SC1-PM-17-2017 - Personalised computer models and in-silico systems for well-being

Grant agreement 777159

OActive

Project full title:

Advanced personalised, multi-scale computer models preventing OsteoArthritis

Project Overview

Prof. Kyriacos Felekkis- University of Nicosia

Osteoarthritis (OA)

- Degenerative disease of the joints and the most common form of arthritis that causes pain and mobility limitations.
- Complex disease- biochemical and biomechanical factors are involved.
- Most important cause of disability in elderly population- ***up 30% of people>65***
- Knee is the most commonly affected joint.

Osteoarthritis (OA)

- Various risk factors are known: age, gender, hormonal status, BMI, family history, occupation, physical activity, past history of knee injury joint operation and depression.
- OA is not easy to ***define, predict or treat***. Progression is poorly understood and that has resulted in a lack of prevention and treatment interventions.

What we set out to do

Perform a holistic multiscale analysis by using a combination of **mechanistic computational models, simulations and machine learnings** in Osteoarthritis (OA)

Integrate patients specific:
Biomarkers
Environmental factors
Behavioral and Social Risk Factors

Augmented Reality (AR) personalized interventions will be developed allowing patients to experience more enjoyable treatment

Technology Validation:
In vitro system
Human populations
Large data registries

… to generate **robust predict**ors for new **personalised interventions** for better diagnosis, delaying onset and/or slowing down progression of knee OA

Who we are

7 countries

5 SMEs

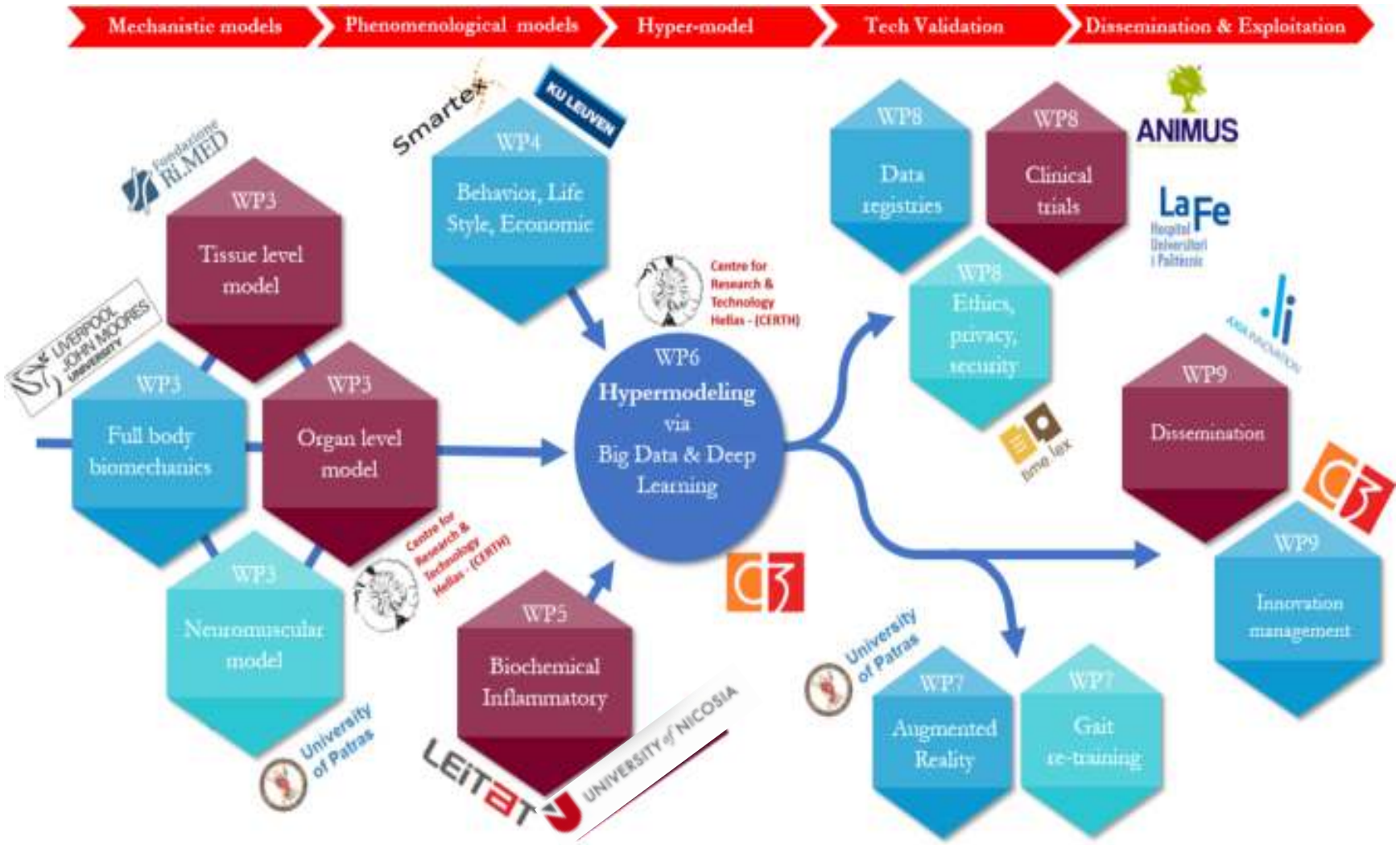
13 partners

8 RTDs

36 months

5M Euros

OACTIVE Approach



Input data:
Three Cohorts and Biobank Databases

Spain

Young patients
Early detection

>100

Cyprus

Elderly patients
Established OA

>130

Greece

Athletes
Post-traumatic OA

>100

USA

OAI

>5000

UK

UKBIOBANK

>10000

Input data: Biomarkers and Social Determinants

Biomarkers of Bone and Cartilage Degradation

- Serum COMP
- Serum HA
- Serum CPII

Inflammatory Biomarkers:

- IL-1β
- TNF-α
- IL-6

Novel Biomarkers:

- miRNAs in urine and blood
- Metagenomic analysis of microbiome

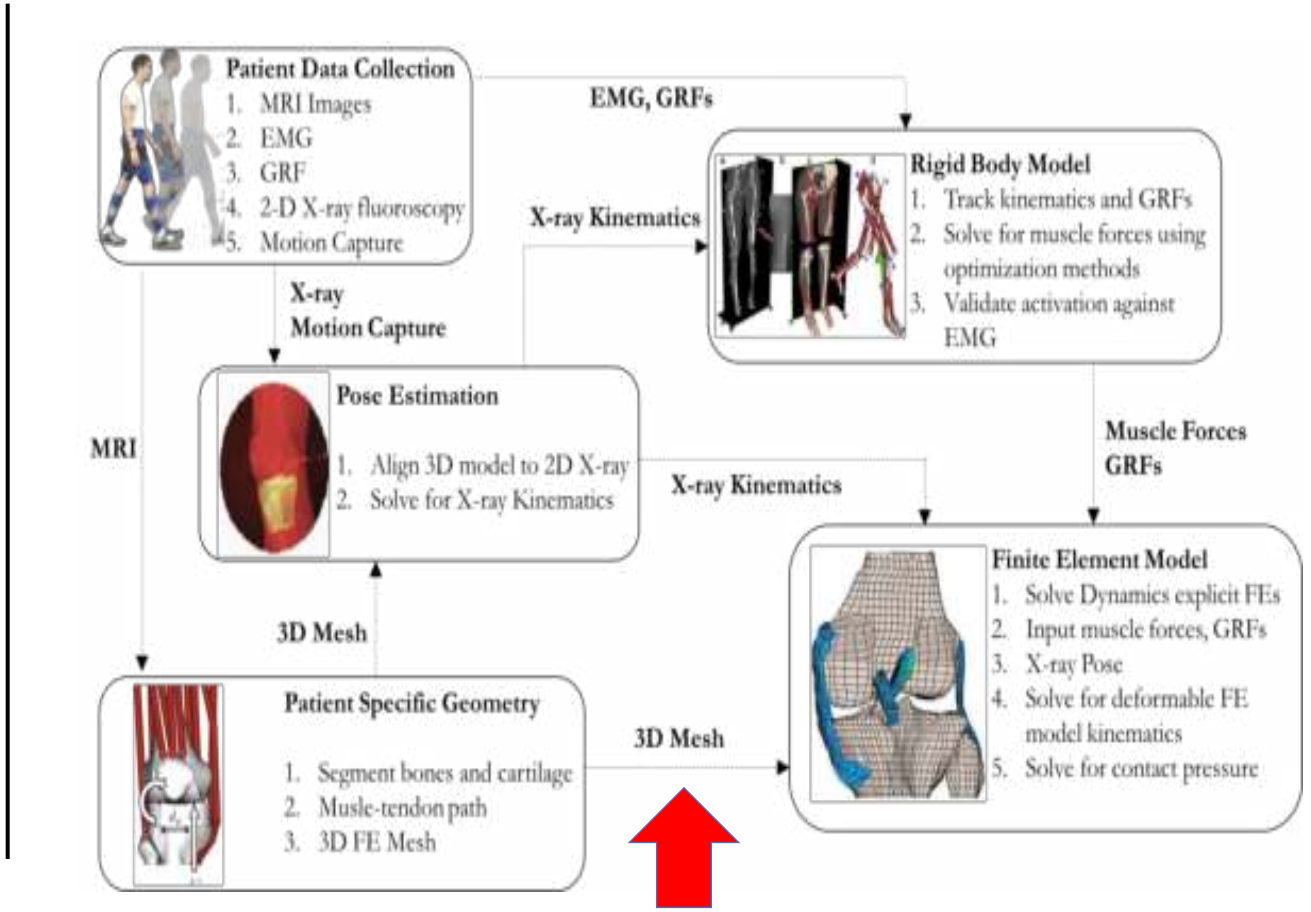
Social Determinants

- Socioeconomic factors
- Environmental factors
- Life Style
- Occupation
- Physical Activity
- etc

Input in the Hypermodel

Input data: Mechanistic Models

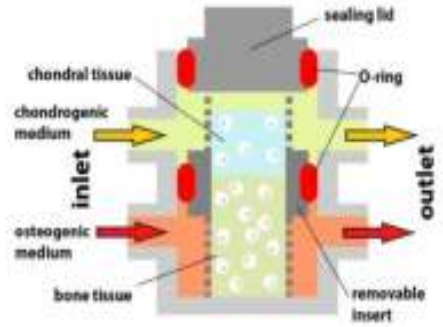
Modeling

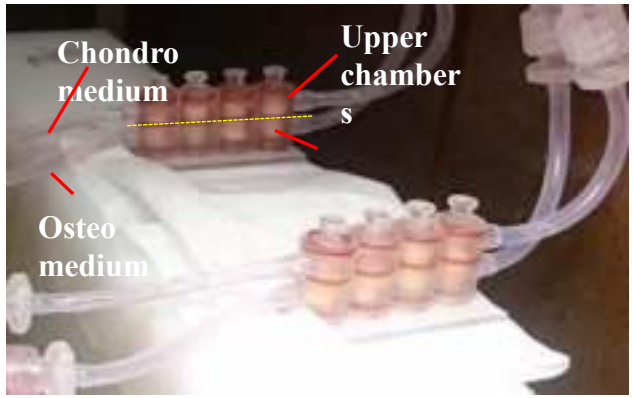


Input into the Hypermodel

Biomechanics: Gait-analysis and Imaging data

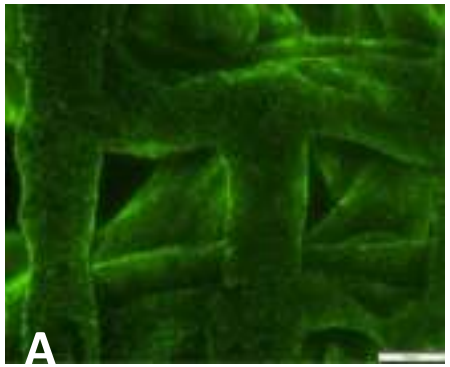
Tissue Level Modeling



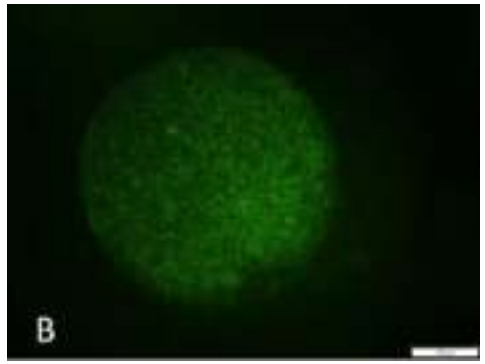


Development of *in vitro* induced OA models Cultured under continuous flow in a bioreactor

Bone-mimic phase

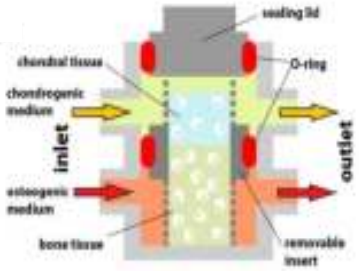


Cartilage-mimic phase



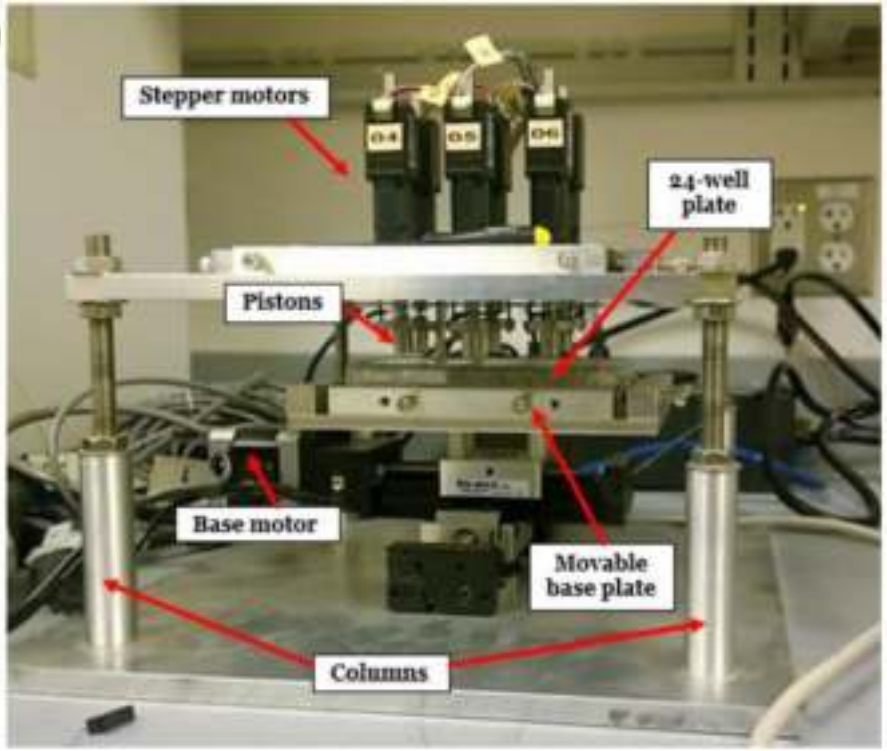
Validate biomechanic data and feed the results to the model

Tissue Level Modeling



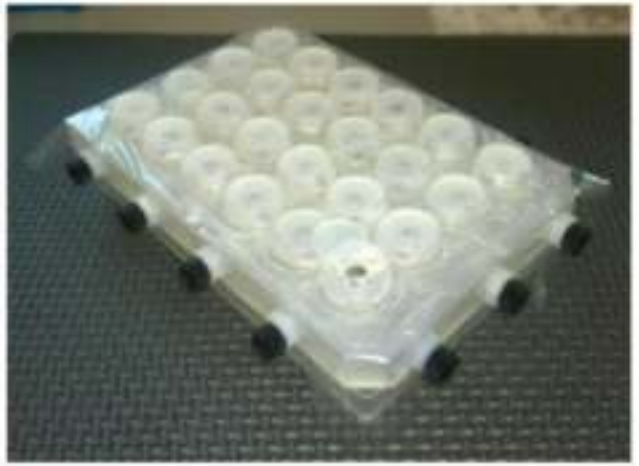
Development of a mechanical actuator fitting 24 wells multiwell plate

a)

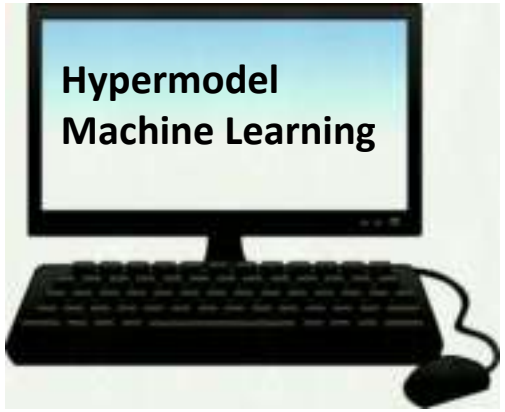


b)

c)

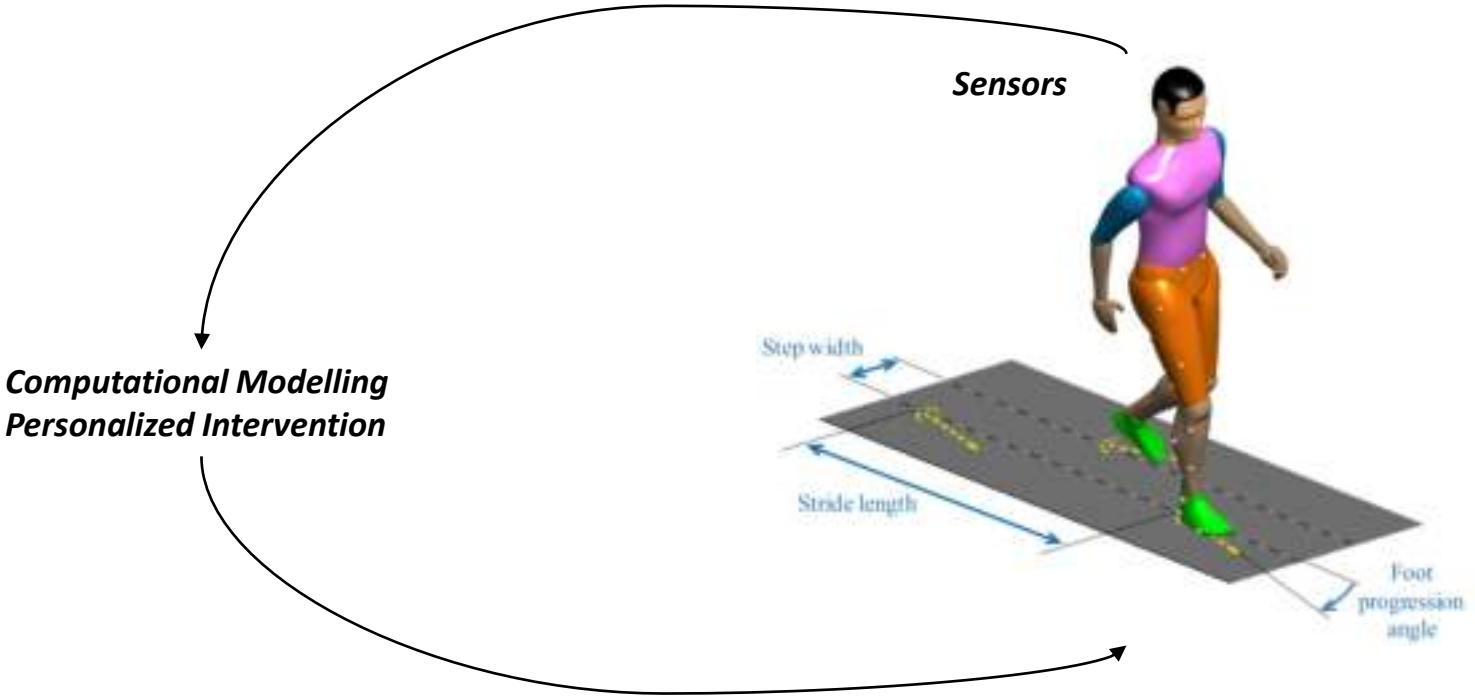


Development of the Hypermodel

DATA → 

→ Personalized Predictors → Intervention AR game

Augmented Reality (AR) Game Personalized Interventions



AR personalized game for gait re-training in real time

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OActive

Thank You

Questions

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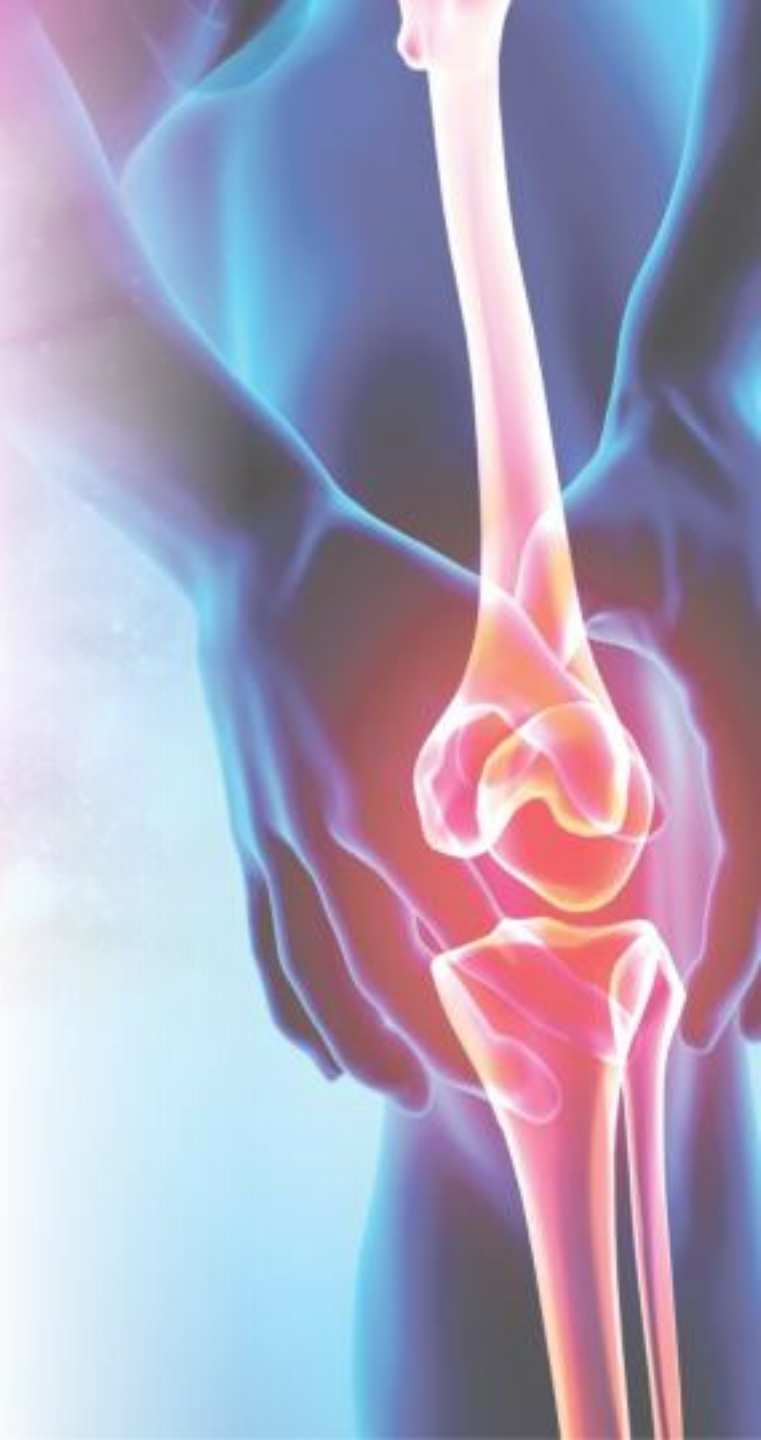
OACTIVE WORKSHOP
PERSONALISED PREDICTIVE MODELS



Exploitation strategy of the OActive project

Ioanna Barouni, Innovation Manager, CETRI, Cyprus

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Exploitation Strategy in Horizon 2020

- Results: Any tangible or intangible output of the action, such as data, knowledge and information whatever their form or nature, whether or not they can be protected.

- Exploitation: The utilization of results in further research activities other than those covered by the action concerned, or in developing, creating and marketing a product or process, or in creating and providing a service, or in standardization activities.

- Can be commercial, societal, political, or for improving public knowledge and action, it also include recommendations for policy making

- Exploitation routes: Spin-off/Start-up, Product, Service, Contribution to Standards, Patent, PhD thesis, Societal activity, Open licenses, Further research, New projects, Policy change, Expanded networks, etc.

Source: 9_dissemination-exploitation-activities_en.pdf (europa.eu)

OActive – Exploitation Strategy

The OActive exploitation strategy is split into two paths:

- The first path seeks to define a longer-term vision for the OActive Integrated System which partners can shape as they see fit (joint exploitation).
- The second path seeks to enable each partner to take their project exploitable results and exploit them for their own ends (individual exploitation).

Joint Exploitation – OActive Integrated System

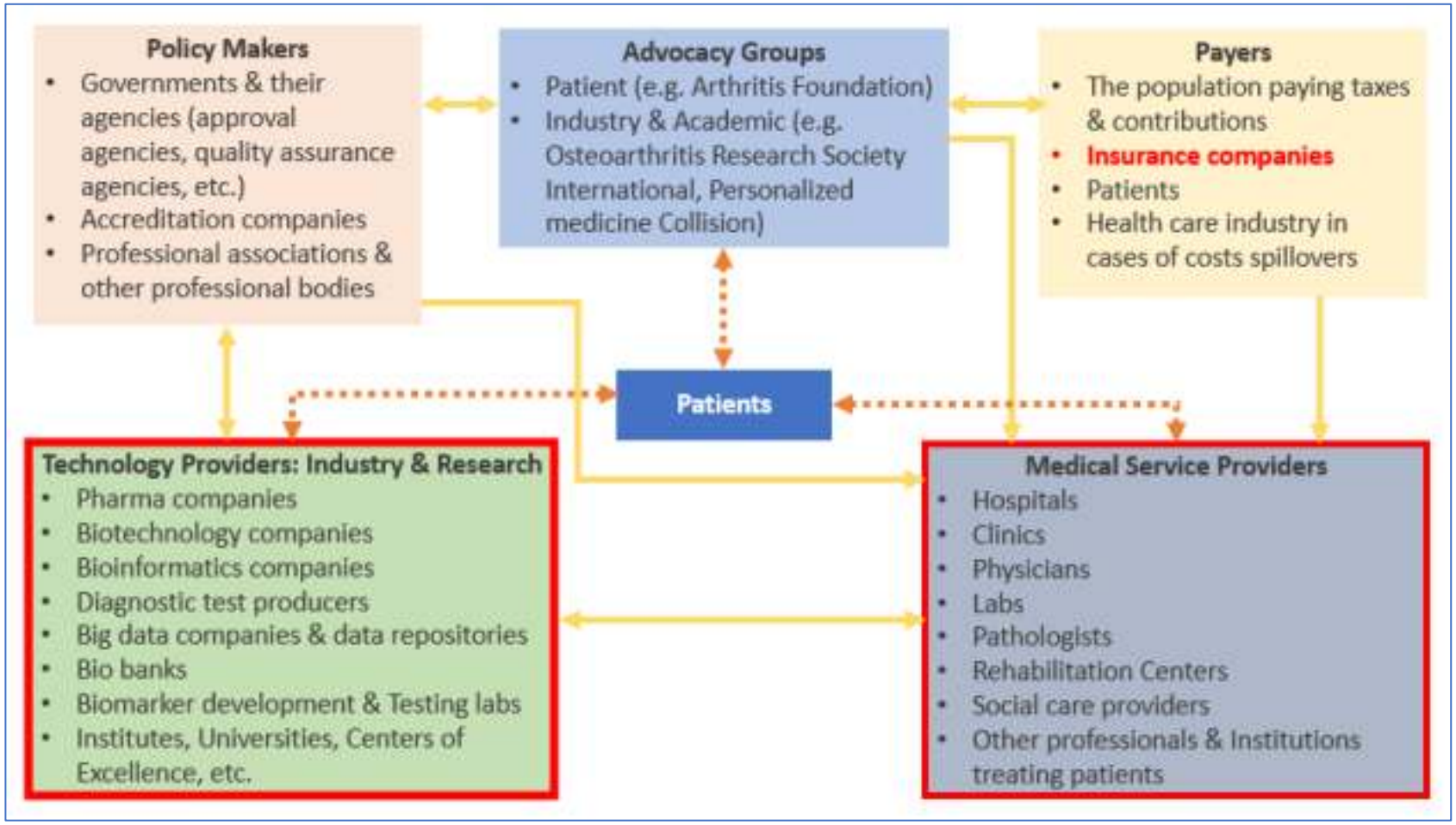
- Market analysis
- Market positioning
- PESTEL analysis
- SWOT analysis
- Porter's 5 forces analysis
- Business model canvas
- End-Users & Industrial stakeholder feedback
- Future funding Sources

Individual Exploitation

- Identification of all individual exploitable results (Key exploitable results)
- Classification into short/medium term & long-term exploitable results
- Identification of the preferred protection & exploitation routes (commercial & non-commercial exploitation)
- Technology watch
- Market analysis, Competition analysis, Porter's Five Forces analysis, SWOT analysis, Business model canvas (for short-term exploitation only)
- End-Users & Industrial stakeholder feedback (where applicable)
- Future funding Sources

Joint Exploitation – OActive Integrated System – Market analysis

- **Personalized Medicine Market**: estimated at USD 1.57 trillion in 2018 and is anticipated to expand at a CAGR of 10.6% up to 2025.
- **Commercial solutions**: Artificial Intelligence supported solutions in the field of musculoskeletal (MSK) radiology & Arthrotest®



Target markets:

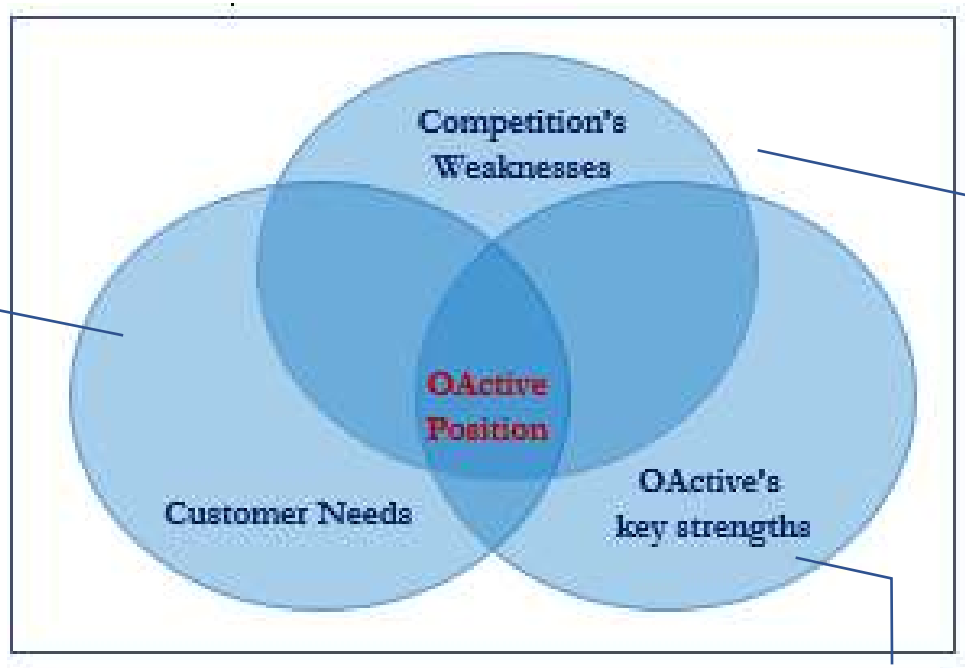
- ✓ **Medical Service providers**: hospitals and clinics, physicians, labs, pathologists, social care providers, etc.

- ✓ **Technology providers**: pharma companies, biotechnology companies, bioinformatics, big data companies and data repositories, diagnostic test producers, bio banks, biomarker development and testing labs, institutes, universities, centres of excellence, etc.

Joint Exploitation – OActive Integrated System – Market positioning

OActive's Market Position lies at the **intersection of the Competition's weaknesses, the Customer needs and OActive's key strengths**.

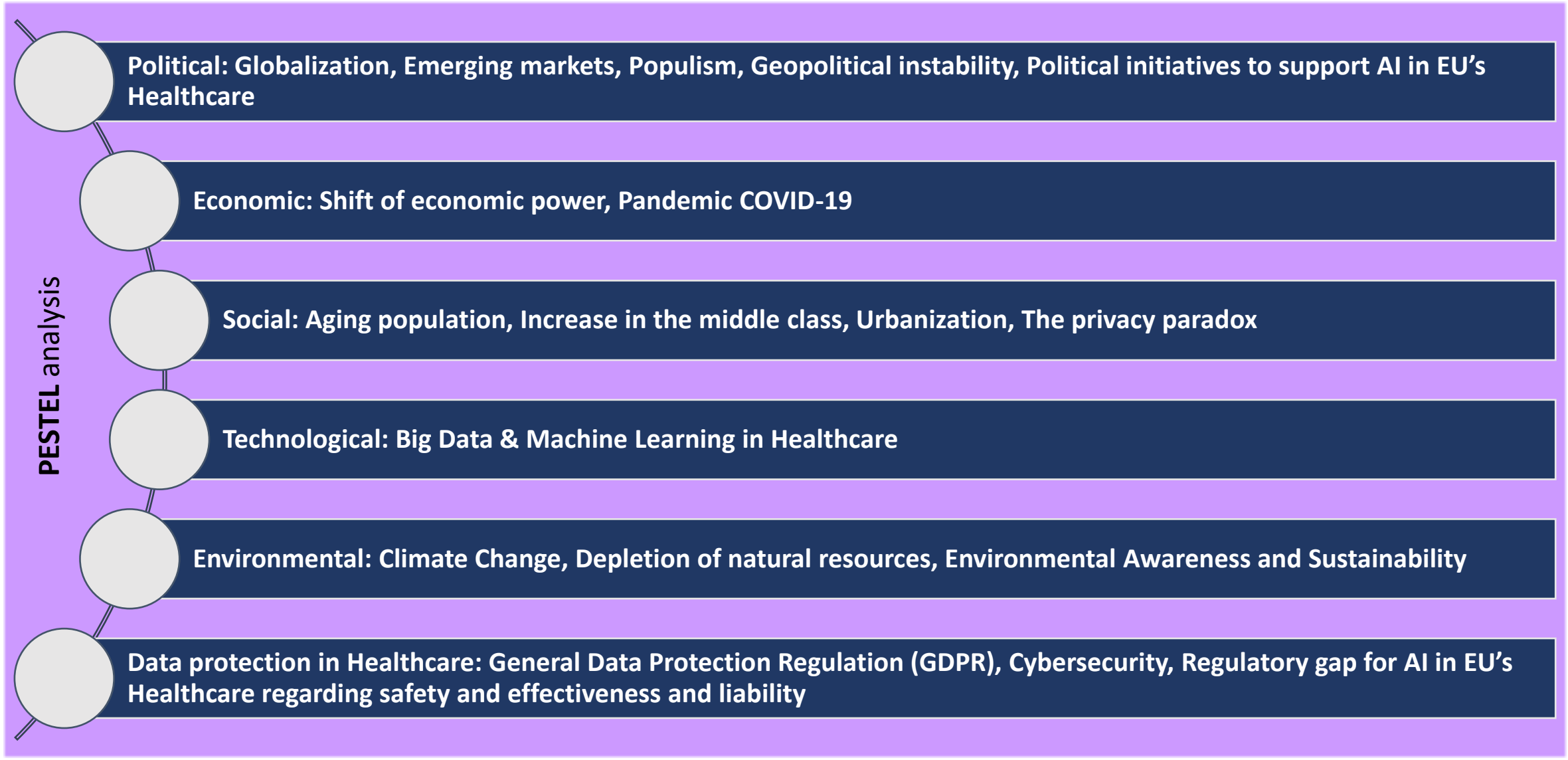
Complex musculoskeletal disorder with impact on patients and the society, including its impact on health care systems, patients' caregivers and their employers



- Criticism with respect to efficacy and safety, especially on a long-term use
- Palliative and reactive, rather than coordinated, proactive and preventive actions

- Shifting the emphasis in OA treatment from reaction to prevention
- Directing targeted therapy and reducing trial-and-error prescribing and adverse drug reactions
- Increasing patient adherence to treatment
- Reducing high-risk invasive testing procedures and surgeries
- Helping to control the overall cost of OA treatment for the society and the patients

Joint Exploitation – OActive Integrated System – PESTEL analysis



Individual Exploitation – IP Registry

An **IP Registry** was created to document all Key Exploitable Results and define the following (per result):

- A meaningful title
- A comprehensive short Description
- The relation to the work structure: Work Package, Task, Deliverable
- The Background IP -if any-, meaning the pre-existing IP, know-how, knowledge or any additional data that is needed for carrying out the project
- The names of the partner(s)/beneficiaries with whom they will be developing the Result
- The **shares of ownership per partner**/beneficiary & the nature of work per partner/beneficiary
- The Technology Readiness Level (TRL) & Short/medium term OR Long-term Exploitation
- The **preferred IP protection route**
- **Exploitation as a component of the OActive Integrated System via a Joint Venture or Collaborative Agreement** (YES/NO)
- **Individual Commercial Exploitation**: Stand - alone PRODUCT/SERVICE and/or PRODUCT/SERVICE formed in combination with other Results in the area of OA management and beyond (YES/NO, other Result(s), Product(s))
- **Individual non-Commercial Exploitation**: Further scientific research in OA and beyond

Individual Exploitation – products, services & non-commercial exploitation

OActive **products, services & non-commercially exploitable results:**

- Novel AR supported gait retraining for other (joint) diseases, such as: Stroke, Traumatic brain injury (TBI), Spinal cord injury (SCI), Cerebral palsy, Multiple sclerosis, Parkinson's disease, Endoprosthesis (e.g. joint replacements), Degenerative joint diseases of the lower limbs (e.g. knee osteoarthritis), Spinal muscular atrophy, Muscle weakness due to lack of mobility, Cardiac conditions if permitted by treating physician, Amputees
- Portable devices for gait analysis as a standalone product to be used in clinical studies but also in other markets
- New diagnostic tools (biosensors) for other bone and cartilage diseases accruing from the knowledge generated on the relation of exosomal & microbiome biomarkers with OA development and progression and on the knowledge generated on the relation of inflammation biomarkers with OA development and progression investigated within OActive.
- Expanded portfolio with new services for Rehabilitation Centers and Hospitals
- Publications on biochemical biomarkers in established OA patients & Publications and follow-up work via Phd theses on microbiota studies
- Agreed collaborations among partners to jointly participate in research projects on chronic diseases
- Further research into the causes of the disease, and the subsequent design and testing of potential therapeutics
- Further research on OA in other parts of the body/joints & on other inflammatory diseases
- New knowledge on the regulatory and ethical challenges in relation to cross border scientific processing of health care data.
- New knowledge on computational modelling, data mining, knowledge discovery and pattern recognition

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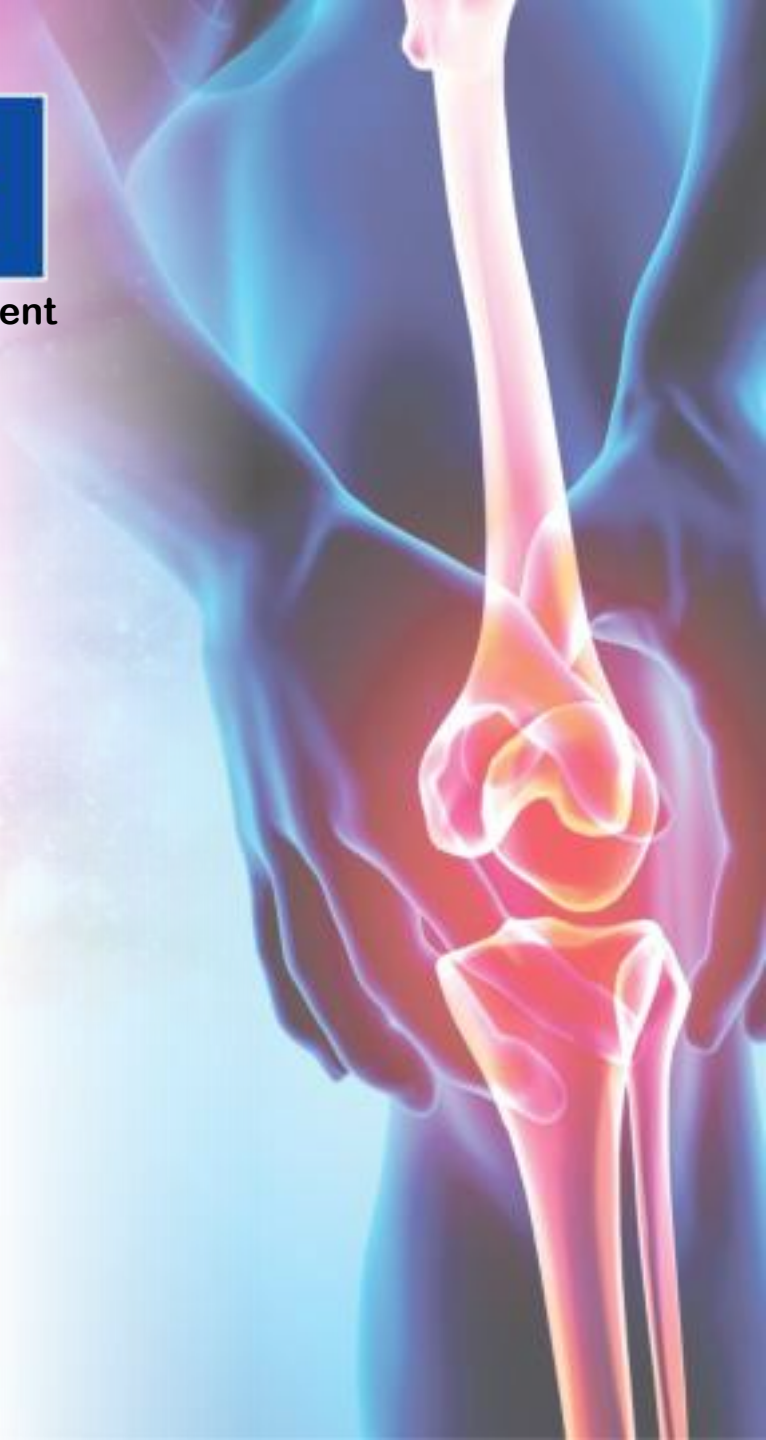
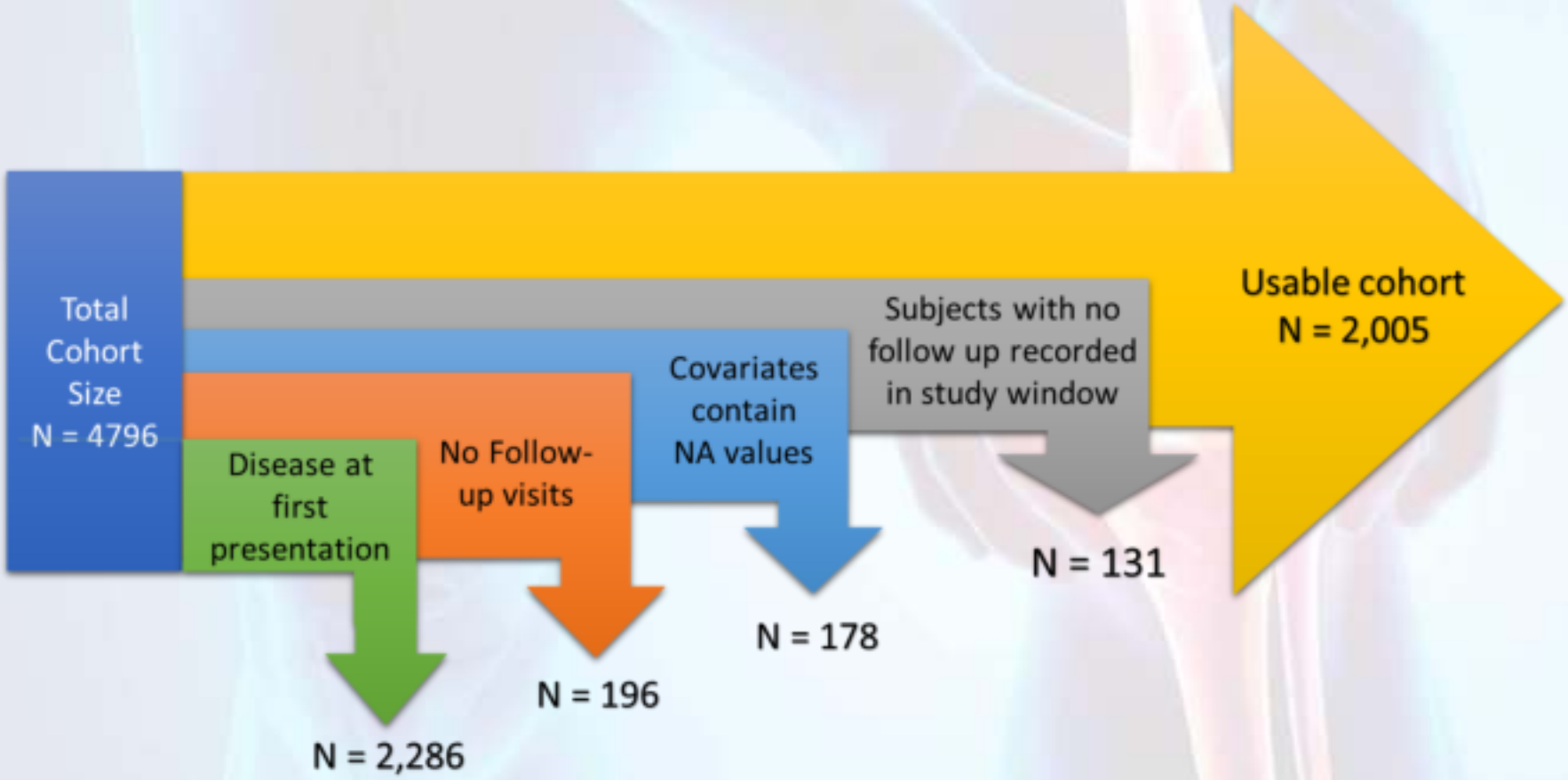


Thank you!

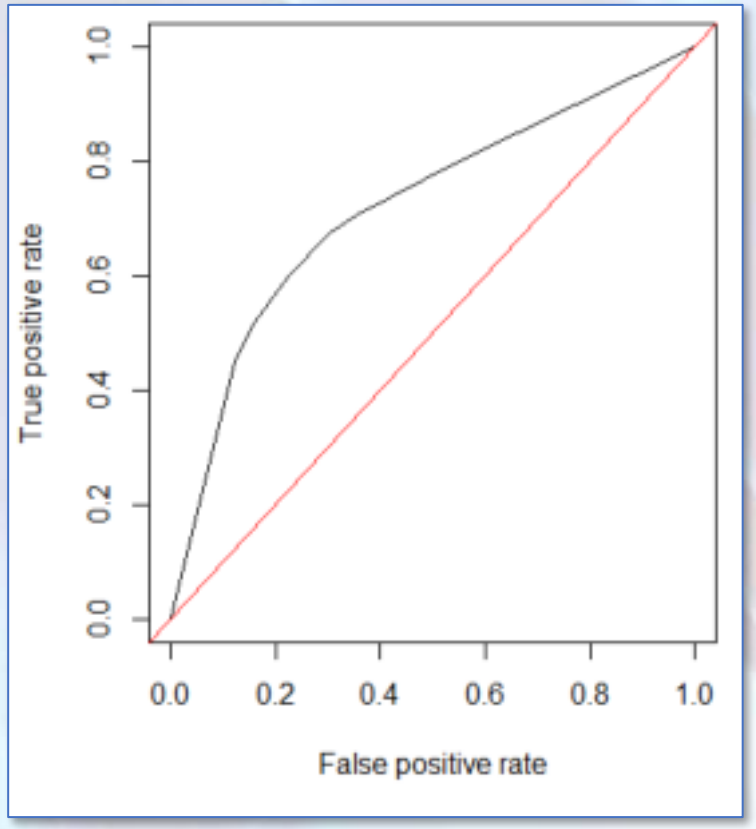
OAI: OsteoArthritis Initiative
Cohort for model development & optimisation



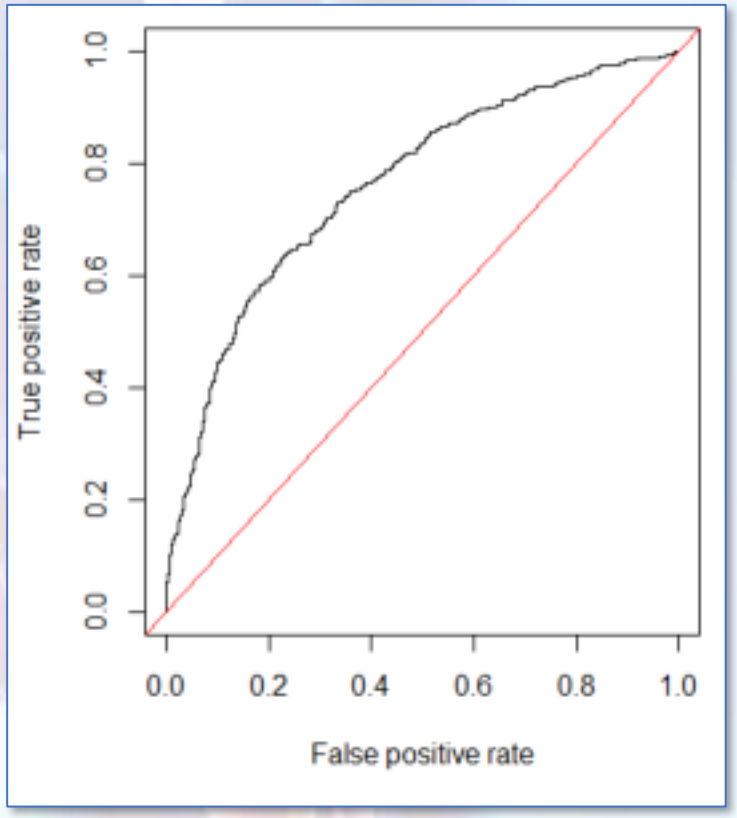
Knowledge discovery

Factors association with KL > 1 at baseline

Data from the OAI



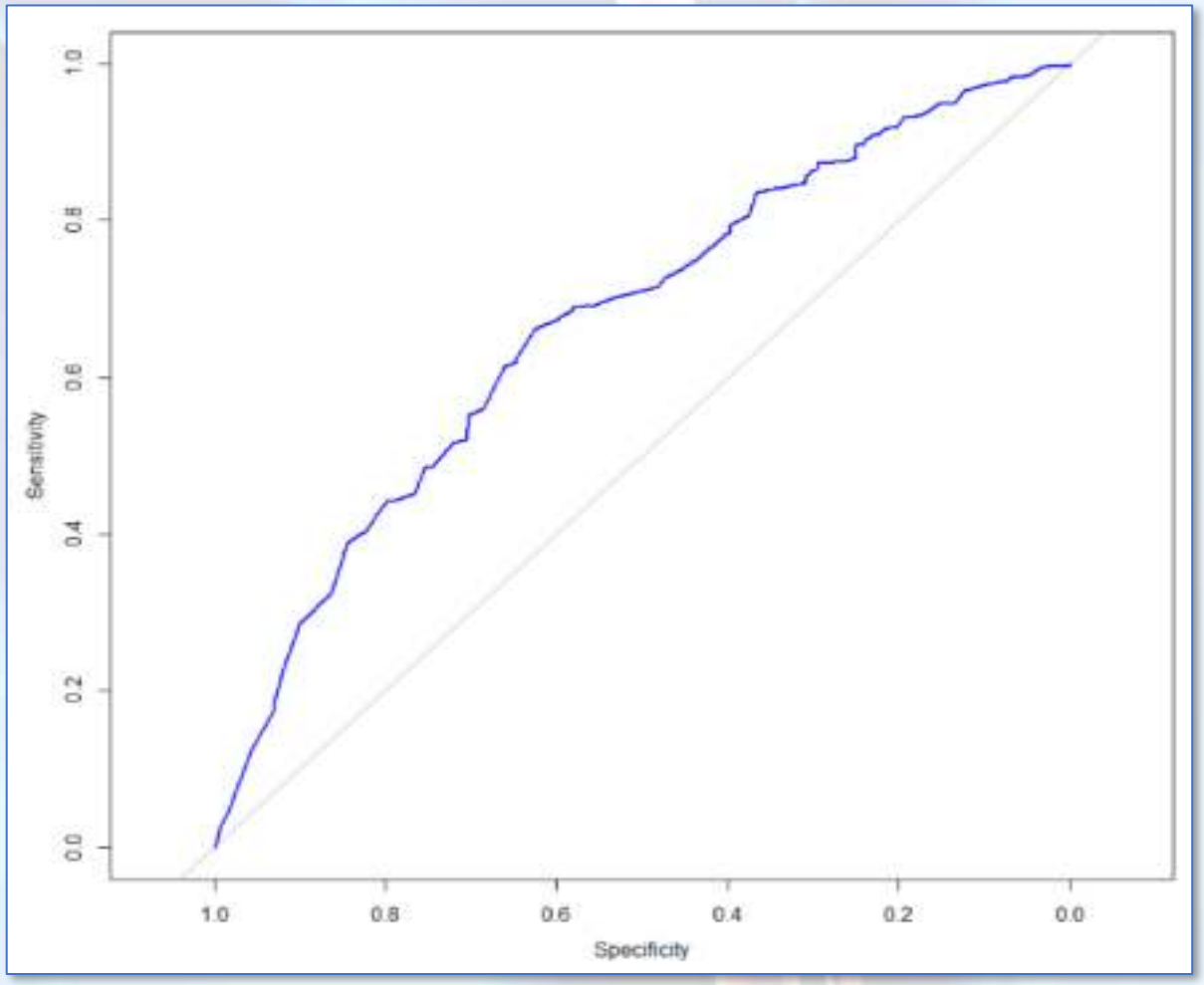
CART: AUC = 0.719



Logistic Regression: AUC = 0.763

Multicenter Osteoarthritis Study (MOST) (n=1175)

Measure	Value
Accuracy	0.6859
Sensitivity	0.9052
Specificity	0.2353
PPV	0.5421
NPV	0.7128
AUROC [CI]	0.6697 [0.631, 0.708]



Web App

Knee Osteoarthritis Diagnosis at First Presentation

Choose Subject Age Braket:

- (•) 45 - 50
- ( ) 50 - 55
- ( ) 55 - 60
- ( ) 60 - 65
- ( ) 65+

Choose Subject BMI score:

BMI less than 25

Select Subject Gender:

Male

B.LINE_SYMP: Does the subject present with symptoms today?

No

KPACT30: Does the subject report having to modify their activity due to knee pain in the last 30 days?

No

diff_upstr: Does the subject have difficulty getting upstairs?

No

Select amount of days Subject reported Knee Stiffness in last 30 days:

- (•) No Knee stiffness
- ( ) 1-7 days of knee stiffness
- ( ) 8-14 days of knee stiffness
- ( ) 15-21 days of knee stiffness
- ( ) 21+ days of knee stiffness

Calculate

Results | About

The subject is aged 45 - 50

The subject's BMI is BMI less than 25

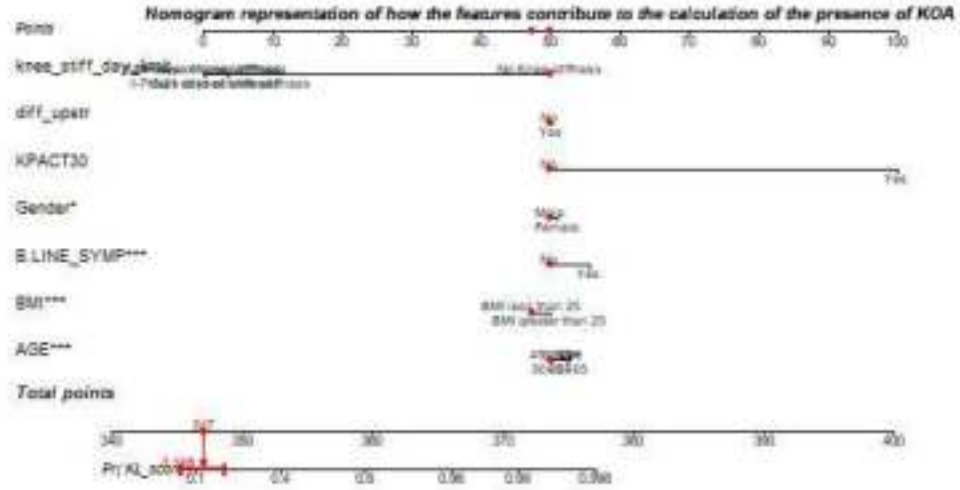
The subject is Male

Subject exhibits symptoms today No

Subject modified activity in previous 30 days No

Subject's difficulty with stairs No

In the last 30 days, the subject has had No Knee stiffness

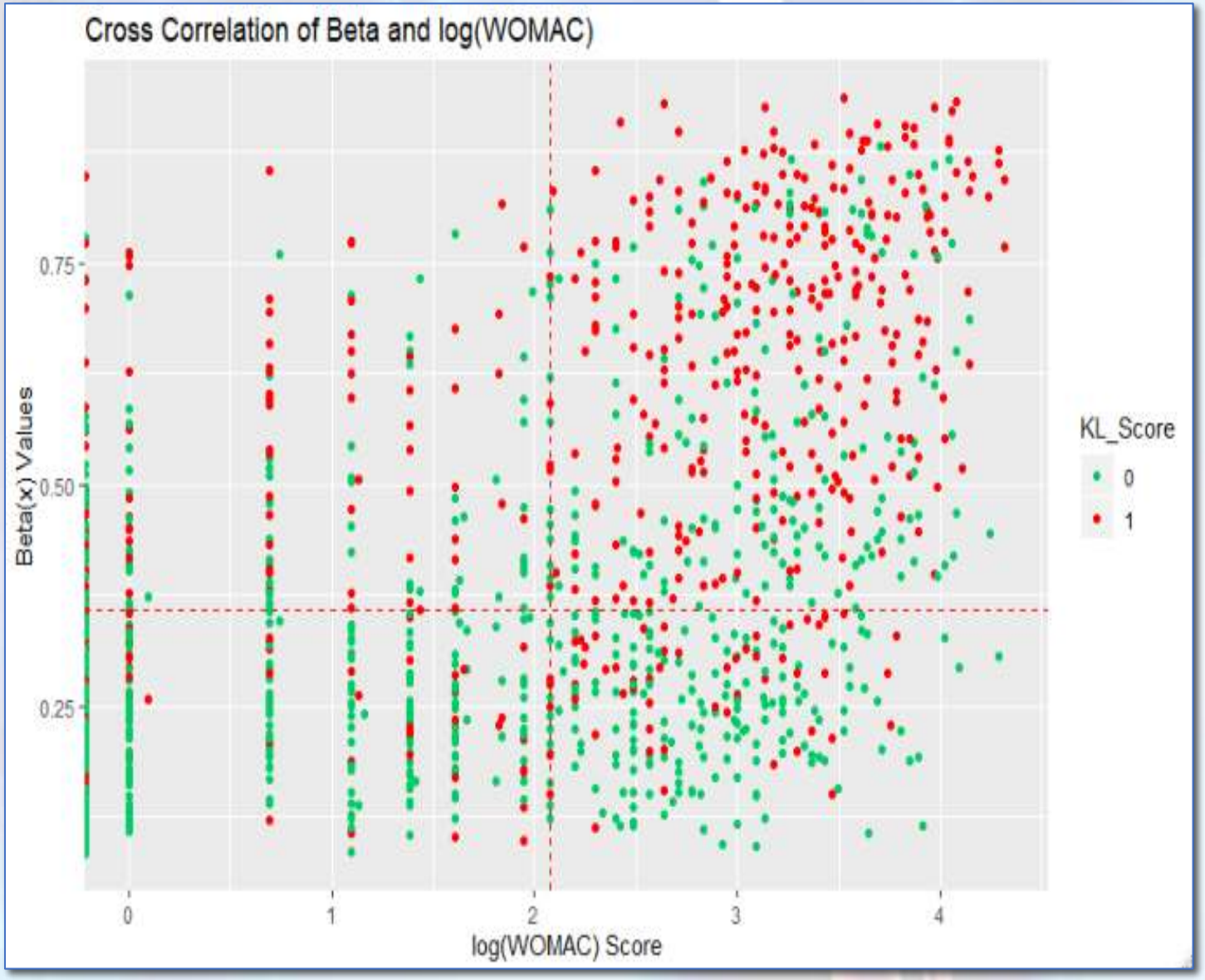


Based on these features, the probability of having KOA is 11.6%.
The prediction is that the subject does not have knee osteoarthritis.
To have KOA the probability threshold is 50%.

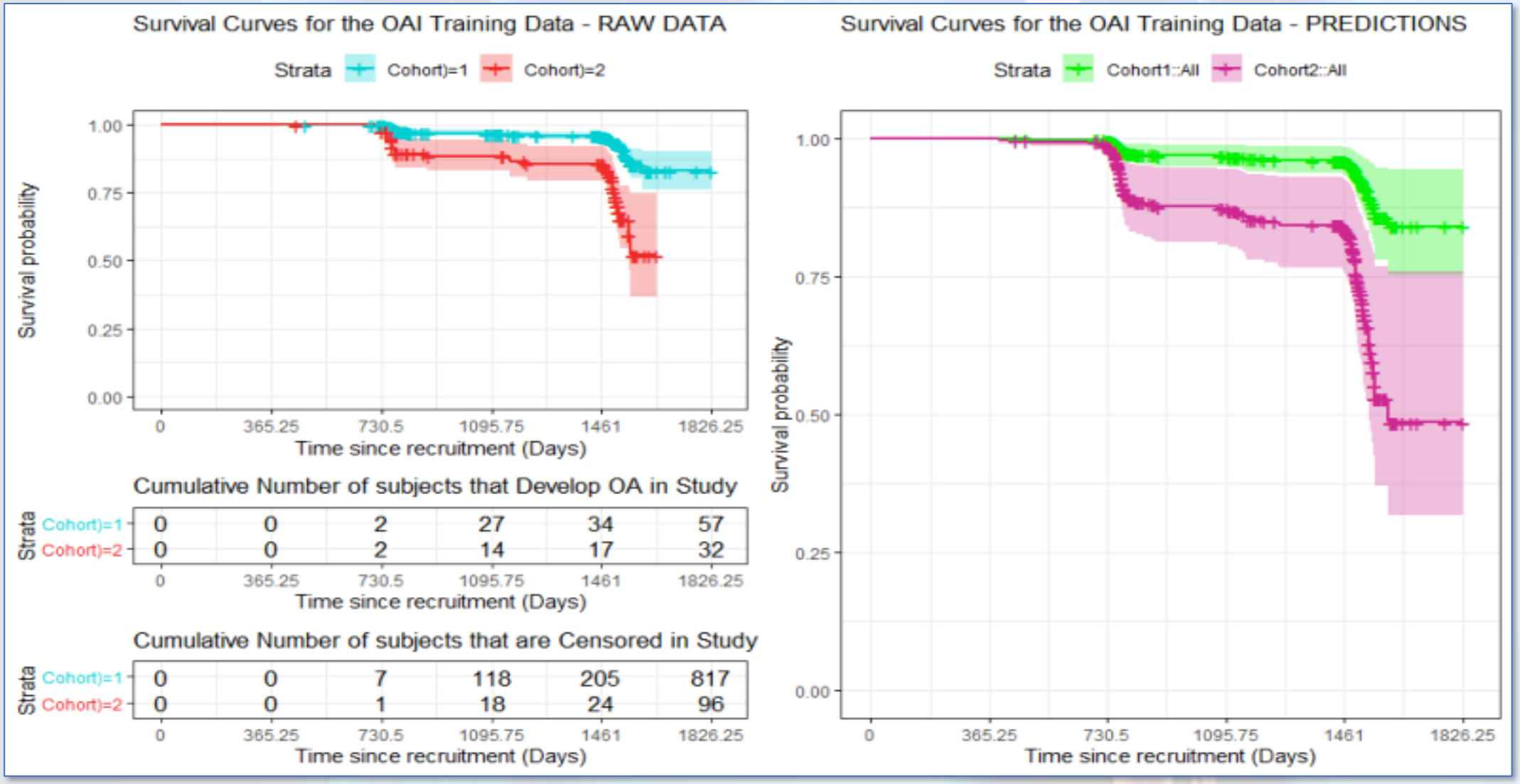
Knowledge discovery: Pain

KL *vs.* WOMAC

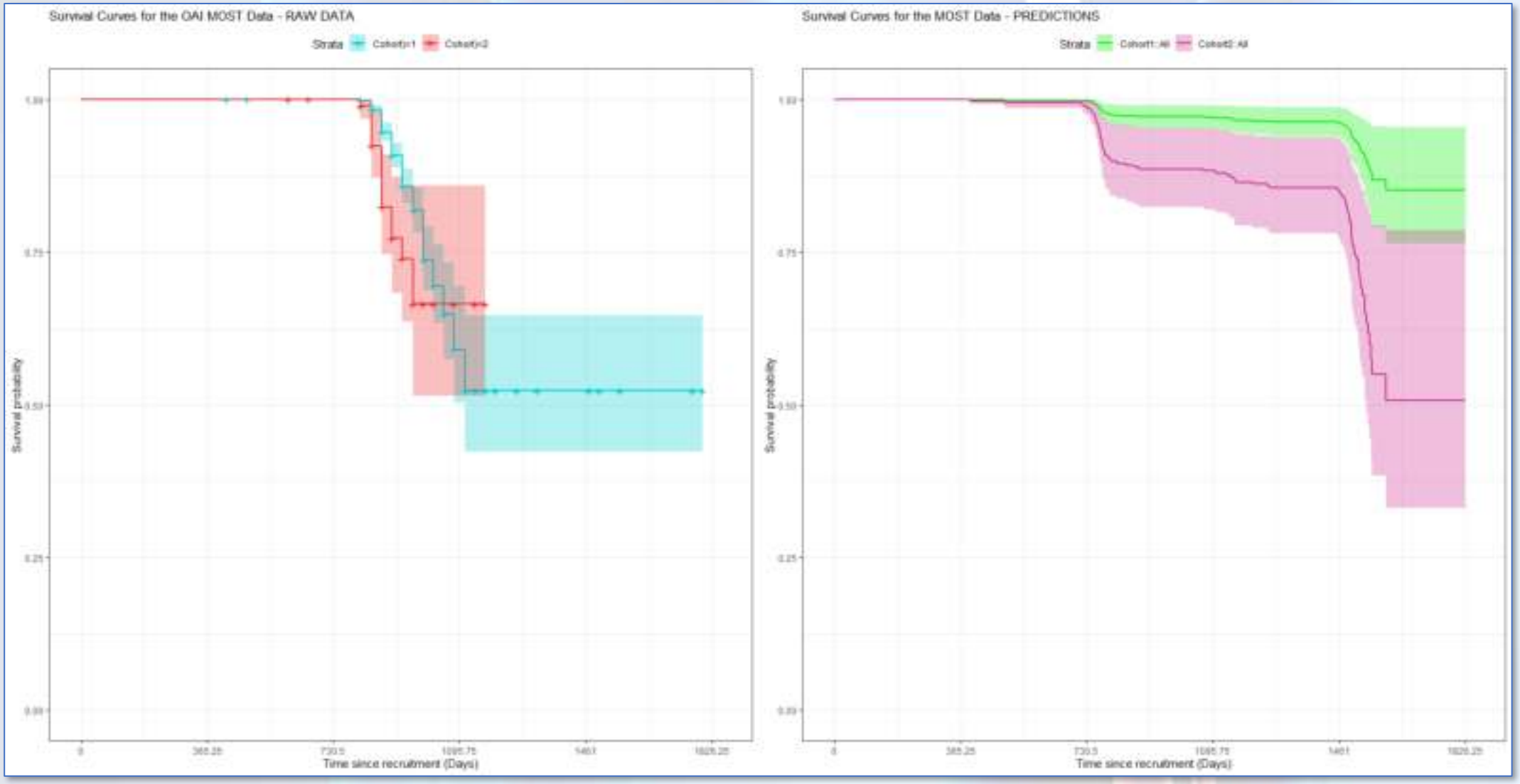
Data from the OAI



Longitudinal modelling. KL {0,1} → KL {2+}



Multicenter Osteoarthritis Study (MOST) (n=1175)



Web App

Knee Osteoarthritis Development in the next 5 years

Does the subject have a family history of knee surgery?

No

Choose Subject BMI score:

BMI_less_than_25

Select Subject Gender:

Male

Does the subject have a history of knee injuries?

No

Does the subject have a history of falling down?

No

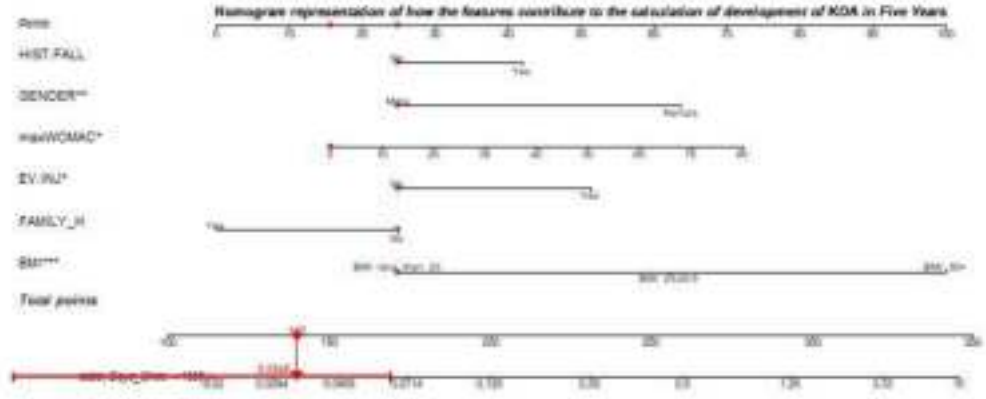
Select the subjects WOMAC score based on the questionnaire

0 — 96

Click here if you need to calculate your WOMAC score

Calculate

Results | About



The score at which a subject crosses the threshold from the low risk to the high risk cohort is an odd ratio of 0.636 (or 269 points).

Subject has a family history of knee surgery: No

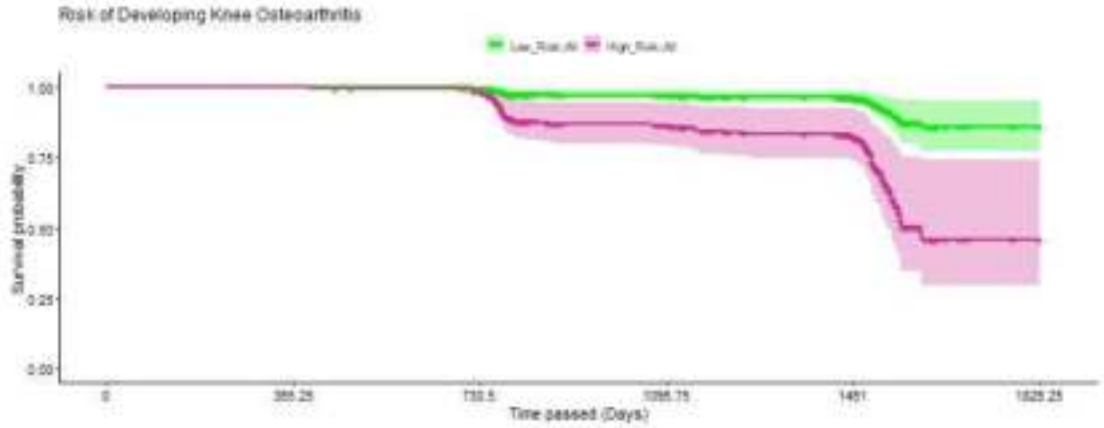
The subject's BMI is BMI_less_than_25

The subject is Male

Subject has has previous knee injuries: No

Subject has a history of falling down: No

Subject's WOMAC score is 0



The prediction is that the subject is at low risk of developing knee osteoarthritis in the next five years, based on these features.

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WP7 - Personalised interventions through augmented reality

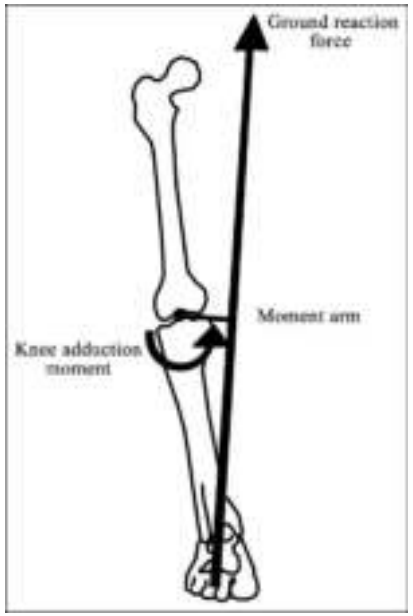
University of Patras (UPAT)
Konstantinos Moustakas (moustakas@ece.upatras.gr)
Georgios Giarmatzis (ggiarmatzis@ece.upatras.gr)

Overview

- Background on gait retraining
- Augmented Reality (AR) Oactive Gait retraining system
  - Hardware configurations
  - Software front-ends

Background

- Knee OA onset/progression related to mechanical forces
- Cartilage degeneration due to mechanical loading
- Suitable ways to reverse knee OA (pharmacological, surgical, etc)
- Reduction of knee medial torque
- Braces
- Gait retraining




Knee OA without bracing


The 3-Point Leverage


Knee OA with bracing

How can I reduce knee loading?

- Increase walking base (keep legs apart)
- Toe-off (toes outwards)
- Lean torso sideways

- Uncomfortable – not sustainable
- What is the optimal way?
  - Maybe a combination?

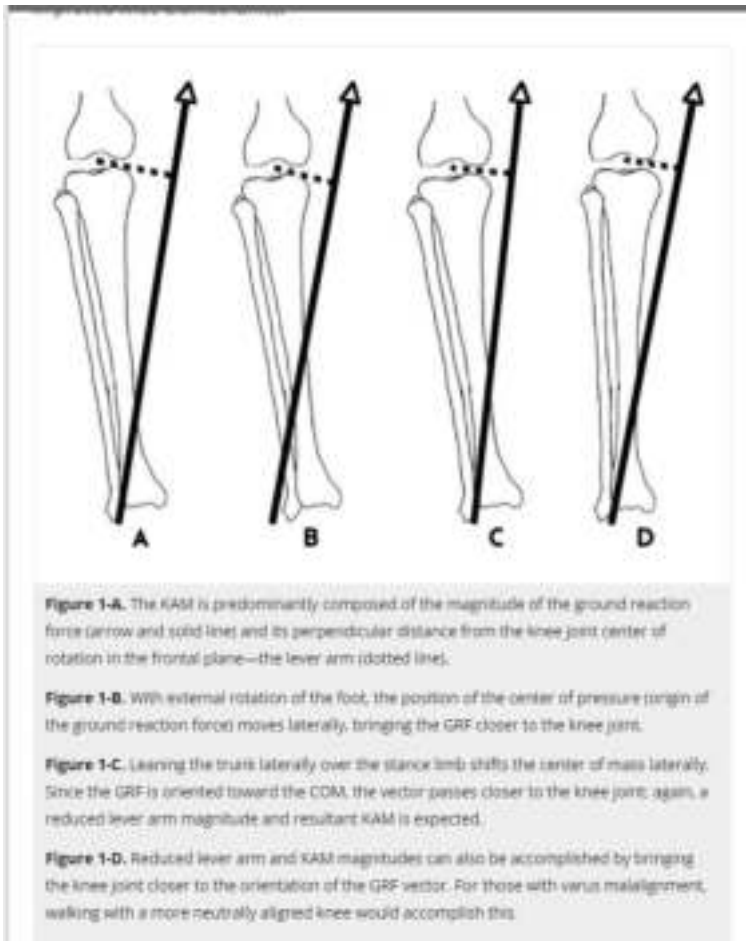


Figure 1-A. The KAM is predominantly composed of the magnitude of the ground reaction force (arrow and solid line) and its perpendicular distance from the knee joint center of rotation in the frontal plane—the lever arm (dotted line).

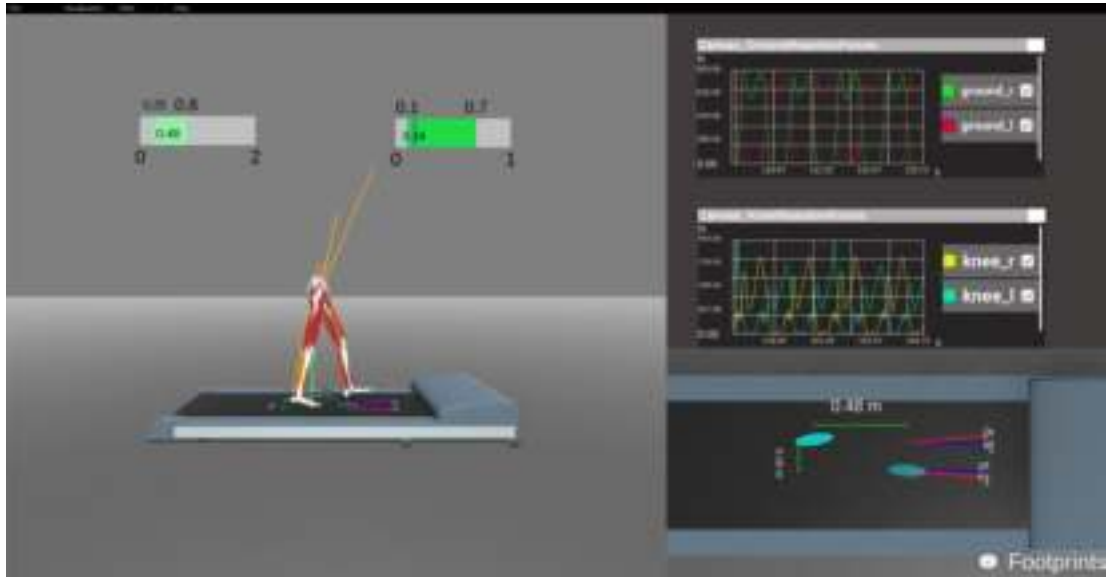
Figure 1-B. With external rotation of the foot, the position of the center of pressure (origin of the ground reaction force) moves laterally, bringing the GRF closer to the knee joint.

Figure 1-C. Leaning the trunk laterally over the stance limb shifts the center of mass laterally. Since the GRF is oriented toward the COM, the vector passes closer to the knee joint; again, a reduced lever arm magnitude and resultant KAM is expected.

Figure 1-D. Reduced lever arm and KAM magnitudes can also be accomplished by bringing the knee joint closer to the orientation of the GRF vector. For those with varus malalignment, walking with a more neutrally aligned knee would accomplish this.

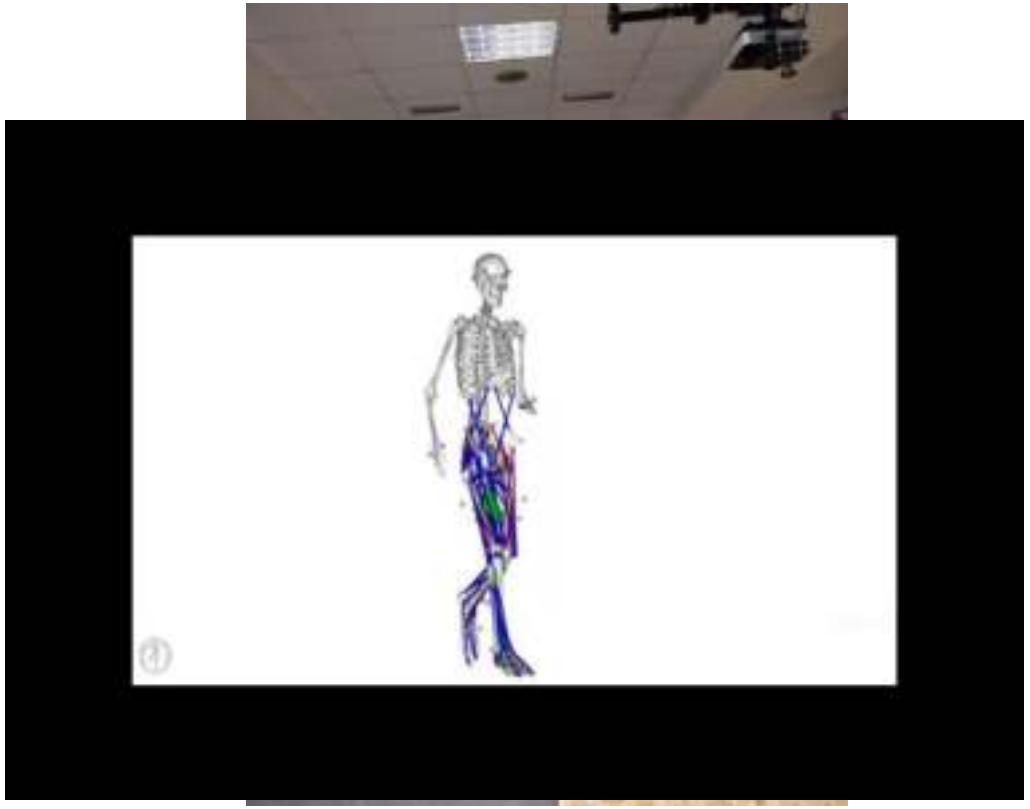
Gait retraining

- Can we make a change in walking strategy maintainable?
- Guidance and feedback
- Real time
- Clinician supervision
- Attractive
- Game-like



Gait retraining – OActive Approach

- Calculation of knee forces
  - Real time
  - Motion capture equipment
    - Markers-based
    - IMU-based
  - Modeling of the musculoskeletal system
    - Fitting a virtual model to each patient
    - Calculation of joint angles – joint torques
    - Calculation of muscle forces
    - Calculation of joint forces



Hardware, software and design decisions

- **Musculoskeletal performance analysis**
  - Indoor solution: Marker-based motion capture
  - Outdoor solution: IMUs and foot pressure sensors
  - OpenSim: open source, high accuracy, modeling and simulation capabilities, publicly available code and models and expertise

- **Augmented reality**
  - Unity engine: open source, multiplatform target and multiple device rendering
  - Meta 2 AR glasses, Microsoft HoloLens 2

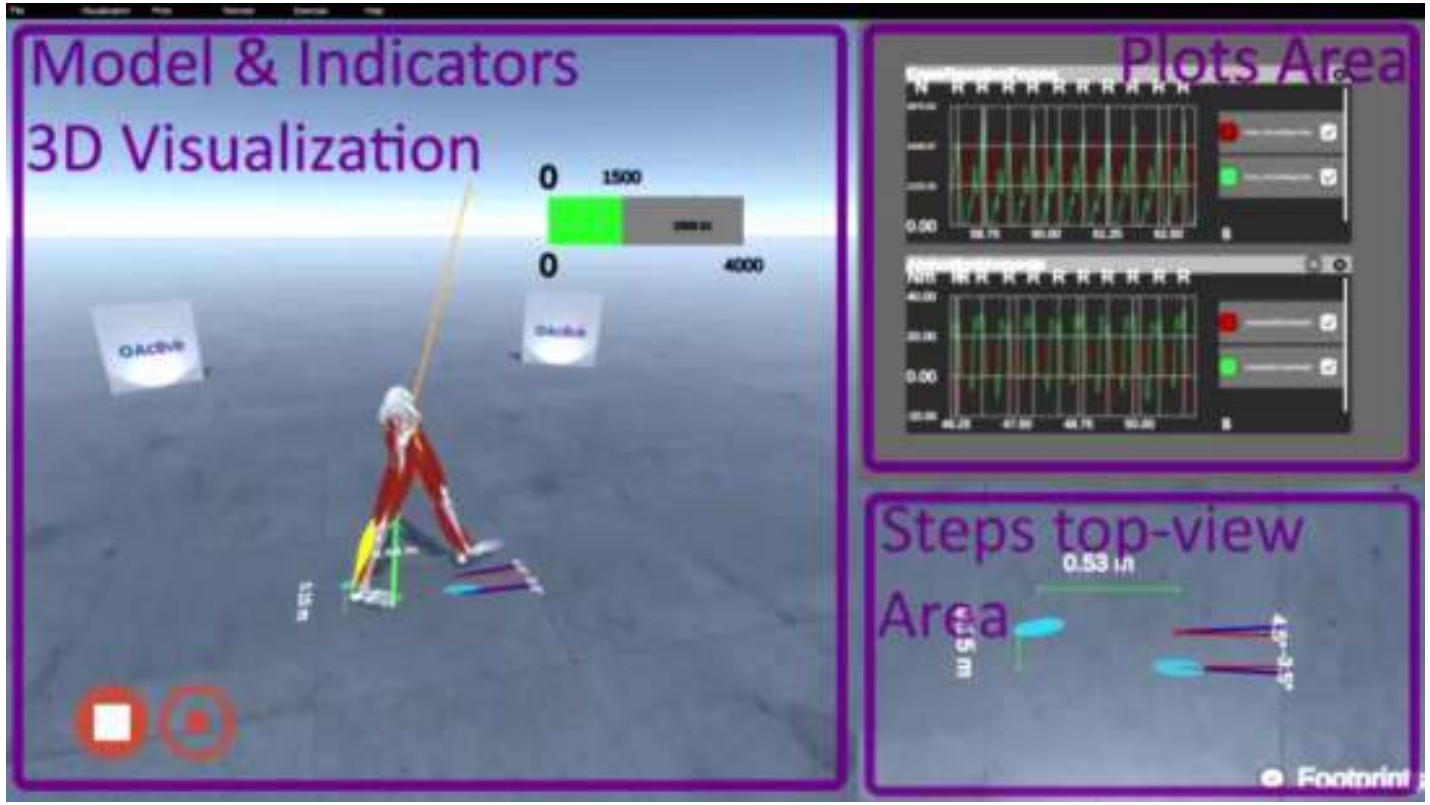
Oactive Gait Retraining System

Work completed

- ✓ Clinician front-end
- ✓ Patient front-end
- ✓ Multiple visualization options
- ✓ Real time

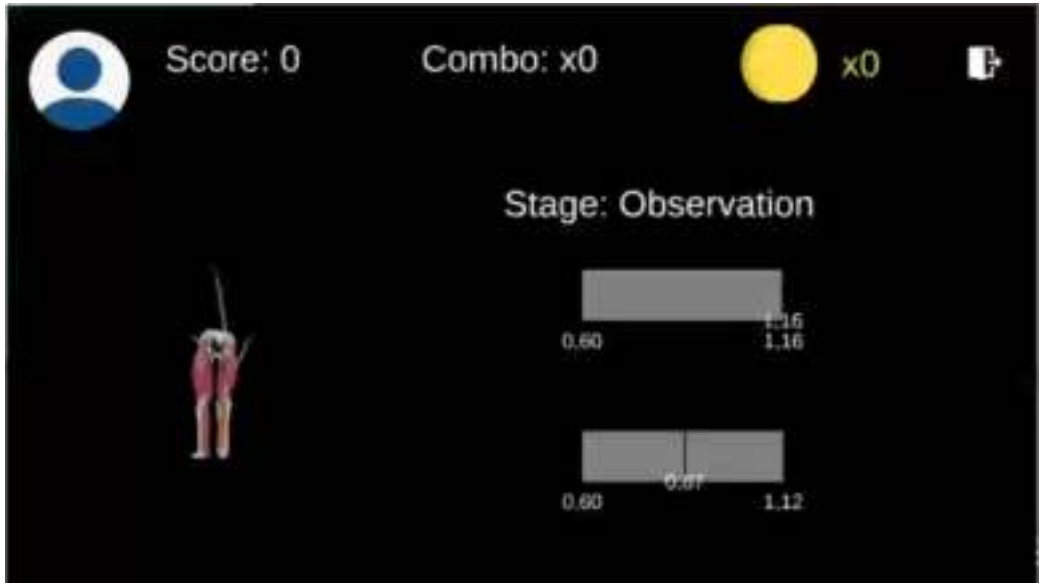
Work in progress

- Vibrotactile feedback using wearable vest or belt



Games development

- ✓ Patient front-end
- ✓ State-of-the-art gamification approaches in clinical settings
- ✓ Game platforms and elements
- ✓ Investigation of game elements that enhance patient motivation and engagement
- ✓ Integration with the gait retraining module
- ✓ Primitive visualization cues
- ✓ Exercise-agnostic gamification elements, based on metrics set by the clinician

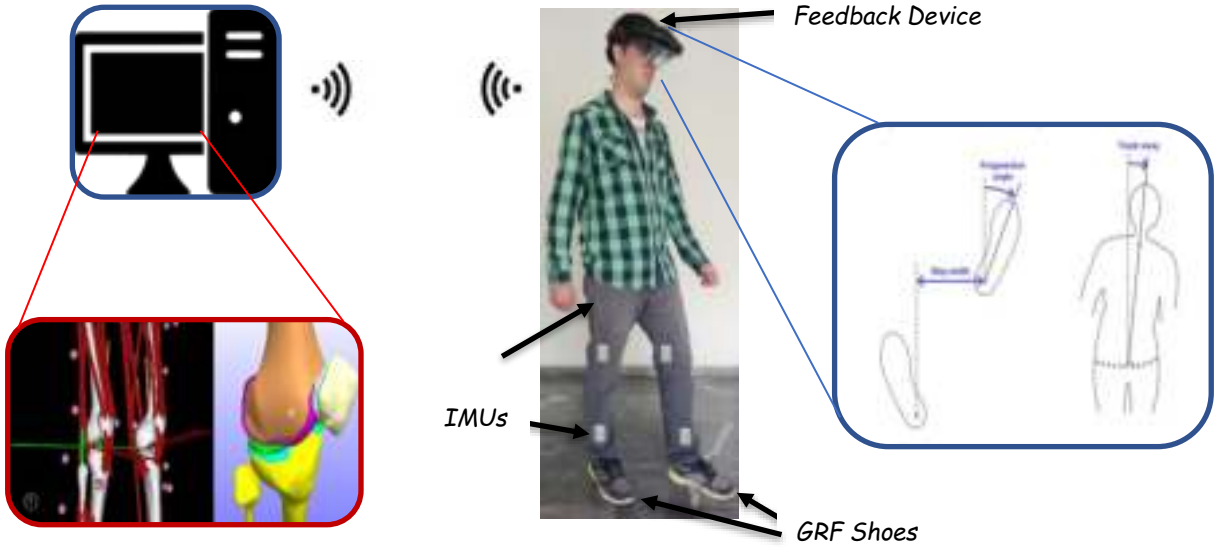


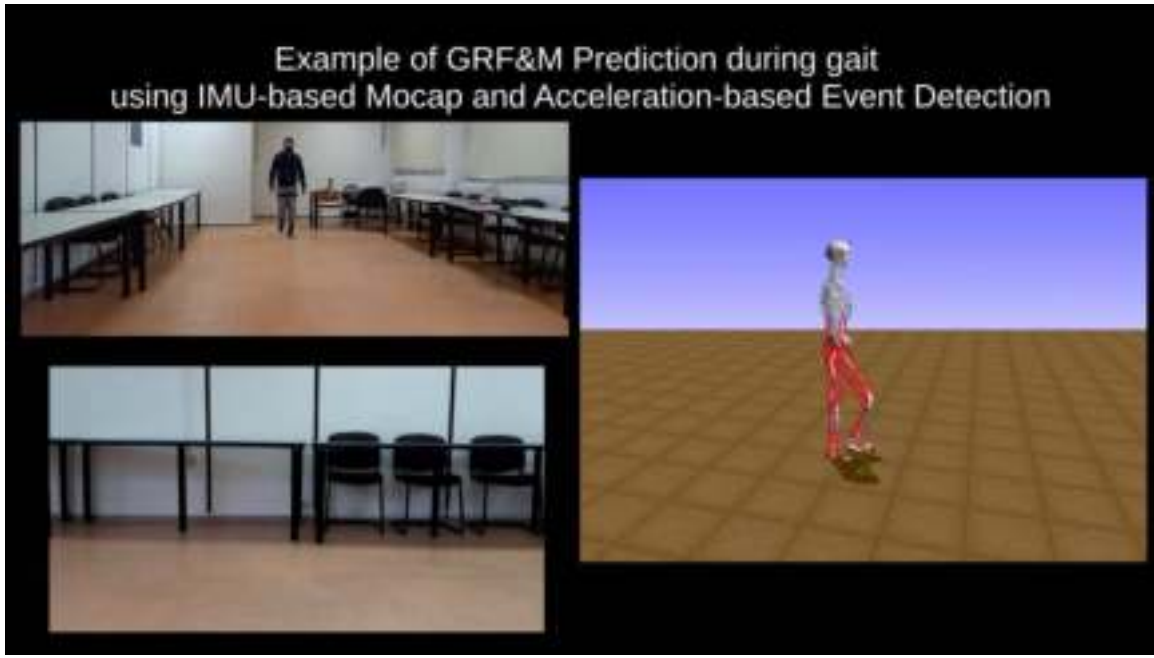
Use case – single leg hop

- Lack of treadmill
- Hopping exercise
- Selected metric:

  jump height

Mobile solution - IMUs



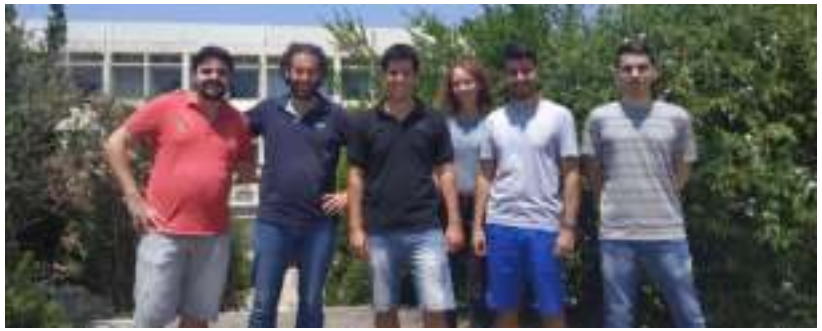


Stanev, D.; Filip, K.; Bitzas, D.; Zouras, S.; Giarmatzis, G.; Tsaopoulos, D.; Moustakas, K. ***Real-Time Musculoskeletal Kinematics and Dynamics Analysis Using Marker- and IMU-Based Solutions in Rehabilitation.*** Sensors 2021, 21, 1804.

Finalist in the category “Tech of Society” for the Innovation Radar Prize 2019

Related work

- Automated segmentation of knee MRI
- Subject-specific modeling
- Simulation and analysis of the knee mechanics in real time
- Loading of soft tissues during motion
- **Informed gait retraining interventions**



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Thank You

Questions