the custom surgical planning process (surgeons, radiologists, engineers, etc.); these steps are not required in the standard platforms, where in addition to the surgeon and the corporate technologist no other professional figures are involved. The web interface is still under development based on the latter; currently, a temporary version has been released, but feedback is being gathered from all parties involved to fully implement the procedural flow steps, including the platform's ease of use. Regarding morphologic evaluations using retrospective cases, morphologic comparisons through distance-map analysis are still in progress. However, preliminary results show a good superimposition between 3D biomodels/prototypes (digital and physical), with sub-millimeter differences between the two models, i.e., far below the accuracy of medical imaging; however, it is planned to finalize evaluations of high tibial osteotomy cases first and then to consider other surgical treatments as well. What has been achieved so far is in line with expectations, especially in terms of timing and operability. The validation process and the obtained results are encouraging and meet the needs and requirements of the Task.

3.10 Next steps

In the next 22 months, researchers are meant to complete the configuration of the platform, run a number of previous High Tibial Osteotomy (HTO) taken from retrospective case studies, and continue to evaluate the operational performance of the platform and the accuracy of 3D modeling in HTO surgical planning. Moreover, a few new surgical cases are meant to be carried out: HTO but also other, more complex, knee osteotomies as well as arrange training of the surgeons and all those involved in the procedural process and improve connections of the platform with 3D printing facilities (in-house and also outside), including different technologies and materials.

4. Task 2.4 – Predicting the risk of bone fracture in patients with metastatic carcinoma

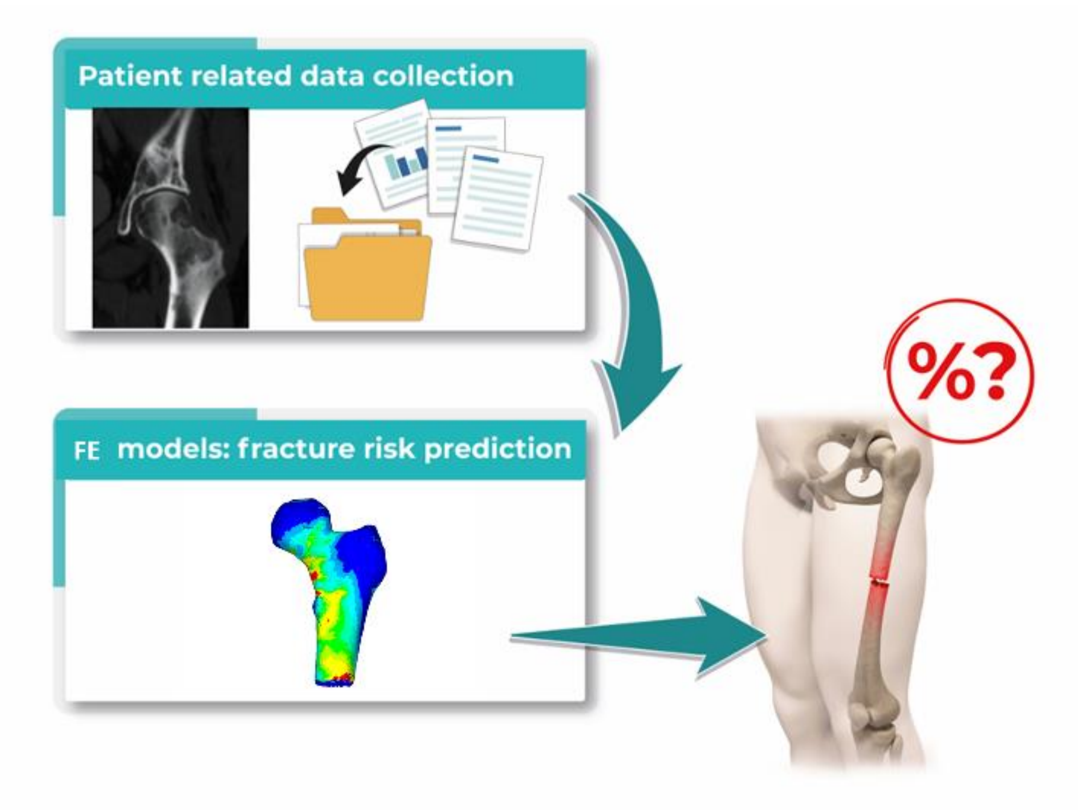
4.1 Task leader

PI: Laura Campanacci (IOR)

4.2 Task keypersons

Laura Campanacci (IOR)
Davide Donati (IOR)
Barbara Dozza (IOR)
Costantino Errani (IOR)
Tommaso Frisoni (IOR)
Antonino Amedeo La Mattina (IOR)
Cristina Curreli (IOR)

4.3 Graphical abstract



4.4 Task summary

The study aims to develop a decision support system capable of predicting the risk of pathological fractures and prognosis in patients with bone metastases, allowing clinicians to select a treatment more tailored to the patient. These researchers will collect retrospective data from patients with metastatic cancer from the IOR database. This database will serve as the foundation for the development of a biomechanical computational model that will provide an objective fracture risk assessment and assist doctors in choosing the most appropriate treatment for the patient.

4.5 Data used for preliminary assessment and validation

Data on patients diagnosed with bone metastases in the proximal femur due to carcinoma between 2004 and 2023 will be retrieved from the institutional archives of the Istituto Ortopedico Rizzoli and used for the preliminary assessment and validation of a decision support system designed to predict the risk of pathological fractures and prognosis in patients with bone metastases. The inclusion criteria are as follows:

- Diagnosis of proximal femoral metastasis from carcinoma
- Male and female patients
- Patients who were not surgically treated and admitted to the Istituto Ortopedico Rizzoli between 01/01/2004 and 31/12/2023 (including follow-up)
- Age ≥ 18 years
- Availability of at least one CT image without fracture (baseline CT) and one image (CT, X-ray, MRI, or PET) performed after the baseline CT
- One or more follow-ups within 12 months from the baseline CT

4.6 Devices employed in the study

Not applicable

4.7 Developed models/algorithms/platforms

The biophysical model will be developed using a subject-specific finite element (FE) model to estimate femoral strength, following the validated Bologna Biomechanical Computed Tomography (BBCT) workflow. Quantitative computed tomography (QCT) scans of the hip region, along with patient data (e.g., weight, height), will inform the personalized computational model, enabling the simulation of proximal femur crack propagation and the prediction of femoral fracture risk at the time of CT acquisition. Various loading scenarios, such as in walking, sideways falls, and stair climbing, will be considered to provide a comprehensive overview of the metastatic femur fracture risk.

The main stages of the computational pipeline include:

i) image segmentation;

ii) anatomical landmarking;

iii) meshing;

iv) mapping of mechanical material properties;

v) definition of boundary conditions;

vi) FE simulations.

4.8 Evaluation metrics and statistical analysis

The prediction and stratification accuracy will be evaluated to demonstrate the validity of the computational pipeline. Specifically, the biomechanical quantities of interest extracted from the simulations (e.g., strain and failure load) will be used to differentiate between fractured and non-fractured patients. These results will be compared with clinical observations. Given the nature of the study, both descriptive and inferential statistics will be applied. Additionally, to assess the credibility of the modeling pipeline, typical verification activities outlined in the ASME VV40 standard and the recently proposed FDA guidance, Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions, will be considered.

4.9 Results and discussion

The study protocol for this clinical trial and all documentation necessary for the submission of the study to the local ethical committee were completed and submitted to the Ethical Committee. The research group received the approval of the Ethical Committee, as well as the necessary "nulla osta" from the General Director of the Institute hosting the study. A preliminary screening of their database identifies approximately 100 potential patients whose data can be processed using the biophysical model. The modeling pipeline has been revised for the identified context of use. In particular, the simulation of crack propagation has been included in the computational workflow.

4.10 Next steps

In the coming months, researchers are planning to apply the computational workflow, refined for the study's specific use case, to the data selected from the database. The prediction and stratification accuracy will be evaluated to demonstrate the validity of the computational pipeline.

5. Task 2.5 – Cardiovascular radiomics analysis to predict coronary arteries and carotids disease in medium and low risk patients

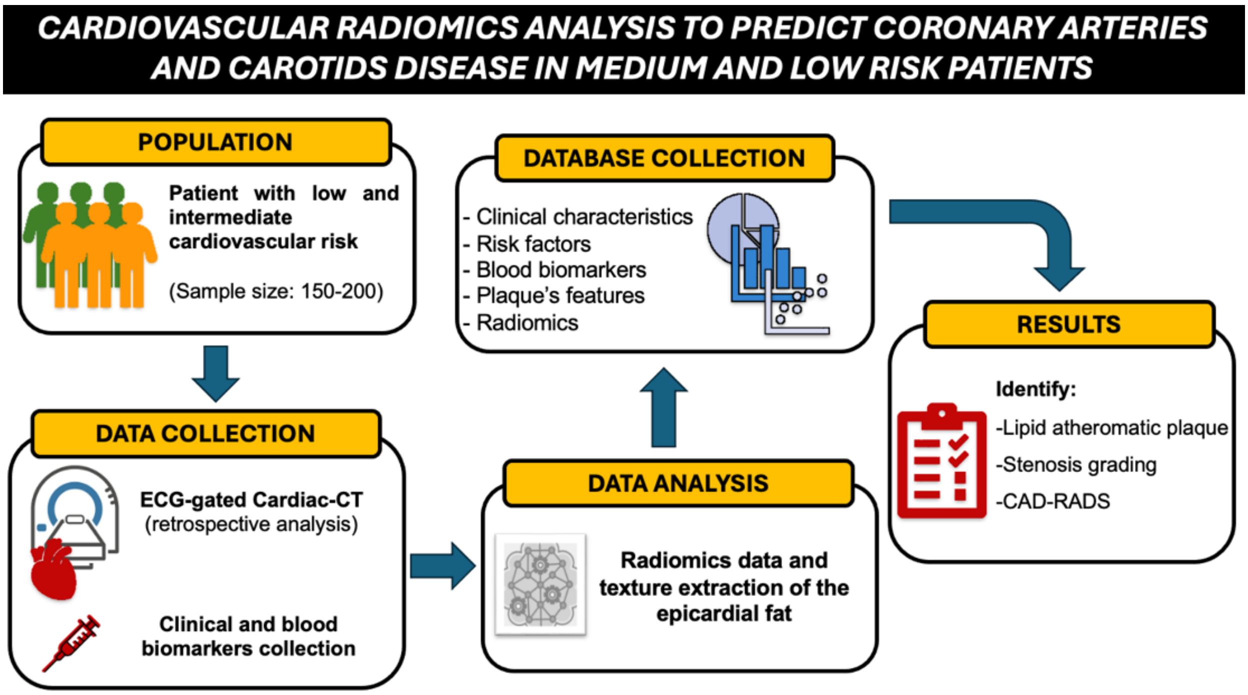
5.1 Task leader

Francesco Garaci (UNIROMA 2)

5.2 Task keypersons

Francesco Garaci (UNIROMA 2)
Eliseo Picchi (UNIROMA 2)

5.3 Graphical abstract



5.4 Task summary

To predict coronary disease in low and middle-risk patients for heart diseases. The radiomic features of the epicardial fat are being extracted from the Computed Tomography (CT) data to predict the presence of lipid atheromatous plaque and the lumen stenosis of the three main coronary vessels (circumflex artery, anterior descending, and right coronary arteries); a correlation with the Coronary Artery Disease-Reporting and Data System (CAD-RADS) score will be investigated, too. By using ensemble-type machine learning models, the features will be processed and analyzed to determine the most predictive variables.

This retrospective single-center analysis will collect and analyze data from the University Hospital of Rome Tor Vergata.

5.5 Data used for preliminary assessment and validation

The study was conducted on 128 patients with low to intermediate cardiovascular risk according to the 2021 European Society of Cardiology (ESC) Guidelines and Heart Score; patients underwent cardiac computed tomography scans without and with contrast medium for known or suspected coronary artery disease.

The demographic features of the enrolled population are reported in the following table.

Age (years old)	52.3 ± 13.3
Gender (M, F)	76M, 52F
Hypertension, n (and %)	75 (59%)
Smoke, n (and %)	56 (44%)
Diabetes, n (and %)	37 (29%)
Dyslipidemia, n (and %)	64 (50%)

Table 1. Demographic features of the enrolled population. M: male; F: female; n: number; %: percentage.

Radiomics features have been extracted using MaZda software 4.6. The data were then processed with the Weka data mining platform (v3.8.5). The risk of overfitting has been reduced by the pre-processing of the extracted radiomics features and selecting the features with the highest correlation with the final event and the lowest correlation between the same features. The "CfsSubsetEval" analysis has been used to identify a subset of features that are highly correlated with the class while having low inter-correlation between them. The dataset was split randomly from R software. No specific techniques have been used to prevent data leakage.

Patients were split into non-overlapping groups to ensure independence:

i) Training: 50% (64 patients)

ii) Validation and Test: 50% (64 patients)

5.6 Devices employed in the study

Device #1	
Model	General Electric Healthcare Revolution Computed Tomography
What is it measuring? What is the role of the device in the study?	Plaque composition and stenosis through workstation Advantage Workstation (AWD) 4.7 (General Electric)
Total number of devices used in the study	1

5.7 Developed models/algorithms/platforms

All the acquired images were collected in the local Picture Archiving and Communication System (PACS), which is starting to interact with Electronic Health Records (EHR) / Electronic Medical Records (EMR) systems. The PACS adheres to DICOM standards.
Data transmission is in DICOM 3.0 format between modalities and PACS, in DICOMWL format between the Radiology Information System (RIS) and modalities, and in Healt Level 7 format between all systems, including those external to the department. Storage is done on fast redundant array of independent disks (RAID) systems, and protection is achieved through compression and encryption.
Access to systems and data occurs via corporate Lightweight Directory Access Protocol (LDAP) authentication, where groups and permissions are defined for what each user is allowed to see, modify, and manage.
The systems are redundant. In parallel, there is a second system with a database and storage aligned with the primary one in production. Furthermore, the data is written on WORM tape stored in a fireproof safety cabinet. The systems are regularly updated with the latest security patches and protected by a specific antivirus.

a. Receiver operating characteristic (ROC) curves of 10 machine learning models were analyzed to create an Ensemble Machine Learning model using models with the best accuracy, sensitivity, and specificity, with an AUC $\geq$ 0.7. The following models were used:
b. The Random Forest model [sensitivity of 0.66; specificity of 0.00; negative predictive value of 0.00; positive predictive value of 0.78; accuracy of 0.76 (95% CI: 0.383, 0.713)].
c. The Naive Baynes model [sensitivity of 0.74; specificity of 0.43 with a negative predictive value of 0.85; positive predictive value of 0.30; accuracy of 0.68 (95% CI: 0.5135, 0.825)].

d. The Support Vector Machine (SVM) model [sensitivity of 0.66; specificity of 0.17; negative predictive value of 0.20; a positive predictive value of 0.63, accuracy of 0.50 (95% CI: 0.3338, 0.6662)].
e. The Smart Vibration-based Machine Learning (SVML) model [sensitivity of 0.64; specificity of 0.10; negative predictive value of 0.01; positive predictive value (ppv) of 0.67, accuracy of 0.50 (95% CI: 0.3338, 0.6662)].
f. The K-Nearest Neighbors (KNN) model [sensitivity of 0.73; a specificity of 0.32; negative predictive value of 0.55; positive predictive value of 0.55, with accuracy of 0.53 (95% CI: 0.3582, 0.6902)].
g. The Classification and Regression Tree (CART) model [sensitivity of 0.70; specificity of 0.00; negative predictive value of 0.00; positive predictive value (ppv) of 0.96; accuracy of 0.68 (95% CI: 0.5135, 0.825)].
h. The General Linear Model (GLM) [sensitivity of 0.71; a specificity of 0.00; negative predictive value of 0.00; positive predictive value (ppv) of 0.00; with accuracy of 0.71 (95% CI: 0.541, 0.8458)].
i. The Partial Least Squares (PLS) model [sensitivity of 0.70; specificity of 0.00; negative predictive value of 0.96; positive predictive value (ppv) of 0.00; accuracy of 0.68 (95% CI: 0.5135, 0.825)].
j. The Linear discriminant analysis (LDA) model [sensitivity of 0.71; a specificity 0.00; negative predictive value of 0.00; positive predictive value of 0.00, with accuracy of 0.71 (95% CI: 0.541, 0.8458)].
k. The Neural Network (NNET) model [sensitivity of 0.65; specificity of 0.00; negative predictive value of 0.00; positive predictive value of 0.00; accuracy of 0.55 (95% CI: 0.383, 0.7138)].
l. The Xtreme Gradient Boosting (XBG) model [sensitivity of 0.66; specificity of 0.00; negative predictive value of 0.00; positive predictive value of 0.78; accuracy of 0.55 (95% CI: 0.383, 0.7138)].

5.8 Evaluation metrics and statistical analysis

The Ensemble Machine Learning model combined with coronary plaque data showed a sensitivity of 1.00 and specificity of 0.93 with a negative predictive value of 1.00 and a positive predictive value of 0.85, with an accuracy of 0.95 (95% CI: 0.9221-1); this Ensemble Machine Learning model is commonly used in the literature to evaluate different conditions.

The score that maximizes the Youden index (sensitivity + specificity -1) was evaluated as the best score to discriminate the two classes.

To summarize the results, a confusion matrix was used to study the overall diagnostic performance of the proposed score.

5.9 Results and discussion

The Ensemble Machine Learning model demonstrated high diagnostic accuracy (95%) and specificity (93%) using data obtained from Random Forest, SVM, and Radial Basis Functions, as reported in Figure 1; furthermore, the sensitivity reaches approximately 99% in predicting lipid-rich plaques causing coronary lumen stenosis of 70% and CAD-RADS >4.

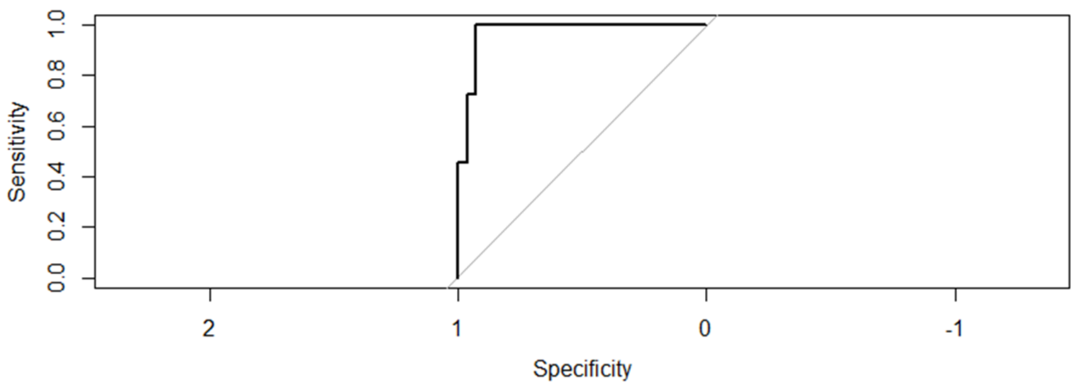


Figure 1. Sensitivity and specificity of the analyzed Ensemble Machine Learning model

Excess lipid deposit in diet-induced obesity and insulin resistance has been shown to be related to adipose tissue with lower CT attenuation with adipocyte hypertrophy and hyperplasia and insulin resistance. This adipose tissue produces many molecules, such as plasminogen activator inhibitor-1 (PAI-1) and monocyte chemoattractant protein-1 (MCP-1), which are associated with low-grade systemic inflammation and an increased risk of vascular inflammation and atherosclerosis progression. Furthermore, low-density EAT is associated with a reduction in the level of adiponectin, a protective factor on inflammation and atherogenesis, thus increasing the risk of acute coronary syndrome and progression of atherosclerosis.

Inflammatory biomolecules not only cause coronary microvascular endothelial inflammation, oxidative stress, reduced nitric oxide, and loss of cardiomyocytes but also directly influence immune cells in the heart, causing chronic local inflammation. Activation of the NLRP3 inflammasome, which causes the secretion of IL-1-β and IL-18, is one of the identified inflammatory patterns. While IL-18 causes fibrosis and cardiac hypertrophy, which can cause diastolic stiffness and concentric remodeling, IL-1-β reduces the expression of SERCA (sarcoplasmic reticulum calcium ATPase) and phospholamban (PLB). Consequently, the relationship between coronary atheromasia and chronic inflammation suggests the possibility of using mediators of these patterns as clinical targets.

Assessing the characteristics of epicardial adipose tissue in patients who undergo a CT scan of the chest even without contrast medium would make it possible to stratify the risk of these patients and to choose which of them are worthy of further diagnostic investigation as they are at greater risk of having coronary artery disease.
The validation process and the obtained results are encouraging and meet the primary endpoint of this task.

5.10 Next steps

During the next months, the data analysis will be extended to over 200 patients, and clinical-anamnestic data (e.g., diabetes, hypercholesterolemia, hypertension, smoking) will be considered and added to the analysis to increase the diagnostic accuracy of the predictive model.

6. Task 2.6 – Risk of Sleep Disorders in Older Sarcopenic and Physical Frail Patients

6.1 Task leader

PI: Marcello Giuseppe Maggio, (UNIPR)

6.2 Task keypersons

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Chiara Cattabiani (AOUPR)

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Valeria Ribatezzato (UNIPR)

Beatrice Tanzi (UNIPR)

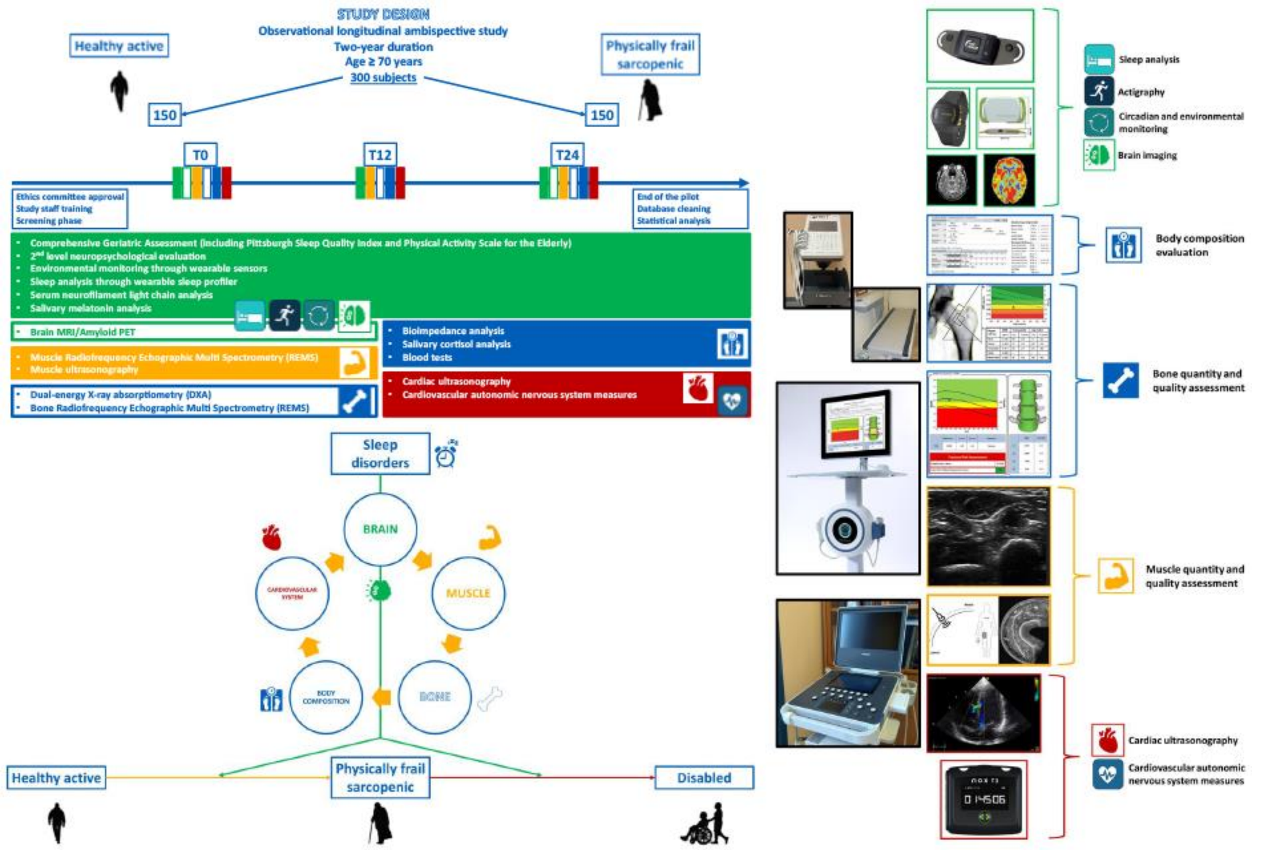
Elisa Galli (UNIPR)

Marta Leone (UNIPR)

Elisabeth Imperatore (UNIPR)

Salvatore Vincenzo Anfuso (UNIPR)

6.3 Graphical abstract



6.4 Task summary

A well-characterized sex-balanced sample of community-dwelling, physically frail, sarcopenic, and healthy, active older people from 70 years of age, not demented and independent in the Basic Activities of Daily Living, will be evaluated.

The role of sleep disorders on physical and cognitive function, as well as bone and muscle metabolism, will be evaluated in an observational and prospective study at baseline and 12 and 24 months later, with certain exceptions.

The following examinations will be performed: brain MRI, amyloid PET, Dual-energy X-ray absorptiometry, bioimpedance analysis, cardiac ultrasonography, sleep analysis, environmental monitoring and actigraphy through wearable devices, blood and salivary tests, muscle ultrasonography, and muscle and bone radiofrequency echographic multi spectrometry (REMS).

The use of the most advanced diagnostic and digital health techniques will allow us to detect, in a comprehensive and translational way, changes in brain, muscle, hormonal milieu, cardiovascular system, skeletal and body composition.

6.5 Data used for preliminary assessment and validation

The research group in charge of the study has experience in conducting both prospective observational studies and randomized clinical trials in populations consisting of healthy active, physically frail, and sarcopenic older subjects (see, for example, the SPRINTT project and the current Trajector-AGE study). To date and based on the available knowledge, an analysis of sleep disorders in this population and for these purposes has never been performed. There is also a lack of data in the Geriatrics field on the usefulness of comprehensive and translational ways by which sleep disorders in this population can be assessed.

By considering the primary objectives (the evaluation of the effect of sleep disorders on the incidence of sarcopenia and physical frailty and mobility disability in community-dwelling healthy active, and physically frail sarcopenic elderly individuals), the statistical power calculation was performed using the relative risk of developing sarcopenia and physical frailty as well as mobility disability in the above-mentioned two groups. The obtained a priori calculation suggests a sample size of 145 subjects per group, rounded to 150 per group to account for possible drop-out.

Researchers will plan to enroll community-dwelling, physically frail sarcopenic and healthy active older adults from 70 years of age and attending the geriatric and sleep medicine outpatient clinics, not demented and independent in the Basic Activities of Daily Living.

6.6 Devices employed in the study

Device #1	
Model	Sleep profiler, X8 29-1001
What is it measuring?	Sleep architecture
What is the role of the device in the study?	Home-based sleep analysis
Total number of devices used in the study	2

Device #2	
Model	Nox T3s
What is it measuring?	Thorax and abdomen respiratory movements Nasal/mask pressure Audio and snoring signal Position Activity SpO2 Pulse Plethysmography

What is the role of the device in the study?	Cardio-respiratory recording during sleep
Total number of devices used in the study	2

Device #3	
Model	GENEActiv
What is it measuring?	Accelerometer Light exposure Skin temperature
What is the role of the device in the study?	Actigraphy and environmental monitoring
Total number of devices used in the study	8

Device #4	
Model	Dynaport 7
What is it measuring?	Accelerometer Gyroscope Barometer Temperature
What is the role of the device in the study?	Actigraphy and environmental monitoring
Total number of devices used in the study	8

Device #5	
Model	5500G
What is it measuring?	Echocardiography and muscle ultrasound
What is the role of the device in the study?	Cardiac morphological and functional assessment Muscle quantity and quality assessment
Total number of devices used in the study	1

Device #6	
Model	EchoS
What is it measuring?	Bone and muscle radiofrequency echographic multi-spectrometry (REMS)
What is the role of the device in the study?	Bone and muscle quality assessment
Total number of devices used in the study	1

Device #7	
Model	InBody S10
What is it measuring?	Bioimpedance analysis
What is the role of the device in the study?	Body composition evaluation
Total number of devices used in the study	1

6.7 Developed models/algorithms/platforms

Data and information from the diagnostic methods used in the pilot project will be stored and transmitted in the manner and standards prescribed by the enrolling institution (University Hospital of Parma) for the respective instruments. The instruments will be inventoried and approved for clinical use by the clinical engineering service of the University-Hospital of Parma.

Authentication and authorization to access the data collected for the different diagnostic platforms will be obtained to make available the information acquired during medical examination and comprehensive geriatric assessment. These data will be stored in a web application (according to the existing rules and standards) for building and managing online databases available to the clinical research service of the enrolling institution.

To mitigate such risks as data breaches and data loss, the research group will adopt the following procedures: a) preliminary evaluation of all diagnostic tools used by the clinical engineering service of the enrolling institution, b) preliminary training of project collaborators, c) constant supervision by the Principal Investigator on the production and storage of the data produced, d) the use of proven and validated safety data collection and storage tools.

6.8 Evaluation metrics and statistical analysis

Incidence, prevalence, and mortality among the groups will be compared using a chi-square test, adjusted for age and sex. Both multivariate logistic regression and Cox multivariate regression analysis will be performed to identify confounding factors influencing the incidence of sarcopenia and physical frailty as well as mobility disability in the two groups. Changes in diagnostic parameters and measures, quality of life, social well-being, and use of healthcare services in the two groups will be compared by ANOVA, if reported as means, or non-parametric tests (Mann–Whitney), whether calculated as medians. Correlations between continuous variables will be tested by multivariate linear regression analysis, adjusted for possible confounders, while skewed distributed values will be log-transformed to approximate normal distribution before entering into regression analysis. All sample sizes mentioned above could cover possible missing values. Statistical significance will be set for $p < 0.05$.

6.9 Results and discussion

The project will allow the analysis of relevant outcomes for the older population to compare the ability of current and innovative digital measurements in predicting trajectories of low physical and cognitive function and quality of life. The expected findings will highlight the importance of sleep as a significant determinant of muscle, brain, and metabolic health.

6.10 Next steps

In the next 18 months, researchers expect to achieve final approval for study initiation by the sponsoring and enrolling institutions, acquisition of all the diagnostic tools needed to conduct the study, as well as their preliminary evaluation by the clinical engineering service of the enrolling institution, the set up of the data collection system by the clinical engineering service of the enrolling institution, completion of enrollment, and reassessment of the statistical power of the study based on preliminary results.

7. Task 2.7 – Physiological models to neurorehabilitation

2.7a Toward a digital twin of postural stability in the elderly

7.1 Task leader

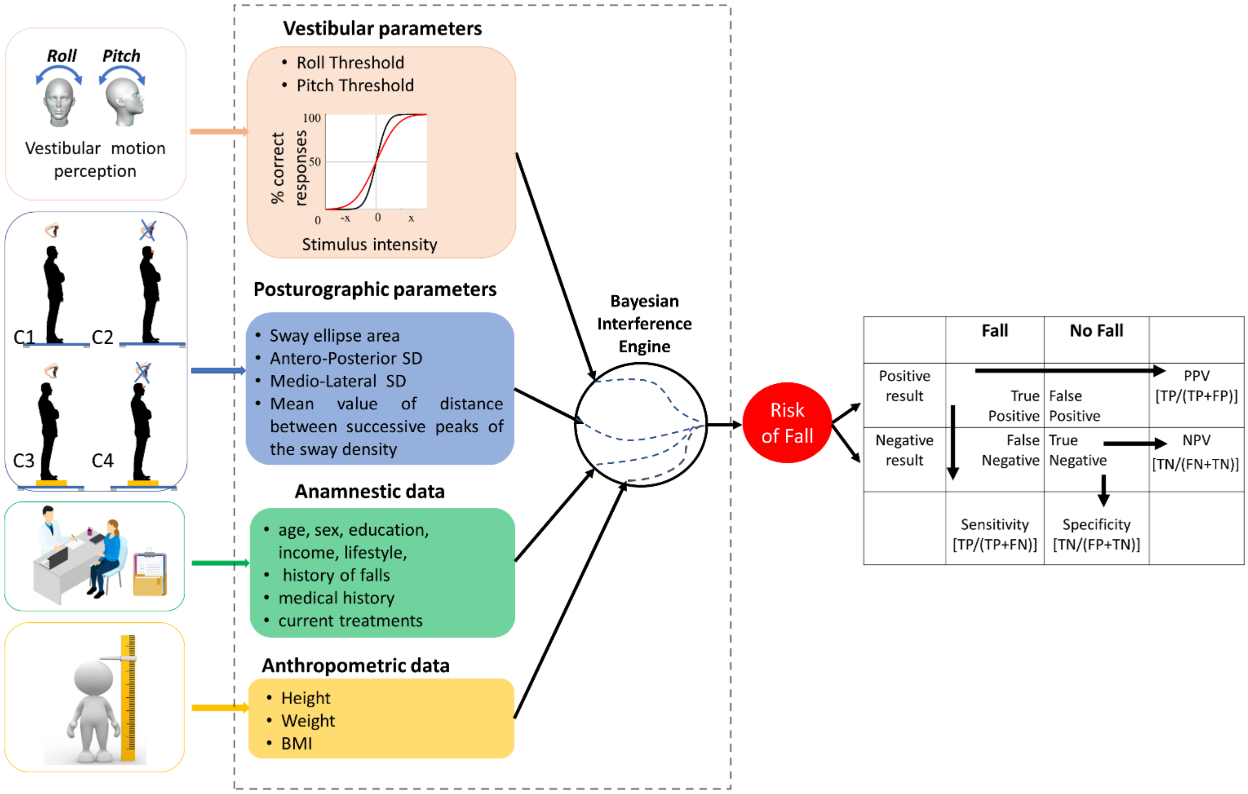
PI: Myrka Zago (UNIROMA 2)

Co-PI: Francesco Lacquaniti (UNIROMA 2)

7.2 Task keypersons

Co-PI Barbara La Scaleia (Laboratory of Neuromotor Physiology, IRCCS Santa Lucia Foundation, Rome)

7.3 Graphical abstract



PCA and cluster analysis

7.4 Task summary

The task aims at assessing the individual posterior probability of fall risk in older adults based on prior data and individual likelihood. A multifactorial model will be developed to predict fall risk, considering the complex interaction of sensory systems and neuromotor mechanisms that regulate balance. The prior is derived from a reference population, while the likelihood for each individual will be estimated using various behavioral, anamnestic, anthropometric, and clinical-hematological parameters. The primary outcome: number of falls recorded over 6 months after posturography. Falls are defined as events in which the person unintentionally comes to rest on the ground or other lower supporting surface unrelated to a medical incident or to an overwhelming external physical force. Secondary outcomes: sway ellipse area, Root Mean Square of sway in the AnteroPosterior and MedioLateral directions

7.5 Data used for preliminary assessment and validation

One hundred thirteen participants (28 females; 85 males) aged 65 to 75 with Type 2 Diabetes (T2D) were recruited, with a sample size based on a pre-test fall probability of 30%. The recruited cohort had an unintentionally uneven sex balance, as men volunteered more frequently to participate.

Age-related and T2D-related declines in neuromuscular, sensory, and cognitive functions can compromise postural control and increase fall risk. The study, therefore, integrates anthropometric, clinical, and laboratory data, together with postural parameters assessed using the Romberg test and vestibular parameters assessed during passive self-motion (vestibular thresholds).

During the Romberg test, participants are asked to maintain balance under four experimental conditions: with feet together and arms crossed, with eyes open or closed, and on either a rigid or compliant surface. The center of pressure oscillations were measured using a force platform. Vestibular thresholds for motion discrimination assess the vestibular system's ability to perceive head and body movements. These thresholds represent the minimum amount of motion required to detect the direction of passive movement reliably.

Posturographic parameters, such as sway ellipse area, anterior-posterior standard deviation, medio-lateral standard deviation, and the mean distance between successive peaks in sway density, along with vestibular thresholds, are evaluated.

7.6 Devices employed in the study

Device #1	
Model	6DOF hexapod motion platform: MOOG MB-E-6DOF/12/1000Kg, East Aurora, New York, USA
What is it measuring? What is the role of the device in the study?	Device used to assess vestibular movement thresholds
Total number of devices used in the study	1

Device #2	
Model	Kistler force plate (Type 9260AA6 Kistler, Winterthur, Switzerland).
What is it measuring? What is the role of the device in the study?	Force plate used to evaluate posturographic parameters
Total number of devices used in the study	1

7.7 Developed models/algorithms/platforms

Posturographic parameters, along with vestibular thresholds, are correlated with participants' medical history, lifestyle, and anthropometric data (age, sex, lifestyle, medical history, current treatments).

Principal Component Analysis (PCA) is employed to reduce the dimensionality of the data related to fall risk factors. First, the correlation between variables is assessed, and in PCA, a subset of variables with a correlation below 90% is retained. Next, cluster analysis is applied to group the data into homogeneous clusters based on the risk factors identified through PCA. This approach enables the identification of different fall risk categories within the study population.

K-means clustering for numerical data was applied, with random initialization of the cluster centroids (performed with 2000 replications to minimize the risk of getting stuck in local minima). When both numerical and categorical data are involved, the K-prototypes method was used to cluster the data. The k-prototype combines k-means (for numerical data) and k-modes (for categorical data). K-prototypes were implemented in R, using 2000 randomly chosen initial cluster prototypes.

7.8 Evaluation metrics and statistical analysis

The normality of the distribution of data with the Kolmogorov-Smirnov test was verified, and the homoscedasticity in different samples was verified with the Bartlett test. When the data were not normally distributed, non-parametric statistics (Wilcoxon rank sum test) were used.

To check for a correlation between the vestibular thresholds in roll and those in pitch, a linear regression was carried out (MATLAB function *fitlm* with option RobustOpts=on, using the bisquare weight function) between the log-transformed threshold values. Multiple logistic regressions were used to model the relationships between the vestibular clusters and the demographic, clinical, and biochemical parameters. Stepwise regression analysis was performed using the MATLAB function *stepwiseglm*, which uses a mixed forward and backward stepwise procedure. The models with the lowest Akaike Information Criterion (AIC) score were retained. The accuracy and predictive capability of the developed

Bayesian model will be evaluated using fall events recorded over 6 months following the subject's assessment. The Bayesian model thus developed will allow the integration of various sources of information and the identification of key risk factors associated with falls, enabling a more accurate assessment of fall risk and better personalization of prevention strategies.

7.9 Results and discussion

Preliminary results suggest that assessing vestibular thresholds helps identify individuals with greater postural instability. Participants with significantly higher thresholds exhibited an increased incidence of postural instability, as assessed through the Romberg Test and posturography. Furthermore, elevated vestibular thresholds were associated with longer diabetes duration, poorer glycemic control (higher HbA1c), and hypertension. Therefore, impaired vestibular perception of self-motion and diabetes as specific risk factors for postural instability were identified. Additionally, quantitative models to correlate vestibular parameters with clinical-biochemical parameters were developed.

7.10 Next steps

In the next 18 months, researchers plan to develop advanced models that establish correlations between vestibular parameters and posturographic metrics. These models will provide a deeper understanding of how vestibular function influences postural stability. To validate the reliability and applicability of developed models, fall diaries from patients will be used, which will serve as a real-world dataset to test and refine predictions. By stratifying fall risk levels based on the classification of individuals according to the key characteristics that describe their behavior, the models' accuracy in identifying fall risks and their predictive power in forecasting future instability events will be evaluated. The ultimate goal is to create robust predictive tools capable of supporting clinical decision-making and personalized interventions for fall prevention.

2.7b Early detection of children with Cerebral Palsy (CP)

7.1 Task leader

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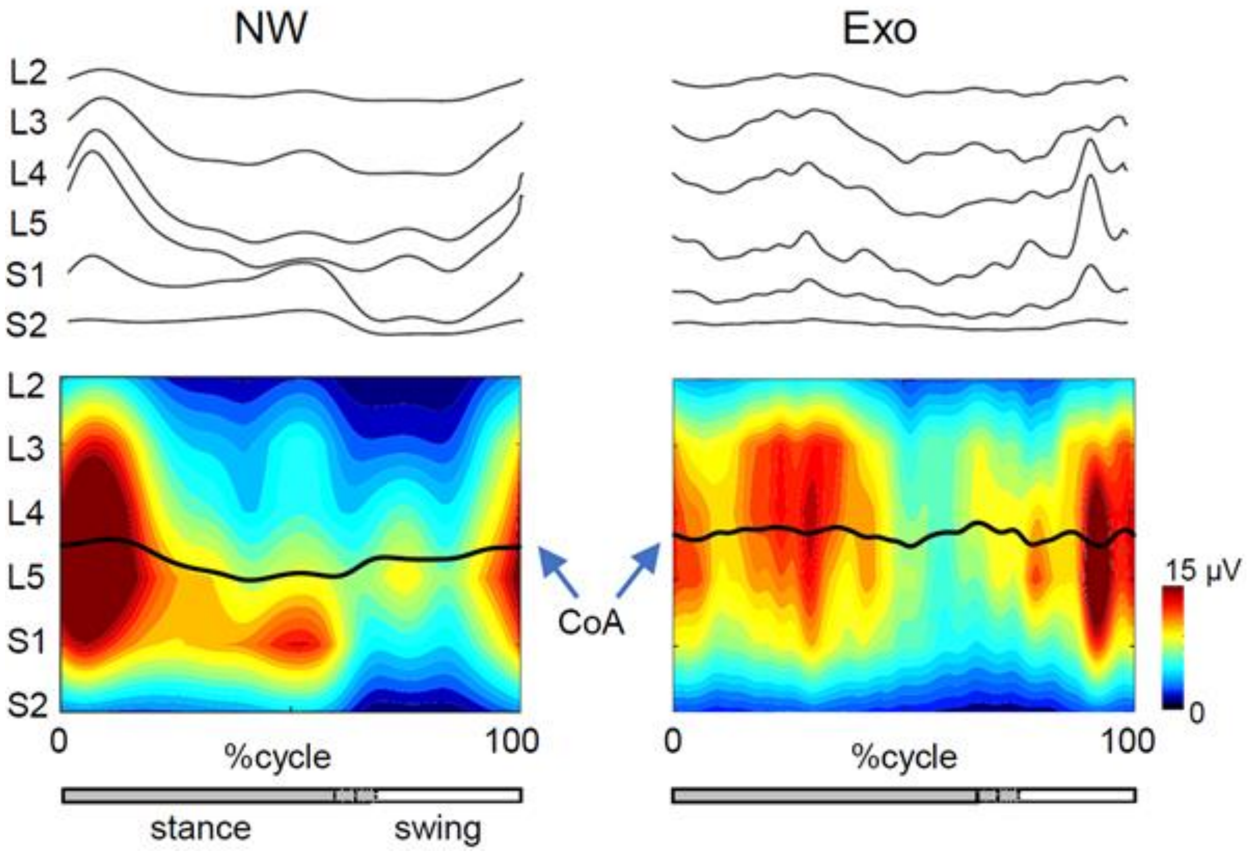
7.3 Graphical abstract



7.4 Task summary

Aims: Detection of pathological patterns of EMG, kinematics, and dynamics in children with Cerebral Palsy (CP) or at risk of developing CP. Assessment of locomotion with exoskeletons.

Results: researchers assessed the effects of a robotic exoskeleton (ExoAtlet Bambini) on gait performance of TD children by recording electromyographic activity of leg muscles and analyzing the corresponding spinal motor pool output.

Conclusions: This work shows promise as a valuable technique for analyzing exoskeleton performance to help children develop their natural gait generation pattern and to guide system optimization in the future for inclusion into clinical care.

7.5 Data used for preliminary assessment and validation

Six healthy children (age range 7-11 years old, height 1.25-1.43 m, weight 29-33 kg) participated in this study. They had no known neurological disorders or other impairments that would have prevented them from walking in the exoskeleton. Experiments were performed in the Laboratory of Neuromotor Physiology of IRCCS Santa Lucia Foundation. The study conformed to the Declaration of Helsinki and was performed according to the procedures of the Ethics Committee of the Santa Lucia Foundation for walking in the exoskeleton. Each child's parents were informed about the study's purpose, duration, and structure, and informed written consent was obtained from the parents of all children.

7.6 Devices employed in the study

Device #1	
Model	ExoAtlet
What is it measuring? What is the role of the device in the study?	Exoskeleton with 6 actuators: hip, knee, and ankle on each leg moving in sagittal plane
Total number of devices used in the study	1

Device #2	
Model	Vicon-Nexus system
What is it measuring? What is the role of the device in the study?	Limb joint markers kinematics
Total number of devices used in the study	1

7.7 Developed models/algorithms/platforms

The exoskeleton was adjusted in two ways. First, the user's anthropometric parameters were matched mechanically: shank and thigh lengths were chosen to match the rotation axes of the exoskeleton with the physical features of the user. Furthermore, the width of the exoskeleton was adjusted to ensure tight and comfortable placement of the user inside the device. Additionally, the construction of the exoskeleton allows adjustment of all leg fasteners in sagittal and frontal planes to match the anthropometric characteristics of the user. The exoskeleton range of motion is capable of supporting all operating modes, from sitting with the knees and hips bent at 90 degrees to standing with 0 degrees of extension. Therefore, the second stage of setting up the exoskeleton included setting the specific gait parameters, making the exercise comfortable for the user. After donning the exoskeleton, the child was moved from a sitting position to a standing position and vice versa using the exoskeleton's sit-to-stand and sit-down control modes, respectively. The exoskeleton comprises 6 motors (hip, knee, and ankle on each leg), allowing enough degrees of freedom to simulate the natural movement of the lower limb during the gait. All motors are independently controlled, allowing adjustments to the gait parameters as needed. During this study, the ankle, although motorized, was not involved in the movement to the full possible extent. Adjustable walking parameters include step length, height, speed, and the time delay between steps. The control modes allow standing still, stepping in place, standing up and sitting down on a chair, level walking with different cycle durations and in combination with functional electrical stimulation of leg muscles, walking on inclined surfaces, backward walking, stepping over obstacles, and comfortable walking up and down stairs. If excessive torque is sensed, sensors embedded into each motor will automatically stop stepping. In this study, researchers used the default settings for forward-level walking at ~0.2 m/s and without a time delay between steps (the latter mode is intended for patients who are either at the beginning of their exoskeleton training regimen or have severe gait and posture abnormalities and need to move more slowly). The exoskeleton was operated with the assistance of the therapist.

7.8 Evaluation metrics and statistical analysis

The raw EMG signals were high-pass filtered (60 Hz), full-wave rectified, and low-pass filtered with a zero-lag fourth-order Butterworth filter (5 Hz) to obtain envelope time series. The processed EMG data were time-interpolated over a normalized 200-point time base t, and were averaged across all cycles. To characterize differences in the timing of EMGs, researchers computed the center of muscle activity (CoMA). The CoMA was calculated using circular statistics as the angle of the vector (1st trigonometric moment) in polar coordinates that point to the center of mass of that circular distribution of each muscle EMG.

7.9 Results and discussion

Mapping the EMG-activity profiles onto the rostrocaudal anatomical location of MN-pools in the lumbosacral spinal cord highlighted specific variations in the spinal maps of α-MN activity during Exo walking. To quantify the similarity of those spinal maps, researchers computed the correlation of individual subjects' CoA with averaged CoA during NW, and a significant difference in the Exo condition ($p < 0.01$, One-way ANOVA) was found. During NW, these correlations were relatively high ($r = 0.74 \pm 0.19$), and the CoA resembled that of adults during level walking, while during Exo walking, the correlations were lower and more variable across children ($r = -0.24 \pm 0.69$). The prominent feature of these maps in NW was a distinct activation of lumbar and sacral segments during early and late stance, respectively. Researchers quantified it by computing the maximum activity timing of the upper lumbar (L3+L4) and sacral (S1+S2) output. The NW condition showed distinct activation of the lumbar and sacral segments during early and late stance ($p < 0.05$, Watson-Williams test), whereas the Exo condition showed no differentiation ($p > 0.05$, Fig. 3B left panels) and a tendency for synchronous activation of the lumbar and sacral segments. Furthermore, the activation of the lumbar and sacral segments during Exo walking showed no or only minor similarities with NW. This suggests that, despite full assistance for leg movements, the child's locomotor controllers can interpret step-related afferent information promoting essential activity in leg muscles. This is most likely explained by the active nature of stepping in the exoskeleton. In terms of the general muscle activity patterns, researchers identified notable variations for the proximal leg muscles, the co-activation of the lumbar and sacral motor pools, and the weak propulsion from the distal extensors at push-off.

7.10 Next steps

In the next 18 months, the research group plans to apply the results to the rehabilitation of children with CP. To this end, a Moonwalker exoskeleton will be used in 20 sessions of walking exercises, followed by 30 minutes of standard motor therapy. The training will then be continued at home for about 5 months. Outcome measures will be monitored at the start of the protocol (T0), after 20 training sessions (T1), and at the completion of at-home activities (T2).

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